

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2023 January 9; 12(1): 1-24



Contents

Bimonthly Volume 12 Number 1 January 9, 2023

REVIEW

- 1 Play therapy in children with autism: Its role, implications, and limitations

Elbeltagi R, Al-Beltagi M, Saeed NK, Alhawamdeh R

LETTER TO THE EDITOR

- 23 Adipocytokine profile in children with Kawasaki disease

Joob B, Wiwanitkit V

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Mohammed Al-Biltagi, PhD, MD, Professor of Pediatrics and Pediatric Cardiology, Faculty of Medicine, Tanta University, Tanta, 31527, Algharbia, Egypt; Senior Consultant Pediatrics, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Bahrain. mohamed.elbeltagi@med.tanta.edu.eg

AIMS AND SCOPE

The primary aim of the *World Journal of Clinical Pediatrics* (WJCP, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCP mainly publishes articles reporting research results and findings obtained in the field of pediatrics and covering a wide range of topics including anesthesiology, cardiology, endocrinology, gastroenterology, hematology, immunology, infections and infectious diseases, medical imaging, neonatology, nephrology, neurosurgery, nursing medicine, perinatology, pharmacology, respiratory medicine, and urology.

INDEXING/ABSTRACTING

The WJCP is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; **Production Department Director:** Xiang Li; **Editorial Office Director:** Yu-Jie Ma.

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2219-2808/editorialboard.htm>

PUBLICATION DATE

January 9, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Play therapy in children with autism: Its role, implications, and limitations

Reem Elbeltagi, Mohammed Al-Beltagi, Nermin Kamal Saeed, Rawan Alhawamdeh

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Liao JX, China;

Masaru T, Hungary

Received: July 27, 2022

Peer-review started: July 27, 2022

First decision: September 5, 2022

Revised: November 8, 2022

Accepted: November 23, 2022

Article in press: November 23, 2022

Published online: January 9, 2023



Reem Elbeltagi, Department of Medicine, Royal College of Surgeons in Ireland - Bahrain, Busaiteen 15503, Bahrain

Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31527, Egypt

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Bahrain

Nermin Kamal Saeed, Pathology Department, Salmaniya Medical Complex, Manama 12, Bahrain

Nermin Kamal Saeed, Pathology Department, Irish Royal College of Surgeon, Bahrain, Busaiteen 15503, Bahrain

Rawan Alhawamdeh, Pediatrics Research and Development Department, Genomics Creativity and Play Center, Manama 0000, Bahrain

Rawan Alhawamdeh, School of Continuing Education, Masters in Psychology, Harvard University, Cambridge, MA 02138, United States

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Academic Editor, Chairman, Consultant Physician-Scientist, Professor, Researcher, Department of Pediatrics, Faculty of Medicine, Tanta University, Al Bahra Street, Tanta 31527, Egypt.

mbelrem@hotmail.com

Abstract

Play is a pleasurable physical or mental activity that enhances the child's skills involving negotiation abilities, problem-solving, manual dexterity, sharing, decision-making, and working in a group. Play affects all the brain's areas, structures, and functions. Children with autism have adaptive behavior, adaptive response, and social interaction limitations. This review explores the different applications of play therapy in helping children with autism disorder. Play is usually significantly impaired in children with autism. Play therapy is mainly intended to help children to honor their unique mental abilities and developmental levels. The main aim of play therapy is to prevent or solve psychosocial difficulties and achieve optimal child-healthy growth and development. Play therapy helps children with autism to engage in play activities of their interest and choice to express themselves in the most comfortable ways. It changes their

way of self-expression from unwanted behaviors to more non-injurious expressive behavior using toys or activities of their choice as their words. Play therapy also helps those children to experience feeling out various interaction styles. Every child with autism is unique and responds differently. Therefore, different types of intervention, like play therapy, could fit the differences in children with autism. Proper evaluation of the child is mandatory to evaluate which type fits the child more than the others. This narrative review revised the different types of play therapy that could fit children with autism in an evidence-based way. Despite weak evidence, play therapy still has potential benefits for patients and their families.

Key Words: Autism; Play therapy; Children; Autism spectrum disorder; Sensory integration therapy; Art-play therapy; Equine-partnered play therapy; Child-centered play therapy; Synergistic play therapy

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Play is a pivotal activity for humans, especially children. It plays an essential role in children's physical and mental development. Play therapy has been used for a long time to manage various diseases. Play therapy helps children with autism to engage in play activities of their interest, express themselves in comfortable ways, and change their self-expression from unwanted behavior to more non-injurious expressive behavior. There are different forms of play therapy. Proper evaluation of the child is mandatory to evaluate which fits the child more. Play therapy has a lot of potential benefits for patients and their families.

Citation: Elbeltagi R, Al-Beltagi M, Saeed NK, Alhawamdeh R. Play therapy in children with autism: Its role, implications, and limitations. *World J Clin Pediatr* 2023; 12(1): 1-22

URL: <https://www.wjgnet.com/2219-2808/full/v12/i1/1.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i1.1>

INTRODUCTION

Play is pleasurable, intrinsically motivating, process-oriented, freely chosen physical or mental activities in which the child actively engages spontaneously, mainly in a safe environment. Children must have fun, or it is not considered a play[1]. Children from the neonatal period to adolescence spend 3%-20% of the day playing. Play is a fundamental daily activity that allows children to learn and master various skills involving negotiation abilities, problem-solving, emotional intelligence, improving their manual dexterity, sharing, decision-making, and working within a group. Play helps children to discover their interests. Play promotes the integration of mental development with social life.

Furthermore, unstructured play allows children to exercise more, spend more calories, avoid sedentary life effects, and remain healthy. Children do not need to learn how to play; they acquire it naturally. Play is developmentally relevant to childhood[2,3].

Consequently, play becomes the child's language, and the toys become the child's words. Play and toys become a medium to prevent or resolve social and/or psychological difficulties that the child may become exposed to. Adults usually underestimate children's capabilities, especially when it comes to playing. Adults usually lead the children during playing with an agenda that seems vital to them without allowing them to play according to what they want or need. There is less opportunity for children to play without directiveness, rules, conditions, and/or agenda. Adults usually change or ruin the child's structure and flow of play[4]. The play could be advocated in educational, medical, mental health systems, and/or community settings. Play became an option when all seriousness occurred. It became a reward despite being crucial and is integrated into healthy child development. Play helps us to communicate with the child's language so that we can enter their world, which is often left silent. Play is the child's language when we start to listen to him[5].

Autism prevalence has been increasing over the last decades. Autism is a spectrum characterized by a wide range of persistent shortages in social interaction, impaired communication skills, restricted-repetitive forms of behavior, and the loss of social interests or activities. These social communication and interaction impairments may be due to impaired social signaling interpretation and failure to guide proper behaviors[6]. The exact mechanisms for these behavioral abnormalities are not yet defined. However, autism results from genetic defects and neuroinflammation of the immature brain. Neuroinflammation could result from a malfunctioning placenta, an immature blood-brain barrier, aberrant maternal immune activation by infection and maternal dysbiosis during pregnancy, a premature delivery, and antenatal exposure to nutritional and toxic metals through mid-fatal development, early

postnatal encephalitis, or a toxic environment[7,8]. There are more mitochondrial disorders and dysfunction incidences in children with autism than in the general population, which commonly occur secondary to environmental factors[9]. In addition, discrepancies in the glutathione redox system are a crucial factor in autism pathophysiology, causing proteotoxic stress and other defects in sulfhydryl-containing enzymes in the blood and brain[10]. This review aims to explore the effects of play in modulating the symptoms of autism and aims to investigate the different applications of play therapy in helping children with autism disorder.

LITERATURE SEARCH

To build an evidence-based view of this aim, we conducted a comprehensive literature review by searching electronic databases, including PubMed, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Scopus, Library, and Information Science Abstracts, and the National Library of Medicine catalog up until June 30, 2022, using the keywords: play, play therapy, autism, autism spectrum disorder. We included full-text research (66 articles), reviews (55 articles), systematic reviews (7 articles), metaanalysis (3 articles), Case reports (7 articles), guidelines (two articles), commentaries (two articles), and book chapters (16), written in English and concerned with using play therapy in the management of children with autism (Figure 1). Reference lists were inspected, and citation searches were performed on the included studies. We also reviewed many review articles concerned with the same topic. We also reviewed the articles that are available as abstracts only. We excluded articles that could have a commercial background.

PLAY IN DIFFERENT STAGES OF CHILDHOOD

Intrauterine fetal play

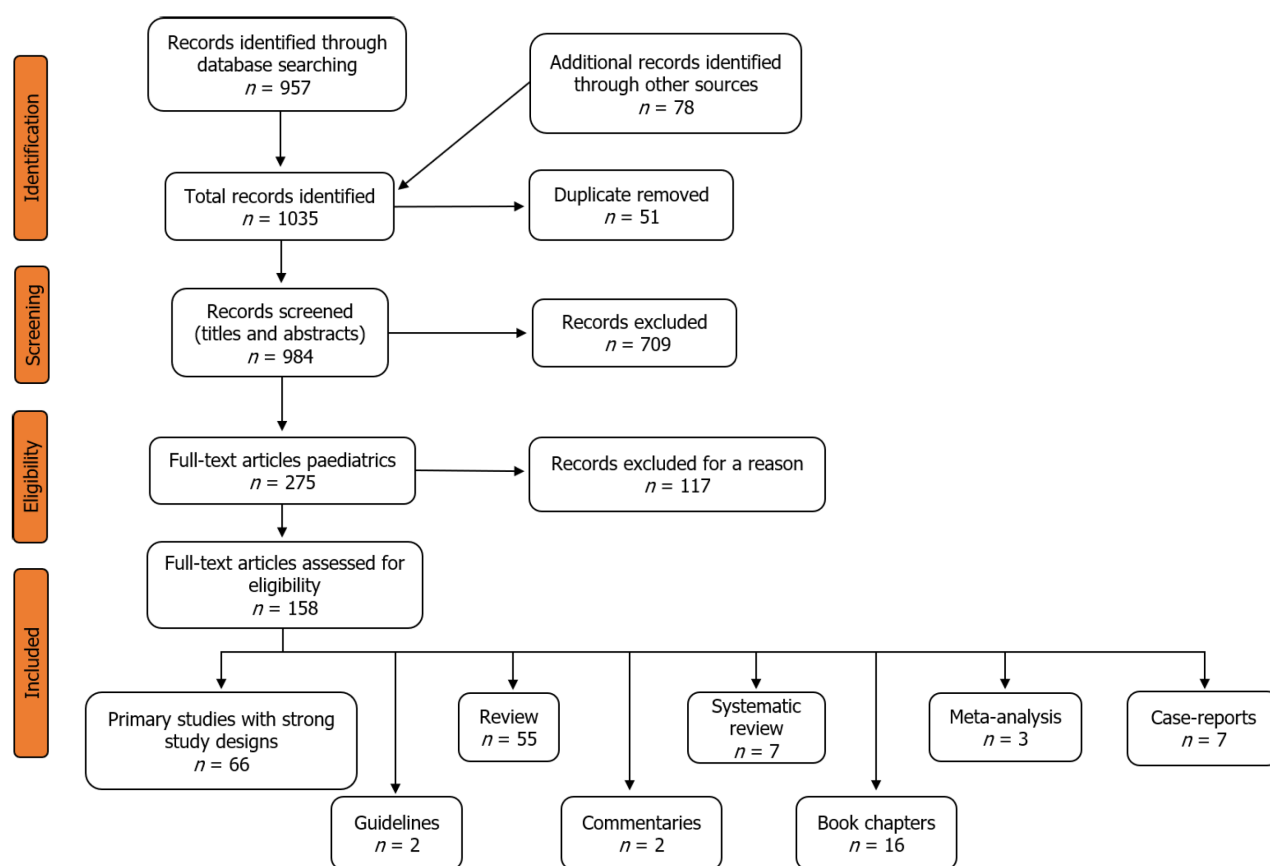
The fetus develops a unique type of sensory play at a very early stage of gestation and begins to develop its tactile system due to the surrounding amniotic fluid. The fetus swims smoothly in a way that activates the vestibular system and sense of direction, which helps to develop a sense of proprioception when kicking and pushing the inner sides of the womb[11]. The fetus starts to hear the mother's body sounds, such as heartbeats or stomach rumbling, by the 18th week of gestation and starts to react to these sounds by the 26th week. After the 32nd week of gestation, the fetus can recognize certain vowel sounds from the mother language, suggesting very early language development even before birth. The fetus can memorize his mother's voice and more complex auditory external sounds with considerable discrimination capacity[12]. Fetuses may startle or even cry when exposed to sudden loud sounds. The mother can start playing with her fetus by touching or rubbing her abdomen in response to fetal movement. The father can massage the fetus's bump if the mother is happy with that. Both can talk, sing and read, so the fetus can get used to sounds[13]. These maneuvers help to strengthen fetomaternal bonding and enhance fetal development. The auditory and olfactory systems also develop in unique ways. A previous study has shown that the baby feels comfortable if his pillow is sprayed with the smell of food that the mother used to eat while she was pregnant with that baby. Babies who ate cereals with carrot flavor showed better facial expressions if the mother consumed carrots during gestation. Moreover, if the baby listens to music that the mother used to hear while she was pregnant with him, he will sleep deeper and more comfortably[14].

Neonatal play

Playing with newborns helps them learn about the new world and how to interact with it. Play permits their brains to grow and develop, build muscles, and develop gross and fine motor skills. The mother's play with the baby helps her understand her baby and helps the baby feel love and build trust with the mother. Play strengthens the bonding between the mother and the newborn. Playing with the newborn needs simple actions such as singing, chatting, tickling, counting toes, blowing raspberries, smiling, laughing, rolling the eyes, or poking the tongue out. Even during the nappy change, the mother could have an excellent chance for face-to-face play[15]. In other words, the mother needs to use what is called "serve and return," in which the child gives action, and the mother or the father must respond right away to keep the child engaged[16]. The mother can use rattles, soft toys, or cloth books with painted pages and different textures. This tactile play helps the neonates to feel different things and learn about the external world. Reading can start soon after birth. The mother should hold books close to the baby's eyes within the visual range of 20 to 30 centimeters. Early reading helps infants get used to sounds and words to build language and enjoyment with books[17,18].

Childhood play

Play is a central component in typical child development and learning and is a fundamental right of every child. Play is the main occupation of children. Play is critical in maintaining children's physical



DOI: 10.5409/wjcp.v12.i1.1 Copyright ©The Author(s) 2023.

Figure 1 The flow chart of the study, according to PRISMA 2009 guidelines.

and mental health. The main intention of the child's play is to have fun; however, play enhances psychosocial development and helps children to discover the surrounding world. It helps children enface reality and adapt it to their wishes[19]. Play enriches the children's physical, social, cognitive, and emotional abilities and sense of well-being. In the meantime, play promotes the children's skills and abilities to study and work. In addition, it hones their relationships with their peers and community and helps them gain independence, confidence, self-esteem, interaction, resilience, curiosity, and coping with challenging situations[20]. The degree of playful behaviors during play varies between 0-100% depending on the presence of purpose, pleasure, and enjoyment degree, and how much the child is process-oriented[21].

Children are affected by day-to-day changes in the world around them. Consequently, the degree of playful activities depends on the child's age, the local culture that impacts the parents' concepts of playing, and the type of the child's play. It is also affected by social class and urban or rurality[22]. Playtime is also affected by the media, local culture and tradition, fashion, books, sex, and ethnicity. Unfortunately, children currently spend less time in actual playing due to the stress of study and school testing, even though play establishes the foundation for effective lifetime learning. Therefore, pediatricians must promote the importance of playful learning to young children by supplying children with rich play practices and assisting the parents to understand better the significance of playful learning in children's lives. Parents playing with their children establish the base for children's ability to play with their peers effectively[23,24].

Play could help to build motivated, happy, and healthy children to be the future of a productive society. There are different types of social play the children can do. In the solitary play, every child plays alone, while in parallel play, the children are engaged in similar activities, but each child plays separately. In associative play, children play individually, but they may share, pay joint attention, and occasionally communicate with each other. Meanwhile, in cooperative play, children are involved in play with a shared goal, and they play together to achieve this goal. Consequently, play helps to increase social interaction, which usually increases over time[25,26].

Object play

In object play, children actively playfully manipulate objects. This active manipulative play is used to either explore or construct objects. With time, manipulating and visualizing objects and toys improves visual-motor integration skills necessary for reading, writing, and many other daily-life activities[16]. It

starts as early as the fifth postnatal month when the infant starts exploratory playing by putting everything in his mouth. By age two, the child starts constructive playing as he can combine objects when playing, such as building a tower from some blocks or lining small cars beside each other[27]. Over the next few years, constructive play increases to be combined with imaginative and pretended play, where children start to construct more complex creative models blending constructive and pretended play together, representing the world around them. Constructive play is established when the child develops a constructional praxis ability[28]. By year four, children spend about half of their free-play time in constructive play, extending to preschool and elementary years. Object Play significantly impacts the children's physical, cognitive, and social development by enhancing fine and gross motor skills and manual dexterity. Interactive, cooperative object playing with adults or peers significantly impacts the child's social development more than solitary, parallel, or associative play[29].

Pretend play

Pretend play is characteristic of early childhood, in which the child creates an imaginary reality alternative to the real world. The child assumes other people's roles or imagines other places, things, or other times. The child can also use objects as a symbol for what is imagined. For example, the child uses the banana as a telephone. Pretend play can occur in a group, where a group of children cooperate and assume complementary characters, which enhances social interaction[30]. Pretend play may appear by twelve months when the infant pretends to sleep. Later, children direct their pretending towards other people and surrounding objects. They may animate the surrounding objects in their imaginative play. They may use models like dolls or stuffed animals in their acting play. The child also can respond to pretend play as early as two years old; for example, when a person pretends to do something, the child may pretend to do a complementary or opposite action[31]. Overt pretend play usually diminishes by middle childhood when the child acquires more interest in organized games. Pretend play performs a crucial role in the cognitive and social development of the child with a marked impact on a wide range of cognitive, cultural, emotional, social, and competence skills. It also helps to enhance the child's creative and problem-solving abilities and language skills[32]. The earlier the pretend play, the better literacy outcomes, especially for reading and comprehension abilities and communication skills, particularly speech and writing. Pretend play is also a prominent factor in developing the child's self-regulating abilities and different aspects of executive function[33]. These abilities, in turn, impact school readiness, memory development, attention empowerment, intelligence enhancement, morality, and emotion regulation. Pretending also helps children to understand others. When they step into the shoes of a character, they imagine what he would say, do, or feel, which helps them to understand other people. Pretending and fantasy could also allow children to express their feelings, regulate their thoughts, and better cope with their emotions[34].

Physical play (locomotor or exercise play)

Physical play involves any physical activity performed in a playful and joyful context, such as running, climbing, skipping, gambol, hopping, kicking a football, and chasing. It has an inverted U-shaped curve, gradually rising from infancy across the school years and then decreasing during adolescence[35]. Physical play is essential nowadays, especially with increasing obesity and insulin resistance rates among children and adolescents. Physical activity improves insulin sensitivity, helps fight obesity, and promotes healthy lifestyles[36]. Encouraging childhood physical play and gross motor skills is essential to boost physical activity levels with enormous health benefits, including aerobic endurance, strengthening muscle growth, better coordination, enhanced growth stimulation of crucial organs, and augmented bone mineral content[37,38]. In addition, physical play improves cognitive, mental, and academic fields, contributes to self-regulation development and expression, and improves school-age children's executive function, particularly with organized and planned activities like sports. It also enhances academic outcomes through increased attention to educational tasks[39,40]. Physical play promotes the sensory integration, incorporation, and processing mechanism between the central nervous system and the body. Thus, sensory integration enhances cognitive, social, emotional, academic, and communication skills to higher levels[41]. Physical play and sensory integration are evidence-based methods that support the development of children in general and children with ASD. **Figure 2** shows the application of sensory play in the Genomics Childhood Sensory Play Center, the first epigenetic play center in the world, based in Manama, Bahrain. Unfortunately, physical play is markedly affected during the COVID-19 pandemic reaching alarming rates. This environmental deprivation affected children's physical, emotional, communication, social, and academic learning abilities[42].

Media play

Technology plays a crucial role in children's lives today, much more than before. Before the COVID-19 era, children younger than three years spent 3-4 h/day on-screen media. This number increased to 7.5 h/d by eight years of age. In the COVID-19 era, the number of hours children spend on media screens has significantly risen[43]. There are contradictory opinions about the effects of media on children's behavior and development. A popular opinion suggests that media and gaming are responsible for



DOI: 10.5409/wjcp.v12.i1.1 Copyright ©The Author(s) 2023.

Figure 2 The application of sensory play in the Genomics Childhood Sensory Play Center, the first epigenetic play center in the world, based in Manama, Bahrain.

increasing obesity rates, reducing social skills development, encouraging violent behavior, and negatively affecting language, social, cognitive, and emotional development[44]. On the other hand, other studies endorse that media and video gaming enhance athletic participation and decrease the rate of obesity. Those studies suggest that video game players are more likely to be open-minded, show more obedience to their parents, have more academically minded friends, and are no more violent or aggressive than non-video game players[45,46]

Technology-based games construct a powerful tool to enhance playful learning, especially when the interest in traditional play starts to wane. In addition to fun, these games allow children to practice high self-control and self-learning with trial and error. These games also varnish their memory, skills, critical thinking, executive function, qualitative thinking, and creativity in problem-solving and advance their knowledge through escalated levels of complexity impregnated into the games. In addition, these games used different tactile, visual, and auditory modalities with increased visuospatial abilities, allowing children to have various learning styles[47,48]. These games teach children to stay on task for longer and be more patient in reaching their goals. For instance, Genomics Childhood Sensory Play Center uses interactive projector games that enable children to use tactile, vestibular, proprioceptive, auditory, and visual systems more effectively.

Moreover, they have specific reaction times to give an adaptive response and functional performance. Thus, they promote self-esteem, self-confidence, mind, brain, and behavior. That being experienced, children achieve higher and innovate throughout their future education, career, family, and life in general. However, the degree of benefit from media and video games is age dependent. For example, television viewing has mostly negative associations for children younger than two years, particularly for executive function and language. Conversely, television viewing has positive and negative outcomes for preschool children[49].

Meanwhile, media play has more positive results in older children. Educational video games targeting middle-school to college students increase learning achievement by 7%-40% more than lecture-based learning[47]. We should also emphasize that technology will never replace traditional play. Children still need outdoor playing, pretending, hard book reading, manual drawing, and other forms of play that enhance manual dexterity. Media and video games should only be considered tools to enhance child play and learning within monitored contexts, age groups, and evidence-based practices. It is critical to mention that the effects of flat-screen media usage on developing brains are detrimental, especially for children below two years old. Children between two to five years old are advised to have no longer than one hour of daily flat-screen use[50].

THE SEXUAL DIFFERENCES IN PLAY

The differences in play between boys and girls are related to many factors, particularly parents and other social influences (*e.g.*, local cultures and media). Physique is also an essential factor in sex differences in play. Tissera *et al*[51] found that adolescent males outperformed females in all off-court fitness characteristics. Sex differences in play appear as early as 18 mo of age. Caldera *et al*[52] and Dinella *et al*[53] showed that these children demonstrated more interest when playing with same-sex-typed or neutral toys than when playing with cross-gender toys. This sex-typed play continues to increase as they get older[52,53].

Boys differ from girls in three aspects of play: preferred play partners, toy choices, and social play. Boys usually prefer dynamic toys such as rocket ships, vehicles, cars, trucks, boats, mechanical sets, and toy weapons such as guns and swords, while girls prefer cosmetics, passive nature – dolls, dress-up costumes, and household toys such as toy stoves and tea sets. Most children (80% and 90%) favor playmates of the same sex. Hence, girls prefer to play with girls, and boys prefer to play with boys. Boys are more physically active than girls, so they also prefer aggressive and rough play, such as chases, fights, wrestling, and other kinds of rough play[54-56]. Lamminmäki *et al*[57] did an exciting study to explain the difference between boys' and girls' play. They correlated the testosterone levels with the play type. They found that testosterone levels in boys significantly and positively correlated with playing with a train and negatively correlated with doll playing.

EFFECT OF THE PLAY ON THE BRAIN

Cortico-cerebellar system is a neural system involved in complex cognition and creating complex behavior, including play[58]. Play induces epigenetic molecular changes, enhancement of neural cell connectivity, behavioral modifications in executive functioning skills, socioemotional status and learning, and adaptive and prosocial behavior. Play affects all the brain's areas, structures, and functions, including the upper and lower brain and the right and left hemispheres, particularly for sensory integration and processing. The prefrontal cortex is the anterior part of the frontal lobe. It is considered the brain's executive control center, involved in cognitive control, planning complex cognitive behavior, decision-making, personality expression, controlling social behavior, managing attention, prospective memory, impulse inhibition, and cognitive flexibility[5]. The more engaging in free play, the more the brain builds new circuits in the prefrontal area to facilitate the navigation of these intricate social interactions. Play through increasing dopamine and gamma-aminobutyric acid (GABA) causes prefrontal cortex changes and increases its wiring, enhancing the executive control system involved in controlling emotions, problem-solving, plan-making abilities, and whole brain sensory integration and information processing speed[59]. Designing special programs with active and dynamic play elements may be more effective in stimulating executive function development due to the influential early motor learning and the social motive aspects of learning[60].

A healthy brain is a well-integrated brain, where various parts of the brain can co-transmit a message to each other and work in harmony as one unit. Play increases whole brain integration, like sensory integration and processing. Play increases physical movement, enhances creative self-expression, and increases self-regulation practice. Therefore, play helps the integration of the left cerebral hemisphere with its logical, analytical, personal narrative, and emotional language with the right cerebral hemisphere with its creativity, expression, and sensations functions[5]. In addition, play triggers the brain's incentive circuitry but not harmful stress responses, enabling proper attention and action[61]. Not only the prefrontal cortex is modified by play, but the lower brain regions as well. Play affects these regions due to motor regulation, emotional engagement, and the children's trials to build a sense of safety and to create physically 'safe' worlds with continuous repetitive motor, emotional and sensory feedback to and fro involving the neural network with a continuous rewiring process, benefiting from the high brain plasticity during childhood. Kerney *et al*[58] found a positive association between the relative size of the cortico-cerebellar system's main components and the amount of play in a sample of primate species.

Play refines the medial prefrontal cortex's dendritic length, density, and spine complexity at the cellular level. Play also stimulates the production of the brain-derived neurotrophic factor (BDNF) in the amygdala, hippocampus, dorsolateral frontal cortex, and pons, supporting existing neurons' survival and promoting the new neurons' and synapses' growth and differentiation[62,63]. A 30-min play can modify the expression of approximately one-third of the 1200 genes (especially the *BDNF* gene) present in the posterior and frontal cortical regions within an hour[64,65]. Two hours of daily play showed significant changes in the weight and efficiency of the experimental animals' brains[66]. Conversely, play deficiency impeded the process of pruning and synaptogenesis with impaired problem-solving and executive functioning skills and less behavioral flexibility[67,68]. Play affects the level of brain neurotransmitters, increasing dopamine levels in substantia nigra and ventral tegmentum neurons, activating norepinephrine which facilitates synaptic learning and improves brain plasticity, and decreases levels of the stress hormone cortisol[5,69].

PLAY THERAPY

Play therapy has been implemented in psychiatry for nearly a century. However, it has been practiced for hundreds or even thousands of years. Play therapy is mainly intended to help children. It is a way in which the children use play to honor their unique mental abilities and developmental levels to window up their feelings, emotions, wishes, wants, desires, joys, fears, anxiety, worries, and communication as a play language. The main aim of play therapy is to prevent or solve psychosocial difficulties and achieve

optimal child-healthy growth and development[70]. It enables the child to overcome different obstacles in the pathway to proper development, helps the child to be more responsible in his behavior, and develops successful strategies and creative solutions to problems. It also trains the child to respect and accept himself and others, learn how to express his feelings and emotions, and respect others' thoughts and feelings[71]. Play therapy can be used as a diagnostic and therapeutic tool. Initially, the play therapist observes the child during playing to identify the child's problem; assess his/her problem. Then, the therapist deals with the problem accordingly by scaffolding and supporting the child to learn and execute self-expression and communicate *via* his/her thoughts of the inner world. The therapist helps overcome unresolved trauma, enables the child to master and execute a new coping mechanism, redirects inappropriate behaviors, and enriches adaptive behavioral responses[59,72].

Although play therapy schools differ in their philosophy and techniques, they all incorporate play's therapeutic effects and developmental assets[73]. Each play therapy session lasts about 30 to 60 min, once a week or so. Play therapy has four primary therapy stages after an initial phase of an interview with the family and child with a preliminary treatment assessment (Table 1 and Figure 3). The number of sessions in each phase depends on the child's needs and response to this type of therapy. Therapy can occur individually or in groups.

The first phase is the initiation phase or exploratory stage, which is the most critical time when the child explores a new atmosphere (the playroom, the play therapist, and the play therapy process) not used to and starts to adapt himself to it. The duration of this phase depends on the child's personality. This phase becomes longer if the child exhibits more shyness and introverted traits. The child usually needs the family's encouragement, so he or she will provide the therapist a chance to begin working. Once the child is comfortable expressing himself, he realizes his role as an active agent and develops a sense of security necessary for advanced therapeutic work; he moves into the next stage of play therapy after being tested for his non-so-socially acceptable behavior. After successful testing, some children may experience the resistant (aggressive) phase when confronted with their maladaptive behavior. In this stage, the child resists change and may actively avoid attending play therapy sessions. Some children may pass this phase rapidly within a few sessions, while others may need months to overcome that[74,75].

After passing the resistant phase, the actual work phase comes, as it is the most crucial and usually the longest part of play therapy. The child is ready in each session to exert the hard work needed for personal growth and recognize his or her problems, how to best solve those problems, and how to survive a much happier and more active life. He improves his self-esteem, communication, behavior, and general attitude toward life[76]. Occasionally, the child may show some regression and step back, but with the parents' and the therapist's support, he overcomes it. When the child shows a consistent demonstration of his new skills easily, achieves the targeted therapeutic goals, and shows emotional and behavioral stability in different situations and environments, we can start the termination phase in which we gradually decrease the frequency of the session to once weekly and then monthly until we discharge the child, provided that the child maintains his progress with less support. Some children may feel frustrated during this phase due to their feeling of being punished for achieving positive outcomes[77].

The play therapist should create and hold a safe space for the child. He should be able to reflect feelings and behaviors with unconditional positive regard. He creates a permissive environment for the child where anything can be expressed. At the same time, he should set boundaries when necessary to ensure an appropriate holding environment. The therapist observes and gains perceptions of the child's problems; then, he can help the child explore his emotions and deal with any unresolved trauma by scaffolding the child and the therapeutic achievement[78]. The therapist uses play to help children redirect unacceptable behaviors, discover and practice new coping mechanisms, and form new functional neuronal circuits and healthier epigenetic mechanisms. Therefore, the therapist should have competent clinical, psychological, and occupational Knowledge, exceptional communication skills, a calm, patient, and friendly manner, with the ability to understand a variety of emotions and behaviors and to adapt to change and handle stressful situations. As play may need physical effort, the therapist should be physically fit to work on the floor or perform various physical activities[72].

Effects of play therapy on the brain

Play is an emotionally pleasing and creative experience that raises oxytocin levels. The Oxytocin hormone boosts feelings of emotional well-being and trust. Thus, Oxytocin facilitates the therapeutic relationship between the play therapist and the child, which helps the child to use his imagination and makes him ready for behavioral change. Play also activates the mirror neurons, which helps the therapist to read and interact with the child's emotional status accurately. Play therapy encourages the formation of new neural circuits and promotes neuroplasticity[79]. Play therapy-induced neuroplasticity through four main pathways: empathic harmony, which provides the ideal chemical environment to develop new neural pathways; emotional provocation, which consolidates and integrates the neural pathways; affect and cognition integration which helps the emergence of complex, elegant neural outlines, and co-constructing nonverbal narratives of self-cognizance and changes[80,81]. Play therapy allows the child to integrate the creative, emotional, and expressive functions of the right brain with the logical, rule-oriented, and analytical functions of the left brain. The brain needs 400 repetitions to

Table 1 Stages of play therapy

Stage order	First	Second	Third	Fouth
Name of stage	Initiation phase or exploratory stage	Resistance phase, negative reaction, aggressive stage	Growing phase, or work phase	Termination phase
Duration	Initial 4-6 sessions	Few sessions to a few months	The longest phase	Gradual decrease the number of sessions to every other week or once a month to see if the child can maintain the progress with less support
Aim	The child gets to know the room, the therapist, and the toys, learn the roles of each participant and what is expected from him and develops a bond with the therapist	To help the child confront his maladaptive behavior, helps the child to express his emotions and learn how to communicate his feeling in his body in an acceptable way to society, and start accepting the new changes	To start learning, healing, stepping out of the child's comfort zone and making changes with an improvement of self-esteem, behaviors, communication, and overall outlook on life	To gradually withdraw the play therapy when the child reaches behavioral and emotional function stability in different situations
Counselor role	Acknowledge the child's presence and let the child be aware of his presence They are building a trusting relationship and fostering a safe environment for the child to express himself freely	The counselor confronts the child with his maladaptive habits and pushes him to decide to put in the work or keep fighting because it feels difficult	To help the child better address and understand his difficulties, how to best overcome these difficulties, and how to live happier and playful life by utilizing practical coping skills with little prompting, demonstrate self-regulation, and build resiliency and flexibility with change	To ensure that the child is consistently demonstrating his new skills with ease, and that behavioral and emotional needs have stabilized in multiple environments To support what the child achieved during the few appointments the child does
Parents Role	The parents may attend the first session to support and encourage him till he is used to the therapist	They can support and encourage the child to give the treatment a chance to begin working	They should practice empathy and remain consistent with their expectations. They should support the child emotionally and remind him of his new skill set	They should compensate for the decreasing number of appointments by building a bridge of trust with their child
Child status	The child explores the playroom and the toys. He may have a desire to touch and try out everything he sees to gain an awareness of what is available to him. He also could be hesitant and uncertain about his role in the playroom and look to the therapist to take the lead. He needs to know what to do and what not to do	The child shifts from the comfortable to the uncomfortable zone with a loss of familiarity and starts the change. The child may no longer want to attend therapy	The child will achieve significant advances. However, he may have regression into some of their pre-existing problem, behaviors, or symptoms. This regression may frustrate both child and parents	The child feels this stage is difficult as the secure relationship he had developed with his therapist will start to change with fewer appointments. He feels as if he is being punished for making positive changes

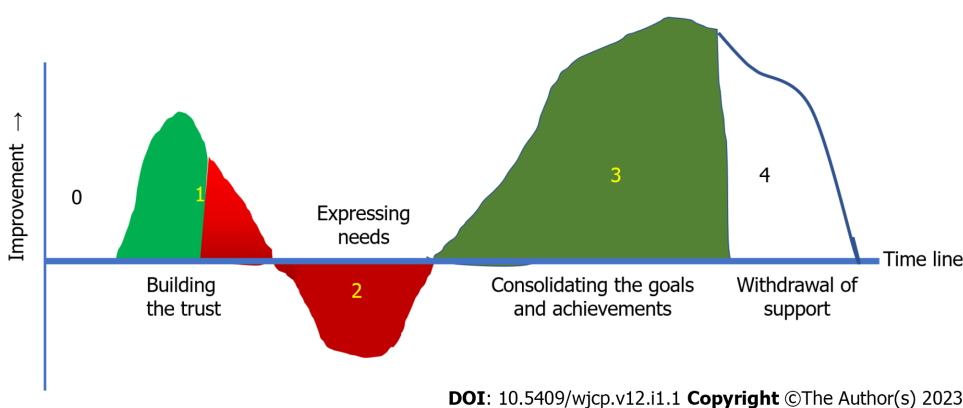


Figure 3 Stages of play therapy. Stage 0: Pre-therapy family and child interview and assessment; Stage 1: The first part in green is the exploratory or Initiation stage, followed by testing for protection (part in gradient red); Stage 2: Resistance phase, negative reaction, or aggressive stage; Stage 3: The growing or work phase; Stage 4: The termination phase.

develop a new synapse; play helps the brain create a synapse for every 10-20 repetitions.

Indication of play therapy

Although play therapy can help people at any age, it is characteristically used to help children 3-12 years of age. Play therapy may be helpful in various circumstances; some examples are mentioned in

Table 2. Play therapy can help three categories of children; healthy kids, children with organic diseases, and children with mental or psychological problems.

Healthy kids

Play therapy can help the child become more responsible for certain behaviors, develop coping strategies, enhance creative problem-solving skills, learn self-respect, respect others, express feelings, and strengthen family relationships. Play therapy is indicated for children passing through a transition time in their lives, such as a change of place of the house or school environment, parental divorce, a loss of a loved person, or the birth of a new sibling. Play therapy also helps children suffering from bullying phenomena, domestic violence or abuse victims, or suffering social withdrawal[82]. It could also help children with functional disorders such as toileting, eating, or sleep disorders[83]. Play therapy helps to release the child's tension and facilitates the adult's communication with the child's inner world. Play can also help prepare the child for routine vaccination. An exciting study by Pontes *et al*[84] showed that children prepared with therapeutic play before vaccination are more cooperative and accept more than those without preparation.

Physically-ill children

Children with a chronic medical condition that needs frequent hospitalization, such as cancer, are more liable to stress, anxiety, and fear related to their illness and treatment. In addition, children who are undergoing major surgery usually encounter significant preoperative anxiety and fear. Play therapy can help minimize the worries caused by hospitalization or surgical procedure, assist in the fight against the disease, and modulate the child's immunity. Play allows proper lymphatic system pumping, boosts the immune system, and decreases stress, reducing the over-responsiveness of the hypothalamic-pituitary-adrenal axis system[85].

Mentally and psychologically-ill children

Children with certain illnesses hampering their emotional and social expressions usually benefit significantly from play therapy. For example, play therapy may have moderate to high positive effects on children with post-traumatic stress disorder (PTSD); however, these effects need more studies[86]. Children with mental and developmental retardation have a reduced attention span, poor eye-hand coordination, restricted memory, and weak concentration. Play is more effective, long-lasting, and understandable than traditional teaching activities[87]. Play also reduces the impact on parents after having their child diagnosed as mentally or developmentally disabled. It also helps to build more bonds and interactions between parents and their disabled children[88]. Children with aggressive behavior have reduced expressive or reflective verbalization capacity, reduced dramatic or imaginative play, and tend to feel highly threatened by the therapist's slightest observation or inquiry. However, play therapy helps reach these children when chosen and performed correctly. It is most helpful when used to assist these children in developing mature adaptive social skills and responses through building nonthreatening relationships[89]. Attention deficit/ hyperactivity disorder (ADHD) is prevalent in children and adolescents. Abdollahian *et al*[90] found that play therapy can significantly decrease the symptoms of ADHD. The significant differences between the experimental and control groups indicate that play therapy could be an effective treatment method for children with ADHD aged 7-9 years[90]. Some children with autism spectrum disorder (ASD) have deficiencies in play. In this article, we will review the efficiency and limitations of play therapy in children with autism.

PLAY DISORDER IN CHILDREN WITH AUTISM

Autism spectrum disorders (ASD) are a spectrum of neurodevelopmental disorders with classic core symptoms of social deficits, language impairment, and repetitive and restricted behaviors. It has an increasing prevalence all over the world (1/1000 population) with wide heterogeneity from one country to another, reaching a very high level in the United States (1/40-60 population)[91]. The exact mechanism of autism is controversial. However, atypical neurobiological mechanisms obviously underlie the disorder with documented defects in the cerebellum, limbic structures, and cortex, especially the frontal lobe[92]. Frontal lobe dysfunction impacts specific cognitive functions of patients with autism, such as memory, learning, face recognition, emotional judgment, and interpreting biological motion cues[93,94]. The social impairments observed in patients with autism may be related to the impairment of social signals interpretation[95-97].

There is difficulty in comprehension and atypical sensory processing in children with autism. They have limitations in their adaptive behavior and impairments in their ability to relate and interact socially with others, with the presence of significant communication challenges and restricted or stereotyped behaviors[98]. As play needs integration of motor, social, language, and communication skills, it is usually significantly impaired and very limited in children with ASD. They prefer to play alone, engage in selected types of repetitive play such as lining up toys, moving objects from a particular place to another one, or playing with the same toys all the time, and they develop rage attacks and/or tantrums

Table 2 Indications of play therapy

Children categories	Indication
Physically and mentally normal kids	Family issues, like divorce, separation, or death of a close family member Natural disasters or traumatic events Domestic violence, abuse, or neglect Grief Functional gastrointestinal disorders such as eating and toileting disorders Substance abuse Before routine childhood vaccination
Physically-ill children	Facing medical procedures, chronic diseases, or palliative care
Mentally and psychologically ill children	Post-traumatic stress disorder Developmental delay or learning disabilities School behavioural problems Aggressive or angry behavior Attention deficit hyperactivity disorder Autism spectrum disorder

when the parents try to remove them[99,100].

Children with autism struggle to share experiences with others, understand the feelings and thoughts of others, pay attention, respond to others, and/or take turns. They may be unaware of the surrounding children. They have challenges learning new play skills *via* observation or communication. They lack symbolic play and joint attention, representing two critical developmental challenges in young children with autism[101]. They also have a problem understanding the non-verbal cues of body language, such as facial expressions, gestures, and voice tones. They have difficulties copying simple actions or exploring the environment. They also have a problem with imaginative and pretend play. They are critical features for successful interactive play. They are unlikely to share in games that need making decisions, cooperation, or social communication[102,103]. Children with autism usually get "jammed" in the earliest forms of solitary play. They prefer purposeless, meaningless, and repetitive actions that mean something to them without meaning to the typical people around them. Children with autism also show symptoms of restricted and repetitive behavior. Atypical play behavior appears early in life and depends on the severity of the autistic features.

When getting older, some children with autism may improve their playing skills and understand some rules of games. However, their behavior during play is still different from their typically developing peers. They may strictly adhere to the game rules, so they may be unable to cope with any logical changes in the game. They also may become obsessed with particular video games that provide solitary play. They also may show over-concentration on and adherence to a particular game point. For example, they may concentrate on the football player's T-shirt color without actually playing the game. These symptoms may develop into obsessive-compulsive disorder if untreated in the long term[102].

PLAY AND OCCUPATIONAL THERAPY FOR CHILDREN WITH AUTISM

Occupational therapy is a well-known therapy used to support the development of children with autism to use their senses (gustatory, olfactory, tactile, vestibular, proprioceptive, auditory, and visual systems) to make sense of their environment. Ayres Sensory Integration is one of the most renowned evidence-based approaches to promoting children's play[59,104]. Sensory integration is a specialty area of occupational therapy based on over 50 years of theory and research originated at USC by A. Jean Ayres. Sensory integration is a process that begins with receiving sensory inputs by the senses and interceptors from the environment and within the body. Then these sensory inputs are perceived, processed, and integrated into the brain to give an adaptive response, functional reaction, adequate communication, and typical behavior right on time[105]. Play therapy blended with sensory integration is a structured therapy commonly used by occupational therapists to involve children and develop emotional well-being, functional development, and typical growth[106].

Despite lacking play skills in children with ASD, they still can learn how to play, especially with the help of their parents and sibling. The parent's role is crucial in managing the child's difficulties. Parental denial or ignorance worsens the symptoms and makes the likelihood of successful therapies minimal or

nil. In addition, the effects of therapy depend on the time of initiation; the earlier, the better[106].

Play therapy in children with autism aims to engage them in playful activities of their choice and interest. It helps them to express themselves freely and comfortably. Play therapy depends on building partnerships and trustable solid relationships between the therapist and the children through involvement in the joyful activities of playing[107]. Play therapy helps children with autism to change their way of self-expression from unwanted behavior such as aggressive, self-injurious, property destructive, or tantrum behavior to more non-injurious expressive behavior using toys or activities of their choice as their words. Since verbal expression is difficult in children with autism, play therapy offers them different ways to express their suppressed emotions. Children with autism have poor social skills, so play therapy emphasizes the relationship-building trust with the person through interaction and having fun with the play therapist[89]. Play therapy also helps children with autism experience how to feel various interaction styles, whether they realize that or not. It also provides those children with a safe environment to learn self-regulatory behavior, which helps to emphasize appropriate behaviors and decrease unwanted ones, such as aggressive or destructive behaviors. At the same time, the child experiences freedom of choice during playing, like choosing what he likes and desires, controlling the speed and time of activities of the session, and deciding what he wants to do. Thus, play helps him develop independence with time, a valuable developmental stimulant[108].

Autism is a spectrum with heterogeneous symptoms; every child with autism is unique and responds differently. Children with autism usually prefer sensory toys such as weighted stuffed animals, fidget toys, and putty, because these toys help calm the children and encourage them to engage their senses during playing positively[109]. Currently, no specific play therapy is standardized for treatment. Because every child responds differently to different things, some traditional play therapy methods have been constantly shown to improve social and emotional skills in children with autism over time. The efficacy of play therapy depends on many factors, as illustrated in Table 3. However, occupational therapy using the sensory integration theory is evidence-based to use a child-friendly playful method to enhance the neuronal connections of the brains of children with ASD[59].

Child-centered play therapy

Child-centered play therapy is one of the most comprehensively studied types of play therapy in children with autism. This type of therapy is a relationship-based intervention, where the therapist enters the child's world and uses the built relationship to intervene rather than train the child. Schottelkorb *et al*[110] investigated the intensive child-centered play therapy effectiveness in children diagnosed with ASD. They found that children who received intensive child-centered play therapy significantly reduced ASD core symptoms and behavioral disorders, such as attention problems, externalizing problems, and aggression, than control group children[110]. Novita *et al*[111] found that child-centered play therapy effectively improved joint attention skills in children with ASD. Joint attention is one of the first types of visible communication that implies the child's ability to coordinate his attention around an object or event with a social partner. It is observed when the child displays evident skills such as alternating gaze between an object and a person, drawing attention to, pointing, or offering to share or show[111].

Carrizales[112] showed that child-centered play therapy showed positive growth in a range of areas in young children with ASD. She studied three children with ASD who showed varying degrees of improvement concerning play skills. Three of them showed more natural play, two of them showed advanced play skills, and one of them showed fewer play skill changes. These findings support the theory that a safe, acceptable environment provides children with ASD with more motivation and capacity to freely and naturally interact intimately with the external environment and improve their self-healing power[112]. This type of therapy is not only child-centered but also therapist-dependent. Goodman *et al*[113] showed that the child's response to the treatment differs according to the therapist, even though the child remains constant. Child-centered play therapy is part of an integrative treatment approach that includes behavioral techniques and parental training. It improves parent education, training, and the child's social skills to improve the child's functioning and correct maladaptive behavior. Child-centered play therapy is a promising intervention in increasing children's emotional and social behaviors with ASD[114]. However, we still need more research to establish whether child-centered play therapy is effective in children with ASD.

Child-led play

Since it is very challenging to direct children with ASD to do specific actions, especially in severe cases, we need to find a way to attract the children's interests while helping to pull them out of their shells; so they do not stick to their repetitive behaviors. This method is called a non-directive approach in which the therapist follows the child's choices and adapts the tools and environment to serve the therapeutic goals. Child-led play is an approach that allows the child to choose the activity they like to do, and the therapist joins them. It is usually helpful in severely affected children with autism, but it takes a longer time to see significant gains[115]. Child-led play therapy has improved children's social and communication skills with severe autism. It differs from child-centered play therapy, in which there is a preset specific thing and rules the therapist will do and not to do and a specific way of being in the playroom. Gengoux *et al*[116] showed the efficacy of a pivotal response treatment package (PRT-P) for

Table 3 Factors affecting the success of the therapy

The child's age at the time of initiation of the therapy
The degree of cooperation, awareness, and adherence of the parents and the family
The severity of the condition
The developmental level
The marital status of the family
The family education and socioeconomic levels
The therapist's competency
The type of play therapy

children with autism. PRT is play-based therapy initiated by the child. They investigated 48 children with Autism with PRT-P for 24 wk. PRT-P demonstrated more significant improvement in child social communication skills and in teaching parents to implement PRT[116]. de Korte *et al*[117] also showed a significant improvement in spontaneous initiations during the 14-wk protocol of PRT with a semi-structured therapist-child interaction and widespread increases in overall clinical functioning[117].

Floor time-play therapy is one of the most famous play therapies to treat children with ASD, discovered by Wieder and Greenspan[118] in 1980. It can be done at home and in the therapist's office, in a calm environment for a session between two to five hours. It can be provided by child psychologists, occupational therapists, speech therapists, special education teachers, parents, or caregivers with adequate training[118]. Essentially, the therapist or a caregiver sits on the floor to play with the child according to the child's own terms. In this therapy, the therapist or caregiver starts playing, following the child's way of playing (non-directive; the therapist follows, and the child leads). Then, the therapist introduces new elements, such as new toys, acts, or some words (hidden directive). This way of playing with back-and-forth conversations between the child and the therapist ultimately helps the child focus his thinking, improve his emotional skills, and expand his communication circles[119]. With the child's progress, floor time play can also be practiced with typically developing peers when done in a preschool setting. The main aim of floor time play therapy is to meet the child's developmental level, build on the child's own comforts, interests, and strengths, and create relationships during the play course[119].

Floor time play can help the child to improve different critical developmental milestones. It provides him with two-way communication that may progress to more complex communication. It helps him to develop inspirational ideas and emotional thinking, which enables him to enjoy intimacy and engage in relationships. Ultimately, it helps the child improve his self-regulation, enhance emotional and intellectual growth, and empower his interest in the world[120]. Studies show that children with autism significantly improved overall development with 25 h of floor time play per week for a minimum of two years. Wieder *et al*[118] showed that spontaneous 'floor time' play sessions for three years helped a young boy improve his attention, engagement in simple and complex gestures, and problem-solving skills to guide the child into the outside world with lots of ideas and improve abstract thinking. Solomon *et al*[121] studied the effects of 8-12 mo of floor time play therapy in 68 children with ASD. They encouraged the parents to deliver 15 h per week of 1:1 floor time interaction. They found that 45.5% of children achieved good to excellent progress in their functional development with significant increases in child subscale scores[121]. Pajareya and Nopmaneejumruslers found that 14 h/week for one year of floor time parenteral playing with their children showed improvement in the development and decreased signs of autism in 47% of 31 children with autism[122]. In addition, Liao *et al*[123] found in a pilot study involving 11 children with ASD that the floor time home-based intervention program for ten weeks significantly improved mean scores for the children's communication, emotional functioning, and daily life living skills with positive changes in the parent-child interactions. However, the success of floor time play depends on many factors. Praphatthanakunwong *et al*[124] showed that being married, with a lower income, and having higher awareness of floor time play theory are associated with higher parent engagement. They also found that the more severe the autism and the longer the treatment continuation, the more parent engagement and child development improvement[124].

Clown therapy or medical clowning

Clown therapy is currently an essential aspect of managing hospitalized children worldwide. Clown doctors help to minimize the child's stress and anxiety related to the hospital atmosphere during surgical procedures or particular devastating therapies[125]. Clown therapy should be differentiated from the clown person that enters the hospital to cheer up kids and alleviate their tension. Clown therapy (or medical clowning) mimics drama therapy, which helps patients to discover their inner clowns and release clown-like behavior in group settings. This therapy helps patients to discover the absurdity and paradoxes in their everyday lives. They also find new communication methods[126]. There are scarce data about using Clown therapy in treating children with ASD. However, Shefer *et al*

[127] showed that medical clowning sessions enhanced communication in children with ASD during the interventions compared with other interventions. It caused a reduction in stereotypic movement frequency in children with ASD over time[127].

3i play therapy (intensive, individual, and interactive)

The 3i play therapy was induced by Catherine de La Presle in 2004 in France to help her grandson, who had autism. It works through play and is conducted at the child's home, with the involvement of many volunteers to provide several hours daily of individual therapeutic relations to the child. It is an educative method with several elements, including the importance of play, with a low-intrusive approach that emphasizes interaction and behavioral dialogue and ensures the child's excellent and long-lasting mental stability. Developing self-consciousness and mental capacities are obtained through developing relations and stimulating the need for communication with others[128]. Tilmont Pittala *et al* [129] studied 20 children with autism using the 3i method for two years. They showed that children treated with the 3i method for two years had significant behavioral and developmental skills improvement with an evident decrease in autism severity. Their results suggested that the 3i method can be a valuable tool for children with ASD by improving their daily interactions and social environment[129]. Brefort *et al*[130] did a more extensive controlled study that involved 90 children with ASD receiving 3i therapy (intensive developmental play therapy) for two years. They found that 3i therapy improves ASD severity with observed interaction, communication, and repetitive behavior improvements[130].

Integrated play groups

This model is a play-dependent intervention intended to develop meaningful peer relationships and adequate play and social-communication skills in children with ASD through adult-facilitated peer interactions. It involves neurotypical children, "expert players," and children with autism ("novice players") playing together so that the latter can learn better social skills. A trained adult facilitator serves as a "play guide" to assist and outline interactions between expert and novice players. The facilitator divides the children into mixed groups. Each group has three to five children's groups. The facilitator sets the tones and rules for the play before they take control[131]. Yang *et al*[132] investigated the effect of integrated play groups (IPGs) on children with ASD playing with typically developing familiar (siblings at home) and unfamiliar peers (at school in Taiwan). They studied the effect of IPGs on the symbolic and social play of two children with ASD in early elementary school. They noted significant gains in symbolic/pretend play and reciprocal social interaction while participating in IPG[132]. Recently, Wolfberg *et al*[133] studied the effects of 12 wk of IPG therapy on 48 children with ASD participating in play groups with typical peers. They found significant increases in symbolic and social play using unsupported play with both familiar and unfamiliar peers, which maximizes the developmental potential and social inclusion in children with ASD[133]. A 30-min IPG session twice weekly for 16 wk can improve the child's ability in pretend play and his interaction with his peers. IPG also helps the child with ASD learn how to use the toys more typically.

Joint attention symbolic play engagement and regulation

Joint attention symbolic play engagement and regulation (JASPER) is a well-studied naturalistic intervention to improve developmental behavior. This method aims to improve the attentiveness of the child with autism by training him to focus on a toy and another person simultaneously (joint attention). This method improves the child's language and play, making it more effective and reactive with his peers, increasing pretending abilities, and expanding the range of play with different toy types. The child may need to spend up to 25 h weekly in a one-to-one meeting with his therapist. In addition, some preschools can provide this type of therapy. Most studies showed that children who received JASPER intervention significantly improved as a minimum outcome related to joint child engagement, joint attention, play, and language skills compared to the control groups[134]. Goods *et al*[135] tested the effects of 30 min of JASPER intervention twice weekly for 12 wk in children 3 to 5 years old. The intervention induced greater play diversity upon standardized assessment. This effect also appeared in the classroom, where participants in the intervention group started showing more signs of engagement and spent less time without than before[135]. Shire *et al*[136] investigated how toddlers with autism engage with their peers. They found that children who experienced peer intervention (JASPER) had more engagement with their peers, more receptive language, and better combination and presymbolic play when an adult was present, but not when the children were left unsupported[136]. JASPER can also be conducted online. Shire *et al*[137] showed that a technology-enabled adaptation of the evidence-based caregiver-mediated JASPER successfully provided the caregivers with online materials that helped them conduct home-based JASPER. The caregivers navigated the content smoothly and gave positive feedback and suggestions to improve the content[137].

However, children may differ in their response to JASPER. Some may show incredible progress, while others may have slow or no progress. Panganiban and Kasari studied 99 preschool-age children with ASD and limited language for their language improvement after JASPER intervention to predict their response to JASPER. They divided the children after the intervention into super responders and

slow responders using traditional standardized assessment tools of behavioral and cognition data. They found that children who could play appropriately with a more comprehensive toy diversity before starting the intervention had the best improvements in their expressive language[138]. However, we need more research to verify whether it can also improve a more comprehensive range of symptoms and outcomes in children with ASD.

Synergetic play therapy

This approach identifies the significance of the comprehensive therapeutic experience the child is exposed to, including different factors in the therapy, such as the child himself, the therapist, the parents, and all other factors that could impact the child's progress. So, this approach that Lisa Dion created tries to use all the details of the child's life to work in harmony to create a balanced and all-encircling response to the problem the child enfaces. This approach determines a specific role for everybody in the child's life, such as a sibling, cousin, classmate, friend, grandparents, and every other tie they live into[139]. This approach is not straightforward as it is a system of life and existing that concentrates on a more natural and comprehensive approach to therapeutic interaction. When done correctly, this synergetic play therapy (SPT) approach helps the child to co-regulate his internal experience, overcoming his challenging, uncomfortable memories, thoughts, and body sensations. So SPT is a comprehensive play therapy approach that concentrates on the child and the therapist realistically interacting with each other and themselves in an attempt to become more thoughtful. This approach allows for better child development and maturation[139]. Dion and Gray[140] showed that SPT provoked significant improvement in emotionally tolerant behaviors percentage in response to trustworthy therapist expressions from the first to third sessions of SPT. SPT also had a 100% success rate in inducing emotionally tolerant behaviors by their fifth session[140]. Unfortunately, there is very scarce data about the effects of SPT on children with autism, and there are no well-controlled studies. Simmons[141] studied two children using SPI, one of them was a nine-year-old boy with high-functioning autism suffering from aggressive behaviors and difficulty managing his emotional range. He had a one-hour session weekly for 13 wk. The boy has made noticeable progress across several parameters; he was more able to control his anger, engage in cooperative play, and make eye contact effectively[141].

Equine-partnered play therapy

Equine-partnered play therapy (EPPT) is a distinctive type of play therapy intended for children aged three to nine. It uses the special relationship between animals and children. This model of therapy is a modified child-centered play therapy (CCPT) that blends Equine Assisted Counselling with CCPT. In CCPT, children see, explore the world, and express themselves through play[142]. In EPPT, the child will express his thoughts, feelings, needs, and wants through horse riding rather than the toys used in play. In EPPT, horses serve as group members, allowing the child to enhance his social skills while getting feedback from the horses. Including miniature horses (small ponies), EPPT can support the child to feel safe and accept to be her/himself[143]. Horse riding helps the child to express complicated feelings, receive nurturing from the horse, receive feedback from the horse to ground the session in reality, gain self-control and decision-making abilities, and enhance personal responsibility, self-expression, self-direction, self-respect, and acceptance. The EPPT team consists of an equine specialist and a play therapist. However, safety and ethical considerations should be in mind while conducting EPPT. The environment should be safe and comfortable for both the horse and the child[144].

Bass *et al*[145], during their controlled study, showed that children with ASD who had horseback riding intervention for 12 wk demonstrated more excellent sensory seeking, sensitivity, and social motivation. They also had less distractibility, inattention, and sedentary behaviors. These results confirmed the therapeutic benefits of horseback riding in treating children with ASD[145]. Harris and Williams[146] showed a significant reduction in the severity of ASD symptoms and hyperactivity and improved social functioning in children with ASD after horse riding sessions of 45 min weekly for seven weeks compared to the control group. Another self-controlled study by Steiner and Kertesz[147] showed significant differences pre- and post-intervention in the length of the gait cycle that became more stable in the sagittal plane in 26 children with ASD who were subjected to horse riding for one month of therapy. A systemic review by McDaniel Peters and Wood showed that four types of equine-assisted therapies were identified from eight studies that reported improvements in motor control and self-care of children and adolescents with ASD[148].

Art-play therapy

Art therapy is a form of expressive and communicative therapy that uses the act of art interest to decrease anxiety, enhance self-esteem and settle any psychological conflicts. This therapy is entirely different from play therapy. However, child art therapy is sometimes confused with play therapy, as many play therapists include art-based activities during play therapy. Meanwhile, some art therapists use specific play tools such as toys, puppets, or even physical games to enforce and promote the child's artistic expression. While play therapy is more valid for children aged 2-12 who can express themselves through movements, creative media, and play, art therapy is more suitable for 3-12, who can use visual

language better than movement. Art therapy can be practiced individually or in groups, with a session usually lasting 30 to 50 min[149-151].

Wypyszyńska *et al*[152] showed that art therapy has a positive therapeutic effect on speech, social relations, and unusual behavior in children and adolescents with ASD than in the control group. A systematic review by Schweizer *et al*[153] showed that art therapy might provide a more compliant and relaxed approach that can empower the self-image and improve the learning and communicative skills of children with ASD. Art therapy can help to overcome poor social communication and repetitive and restricted behavior patterns in subjects with ASD. Art therapy, with its sensory experiences such as sight and touch, can increase flexibility and attention abilities and improve the social behavior of children with ASD[153]. Moghaddam *et al*[154] investigated the effects of family-based art therapy with the enforcement of verbal interaction, imitation, and phonation in children with autism. They showed that these practices helped children with autism to use art to express their connotations and feelings. Family-based art therapy also effectively reduces stereotypical behaviors and increases social interaction in children with ASD[154]. However, there is a strong need for further empirical well-controlled research to confirm the outcome of art therapy in autism.

Tele-play therapy

With the rise of the COVID-19 pandemic, there was a significant increase in the number of children with special needs, including those with autism. Besides the high morbidity and mortality related to COVID-19-, the pandemic negatively impacted the health and educational-related issues of children with autism. The lockdown negatively altered cognitive abilities, sensory-motor development, sleep, morale, and social and behavioral interactions in about 50% of children with special needs[155]. With the need to continue the services provided to children with autism, telemedicine, including teleplay therapy, provides significant help during the pandemic. Despite teleplay therapy being initially created to provide services to those in remote geographical locations, the pandemic experience paved the way for a new virtual platform where therapeutic play can continue regardless of the place and be provided across borders. Therapists can provide their services to another country and continue their services when traveling or when the child in need of the therapy travels. So, teleplay therapy decreases users' barriers to the therapists and the therapy procedure. Through teleplay therapy, children continue interacting with the world, communicating with others, practicing problem-solving, discovering their emotions and empathy, and provoking their brilliant imagination[156]. However, we emphasize that virtual play therapy does not replace face-to-face play therapy. It needs specific considerations to be followed to ensure safety, accessibility, and efficacy while conducting teleplay therapy. Despite many advantages, such as exploring the child's environment and less anxiety when enfacing strange people, teleplay therapy has many disadvantages. Teleplay therapy may enfance various problems, including privacy, possible easy distraction, technological problems such as digital ecosystem malfunction, and connectivity problems[157,158].

LIMITATIONS OF THE REVIEW

Despite our effort to review all that was published, the research regarding play therapy in children with autism is minimal, and the number of cases in many studies is very few to make a solid conclusion. Therefore, we still have a long way to go to prove the efficacy of teleplay therapy with more well-designed controlled studies.

CONCLUSION

Play therapy is an effective tool in the management of children with ASD. However, it depends on many factors. Play therapy should be continuous as the effect may wane with discontinuation. It is hard to make a conclusion from the previous studies due to many limitations, including the weak experimental design, which makes the generalization of their results to the larger community difficult. Play therapy is usually conducted as a part of a comprehensive intervention, so it is hard to claim that the improvement in the participant's behavior was related to the play therapy intervention. More well-designed controlled studies are needed to understand and judge play therapy's effects on this particular group of children. Despite the weak evidence, play therapy still has a lot of potential benefits for patients and their families. It helps improve the child's social skills and communication in a relaxed environment, integrates the parents, strengthens the child-parent bond, and decreases the tension over the shoulder of the parents. In addition, play therapy has no significant side effects and is cost-effective. More research is needed to experiment with evidence-based therapeutic models on sensory integration play models, neuroscience, and developmental psychology to support children with ASD, the typical ones, and others during and after the COVID-19 pandemic. It is also worth studying the effects of play therapy on frontal lobe functions and neurobiology in children with autism.

ACKNOWLEDGEMENTS

We thank the editors and the anonymous referees for their valuable suggestions.

FOOTNOTES

Author contributions: Elbeltagi R, Al-Biltagi M, Saeed NK, and Alhawamdeh R collected the data and wrote and revised the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Egypt

ORCID number: Reem Elbeltagi 0000-0001-9969-5970; Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207; Rawan Alhawamdeh 0000-0003-3501-6275.

S-Editor: Gong ZM

L-Editor: A

P-Editor: Gong ZM

REFERENCES

- Burghardt GM. Defining and recognizing play. In Pellegrini AD (Ed.), *The Oxford handbook of the development of play*. Oxford: Oxford University Press, 2011: 9-18 [DOI: [10.1093/oxfordhb/9780195393002.013.0002](https://doi.org/10.1093/oxfordhb/9780195393002.013.0002)]
- Campbell SB, Denham SA, Howarth GZ, Jones SM, Whittaker JV, Williford AP, Willoughby MT, Yudron M, Darling-Churchill K. Commentary on the review of measures of early childhood social and emotional development: Conceptualization, critique, and recommendations. *J Appl Dev Psychol* 2016; **45**: 19-41 [DOI: [10.1016/j.appdev.2016.01.008](https://doi.org/10.1016/j.appdev.2016.01.008)]
- Milteer RM, Ginsburg KR; Council on Communications and Media; Committee on Psychosocial Aspects of Child and Family Health. The importance of play in promoting healthy child development and maintaining strong parent-child bond: focus on children in poverty. *Pediatrics* 2012; **129**: e204-e213 [PMID: [22201149](https://pubmed.ncbi.nlm.nih.gov/22201149/) DOI: [10.1542/peds.2011-2953](https://doi.org/10.1542/peds.2011-2953)]
- Vedechkina M, Borgonovi F. A Review of Evidence on the Role of Digital Technology in Shaping Attention and Cognitive Control in Children. *Front Psychol* 2021; **12**: 611155 [PMID: [33716873](https://pubmed.ncbi.nlm.nih.gov/33716873/) DOI: [10.3389/fpsyg.2021.611155](https://doi.org/10.3389/fpsyg.2021.611155)]
- Yogman M, Garner A, Hutchinson J, Hirsh-Pasek K, Golinkoff RM; Committee on Psychosocial Aspects of Child and Family Health; Council on Communications and Media. The Power of Play: A Pediatric Role in Enhancing Development in Young Children. *Pediatrics* 2018; **142** [PMID: [30126932](https://pubmed.ncbi.nlm.nih.gov/30126932/) DOI: [10.1542/peds.2018-2058](https://doi.org/10.1542/peds.2018-2058)]
- Tanaka M, Szabó Á, Spekter E, Polyák H, Tóth F, Vécsei L. Mitochondrial Impairment: A Common Motif in Neuropsychiatric Presentation? *Cells* 2022; **11** [PMID: [36010683](https://pubmed.ncbi.nlm.nih.gov/36010683/) DOI: [10.3390/cells11162607](https://doi.org/10.3390/cells11162607)]
- Lee GA, Lin YK, Lai JH, Lo YC, Yang YSH, Ye SY, Lee CJ, Wang CC, Chiang YH, Tseng SH. Maternal Immune Activation Causes Social Behavior Deficits and Hypomyelination in Male Rat Offspring with an Autism-Like Microbiota Profile. *Brain Sci* 2021; **11** [PMID: [34439704](https://pubmed.ncbi.nlm.nih.gov/34439704/) DOI: [10.3390/brainsci11081085](https://doi.org/10.3390/brainsci11081085)]
- Ratajczak HV. Theoretical aspects of autism: causes--a review. *J Immunotoxicol* 2011; **8**: 68-79 [PMID: [21299355](https://pubmed.ncbi.nlm.nih.gov/21299355/) DOI: [10.3109/1547691X.2010.545086](https://doi.org/10.3109/1547691X.2010.545086)]
- Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. *Mol Psychiatry* 2012; **17**: 290-314 [PMID: [21263444](https://pubmed.ncbi.nlm.nih.gov/21263444/) DOI: [10.1038/mp.2010.136](https://doi.org/10.1038/mp.2010.136)]
- Björklund G, Doşa MD, Maes M, Dadar M, Frye RE, Peana M, Chirumbolo S. The impact of glutathione metabolism in autism spectrum disorder. *Pharmacol Res* 2021; **166**: 105437 [PMID: [33493659](https://pubmed.ncbi.nlm.nih.gov/33493659/) DOI: [10.1016/j.phrs.2021.105437](https://doi.org/10.1016/j.phrs.2021.105437)]
- Mennella JA, Jagnow CP, Beauchamp GK. Prenatal and postnatal flavor learning by human infants. *Pediatrics* 2001; **107**: E88 [PMID: [11389286](https://pubmed.ncbi.nlm.nih.gov/11389286/) DOI: [10.1542/peds.107.6.e88](https://doi.org/10.1542/peds.107.6.e88)]
- Chelli D, Chanoufi B. [Fetal audition. Myth or reality?]. *J Gynecol Obstet Biol Reprod (Paris)* 2008; **37**: 554-558 [PMID: [18657916](https://pubmed.ncbi.nlm.nih.gov/18657916/) DOI: [10.1016/j.jgyn.2008.06.007](https://doi.org/10.1016/j.jgyn.2008.06.007)]
- Marx V, Nagy E. Fetal Behavioural Responses to Maternal Voice and Touch. *PLoS One* 2015; **10**: e0129118 [PMID: [26053388](https://pubmed.ncbi.nlm.nih.gov/26053388/) DOI: [10.1371/journal.pone.0129118](https://doi.org/10.1371/journal.pone.0129118)]
- Marlier L, Schaal B, Soussignan R. Bottle-fed neonates prefer an odor experienced in utero to an odor experienced postnatally in the feeding context. *Dev Psychobiol* 1998; **33**: 133-145 [PMID: [9742408](https://pubmed.ncbi.nlm.nih.gov/9742408/)]
- Aguiar R. Infantile experience and play motivation. *Soc Neurosci* 2010; **5**: 422-440 [PMID: [20711936](https://pubmed.ncbi.nlm.nih.gov/20711936/) DOI: [10.1080/17470919.2010.503618](https://doi.org/10.1080/17470919.2010.503618)]
- Committee on the Science of Children Birth to Age 8: Deepening and Broadening the Foundation for Success;

- Board on Children, Youth, and Families; Institute of Medicine; National Research Council; Allen L, Kelly BB, editors. Transforming the Workforce for Children Birth Through Age 8: A Unifying Foundation. Washington (DC): National Academies Press (US); 2015 [PMID: [26269871](#) DOI: [10.17226/19401](#)]
- 17 **Tobar FL**, Lencina MJ. The "Learning Through Play" project. Importance of interdisciplinary work among children born prematurely and their family groups in an area of high socio-environmental risk. *Arch Argent Pediatr* 2017; **115**: 588-594 [PMID: [29087120](#) DOI: [10.5546/aap.2017.eng.588](#)]
- 18 **Chang MC**, Weng CY, Yu JH, Cheng WL, Chu SY. [The Effectiveness of a Shared Reading Program Among Parents of Newborns]. *Hu Li Za Zhi* 2022; **69**: 73-82 [PMID: [35080000](#) DOI: [10.6224/JN.202202_69\(1\).10](#)]
- 19 **Cooke BM**, Shukla D. Double helix: reciprocity between juvenile play and brain development. *Dev Cogn Neurosci* 2011; **1**: 459-470 [PMID: [22436567](#) DOI: [10.1016/j.dcn.2011.07.001](#)]
- 20 **Fisch SM**. Cross-platform learning: on the nature of children's learning from multiple media platforms. *New Dir Child Adolesc Dev* 2013; **2013**: 59-70 [PMID: [23483694](#) DOI: [10.1002/cad.20032](#)]
- 21 **Pellegrini AD**. The role of play in human development. New York: Oxford University Press, 2009 [DOI: [10.1093/acprof:oso/9780195367324.001.0001](#)]
- 22 **Chawla L**. Childhood nature connection and constructive hope: A review of research on connecting with nature and coping with environmental loss. *People Nat* 2020; **2**: 619-642 [DOI: [10.1002/pan3.10128](#)]
- 23 **Marino AJ**, Fletcher EN, Whitaker RC, Anderson SE. Amount and environmental predictors of outdoor playtime at home and school: a cross-sectional analysis of a national sample of preschool-aged children attending Head Start. *Health Place* 2012; **18**: 1224-1230 [PMID: [23000895](#) DOI: [10.1016/j.healthplace.2012.08.004](#)]
- 24 **Ridgers ND**, Stratton G, Fairclough SJ. Physical activity levels of children during school playtime. *Sports Med* 2006; **36**: 359-371 [PMID: [16573359](#) DOI: [10.2165/00007256-200636040-00005](#)]
- 25 **Scott HK**, Cogburn M. Peer Play. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [PMID: [30020595](#)]
- 26 **Broadhead P**, Howard J, Wood E (eds). Play and Learning in the Early Years: From Research to Practice. London: SAGE Publications Ltd, 2010 [DOI: [10.4324/9780203465257](#)]
- 27 **Orr E**. Object play as a mediator of the role of exploration in communication skills development. *Infant Behav Dev* 2020; **60**: 101467 [PMID: [32682122](#) DOI: [10.1016/j.infbeh.2020.101467](#)]
- 28 **Serrada-Tejeda S**, Santos-Del-Riego S, May-Benson TA, Pérez-de-Heredia-Torres M. Influence of Ideational Praxis on the Development of Play and Adaptive Behavior of Children with Autism Spectrum Disorder: A Comparative Analysis. *Int J Environ Res Public Health* 2021; **18** [PMID: [34073380](#) DOI: [10.3390/ijerph18115704](#)]
- 29 **Lee RLT**, Lane S, Brown G, Leung C, Kwok SWH, Chan SWC. Systematic review of the impact of unstructured play interventions to improve young children's physical, social, and emotional wellbeing. *Nurs Health Sci* 2020; **22**: 184-196 [PMID: [32358875](#) DOI: [10.1111/nhs.12732](#)]
- 30 **Weisberg DS**. Pretend play. *Wiley Interdiscip Rev Cogn Sci* 2015; **6**: 249-261 [PMID: [26263228](#) DOI: [10.1002/wcs.1341](#)]
- 31 **Gelman SA**. Learning from others: children's construction of concepts. *Annu Rev Psychol* 2009; **60**: 115-140 [PMID: [18631027](#) DOI: [10.1146/annurev.psych.59.103006.093659](#)]
- 32 **Richard S**, Baud-Bovy G, Clerc-Georgy A, Gentaz E. The effects of a 'pretend play-based training' designed to promote the development of emotion comprehension, emotion regulation, and prosocial behaviour in 5- to 6-year-old Swiss children. *Br J Psychol* 2021; **112**: 690-719 [PMID: [33314057](#) DOI: [10.1111/bjop.12484](#)]
- 33 **Skibbe LE**, Montroy JJ, Bowles RP, Morrison FJ. Self-regulation and the Development of Literacy and Language Achievement from Preschool through Second Grade. *Early Child Res Q* 2019; **46**: 240-251 [PMID: [30636841](#) DOI: [10.1016/j.ecresq.2018.02.005](#)]
- 34 **Garber J**, Frankel SA, Herrington CG. Developmental Demands of Cognitive Behavioral Therapy for Depression in Children and Adolescents: Cognitive, Social, and Emotional Processes. *Annu Rev Clin Psychol* 2016; **12**: 181-216 [PMID: [27019397](#) DOI: [10.1146/annurev-clinpsy-032814-112836](#)]
- 35 **Jago R**, Tibbitts B, Willis K, Sanderson E, Kandiyali R, Reid T, MacNeill S, Kipping R, Campbell R, Sebire SJ, Hollingworth W. Peer-led physical activity intervention for girls aged 13 to 14 years: PLAN-A cluster RCT. Southampton (UK): NIHR Journals Library; 2022 [PMID: [35377571](#) DOI: [10.3310/ZJQW2587](#)]
- 36 **Al-Beltagi M**, Bediwy AS, Saeed NK. Insulin-resistance in paediatric age: Its magnitude and implications. *World J Diabetes* 2022; **13**: 282-307 [PMID: [35582667](#) DOI: [10.4239/wjd.v13.i4.282](#)]
- 37 **Committee on Physical Activity and Physical Education in the School Environment**; Food and Nutrition Board; Institute of Medicine. Educating the Student Body: Taking Physical Activity and Physical Education to School. Kohl HW III, Cook HD, editors. Washington (DC): National Academies Press (US); 2013 [PMID: [24851299](#) DOI: [10.17226/18314](#)]
- 38 **Gunter K**, Baxter-Jones AD, Mirwald RL, Almstedt H, Fuchs RK, Durski S, Snow C. Impact exercise increases BMC during growth: an 8-year longitudinal study. *J Bone Miner Res* 2008; **23**: 986-993 [PMID: [18072874](#) DOI: [10.1359/jbmr.071201](#)]
- 39 **Best JR**. Effects of Physical Activity on Children's Executive Function: Contributions of Experimental Research on Aerobic Exercise. *Dev Rev* 2010; **30**: 331-551 [PMID: [21818169](#) DOI: [10.1016/j.dr.2010.08.001](#)]
- 40 **Tomprowski PD**, Lambourne K, Okumura MS. Physical activity interventions and children's mental function: an introduction and overview. *Prev Med* 2011; **52** Suppl 1: S3-S9 [PMID: [21420981](#) DOI: [10.1016/j.ypmed.2011.01.028](#)]
- 41 **Pfeiffer BA**, Koenig K, Kinnealey M, Sheppard M, Henderson L. Effectiveness of sensory integration interventions in children with autism spectrum disorders: a pilot study. *Am J Occup Ther* 2011; **65**: 76-85 [PMID: [21309374](#) DOI: [10.5014/ajot.2011.09205](#)]
- 42 **Meherali S**, Punjani N, Louie-Poon S, Abdul Rahim K, Das JK, Salam RA, Lassi ZS. Mental Health of Children and Adolescents Amidst COVID-19 and Past Pandemics: A Rapid Systematic Review. *Int J Environ Res Public Health* 2021; **18** [PMID: [33810225](#) DOI: [10.3390/ijerph18073432](#)]
- 43 **Kim SJ**, Lee S, Han H, Jung J, Yang SJ, Shin Y. Parental Mental Health and Children's Behaviors and Media Usage during COVID-19-Related School Closures. *J Korean Med Sci* 2021; **36**: e184 [PMID: [34184439](#) DOI: [10.1007/s12265-021-00900-0](#)]

- 10.3346/jkms.2021.36.e184]
- 44 **Robidoux H**, Ellington E, Lauener J. Screen Time: The Impact of Digital Technology on Children and Strategies in Care. *J Psychosoc Nurs Ment Health Serv* 2019; **57**: 15-20 [PMID: 31670830 DOI: 10.3928/02793695-20191016-04]
 - 45 **Priyam P**, Sil A. Burnout: The Resident Evil - Perspectives from the Horses' Mouth! *Indian Dermatol Online J* 2020; **11**: 816-817 [PMID: 33235854 DOI: 10.1037/a0018941]
 - 46 **Williams D**, Yee N, Caplan SE. Who plays, how much, and why? *J Comput Mediat Commun* 2008; **13**: 993-1018 [DOI: 10.1111/j.1083-6101.2008.00428.x]
 - 47 **Mayo MJ**. Video games: a route to large-scale STEM education? *Science* 2009; **323**: 79-82 [PMID: 19119223 DOI: 10.1126/science.1166900]
 - 48 **Goldstein J**. Technology and play. In Pellegrini A (Ed.). *The Oxford handbook of the development of play*. New York: Oxford University Press, 2011: 323-337 [DOI: 10.1093/oxfordhb/9780195393002.001.0001]
 - 49 **Anderson DR**, Subrahmanyam K; Cognitive Impacts of Digital Media Workgroup. Digital Screen Media and Cognitive Development. *Pediatrics* 2017; **140**: S57-S61 [PMID: 29093033 DOI: 10.1542/peds.2016-1758C]
 - 50 **Canadian Paediatric Society**, Digital Health Task Force, Ottawa, Ontario. Screen time and young children: Promoting health and development in a digital world. *Paediatr Child Health* 2017; **22**: 461-477 [PMID: 29601064 DOI: 10.1093/pch/pxx123]
 - 51 **Tissera KM**, Naughton GA, Gabbett TJ, Krause LM, Moresi MP, Benson AC. Sex Differences in Physical Fitness Characteristics and Match-Play Demands in Adolescent Netball: Should Male and Female Adolescents Co-compete in Netball? *J Strength Cond Res* 2019; **33**: 846-856 [PMID: 30399115 DOI: 10.1519/JSC.0000000000002947]
 - 52 **Caldera YM**, Huston AC, O'Brien M. Social interactions and play patterns of parents and toddlers with feminine, masculine, and neutral toys. *Child Dev* 1989; **60**: 70-76 [PMID: 2702876 DOI: 10.1111/j.1467-8624.1989.tb02696.x]
 - 53 **Dinella LM**, Weisgram ES, Fulcher M. Children's Gender-Typed Toy Interests: Does Propulsion Matter? *Arch Sex Behav* 2017; **46**: 1295-1305 [PMID: 27896564 DOI: 10.1007/s10508-016-0901-5]
 - 54 **Barbu S**, Cabanes G, Le Maner-Idrissi G. Boys and girls on the playground: sex differences in social development are not stable across early childhood. *PLoS One* 2011; **6**: e16407 [PMID: 21297987 DOI: 10.1371/journal.pone.0016407]
 - 55 **Coplan RJ**, Gavinski-Molina MH, Lagacé-Séguin DG, Wichmann C. When girls versus boys play alone: nonsocial play and adjustment in kindergarten. *Dev Psychol* 2001; **37**: 464-474 [PMID: 11444483 DOI: 10.1037/0012-1649.37.4.464]
 - 56 **Fabes RA**, Martin CL, Hanish LD. Young children's play qualities in same-, other-, and mixed-sex peer groups. *Child Dev* 2003; **74**: 921-932 [PMID: 12795398 DOI: 10.1111/1467-8624.00576]
 - 57 **Lamminmäki A**, Hines M, Kuiri-Hänninen T, Kilpeläinen L, Dunkel L, Sankilampi U. Testosterone measured in infancy predicts subsequent sex-typed behavior in boys and in girls. *Horm Behav* 2012; **61**: 611-616 [PMID: 22373494 DOI: 10.1016/j.yhbeh.2012.02.013]
 - 58 **Kerney M**, Smaers JB, Schoenemann PT, Dunn JC. The coevolution of play and the cortico-cerebellar system in primates. *Primates* 2017; **58**: 485-491 [PMID: 28620843 DOI: 10.1007/s10329-017-0615-x]
 - 59 **Lane SJ**, Mailloux Z, Schoen S, Bundy A, May-Benson TA, Parham LD, Smith Roley S, Schaaf RC. Neural Foundations of Ayres Sensory Integration®. *Brain Sci* 2019; **9** [PMID: 31261689 DOI: 10.3390/brainsci9070153]
 - 60 **Shaheen S**. How child's play impacts executive function--related behaviors. *Appl Neuropsychol Child* 2014; **3**: 182-187 [PMID: 25010084 DOI: 10.1080/21622965.2013.839612]
 - 61 **Wang S**, Aamodt S. Play, stress, and the learning brain. *Cerebrum* 2012; **2012**: 12 [PMID: 23447798]
 - 62 **Diamond MC**, Krech D, Rosenzweig MR. The effects of an enriched environment on the histology of the rat cerebral cortex. *J Comp Neurol* 1964; **123**: 111-120 [PMID: 14199261 DOI: 10.1002/cne.901230110]
 - 63 **Gordon NS**, Burke S, Akil H, Watson SJ, Panksepp J. Socially-induced brain 'fertilization': play promotes brain derived neurotrophic factor transcription in the amygdala and dorsolateral frontal cortex in juvenile rats. *Neurosci Lett* 2003; **341**: 17-20 [PMID: 12676333 DOI: 10.1016/s0304-3940(03)00158-7]
 - 64 **Burgdorf J**, Kroes RA, Beinfeld MC, Panksepp J, Moskal JR. Uncovering the molecular basis of positive affect using rough-and-tumble play in rats: a role for insulin-like growth factor I. *Neuroscience* 2010; **168**: 769-777 [PMID: 20350589 DOI: 10.1016/j.neuroscience.2010.03.045]
 - 65 **Gordon NS**, Kollack-Walker S, Akil H, Panksepp J. Expression of c-fos gene activation during rough and tumble play in juvenile rats. *Brain Res Bull* 2002; **57**: 651-659 [PMID: 11927369 DOI: 10.1016/s0361-9230(01)00762-6]
 - 66 **Bell HC**, Pellis SM, Kolb B. Juvenile peer play experience and the development of the orbitofrontal and medial prefrontal cortices. *Behav Brain Res* 2010; **207**: 7-13 [PMID: 19786051 DOI: 10.1016/j.bbr.2009.09.029]
 - 67 **Pellis SM**, Pellis VC, Himmler BT. How play makes for a more adaptable brain: a comparative and neural perspective. *Am J Play* 2014; **7**: 73-98 [DOI: 10.1016/b978-0-12-804036-2.00012-1]
 - 68 **Einon DF**, Morgan MJ, Kibbler CC. Brief periods of socialization and later behavior in the rat. *Dev Psychobiol* 1978; **11**: 213-225 [PMID: 658602 DOI: 10.1002/dev.420110305]
 - 69 **Vanderschuren LJ**, Niesink RJ, Van Ree JM. The neurobiology of social play behavior in rats. *Neurosci Biobehav Rev* 1997; **21**: 309-326 [PMID: 9168267 DOI: 10.1016/s0149-7634(96)00020-6]
 - 70 **Johnson JL**. The History of Play Therapy. In: O'Connor KJ, Schaefer CE, Braverman LD (eds). *Handbook of Play Therapy*. John Wiley & Sons, Inc., 2015: 17-34 [DOI: 10.1002/9781119140467]
 - 71 **Dougherty J**, Ray D. Differential impact of play therapy on developmental levels of children. *Int J Play Ther* 2007; **16**: 2-19 [DOI: 10.1037/1555-6824.16.1.2]
 - 72 **Koukourikos K**, Tsaloglidou A, Tzehe L, Iliadis C, Frantzana A, Katsimbeli A, Kourkouta L. An Overview of Play Therapy. *Mater Sociomed* 2021; **33**: 293-297 [PMID: 35210953 DOI: 10.5455/msm.2021.33.293-297]
 - 73 **Reddy RP**, Hirisave U. Child's Play: Therapist's Narrative. *Indian J Psychol Med* 2014; **36**: 204-207 [PMID: 24860228 DOI: 10.4103/0253-7176.130998]
 - 74 **Moss L**, Hamlet HS. An Introduction To Child-Centered Play Therapy. *Ther Person-Centered J* 2020; **25**: 91-103 [DOI: 10.1080/14779757.2014.952899]
 - 75 **Pidgeon K**, Parson J, Mora L, Anderson J, Stagnitti K, Mountain V. Play Therapy. In: Noble C, Day E (Editors).

- Psychotherapy and Counselling: Reflections on Practice. Oxford University Press. 2015: 1-30 [DOI: [10.4324/9780429453083-4](https://doi.org/10.4324/9780429453083-4)]
- 76 Senko K, Bethany H. PLAY THERAPY: An Illustrative Case. *Innov Clin Neurosci* 2019; **16**: 38-40 [PMID: [31440400](https://pubmed.ncbi.nlm.nih.gov/31440400/)]
- 77 Frick-Helms SB, Drewes AA. Introduction to play therapy research theme issue. *Int J Play Ther* 2010; **19**: 1-3 [DOI: [10.1037/a0018496](https://doi.org/10.1037/a0018496)]
- 78 Jayne KM, Purswell KE, Stulmaker HL. Facilitating congruence, empathy, and unconditional positive regard through therapeutic limit-setting: Attitudinal conditions limit-setting model (ACLM). *Int J Play Ther* **28**: 238-249 [DOI: [10.1037/pla0000101](https://doi.org/10.1037/pla0000101)]
- 79 Stewart AL, Field TA, Echterling LG. Neuroscience and the Magic of Play Therapy. *Int J Play Ther* 2016; **25**: 4-13 [DOI: [10.1037/pla0000016](https://doi.org/10.1037/pla0000016)]
- 80 Lambert MJ, Barley DE. Research summary on the therapeutic relationship and psychotherapy outcome. *Psychotherapy* 2001; **38**: 357-361 [DOI: [10.1037/0033-3204.38.4.357](https://doi.org/10.1037/0033-3204.38.4.357)]
- 81 Shirk SR, Karver MS, Brown R. The alliance in child and adolescent psychotherapy. *Psychotherapy* 2011; **48**: 17-24 [DOI: [10.1037/a0022181](https://doi.org/10.1037/a0022181)]
- 82 Ogundele MO. Behavioural and emotional disorders in childhood: A brief overview for paediatricians. *World J Clin Pediatr* 2018; **7**: 9-26 [PMID: [29456928](https://pubmed.ncbi.nlm.nih.gov/29456928/) DOI: [10.5409/wjcp.v7.i1.9](https://doi.org/10.5409/wjcp.v7.i1.9)]
- 83 Sampaio F, Bonnert M, Olén O, Hedman E, Lalouni M, Lenhard F, Ljótsson B, Ssegonga R, Serlachius E, Feldman I. Cost-effectiveness of internet-delivered cognitive-behavioural therapy for adolescents with irritable bowel syndrome. *BMJ Open* 2019; **9**: e023881 [PMID: [30679293](https://pubmed.ncbi.nlm.nih.gov/30679293/) DOI: [10.1136/bmjopen-2018-023881](https://doi.org/10.1136/bmjopen-2018-023881)]
- 84 Pontes JE, Tabet E, Folkmann MÁ, Cunha ML, Almeida Fde A. Therapeutic play: preparing the child for the vaccine. *Einstein (Sao Paulo)* 2015; **13**: 238-242 [PMID: [26154545](https://pubmed.ncbi.nlm.nih.gov/26154545/) DOI: [10.1590/S1679-45082015AO2967](https://doi.org/10.1590/S1679-45082015AO2967)]
- 85 Koukourikos K, Tzehe L, Pantelidou P, Tsaloglidou A. The importance of play during hospitalization of children. *Mater Sociomed* 2015; **27**: 438-441 [PMID: [26889107](https://pubmed.ncbi.nlm.nih.gov/26889107/) DOI: [10.5455/msm.2015.27.438-441](https://doi.org/10.5455/msm.2015.27.438-441)]
- 86 Rusmana N, Hafina A, Suryana D. Group Play Therapy for Preadolescents: Post-Traumatic Stress Disorder of Natural Disaster Victims in Indonesia. *Open Psychol J* 2020; **13**: 213-222 [DOI: [10.2174/1874350102013010213](https://doi.org/10.2174/1874350102013010213)]
- 87 Rathnakumar D. Play Therapy and Children with Intellectual Disability. *Shanlax Int J Educ* 2020; **8**: 35-42 [DOI: [10.34293/education.v8i2.2299](https://doi.org/10.34293/education.v8i2.2299)]
- 88 Paul O. [Parental Resolution of the Child's Disability Diagnosis in the Reaction to Diagnosis Interview (RDI) and Effects on the Play Interaction with the Child]. *Prax Kinderpsychol Kinderpsychiatr* 2020; **69**: 625-642 [PMID: [33146086](https://pubmed.ncbi.nlm.nih.gov/33146086/) DOI: [10.13109/prkk.2020.69.7.625](https://doi.org/10.13109/prkk.2020.69.7.625)]
- 89 Kennedy-Behr A, Rodger S, Mickan S. Aggressive interactions during free-play at preschool of children with and without developmental coordination disorder. *Res Dev Disabil* 2013; **34**: 2831-2837 [PMID: [23796458](https://pubmed.ncbi.nlm.nih.gov/23796458/) DOI: [10.1016/j.ridd.2013.05.033](https://doi.org/10.1016/j.ridd.2013.05.033)]
- 90 Abdollahian E, Mokhber N, Balaghi A, Moharrari F. The effectiveness of cognitive-behavioural play therapy on the symptoms of attention-deficit/hyperactivity disorder in children aged 7-9 years. *Atten Defic Hyperact Disord* 2013; **5**: 41-46 [PMID: [23179507](https://pubmed.ncbi.nlm.nih.gov/23179507/) DOI: [10.1007/s12402-012-0096-0](https://doi.org/10.1007/s12402-012-0096-0)]
- 91 Al-Beltagi M. Autism medical comorbidities. *World J Clin Pediatr* 2021; **10**: 15-28 [PMID: [33972922](https://pubmed.ncbi.nlm.nih.gov/33972922/) DOI: [10.5409/wjcp.v10.i3.15](https://doi.org/10.5409/wjcp.v10.i3.15)]
- 92 Lainhart JE, Piven J. Diagnosis, treatment, and neurobiology of autism in children. *Curr Opin Pediatr* 1995; **7**: 392-400 [PMID: [7581642](https://pubmed.ncbi.nlm.nih.gov/7581642/) DOI: [10.1097/00008480-199508000-00009](https://doi.org/10.1097/00008480-199508000-00009)]
- 93 Golarai G, Grill-Spector K, Reiss AL. Autism and the development of face processing. *Clin Neurosci Res* 2006; **6**: 145-160 [PMID: [18176635](https://pubmed.ncbi.nlm.nih.gov/18176635/) DOI: [10.1016/j.cnr.2006.08.001](https://doi.org/10.1016/j.cnr.2006.08.001)]
- 94 Mazzoni N, Ricciardelli P, Actis-Grosso R, Venuti P. Difficulties in Recognising Dynamic but not Static Emotional Body Movements in Autism Spectrum Disorder. *J Autism Dev Disord* 2022; **52**: 1092-1105 [DOI: [10.1007/s10803-021-05015-7](https://doi.org/10.1007/s10803-021-05015-7)]
- 95 Candini M, Battaglia S, Benassi M, di Pellegrino G, Frassinetti F. The physiological correlates of interpersonal space. *Sci Rep* 2021; **11**: 2611 [PMID: [33510396](https://pubmed.ncbi.nlm.nih.gov/33510396/) DOI: [10.1038/s41598-021-82223-2](https://doi.org/10.1038/s41598-021-82223-2)]
- 96 Ellena G, Battaglia S, Ládavas E. The spatial effect of fearful faces in the autonomic response. *Exp Brain Res* 2020; **238**: 2009-2018 [PMID: [32617883](https://pubmed.ncbi.nlm.nih.gov/32617883/) DOI: [10.1007/s00221-020-05829-4](https://doi.org/10.1007/s00221-020-05829-4)]
- 97 Borgomaneri S, Vitale F, Battaglia S, Avenanti A. Early Right Motor Cortex Response to Happy and Fearful Facial Expressions: A TMS Motor-Evoked Potential Study. *Brain Sci* 2021; **11**: 1203 [PMID: [34573224](https://pubmed.ncbi.nlm.nih.gov/34573224/) DOI: [10.3390/brainsci11091203](https://doi.org/10.3390/brainsci11091203)]
- 98 Woodard CR, Chung J. Feasibility of a play-based intervention set for toddlers with autism. *Res Dev Disabil* 2018; **80**: 24-34 [PMID: [29890299](https://pubmed.ncbi.nlm.nih.gov/29890299/) DOI: [10.1016/j.ridd.2018.05.010](https://doi.org/10.1016/j.ridd.2018.05.010)]
- 99 McCleery JP, Elliott NA, Sampanis DS, Stefanidou CA. Motor development and motor resonance difficulties in autism: relevance to early intervention for language and communication skills. *Front Integr Neurosci* 2013; **7**: 30 [PMID: [23630476](https://pubmed.ncbi.nlm.nih.gov/23630476/) DOI: [10.3389/fnint.2013.00030](https://doi.org/10.3389/fnint.2013.00030)]
- 100 Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. *Lancet* 2018; **392**: 508-520 [PMID: [30078460](https://pubmed.ncbi.nlm.nih.gov/30078460/) DOI: [10.1016/S0140-6736\(18\)31129-2](https://doi.org/10.1016/S0140-6736(18)31129-2)]
- 101 Kasari C, Freeman S, Paparella T. Joint attention and symbolic play in young children with autism: a randomized controlled intervention study. *J Child Psychol Psychiatry* 2006; **47**: 611-620 [PMID: [16712638](https://pubmed.ncbi.nlm.nih.gov/16712638/) DOI: [10.1111/j.1469-7610.2005.01567.x](https://doi.org/10.1111/j.1469-7610.2005.01567.x)]
- 102 Correction and Republication: Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR Morb Mortal Wkly Rep* 2018; **67**: 1279 [PMID: [30439872](https://pubmed.ncbi.nlm.nih.gov/30439872/) DOI: [10.15585/mmwr.mm6745a7](https://doi.org/10.15585/mmwr.mm6745a7)]
- 103 Abrams DA, Lynch CJ, Cheng KM, Phillips J, Supekar K, Ryali S, Uddin LQ, Menon V. Underconnectivity between voice-selective cortex and reward circuitry in children with autism. *Proc Natl Acad Sci USA* 2013; **110**: 12060-12065 [PMID: [23776244](https://pubmed.ncbi.nlm.nih.gov/23776244/) DOI: [10.1073/pnas.1302982110](https://doi.org/10.1073/pnas.1302982110)]
- 104 Tomchek S, Koenig KP, Arbesman M, Lieberman D. Occupational Therapy Interventions for Adolescents With Autism

- Spectrum Disorder. *Am J Occup Ther* 2017; **71**: 7101395010p1-7101395010p3 [PMID: 28027049 DOI: 10.5014/ajot.2017.711003]
- 105 **Kuhaneck H**, Spitzer SL, Bodison SC. A Systematic Review of Interventions to Improve the Occupation of Play in Children With Autism. *OTJR (Thorofare N J)* 2020; **40**: 83-98 [PMID: 31642399 DOI: 10.1177/1539449219880531]
 - 106 **Yahaya A**, Mahir IB, Lee GM, Maakip I, Arus BM, Voo P, Kwan SS. Shelter house play therapy for a child with autism. *IJASOS* 2018; **4**: 299-307 [DOI: 10.18769/IJASOS.455640]
 - 107 **Hyman SL**, Levy SE, Myers SM; Council on Children with Disabilities, Section on Developmental and Behavioral Pediatrics. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics* 2020; **145**: e20193447 [PMID: 31843864 DOI: 10.1542/peds.2019-3447]
 - 108 **Donnellan AM**, Hill DA, Leary MR. Rethinking autism: implications of sensory and movement differences for understanding and support. *Front Integr Neurosci* 2012; **6**: 124 [PMID: 23372546 DOI: 10.3389/fnint.2012.00124]
 - 109 **Kashefimehr B**, Kayihan H, Huri M. The Effect of Sensory Integration Therapy on Occupational Performance in Children With Autism. *OTJR (Thorofare N J)* 2018; **38**: 75-83 [PMID: 29281930 DOI: 10.1177/1539449217743456]
 - 110 **Schottelkorb AA**, Swan KL, Ogawa Y. Intensive Child-Centered Play Therapy for Children on the Autism Spectrum: A Pilot Study. *J Counsell Dev* 2020; **98**: 63-73 [DOI: 10.1002/jcad.12300]
 - 111 **Novita M**, Atmodiwirjo ET, Basaria D. The Effectiveness of Child-Centered Play Therapy to Improve Joint Attention Skills in Children with Autism Spectrum Disorder. The Asian Conference on Education 2017. [Accessed Jul 22, 2022] [DOI: 10.24912/jmishumsen.v1i2.922]
 - 112 **Carrizales KE**. Transcendence Through Play: Child-Centered Play Therapy and Young Children with Autism. Published Doctor of Philosophy dissertation, University of Northern Colorado, 2015
 - 113 **Goodman G**, Chung H, Fischel L, Athey-Lloyd L. Simulation modeling analysis of sequential relations among therapeutic alliance, symptoms, and adherence to child-centered play therapy between a child with autism spectrum disorder and two therapists. *Clin Child Psychol Psychiatry* 2017; **22**: 455-466 [PMID: 28191795 DOI: 10.1177/1359104517691082]
 - 114 **Kenny MC**, Dinehart LH, Winick CB. Child-centered play therapy for children with autism spectrum disorder. In: Drewes AA, Schaefer CE (Eds.). *Play therapy in middle childhood*. American Psychological Association. 2016: 257-274 [DOI: 10.1037/14776-014]
 - 115 **Baum RA**. Learning to Play and Playing to Learn: Enhancing Interactions in Young Children With ASD. *Pediatrics* 2019; **144** [PMID: 31387869 DOI: 10.1542/peds.2019-1270]
 - 116 **Gengoux GW**, Abrams DA, Schuck R, Millan ME, Libove R, Ardel CM, Phillips JM, Fox M, Frazier TW, Hardan AY. A Pivotal Response Treatment Package for Children With Autism Spectrum Disorder: An RCT. *Pediatrics* 2019; **144** [PMID: 31387868 DOI: 10.1542/peds.2019-0178]
 - 117 **de Korte MWP**, van Dongen-Boomsma M, Oosterling IJ, Buitelaar JK, Staal WG. Pivotal Response Treatment (PRT) parent group training for young children with autism spectrum disorder: a pilot study. *Sci Rep* 2022; **12**: 7691 [PMID: 35546154 DOI: 10.1038/s41598-022-10604-2]
 - 118 **Wieder S**, Greenspan SI. Climbing the symbolic ladder in the DIR model through floor time/interactive play. *Autism* 2003; **7**: 425-435 [PMID: 14678681 DOI: 10.1177/1362361303007004008]
 - 119 **Lal R**, Chhabria R. Early Intervention of Autism: A Case for Floor Time Approach. In: Fitzgerald M. *Recent Advances in Autism Spectrum Disorders*. 2013 [DOI: 10.5772/54378]
 - 120 **Dionne M**, Martini R. Floor time play with a child with autism: a single-subject study. *Can J Occup Ther* 2011; **78**: 196-203 [PMID: 21699014 DOI: 10.2182/cjot.2011.78.3.8]
 - 121 **Solomon R**, Necheles J, Ferch C, Bruckman D. Pilot study of a parent training program for young children with autism: the PLAY Project Home Consultation program. *Autism* 2007; **11**: 205-224 [PMID: 17478575 DOI: 10.1177/1362361307076842]
 - 122 **Pajareya K**, Nopmaneejumrulers K. A one-year prospective follow-up study of a DIR/Floortime parent training intervention for pre-school children with autistic spectrum disorders. *J Med Assoc Thai* 2012; **95**: 1184-1193 [PMID: 23140036]
 - 123 **Liao ST**, Hwang YS, Chen YJ, Lee P, Chen SJ, Lin LY. Home-based DIR/Floortime intervention program for preschool children with autism spectrum disorders: preliminary findings. *Phys Occup Ther Pediatr* 2014; **34**: 356-367 [PMID: 24865120 DOI: 10.3109/01942638.2014.918074]
 - 124 **Prapthathanakunwong N**, Kiatrungrit K, Hongsangunsri S, Nopmaneejumrulers K. Factors associated with parent engagement in DIR/Floortime for treatment of children with autism spectrum disorder. *Gen Psychiatr* 2018; **31**: e000009 [PMID: 30582122 DOI: 10.1136/gpsych-2018-000009]
 - 125 **Boscarelli A**. Clown therapy: not only a pediatric matter. *Transl Pediatr* 2017; **6**: 111-112 [PMID: 28503418 DOI: 10.21037/tp.2017.03.03]
 - 126 **Gordon J**, Shenar Y, Pendzik S. Clown therapy: A drama therapy approach to addiction and beyond. *Arts Psychother* 2018; **57**: 88-94 [DOI: 10.1016/j.aip.2017.12.001]
 - 127 **Shefer S**, Leon Attia O, Rosenan R, Wald OA, Ende H, Gabis LV. Benefits of medical clowning in the treatment of young children with autism spectrum disorder. *Eur J Pediatr* 2019; **178**: 1283-1289 [PMID: 31243575 DOI: 10.1007/s00431-019-03415-7]
 - 128 **Gardziel A**, Ozaist P, Sitnik E. Method 3i in ASD therapy. *Psychoterapia* 2015; **172**: 37-45 [DOI: 10.12740/pt/31765]
 - 129 **Tilmont Pittala E**, Saint-Georges-Chaumet Y, Favrot C, Tanet A, Cohen D, Saint-Georges C. Clinical outcomes of interactive, intensive and individual (3i) play therapy for children with ASD: a two-year follow-up study. *BMC Pediatr* 2018; **18**: 165 [PMID: 29753322 DOI: 10.1186/s12887-018-1126-7]
 - 130 **Brefort E**, Saint-Georges-Chaumet Y, Cohen D, Saint-Georges C. Two-year follow-up of 90 children with autism spectrum disorder receiving intensive developmental play therapy (3i method). *BMC Pediatr* 2022; **22**: 373 [PMID: 35764975 DOI: 10.1186/s12887-022-03431-x]
 - 131 **Green E**. Integrated Play Groups (IPG) Model. In: Volkmar FR (eds). *Encyclopedia of Autism Spectrum Disorders*. Springer, New York, NY. 2013 [DOI: 10.1007/978-3-319-91280-6_781]

- 132 **Yang TR**, Wolfberg PJ, Wu SC, Hwu PY. Supporting children on the autism spectrum in peer play at home and school: piloting the integrated play groups model in Taiwan. *Autism* 2003; **7**: 437-453 [PMID: [14678682](#) DOI: [10.1177/1362361303007004009](#)]
- 133 **Wolfberg P**, DeWitt M, Young GS, Nguyen T. Integrated play groups: promoting symbolic play and social engagement with typical peers in children with ASD across settings. *J Autism Dev Disord* 2015; **45**: 830-845 [PMID: [25231289](#) DOI: [10.1007/s10803-014-2245-0](#)]
- 134 **Waddington H**, Reynolds JE, Macaskill E, Curtis S, Taylor LJ, Whitehouse AJ. The effects of JASPER intervention for children with autism spectrum disorder: A systematic review. *Autism* 2021; **25**: 2370-2385 [PMID: [34348479](#) DOI: [10.1177/13623613211019162](#)]
- 135 **Goods KS**, Ishijima E, Chang YC, Kasari C. Preschool based JASPER intervention in minimally verbal children with autism: pilot RCT. *J Autism Dev Disord* 2013; **43**: 1050-1056 [PMID: [22965298](#) DOI: [10.1007/s10803-012-1644-3](#)]
- 136 **Shire SY**, Shih W, Bracaglia S, Kodjoe M, Kasari C. Peer engagement in toddlers with autism: Community implementation of dyadic and individual Joint Attention, Symbolic Play, Engagement, and Regulation intervention. *Autism* 2020; **24**: 2142-2152 [PMID: [32643385](#) DOI: [10.1177/1362361320935689](#)]
- 137 **Shire SY**, Arbuckle S, Bao W. Development and Usability Testing of a Web-Based Adaptation of the Joint Attention, Symbolic Play, Engagement, and Regulation Social Communication Intervention. *Perspectives* 2022; **7**: 310-323 [DOI: [10.1044/2021_persp-21-00222](#)]
- 138 **Panganiban J**, Kasari C. Super responders: Predicting language gains from JASPER among limited language children with autism spectrum disorder. *Autism Res* 2022; **15**: 1565-1575 [PMID: [35437928](#) DOI: [10.1002/aur.2727](#)]
- 139 **Schaad J**, Dion L. Synergetic Play Therapy Combined With EMDR Therapy, In: Beckley-Forest A, Monaco A. EMDR with Children in the Play Therapy Room. Springer Publishing Company, New York. 2020: 109-144 [DOI: [10.1891/9780826175939.0004](#)]
- 140 **Dion L**, Gray K. Impact of therapist authentic expression on emotional tolerance in synergetic play therapy. *Int J Play Ther* 2014; **23**: 55-67 [DOI: [10.1037/a0035495](#)]
- 141 **Simmons J**. Moving Toward Regulation Using Synergetic Play Therapy. *Canadian J Counsell Psychother* 2020; **54**: 242-258 [DOI: [10.4324/9781315752457-6](#)]
- 142 **Sheade H**. Equine-Partnered Play Therapy™ for Children with Oppositional Behavior. In: Equine-Assisted Mental Health Interventions, First edition, Routledge, 2018: 1-8 [DOI: [10.4324/9781315164144-12](#)]
- 143 **Chandler CK**. Animal-Assisted Therapy in Counseling, 3rd Edition, Routledge Company, 2017 [DOI: [10.4324/9781315673042-8](#)]
- 144 **Roberts F**, Bradberry J, Williams C. Equine-facilitated psychotherapy benefits students and children. *Holist Nurs Pract* 2004; **18**: 32-35 [PMID: [14765690](#) DOI: [10.1097/00004650-200401000-00006](#)]
- 145 **Bass MM**, Duchowny CA, Llabre MM. The effect of therapeutic horseback riding on social functioning in children with autism. *J Autism Dev Disord* 2009; **39**: 1261-1267 [PMID: [19350376](#) DOI: [10.1007/s10803-009-0734-3](#)]
- 146 **Harris A**, Williams JM. The Impact of a Horse Riding Intervention on the Social Functioning of Children with Autism Spectrum Disorder. *Int J Environ Res Public Health* 2017; **14** [PMID: [28708075](#) DOI: [10.3390/ijerph14070776](#)]
- 147 **Steiner H**, Kertesz Z. Effects of therapeutic horse riding on gait cycle parameters and some aspects of behavior of children with autism. *Acta Physiol Hung* 2015; **102**: 324-335 [PMID: [26551748](#) DOI: [10.1556/036.102.2015.3.10](#)]
- 148 **McDaniel Peters BC**, Wood W. Autism and Equine-Assisted Interventions: A Systematic Mapping Review. *J Autism Dev Disord* 2017; **47**: 3220-3242 [PMID: [28733851](#) DOI: [10.1007/s10803-017-3219-9](#)]
- 149 **Bosgraaf L**, Spreen M, Pattiselanno K, van Hooren S. Art Therapy for Psychosocial Problems in Children and Adolescents: A Systematic Narrative Review on Art Therapeutic Means and Forms of Expression, Therapist Behavior, and Supposed Mechanisms of Change. *Front Psychol* 2020; **11**: 584685 [PMID: [33132993](#) DOI: [10.3389/fpsyg.2020.584685](#)]
- 150 **Hermann C**. Bonsai as a group art therapy intervention among traumatized youth in KwaZulu-Natal. *Psych J* 2021; **10**: 177-186 [PMID: [33751848](#) DOI: [10.1002/pchj.440](#)]
- 151 **West C**. Art therapy. *Nurs Older People* 2008; **20**: 18-19 [PMID: [18853545](#)]
- 152 **Wypyszyńska J**, Zaboklicka N, Stachura M, Sito Z, Męcik-Kronenberg T. Opinions of parents of children with autism spectrum disorders on art therapy in the improvement of their functioning. *Wiad Lek* 2021; **74**: 2452-2459 [PMID: [34897003](#)]
- 153 **Schweizer C**, Knorth E J, Spreen M. Art therapy with children with Autism Spectrum Disorders: A review of clinical case descriptions on 'what works'. *Arts Psychother* 2014; **41**: 577-593 [DOI: [10.1016/j.aip.2014.10.009](#)]
- 154 **Moghaddam K**, Zadeh Mohammadi A, Sharifi Daramadi P, Afrooz G. Effect of the Family-based Art Therapy Program on the Social Interactions, Verbal Skills and Stereotypic Behaviors of Children with Autism Spectrum Disorders (ASD). *Iran J Public Health* 2016; **45**: 830-832 [PMID: [27648433](#)]
- 155 **Al-Beltagi M**, Saeed NK, Bediwy AS, Alhawamdeh R, Qaraghuli S. The Effects of COVID-19 on children with Autism. *World J Virol* 2022; In press
- 156 **Schueller SM**, Stiles-Shields C, Yarosh L. Online Treatment and Virtual Therapists in Child and Adolescent Psychiatry. *Child Adolesc Psychiatr Clin N Am* 2017; **26**: 1-12 [PMID: [27837935](#) DOI: [10.1016/j.chc.2016.07.011](#)]
- 157 **Renshaw KL**, Parson JA. Tele-Play Therapy. In: Play Therapy and Expressive Arts in a Complex and Dynamic World. First Edition. Routledge, 2020: 27 [DOI: [10.4324/9781003252375-5](#)]
- 158 **Tuber S**, Da Costa R, Eidman J, Feldman H, Hadar O, Kaur N, Zanotti P, Schulder T, Tocatly K. Dialectical Reflections on the Advantages and Disadvantages of Tele-Play Therapy. *J Infant, Child, Adol Psychother* 2022; **21**: 19-26 [DOI: [10.1080/15289168.2022.2043058](#)]

Adipocytokine profile in children with Kawasaki disease

Beuy Joob, Viroj Wiwanitkit

Specialty type: Infectious diseases

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ali A; Govindarajan KK, India; Huang J; Mallineni SK, Saudi Arabia

Received: September 8, 2022

Peer-review started: September 8, 2022

First decision: October 12, 2022

Revised: October 18, 2022

Accepted: November 29, 2022

Article in press: November 29, 2022

Published online: January 9, 2023



Beuy Joob, Medical Center, Sanitation Medical Academic Center, Bangkok 10203043, Thailand

Viroj Wiwanitkit, Community Medicine, Dy Patil University, Pune 73949393, India

Corresponding author: Beuy Joob, PhD, Adjunct Professor, Senior Researcher, Medical Center, Sanitation Medical Academic Center, Bangkok, Bangkok 10203043, Thailand.

beuyjoob@hotmail.com

Abstract

This letter to editor discusses on the publication on adipocytokine profile in children with Kawasaki disease. Concerns on confounding factors are raised and discussed.

Key Words: Pediatric; Adipocytokine; Kawasaki disease

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This letter to editor discussing on the publication on adipocytokine profile in children with Kawasaki disease. Concerns on confounding factors are raised and discussed.

Citation: Joob B, Wiwanitkit V. Adipocytokine profile in children with Kawasaki disease. *World J Clin Pediatr* 2023; 12(1): 23-24

URL: <https://www.wjgnet.com/2219-2808/full/v12/i1/23.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i1.23>

TO THE EDITOR

We would like to share ideas on the publication "Adipocytokine profile in children with Kawasaki disease (KD) at a mean follow-up period of 5.5 years: A study from North India[1]." When compared to controls, patients with KD had significantly higher serum resistin levels throughout the convalescent phase, according to Praharaj *et al*[1]. Serum leptin levels looked to be higher in KD patients, according to Praharaj *et al*[1], even if the difference was not statistically significant. Adiponectin levels were similar in both patients and controls, according to Praharaj *et al*[1] Raised levels of resistin and leptin may help to explain some of the lipid abnormalities seen during the

convalescent phase of KD.

The pathophysiology of Kawasaki illness is still unknown at this time, particularly given its risk factors for complicating coronary artery injury. One of the hot topics in contemporary study is whether or not children with Kawasaki disease have aberrant lipid metabolism, as well as its significance in the onset and progression of the disease. In terms of lipid metabolism, this study has some clinical utility in identifying potential Kawasaki disease biomarkers.

We agree that adiponectin levels might be an important biomarker in KD. However, it is necessary to recognize the effect of confounding factors. The underdiagnosed co-morbidity might affect adiponectin levels. Basically, underlying genetic factors can also play a role. For example, the adiponectin +276G/T polymorphism is associated with adiponectin level[2]. Clinically, the adiponectin +276G/T polymorphism is also associated with the development of KD[3]. Nevertheless, the other common inherited disorder such as hemoglobin disorder is also reported for association with high adiponectin level[4].

FOOTNOTES

Author contributions: Joob B gave ideas, wrote, analyzed and approved final submission. Wiwanitkit V gave ideas, revised, supervised and approved final submission.

Conflict-of-interest statement: The authors declare for no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Thailand

ORCID number: Beuy Joob 0000-0002-5281-0369; Viroj Wiwanitkit 0000-0003-1039-3728.

S-Editor: Ma YJ

L-Editor: A

P-Editor: Ma YJ

REFERENCES

- 1 **Praharaj DL**, Rawat A, Gupta A, Arora K, Pilania RK, Bhattad S, Singh S. Adipocytokine profile in children with Kawasaki disease at a mean follow-up period of 5.5 years: A study from North India. *World J Clin Pediatr* 2022; **11**: 360-368 [PMID: 36052116 DOI: 10.5409/wjcp.v11.i4.360]
- 2 **de Faria AP**, Modolo R, Sabbatini AR, Barbaro NR, Corrêa NB, Brunelli V, Tanus-Santos JE, Fontana V, Moreno H. Adiponectin -11377C/G and +276G/T polymorphisms affect adiponectin levels but do not modify responsiveness to therapy in resistant hypertension. *Basic Clin Pharmacol Toxicol* 2015; **117**: 65-72 [PMID: 25546819 DOI: 10.1111/bcpt.12368]
- 3 **Huang M**, Dong GQ, Xiao F, Su YY, Li MZ. [Association of +45 and +276 polymorphisms in the adiponectin gene with the development of Kawasaki disease]. *Zhongguo Dang Dai Er Ke Za Zhi* 2018; **20**: 549-553 [PMID: 30022756 DOI: 10.7499/j.issn.1008-8830.2018.07.007]
- 4 **El-Rasheidy FH**, Essa ES, Mahmoud AA, Nada Ael-W. Elevated serum adiponectin is related to elevated serum ferritin and interleukin-6 in β -thalassaemia major children. *J Pediatr Endocrinol Metab* 2016; **29**: 953-958 [PMID: 27235671 DOI: 10.1515/jpem-2016-0014]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2023 March 9; 12(2): 25-56



OPINION REVIEW

- 25 Higher rates of autism and attention deficit/hyperactivity disorder in American children: Are food quality issues impacting epigenetic inheritance?

Dufault RJ, Crider RA, Deth RC, Schnoll R, Gilbert SG, Lukiw WJ, Hitt AL

ORIGINAL ARTICLE**Clinical and Translational Research**

- 38 Factors associated with subsequent surgery after septic arthritis of the knee in children

O'Donnell JM, Ekunseitan E, Swarup I

Retrospective Cohort Study

- 45 Vaccination coverage in children with juvenile idiopathic arthritis, inflammatory bowel diseases, and healthy peers: Cross-sectional electronic survey data

Makarova E, Khabirova A, Volkova N, Gabrusskaya T, Ulanova N, Sakhno L, Revnova M, Kostik M

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Setila Dalili, MD, Associate Professor, Department of Pediatric Endocrinology, Pediatric Diseases Research Center, 17 Shahrivar Hospital, Guilan University of Medical Sciences, Iran, Siadati Street, Rasht, Iran. setiladalili1346@yahoo.com

AIMS AND SCOPE

The primary aim of the *World Journal of Clinical Pediatrics* (WJCP, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCP mainly publishes articles reporting research results and findings obtained in the field of pediatrics and covering a wide range of topics including anesthesiology, cardiology, endocrinology, gastroenterology, hematology, immunology, infections and infectious diseases, medical imaging, neonatology, nephrology, neurosurgery, nursing medicine, perinatology, pharmacology, respiratory medicine, and urology.

INDEXING/ABSTRACTING

The WJCP is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; **Production Department Director:** Xiang Li; **Editorial Office Director:** Yu-Jie Ma.

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2219-2808/editorialboard.htm>

PUBLICATION DATE

March 9, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Higher rates of autism and attention deficit/hyperactivity disorder in American children: Are food quality issues impacting epigenetic inheritance?

Renee J Dufault, Raquel A Crider, Richard C Deth, Roseanne Schnoll, Steven G Gilbert, Walter J Lukiw, Amanda L Hitt

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Liao JX, China; Nasrallah O, Syria

Received: November 27, 2022

Peer-review started: November 27, 2022

First decision: December 13, 2022

Revised: December 25, 2022

Accepted: January 9, 2023

Article in press: January 9, 2023

Published online: March 9, 2023



Renee J Dufault, Raquel A Crider, Roseanne Schnoll, Steven G Gilbert, Department of Research, Food Ingredient and Health Research Institute, Naalehu, HI 96772, United States

Renee J Dufault, College of Graduate Health Studies, A.T. Still University, Kirksville, MO 63501, United States

Richard C Deth, Department of Pharmaceutical Sciences, Nova Southeastern University, Fort Lauderdale, FL 33314, United States

Roseanne Schnoll, Department of Health and Nutrition Sciences, Brooklyn College of CUNY, Brooklyn, NY 11210, United States

Steven G Gilbert, Department of Research, Institute of Neurotoxicology and Neurological Disorders, Seattle, WA 98105, United States

Walter J Lukiw, LSU Neuroscience Center, Louisiana State University Health Sciences Center, New Orleans, LA 70112, United States

Amanda L Hitt, Food Integrity Campaign, Government Accountability Project, Columbia, WA 20006, United States

Amanda L Hitt, Department of Legal, Food Ingredient and Health Research Institute, Naalehu, HI 96772, United States

Corresponding author: Renee J Dufault, PhD, Doctor, Department of Research, Food Ingredient and Health Research Institute, PO Box 1055, Naalehu, HI 96772, United States.

rdufault@foodingredient.info

Abstract

In the United States, schools offer special education services to children who are diagnosed with a learning or neurodevelopmental disorder and have difficulty meeting their learning goals. Pediatricians may play a key role in helping children access special education services. The number of children ages 6-21 in the United States receiving special education services increased 10.4% from 2006 to 2021. Children receiving special education services under the autism category increased 242% during the same period. The demand for special education services for

children under the developmental delay and other health impaired categories increased by 184% and 83% respectively. Although student enrollment in American schools has remained stable since 2006, the percentage distribution of children receiving special education services nearly tripled for the autism category and quadrupled for the developmental delay category by 2021. Allowable heavy metal residues remain persistent in the American food supply due to food ingredient manufacturing processes. Numerous clinical trial data indicate heavy metal exposures and poor diet are the primary epigenetic factors responsible for the autism and attention deficit hyperactivity disorder epidemics. Dietary heavy metal exposures, especially inorganic mercury and lead may impact gene behavior across generations. In 2021, the United States Congress found heavy metal residues problematic in the American food supply but took no legislative action. Mandatory health warning labels on select foods may be the only way to reduce dietary heavy metal exposures and improve child learning across generations.

Key Words: Lead exposure; Mercury; Oxidative stress; Methylation patterns; Epigenetic inheritance; Autism

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Heavy metal residues are pervasive in the food supply and allowed by the Code of Federal Regulations because of food ingredient manufacturing processes. Children fed food with heavy metal residues may bioaccumulate inorganic mercury and lead in their blood and exhibit symptoms of autism or attention deficit/hyperactivity-disorder. Prenatal dietary exposures to heavy metals may impact gene activity in children and create learning difficulties requiring special education services. Educators see an increase in the prevalence of autism and developmental delay with cases doubling or tripling since 2006. Food quality issues may be impacting epigenetic inheritance of autism and related disorders.

Citation: Dufault RJ, Crider RA, Deth RC, Schnoll R, Gilbert SG, Lukiw WJ, Hitt AL. Higher rates of autism and attention deficit/hyperactivity disorder in American children: Are food quality issues impacting epigenetic inheritance? *World J Clin Pediatr* 2023; 12(2): 25-37

URL: <https://www.wjgnet.com/2219-2808/full/v12/i2/25.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i2.25>

INTRODUCTION

The special education system in the United States began developing in the 1970s and is mandated by Congress through the Individuals with Disabilities Education Act (IDEA). This act is codified in title 34 of the Code of Federal Regulations and governs how states must meet the educational needs of students between the ages of 3 and 21 who are developmentally impaired, either cognitively or intellectually, and have difficulty learning in the general education classroom. IDEA requires states to provide a free and appropriate public education to each disabled student at no cost to the parents. Through IDEA, the United States Department of Education is authorized to provide federal funding to states in the form of grants which are distributed each year and based on the child count or number of children in each state in need of special education services[1]. The funding is used by states to pay for special education teachers who provide academic services, school psychologists, occupational therapists, transportation, classroom aides, instructional materials, and parent education[2].

Under IDEA, there are 13 disability categories states must use to determine student eligibility for special education and related services[3]. Young children with autism are found eligible for services under different disability categories depending on their age and dominant behaviors[4]. Typical disability categories used to determine eligibility for children exhibiting symptoms of autism include Autism, Developmental Delay, Speech/Language Impairment, or other health impaired (OHI) if attention deficit hyperactivity disorder (ADHD) is a co-morbid condition[5]. In a 2009 review of the literature, Yerys *et al*[6] estimated 30% of children with autism also meet diagnostic criteria for ADHD and another 20% of children with autism exhibit subthreshold clinical symptoms for ADHD. This review provides up-to-date analyses of the prevalence data for disability categories made available to the public by the United States government. Etiology of autism and ADHD and future trends will be discussed from an epigenetic perspective.

CURRENT AUTISM AND ADHD PREVALENCE IN THE UNITED STATES

Medical researchers at the United States Center for Disease Control (CDC) and Prevention have been monitoring the prevalence of autism and developmental disabilities in eight-year-old children living in select communities in up to eleven states since 2000. Between 2000 and 2002, the estimated autism prevalence among eight-year-old children living in these communities was 1/150 or 6.7/1000[7]. By 2018, the autism prevalence in eight-year-old children living in these communities had increased to 1/44 or 23/1000[7]. Autism was 4.2 times more prevalent in boys than girls[7]. CDC researchers collect their autism prevalence data through federal contracts with community medical and educational service providers in CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network.

Our review of the data collected by CDC's ADDM network revealed the prevalence of autism among children aged 8 years has increased 70% from 2000 to 2018[8]. Although the increase over the entire period is substantial, more noteworthy is the fact that the rate of change is increasing. From 2000 to 2010, the rate of change was 1.6/1000 per 2-year measurement period. From 2012 to 2018, the rate of change nearly doubled as it increased to 2.7/1000 per 2-year measurement period. Table 1 clearly shows these changes.

The CDC has not set up a network to track ADHD prevalence in any age group or community, however, periodically, the agency studies the prevalence of ADHD using data gathered from the National Health Interview Survey (NHIS)[9]. The most recent analysis of the NHIS data ($n = 146457$) was conducted by Xu *et al*[10] who found a significant increase in the prevalence of ADHD in a representative sample of United States children aged 4-17 with 14% of boys and 6.3% of girls given the diagnosis in 2015-2016.

Public policy and medical researchers can better understand the magnitude of the problem of autism and ADHD across the United States by studying the special education data collected by the United States Department of Education each year. Newschaffer *et al*[11] first used this data set to determine increasing autism and ADHD prevalence over time in United States children between the ages of 6 and 17 from 1992 to 2001. ADHD prevalence trends can be determined by tracking the children receiving special education services under the OHI category[11,12]. Dufault *et al*[12] reviewed the special education data set available for the years 2005-2010 and found the number of children in the United States between the ages 6-21 receiving services under the IDEA categories of autism and OHI increased 91% and 26% respectively. We conducted an assessment and analysis of the special education data currently available at the United States Department of Education for the years 2006[13], 2011[13], and 2021[14] in preparation for this review and present our results in Table 2.

The overall number of children ages 6-21 in the United States receiving special education services increased 10.4% from 2006 to 2021. The number of children receiving special education services under the autism category increased 242% during the same period. The demand for special education services for children with developmental delay and OHI increased by 184% and 83% respectively. These increases should be alarming to policymakers, teachers, parents, and others who are responsible for educating these learning-disabled children in classrooms across the country given the stable student enrollment in public schools during the last fifteen years. The National Center for Education Statistics (NCES) reported a total enrollment of 49.5 million children in public elementary and secondary schools in grades pre-k to 12 during the fall of 2021[15]. Prior to the COVID pandemic, public school enrollment in grades pre-k to 12 ranged from 49.5 million students in the fall of 2010 to 50.8 million students in the fall of 2019[15]. The NCES created Figure 1 to provide a visual representation of the student enrollment trends in the United States since 2003[16].

While student enrollment in United States schools has remained stable since the early 2000s, our data shows the percentage distribution of children receiving special education services in the autism disability category has nearly tripled between 2006 and 2021. The percentage distribution of children receiving special education services in the developmental delay category has quadrupled over the same period. Figure 2, created using the data in Table 2, shows the burden of care required for children in special education disability categories associated with ADHD and autism compared to all other disability categories in 2006 and 2021. The burden of care for American children with autism or ADHD related special education services has increased dramatically between 2006-2021 even as student enrollment remains stable.

Data collected through the ADDM network and analyzed by CDC medical researchers reveal autism prevalence rates in the United States vary by geographic location[7]. Dufault *et al*[12] analyzed autism prevalence data from the United States and Italy and proposed a macroepigenetic model to explain why autism prevalence may vary across geographic regions depending on nutrition deficits in the population under study, exposure to organophosphate (OP) pesticides, and the influence of various dietary factors known to impact gene expression. Such dietary factors may include high intake of high fructose corn syrup (HFCS) and exposures to heavy metal residues from the consumption of processed foods[12]. Dietary epigenetic factors vary between countries due to policies and regulations that determine allowable exposures to heavy metal and pesticide residues in food and food ingredients[17].

A recent review of the literature indicates the primary factors involved in the development of autism, ADHD, and disruptive child behaviors are exposures to heavy metals[18-21]. Recent clinical trial data collected from cohort studies around the world show mercury is the most common heavy metal

Table 1 Rate of change in Center for Disease Control prevalence estimates among 8-year-old children between 2000-2018

Year	Autism prevalence estimate among 8-year-old children (CDC)	Rate of change
2000	6.7/1000	
2002	6.6/1000	
2004	8/1000	
2006	9/1000	
2008	11.3/1000	
2010	14.7/1000	1.6/1000 (from 2000-2010)
2012	14.5/1000	
2014	16.8/1000	
2016	18.5/1000	
2018	23/1000	2.7/1000 (from 2012-2018)

CDC: Center for Disease Control.

Table 2 Number of United States students ages 6-21 served under Individuals with Disabilities Education Act by disability category & year

Year	Autism	OHI (including ADHD)	Speech/language	Developmental delay (3-9 yr only)	All disabilities
2006	224594	599494	1160904	89931	6081890
2011	407214	734348	1071555	115642	5789884
2021	768179	1097251	1183310	255787	6712010
% Change (2006-2021)	+242.0%	+83.0%	+1.9%	+184.4%	+10.4%

OHI: Other health impaired; ADHD: Attention deficit hyperactivity disorder.

exposure of concern in the development of autism[22,23] and lead is the most common heavy metal exposure of concern in children with ADHD[24-27].

SOURCES OF HEAVY METAL EXPOSURES IN THE UNITED STATES FOOD SUPPLY

Ingredients in the American food supply with allowable lead, arsenic, and mercury residues are abundant[28]. The allowed heavy metal residues are based on the individual food ingredient manufacturing processes. For example, food colors made from petroleum[29] are expected to contain trace amounts of heavy metals because petroleum is extracted from beneath the earth's crust where heavy metals are found[28]. The United States Food and Drug Administration (FDA) therefore has a process in place to ensure the petroleum-based food colors do not contain more than the "allowable" levels of inorganic mercury (≤ 1 ppm Hg), lead (≤ 10 ppm Pb), and arsenic (≤ 3 ppm As)[30]. FDA regulations require manufacturers to test and certify each batch of food coloring to ensure the allowable levels of heavy metals are not exceeded[30]. All food colors requiring FDA certification are referred to as "certified food colors".

In addition to certified food colors, other food ingredients may contain various levels of heavy metal residues. Some preservatives and a few food colors exempt from the FDA certification requirements have legally allowable levels of arsenic, lead, cadmium, or inorganic mercury[28]. Corn sweetener products such as HFCS may also be at risk of mercury contamination due to their manufacturing process which may involve the use of mercury cell chlor-alkali products[31-33] or the direct application of mercuric chloride onto the corn starch at the front end of the refining process[34]. Vegetable oils risk heavy metal contamination from a variety of sources including the use of fertilizers and pesticides during farming and the use of process aids (*e.g.*, phosphoric acid, citric acid) during refining[35]. The use of phosphoric acid may introduce up to 10 ppm Pb and 1 ppm As while the use of citric acid may introduce up to 1 ppm Pb during the vegetable oil refining process[35].

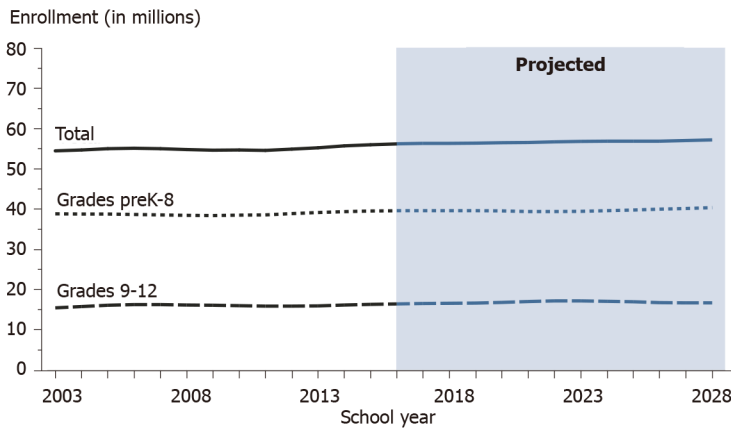


Figure 1 Actual and projected numbers for enrollment in elementary and secondary schools, by grade level: Fall 2003 through fall 2028. Pre-K: Pre-kindergarten. Citation: Hussar WJ, Bailey TM. Projections of education statistics to 2028. Washington: National Center for Education Statistics. Copyright © U.S. Department of Education 2020. Published by National Center for Education Statistics. The authors have obtained the permission for figure using from the National Center for Education Statistics (Supplementary material).

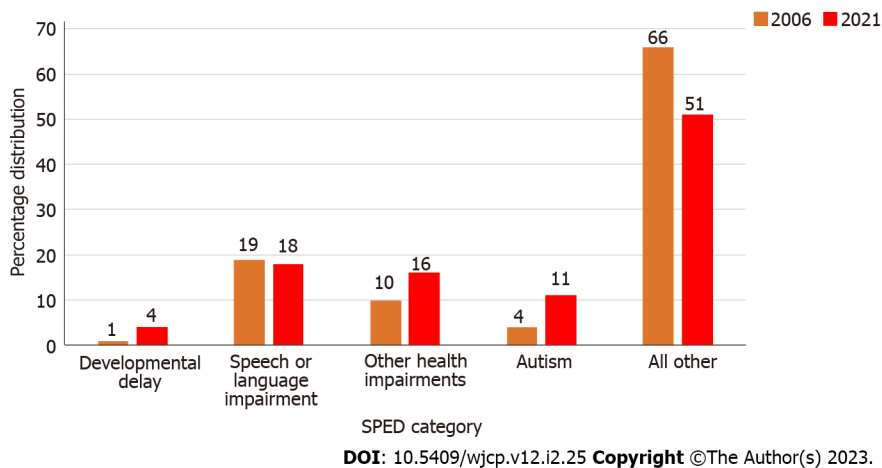


Figure 2 Percentage distribution of American children receiving special education services, 2006 and 2021. SPED: Special education.

The risk of heavy metal exposure in humans from eating foods containing heavy metal residues was first demonstrated by Khan *et al*[36] who found heavy metal concentrations in foodstuffs significantly correlated with the same heavy metals detected in human blood. Wells *et al*[37] analyzed data ($n = 1770$ for non-fish eaters, $n = 5427$ for fish/seafood eaters) from the CDC's National Health and Nutrition Examination Survey (NHANES) and verified mercury exposure from non-fish food occurs in the American population through the consumption of vegetable oil, an ingredient found in many processed foods. In another study using NHANES data ($n = 11354$), Raehsler *et al*[38] determined a diet high in ultra-processed foods[39], such as a gluten-free diet, may lead to significantly higher levels of mercury, cadmium, and lead in blood.

Vegetable oils, HFCS, and corn syrup solids are common ingredients used in the ultra-processed food supply[40]. The United States Department of Agriculture (USDA) provides estimates of the annual per capita dietary intake of corn sweeteners ("sugar") and vegetable oils ("fat") *via* the Food Availability (Per Capita) Data System[41]. We were able to extract the most current data available from the system to determine the average American consumed 21.6 pounds per year of HFCS in 2019 and 36 pounds per year vegetable oil ("salad and cooking oils") in 2010[41]. Unfortunately, the USDA does not analyze corn sweeteners or vegetable oil products to determine heavy metal residue levels. The USDA also does not track "corn syrup solid" consumption trends. Corn syrup solids and vegetable oils are the primary ingredients in many baby formula food products[42,43].

In 2019, the United States Congress investigated consumer reports alleging elevated levels of toxic heavy metals in the American baby food supply[44]. In response, seven of the largest baby food manufacturers provided internal documents and baby food test results to Congress[44]. After reviewing the manufacturers' information, the United States Congress issued a report in February 2021 that included the following findings: Arsenic, lead, and cadmium residues were present in baby foods made by all the responding companies and mercury residues were detected by the one company that tested

for it[44]. The mercury levels were reported at higher concentrations many times higher than allowed under existing regulations[44]. The United States Congress issued a second report in September 2021 with the recommendation that baby food manufacturers should “voluntarily find substitutes for ingredients that are high in toxic heavy metals”[45].

In addition to the United States Congressional reports, we identified a few other studies conducted to determine heavy metal exposures in baby formula or baby foods. Dabeka and McKenzie[46] measured total mercury levels in 150 infant formula products sold in Canada in 2003. Using the measurement method available at the time, mercury concentrations in 76% of the samples fell below the limit of detection[46]. There were, however, clear cases of low-level mercury contamination (up to 1.5 ng/g) in individual lots of powdered formula[46]. In a sample size of 87, Martins *et al*[47] identified median total mercury concentrations of 0.50 ug/kg in baby formula analyzed in Portugal. In a more recent study, Gardener *et al*[48] analyzed 564 baby food (including infant formula, cereals, meals, juices, snacks) products for cadmium and lead. While lead was only detected in 37% of the samples, cadmium was detected in 57% of the samples collected from the United States food supply[48].

The multiple findings of heavy metal residues in the food supply are important because children diagnosed with symptoms of autism have difficulty metabolizing and excreting heavy metals from their bloodstream due to their biologically embedded epigenome[17]. In the most recent study, Hassan *et al* [49] found higher aluminum, mercury, and lead levels in the blood of children with autism ($n = 73$) compared to children serving in a healthy age- and sex- matched control group ($n = 73$). The finding of higher aluminum in this case-control study is alarming because a novel laboratory experiment recently showed significant synergism in the toxicity of aluminum and mercury when added together in a culture of human brain cells[50]. Alabdali *et al*[51] demonstrated the levels of mercury and lead in the blood of children with autism correlate with the severity of their symptoms to include social and cognitive impairment. The synergistic neurotoxic damage caused by dietary inorganic mercury, lead, and cadmium exposures was recently demonstrated in a study conducted on rats[52]. Co-exposures to specific heavy metals cause more extensive damage to brain cells. When studied alone, however, mercury exposure is a significant factor in the development of autism. In agreement with Alabdali *et al* [51], Mostafa *et al*[53] also found mercury levels were significantly higher ($P < 0.001$) in the blood of children with autism ($n = 84$) compared to the healthy matched controls ($n = 84$). There was also a significant ($P < 0.0001$) and positive linear relationship between mercury in the blood of children with autism and symptom severity[53].

Children diagnosed with ADHD bioaccumulate lead in their blood because of dietary calcium and zinc deficits or losses, in conjunction with lead exposures[17]. In an analysis of NHANES data gathered between 1976-1980 ($n = 2926$), Mahaffey *et al*[54] found an inverse relationship exists between lead in blood and dietary calcium intake. More recently, Gulson *et al*[55] found a positive association between lead content in the diets of 108 children over a 5-year period and the lead concentration in their blood. There was also a statistically significant inverse relationships between dietary zinc and calcium and lead levels in the children’s blood[55]. As dietary zinc and calcium levels increased, the blood lead levels decreased[55]. Lead exposure has historically been recognized by governments and public health agencies to adversely impact child neurodevelopment. According to the CDC, no safe level of lead in blood has been identified and even low levels of lead in blood can negatively impact child intelligence and ability to learn[56].

ETIOLOGY OF AUTISM AND ADHD: AN EPIGENETIC PERSPECTIVE ON HEAVY METAL EXPOSURES AND POOR DIET

Food ingredients with allowable lead, arsenic, cadmium, and mercury residues may impact gene behavior by synergistically interfering with heavy metal excretion[57]. For example, in addition to being a source of lead, arsenic, and mercury exposure, the food color tartrazine (yellow 5) has been shown to negatively impact zinc status of children with ADHD[58,59]. Lower levels of zinc may downregulate metallothionein (MT) gene expression, thereby further reducing heavy metal detoxification and elimination[57,60], especially in children with autism[60,61]. The MT gene promotes the synthesis of the MT protein which is zinc dependent because it requires up to seven zinc atoms per molecule[62]. Hundreds of molecules bind together to make a MT protein strand. With adequate zinc reserves, the MT transporter protein prevents heavy metal accumulation as it continuously swaps zinc for lead, mercury, arsenic, or cadmium as part of the body’s metal detoxification and elimination process[63]. Dietary zinc is therefore crucial for supporting the body’s effort to rid itself of harmful metals that create conditions for oxidative stress and the development of various disease conditions[64]. The more zinc deficient a child is, or becomes because of his/her diet, the more likely he/she will accumulate heavy metals in his bloodstream due to the disruption in MT gene activity[57]. Zinc is an important macromineral; it is a dietary element needed by the body in copious amounts. Food ingredients, such as yellow 5, that are a source of heavy metal exposure and lead to zinc loss may be eliminated from the food supply to improve child health and learning outcomes.

Another example of a food ingredient that can disrupt macromineral homeostasis in humans is HFCS [57,65]. In a study conducted by the USDA, Milne and Nielsen[65] fed eleven men a mixed Western diet for four 42-d dietary periods. When fed a high fructose diet, the men showed significant calcium ($P < 0.007$) and phosphorus ($P < 0.005$) losses, especially when dietary magnesium intake was low[65]. In their conclusion, Milne and Nielsen[65] suggested further studies are needed to see if a high fructose diet with the accompanied calcium loss and low dietary magnesium lead to the development of osteoporosis. With respect to child health, there is a need to conduct other studies. Because HFCS consumption may lead to calcium losses, its overconsumption by children may result in the bioaccumulation of lead stores in the body[54,55]. More research needs to be done to determine if HFCS consumption adversely impacts children with ADHD or autism by contributing to calcium losses and the bioaccumulation of lead.

The calcium losses that resulted from the consumption of HFCS is a finding of concern especially when the average American consumed 21.6 pounds of HFCS in 2019. Calcium is required by the body in copious amounts to conduct important processes. For example, the paraoxonase (PON1) gene relies on calcium to synthesize the PON1 enzymes that break down and detoxify the metabolites of OP pesticides [66]. PON1 gene expression varies in children with autism and ADHD[67] and can be inhibited by dietary factors such as fructose and heavy metal (*e.g.*, lead, inorganic mercury, or cadmium) intake[66, 68,69]. Children with autism and ADHD have nutrient poor diets and are thus thought to be more susceptible to the neurotoxic effects of OP pesticide exposure especially when concurrently exposed to heavy metals[17,67]. A search of the literature did not yield even one study on humans to determine the effect of concurrent or co-exposures to multiple xenobiotic agents found in the food supply.

However, Zhou *et al*[70] conducted a recent case-control study on pregnant rats to determine if low concurrent exposures to lead, cadmium, and inorganic mercury *via* diet resulted in adverse outcomes among the pups. The low dose exposures to the heavy metals induced damage to several organs including brain tissue in both the dosed rats and their pups[70]. The heavy metal concentration in blood and brain tissue significantly increased in a dose dependent manner[70]. Zhou *et al*[70] also observed significant increases in oxidative stress, intracellular free calcium, and cell apoptosis in the brain tissue of the cases compared to the controls. Learning and memory deficits and sensory perception issues were also observed in the behavior of the prenatally dosed pups along with the histopathological changes in hippocampus morphology[70]. This is the first study showing dietary low-level lead, cadmium, and inorganic mercury co-exposures in rats are a relevant model for evaluating human dietary heavy metal exposure levels that adversely impact child neurobehavior and development[70]. Zhou *et al*[70] also identified changes in the behavior of select genes in select organs in response to the concurrent heavy metal exposures. Figure 3 shows the updated epigenetic model for how autism and ADHD may develop in children because of concurrent exposures to heavy metals in the food supply.

Dietary nutritional deficits, exposures to food ingredients that induce macromineral imbalances, and heavy metal exposures may impact gene behavior through a variety of mechanisms such as histone or DNA methylation[71,72]. Methylation patterns in the cellular environment may change under conditions of oxidative stress which simply means the cell contains too many molecules made up of reactive oxygen species (ROS). The primary ROS (molecular species) are hydrogen peroxide, superoxide anion, hydroxyl radical. When the cell does not contain enough of the molecules (antioxidants) it needs to neutralize the ROS, it is under oxidative stress and the DNA or RNA methylation pattern can change along with gene behavior. The formation of ROS and the development of oxidative stress can be induced by the presence of heavy metals (*e.g.*, inorganic mercury, lead) in the cellular environment.

As heavy metals accumulate in red blood cells, oxidative stress occurs, and methylation patterns may change. Oxidative stress caused by heavy metal exposure may be alleviated with the introduction of nutrients that serve as antioxidants. Examples of such nutrients include zinc[73] and selenium[74]. It is important to reduce dietary heavy metal intake and improve diet to prevent the bioaccumulation of heavy metals in the blood cells of children who exhibit symptoms associated with autism and/or ADHD[17]. In addition to creating conditions for symptomatic autism and ADHD in childhood[17], heavy metal exposures can create changes in DNA methylation patterns that impact child neurodevelopment in the womb[75-78] and contribute to adverse health outcomes in adulthood[78]. DNA methylation is an important regulator of gene expression; a methyl group which is a molecule made up of one carbon and three hydrogen atoms (CH_3) attaches to DNA and serves as a switch to turn a gene on or off from one generation to the next for better or worse.

EMERGING TRANSGENERATIONAL EPIGENETIC INHERITANCE PATTERNS MAY EXPLAIN INCREASING AUTISM AND ADHD

Changes in methylation patterns and gene behavior that occur in response to heavy metal exposures and nutritional factors are common in the development of disease conditions across generations[79]. The term used to describe these cross generational changes in methylation patterns is “transgenerational epigenetic inheritance[79]”. Methylation patterns on genes vary among humans and can be modified by useful or harmful dietary factors[79]. For example, folate and vitamins B6 and B12 are useful dietary

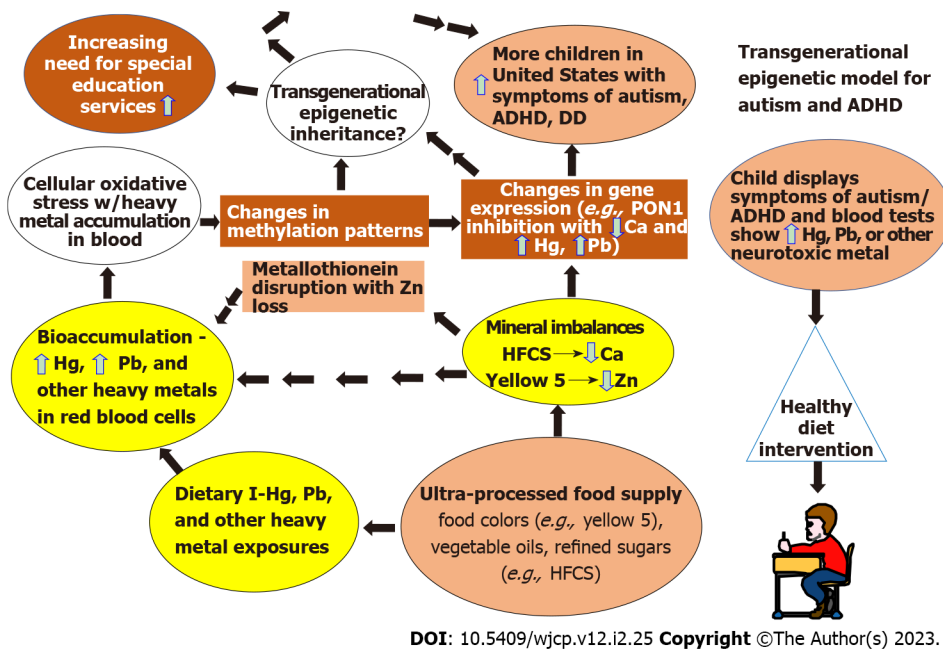


Figure 3 Transgenerational epigenetic model for autism and attention deficit/hyperactivity disorder. ADHD: Attention deficit/hyperactivity disorder; HFCS: High fructose corn syrup; I-Hg: Inorganic mercury; Pb: Lead; Ca: Calcium; Zn: Zinc; PON1: Paraoxonase; DD: Developmental delay.

factors that induce the formation of the methyl donor (CH_3) in DNA methylation[79]. Conversely, prenatal inorganic mercury exposure may be a harmful dietary factor because it has been shown to induce changes in methylation levels of the PON1 gene that persist into early childhood[77]. Cardenas *et al*[77] showed changes in methylation levels of PON1 in cord blood from mercury exposures could be used to predict lower cognitive scores in childhood. These findings are not surprising in the child neurodevelopment field of study because we know suppression of the PON1 gene and/or the bioaccumulation of heavy metals create conditions for oxidative stress which is a hallmark feature of autism[80, 81] along with impaired or decreased DNA methylation capacity[12]. The emerging evidence strongly suggests DNA methylation patterns altered by dietary stimuli may be stable or passed on to the next generation and this is of great concern[82].

Changes in DNA methylation patterns during pregnancy, infancy, and adult life can lead to the inheritance of disease conditions such as obesity and diabetes[82]. Ando *et al*[83] recently conducted a rat study and found changes in DNA methylation patterns on a specific gene led to the development of insulin resistance and hyperlipidemia in offspring when pregnant rats were fed a diet consisting of 20% HFCS[83]. This transgenerational epigenetic inheritance of metabolic abnormalities observed in rats has not yet been studied in humans to determine which gene(s) may be impacted by the consumption of HFCS[83]. In the case of autism and ADHD, however, the literature strongly supports the idea that changes in DNA methylation patterns from prenatal exposures to lead and mercury may lead to the inheritance of the same methylation patterns in human offspring[75].

Bozack *et al*[75] investigated the epigenome-wide associations of maternal heavy metal measurements in blood ($n = 361$) with cord blood DNA methylation ($n = 361$) and persistent DNA methylation changes in mid-childhood ($n = 333$, 6-10 years). Of the twelve metals studied, Bozack *et al*[75] found evidence that prenatal exposures to lead and manganese are associated with changes in cord blood DNA methylation patterns which may persist in children when measured at mid-childhood[75]. In a separate meta-analysis of epigenome-wide association studies involving the cord blood of 2477 children, Neumann *et al*[76] found evidence that DNA methylation at birth is strongly associated with the development of ADHD ($P = 1 \times 10^{-7}$).

Persistent DNA methylation changes resulting from prenatal mercury exposures ($n = 321$) were observed in a study of epigenome-wide methylation patterns conducted by Cardenas *et al*[77]. Among male children, prenatal mercury exposures were associated with cord blood methylation at the PON1 gene locus and lower cognitive test scores measured in early childhood[77]. Cord blood DNA methylation levels at the PON1 gene locus is widely known to be associated with lower PON1 gene activity[77]. In a commentary citing elements of the macroepigenetic model, Dufault and Gilbert[84] explain that because male children have lower PON1 gene activity, prenatal mercury exposure associated with cord blood methylation at the PON1 gene may explain why autism impacts males more often than females. This observation is relevant; CDC reported the finding that autism was 4.2 times more prevalent in boys than girls in 2018[7].

PERSPECTIVES ON FUTURE RESEARCH AND ACTIONS

Research evidence presented in a recent review suggests heavy metal exposures are among the most significant environmental agents impacting human health[85]. Prenatal exposures to lead, inorganic mercury and other heavy metals can induce developmental epigenetic programming in the human population[85]. Research evidence provided in this review supports the idea that food quality issues are impacting epigenetic inheritance. Fortunately, developmental epigenetic modifications, including methylation patterns, may be reversible. More research is needed to identify what intervention measures can be taken to lower dietary heavy metal exposures in children and whether such measures may reverse methylation patterns and gene behaviors.

Switching to a healthy diet and eliminating the intake of ultra-processed foods is currently one intervention used to reduce heavy metals in blood and improve behaviors and learning among children with autism or ADHD[17]. In the current political environment, interventions for mitigating climate change are on the rise along with the trend towards adopting a plant-based animal product alternative (PB-APA) diet[86]. Unfortunately, PB-APA foods tend to be ultra-processed so this trend to increase ultra-processed food intake may have detrimental effects on children. It is important to ensure these “ultra-processed” PB-APA foods do not contribute to child heavy metal exposures. Studies need to be conducted to determine whether the ultra-processed PB-APA food products and the ingredients they are made of are at risk of heavy metal contamination.

The impact of specific food ingredients on macro and micro mineral balance in the human body needs further study. To date only two food ingredients are known to create mineral imbalances: Yellow 5 (tartrazine) and HFCS. There are many more ingredients commonly found in the ultra-processed food supply that could impact mineral balance. Yellow 6 is similar to yellow 5 with the same allowable lead, inorganic mercury, and arsenic residue levels in each manufactured batch; its overconsumption may also lead to zinc loss. A case-control study could be designed to determine the impact of yellow 5 and/or yellow 6 intake on zinc balance, methylation patterns, and MT gene activity levels. Determining how mineral imbalances and dietary exposures to heavy metals impact DNA methylation and gene expression in children with autism or ADHD would be useful.

The mechanisms by which heavy metals bioaccumulate in children with autism and/or ADHD are poorly understood. Dietary factors such as zinc, calcium, and HFCS intake could be key to understanding how dietary heavy metals bioaccumulate in a child’s blood. Intervention studies could be designed to consider pre-post intervention dietary intake (survey intake of whole foods and dairy *vs* ultra-processed foods including those with HFCS, vegetable oils, food colors, preservatives), pre-post intervention heavy metal exposures (heavy metal measurements in blood), pre-post intervention DNA methylation patterns, pre-post intervention gene activity levels (*e.g.*, PON1, MT). Instructions for creating a healthy diet intervention that reduces dietary heavy metal exposures are available[17].

With autism and ADHD prevalence climbing at alarming rates with each successive generation it is clear more must be done to reduce dietary heavy metal exposures and improve child nutrition. Unfortunately, until advancements are made on the epigenomic front, we can only moderate the increasing autism and ADHD prevalence through the introduction of policies and laws that eliminate exposures to certain harmful food ingredients and reduce dietary exposures to heavy metal residues.

The United States Congress has taken an excellent first step in collecting heavy metal residue data from food manufacturers[44,45]. Decisive action is needed now to address the autism and ADHD epidemic in the United States. Ethical considerations need to guide the decision making among Congressional members. We must acknowledge what we know and what we don’t know about the contaminants in the food supply. In the case of lead and inorganic mercury, we know there is no safe level of exposure, and any exposure is harmful to the developing fetus[87]. With the knowledge that widespread heavy metal contamination exists in the United States food supply, Congress could now choose to ban food ingredients with allowable heavy metals. Alternatively, Congress could mandate warning labels on foods that contain ingredients with allowable heavy metal residues. At least warning labels would serve to inform consumers and expectant parents of the health risks associated with eating food ingredients with allowable lead and inorganic mercury residues.

There is compelling evidence to suggest that mandatory health warning labels do encourage consumers to adopt more healthful purchasing behaviors[88]. Song *et al*[88] conducted a meta-analysis of the impact of color-coded and warning nutrition labelling schemes on consumer behavior. Of the 134 studies analyzed, the traffic light labelling system, nutrient warning, and health warning labels were the most effective front-of-package labeling methods for influencing consumers’ purchasing choices[88]. Health warning labels reduced consumers’ perception of the healthfulness of less healthful products while increasing their perceived disease risk from eating unhealthful products[88].

Mandatory health warning labels on foods containing ingredients with allowable heavy metal residues would direct parent purchasing behaviors away from unhealthful food products in the United States free market system. Movement away from the consumption of these foods could lead to significant reductions in child heavy metal exposures. Without any changes in United States food safety law, however, unabated dietary exposures to inorganic mercury and lead will continue to occur because of the adulterated American food supply. Autism and ADHD prevalence will continue to rise as transgenerational epigenetic inheritance becomes the norm.

CONCLUSION

The American food supply is contaminated with allowable heavy metals in specific food ingredients. Americans continue to be exposed to inorganic mercury and lead over time which can impact the national epigenome. The United States Congress has confirmed heavy metal exposures are occurring in American children due to contaminants in the food supply. We are seeing sustainable and alarming increases in autism and ADHD prevalence with cases doubling or tripling in one generation. Congress may act now to mandate the health warning label on foods containing food ingredients with allowable heavy metal residues before child intellectual development and learning erodes any further.

FOOTNOTES

Author contributions: Dufault RJ developed and wrote the original and revised manuscripts, compiled, and analyzed the dataset for table 2, created figure 3, obtained and verified public use of figure 1; Crider RA compiled and analyzed the dataset for table 1, created figure 2, provided comments on both manuscripts; Deth RC provided input on oxidative stress for revision; Schnoll R provided input on zinc metabolism and title for revision; Gilbert SG provided input on ethical considerations for revision; Lukiw WJ provided input on concurrent exposures to heavy metals for revision; Hitt AL provided insights on plant based animal product alternatives for revision; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United States

ORCID number: Renee J Dufault 0000-0002-8299-3768; Raquel A Crider 0000-0003-2217-1356; Richard C Deth 0000-0002-7717-7037; Roseanne Schnoll 0000-0002-5051-550X; Steven G Gilbert 0000-0002-0087-3974; Walter J Lukiw 0000-0001-5500-4402; Amanda L Hitt 0000-0001-5903-4131.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

REFERENCES

- 1 **Individuals with Disabilities Education Act.** About IDEA. [cited 7 November 2022]. Available from: <https://sites.ed.gov/idea/about-idea/>
- 2 **Hawaii State Department of Education.** Special education: what is special education? [cited 7 November 2022]. Available from: <https://www.hawaiipublicschools.org/TeachingAndLearning/SpecializedPrograms/SpecialEducation/Pages/home.aspx>
- 3 **Individuals with Disabilities Education Act.** Sec. 300.8 child with a disability. [cited 7 November 2022]. Available from: <https://sites.ed.gov/idea/regs/b/a/300.8>
- 4 **Brock S.** An examination of the changing rates of autism in special education. *California School Psychol* 2006; **11**: 31-40
- 5 **The Committee on Nomenclature and Statistics of the American Psychiatric Association,** Gruenberg EM. Diagnostic and Statistical Manual of Mental Disorders 5th Edition. Washington: American Psychiatric Association, 2013
- 6 **Yerys BE,** Wallace GL, Sokoloff JL, Shook DA, James JD, Kenworthy L. Attention deficit/hyperactivity disorder symptoms moderate cognition and behavior in children with autism spectrum disorders. *Autism Res* 2009; **2**: 322-333 [PMID: 19998356 DOI: 10.1002/aur.103]
- 7 **Maenner MJ,** Shaw KA, Bakian AV, Bilder DA, Durkin MS, Esler A, Furnier SM, Hallas L, Hall-Lande J, Hudson A, Hughes MM, Patrick M, Pierce K, Poynter JN, Salinas A, Shenouda J, Vehorn A, Warren Z, Constantino JN, DiRienzo M, Fitzgerald RT, Grzybowski A, Spivey MH, Pettygrove S, Zahorodny W, Ali A, Andrews JG, Baroud T, Gutierrez J, Hewitt A, Lee LC, Lopez M, Mancilla KC, McArthur D, Schwenk YD, Washington A, Williams S, Cogswell ME. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018. *MMWR Surveill Summ* 2021; **70**: 1-16 [PMID: 34855725 DOI: 10.15585/mmwr.ss7011a1]
- 8 **Centers for Disease Control and Prevention.** Data and statistics on autism spectrum disorder. [cited 2 March 2022]. Available from: <https://www.cdc.gov/ncbddd/autism/data.html>
- 9 **Centers for Disease Control and Prevention.** About the National Health Interview Survey. [cited 3 March 2022]. Available from: https://www.cdc.gov/nchs/nhis/about_nhis.htm
- 10 **Xu G,** Strathearn L, Liu B, Yang B, Bao W. Twenty-Year Trends in Diagnosed Attention-Deficit/Hyperactivity Disorder

- Among US Children and Adolescents, 1997-2016. *JAMA Netw Open* 2018; **1**: e181471 [PMID: 30646132 DOI: 10.1001/jamanetworkopen.2018.1471]
- 11 **Newschaffer CJ**, Falb MD, Gurney JG. National autism prevalence trends from United States special education data. *Pediatrics* 2005; **115**: e277-e282 [PMID: 15741352 DOI: 10.1542/peds.2004-1958]
 - 12 **Dufault R**, Lukiw WJ, Crider R, Schnoll R, Wallinga D, Deth R. A macroepigenetic approach to identify factors responsible for the autism epidemic in the United States. *Clin Epigenetics* 2012; **4**: 6 [PMID: 22490277 DOI: 10.1186/1868-7083-4-6]
 - 13 **United States Department of Education**. IDEA Section 618 State Level Data Files Part B Child Count. [cited 7 November 2022]. Available from: <https://data.ed.gov/dataset/idea-section-618-state-level-data-files-part-b-child-count>
 - 14 **United States Department of Education**. IDEA Section 618 State Part B Child Count and Educational Environments. [cited 7 November 2022]. Available from: <https://data.ed.gov/dataset/idea-section-618-state-part-b-child-count-and-educational-environments>
 - 15 **National Center for Education Statistics**. Fast facts: enrollment trends. [cited 7 November 2022]. Available from: <https://nces.ed.gov/fastfacts/display.asp?id=372>
 - 16 **Hussar WJ**, Bailey TM. Projections of education statistics to 2028. Washington: National Center for Education Statistics, 2020
 - 17 **Dufault RJ**, Wolle MM, Kingston HMS, Gilbert SG, Murray JA. Connecting inorganic mercury and lead measurements in blood to dietary sources of exposure that may impact child development. *World J Methodol* 2021; **11**: 144-159 [PMID: 34322366 DOI: 10.5662/wjm.v11.i4.144]
 - 18 **Yassa HA**. Autism: a form of lead and mercury toxicity. *Environ Toxicol Pharmacol* 2014; **38**: 1016-1024 [PMID: 25461563 DOI: 10.1016/j.etap.2014.10.005]
 - 19 **Lee MJ**, Chou MC, Chou WJ, Huang CW, Kuo HC, Lee SY, Wang LJ. Heavy Metals' Effect on Susceptibility to Attention-Deficit/Hyperactivity Disorder: Implication of Lead, Cadmium, and Antimony. *Int J Environ Res Public Health* 2018; **15** [PMID: 29890770 DOI: 10.3390/ijerph15061221]
 - 20 **Desrochers-Couture M**, Courtemanche Y, Forget-Dubois N, Bélanger RE, Boucher O, Ayotte P, Cordier S, Jacobson JL, Jacobson SW, Muckle G. Association between early lead exposure and externalizing behaviors in adolescence: A developmental cascade. *Environ Res* 2019; **178**: 108679 [PMID: 31454729 DOI: 10.1016/j.envres.2019.108679]
 - 21 **Choi WJ**, Kwon HJ, Lim MH, Lim JA, Ha M. Blood lead, parental marital status and the risk of attention-deficit/hyperactivity disorder in elementary school children: A longitudinal study. *Psychiatry Res* 2016; **236**: 42-46 [PMID: 26774190 DOI: 10.1016/j.psychres.2016.01.002]
 - 22 **Li H**, Li H, Li Y, Liu Y, Zhao Z. Blood Mercury, Arsenic, Cadmium, and Lead in Children with Autism Spectrum Disorder. *Biol Trace Elem Res* 2018; **181**: 31-37 [PMID: 28480499 DOI: 10.1007/s12011-017-1002-6]
 - 23 **Hessabi M**, Rahbar MH, Dobrescu I, Bach MA, Kobylinska L, Bressler J, Grove ML, Loveland KA, Mihailescu I, Nedelcu MC, Moisesescu MG, Matei BM, Matei CO, Rad F. Concentrations of Lead, Mercury, Arsenic, Cadmium, Manganese, and Aluminum in Blood of Romanian Children Suspected of Having Autism Spectrum Disorder. *Int J Environ Res Public Health* 2019; **16** [PMID: 31261817 DOI: 10.3390/ijerph16132303]
 - 24 **Park JH**, Seo JH, Hong YS, Kim YM, Kang JW, Yoo JH, Chueh HW, Lee JH, Kwak MJ, Kim J, Woo HD, Kim DW, Bang YR, Choe BM. Blood lead concentrations and attention deficit hyperactivity disorder in Korean children: a hospital-based case control study. *BMC Pediatr* 2016; **16**: 156 [PMID: 27659349 DOI: 10.1186/s12887-016-0696-5]
 - 25 **Huang S**, Hu H, Sánchez BN, Peterson KE, Ettinger AS, Lamadrid-Figueroa H, Schnaas L, Mercado-García A, Wright RO, Basu N, Cantonwine DE, Hernández-Avila M, Téllez-Rojo MM. Childhood Blood Lead Levels and Symptoms of Attention Deficit Hyperactivity Disorder (ADHD): A Cross-Sectional Study of Mexican Children. *Environ Health Perspect* 2016; **124**: 868-874 [PMID: 26645203 DOI: 10.1289/ehp.1510067]
 - 26 **Lin Y**, Huang L, Xu J, Specht AJ, Yan C, Geng H, Shen X, Nie LH, Hu H. Blood lead, bone lead and child attention-deficit-hyperactivity-disorder-like behavior. *Sci Total Environ* 2019; **659**: 161-167 [PMID: 30597466 DOI: 10.1016/j.scitotenv.2018.12.219]
 - 27 **Ji Y**, Hong X, Wang G, Chatterjee N, Riley AW, Lee LC, Surkan PJ, Bartell TR, Zuckerman B, Wang X. A Prospective Birth Cohort Study on Early Childhood Lead Levels and Attention Deficit Hyperactivity Disorder: New Insight on Sex Differences. *J Pediatr* 2018; **199**: 124-131.e8 [PMID: 29752174 DOI: 10.1016/j.jpeds.2018.03.076]
 - 28 **Dufault RJ**. Unsafe at any meal: what the FDA does not want you to know about the foods you eat. Garden City Park: Square One Pub, 2017: 59-75
 - 29 **United States Food and Drug Administration**. Color additives history. [cited 3 November 2022]. Available from: <https://www.fda.gov/industry/color-additives/color-additives-history>
 - 30 **Code of Federal Regulations**. Part 74: listing of color additives subject to certification. United States Government. [cited 2 November 2022]. Available from: <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-74?toc=1>
 - 31 **Dufault R**, LeBlanc B, Schnoll R, Cornett C, Schweitzer L, Wallinga D, Hightower J, Patrick L, Lukiw WJ. Mercury from chlor-alkali plants: measured concentrations in food product sugar. *Environ Health* 2009; **8**: 2 [PMID: 19171026 DOI: 10.1186/1476-069X-8-2]
 - 32 **Rideout K**, Sahni V, Copes R, Wylie M, Kosatsky T. Comment on the paper by Dufault et al: Mercury in foods containing high fructose corn syrup in Canada. *Environ Health* 2010. Available from: <https://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-8-2/comments>
 - 33 **Wallinga D**, Sorensen J, Mottl P, Yablon B. Not so sweet: missing mercury and high fructose corn syrup. Institute for Agriculture and Trade Policy (IATP). [cited 3 November 2022]. Available from: <https://www.iatp.org/documents/not-so-sweet-missing-mercury-and-high-fructose-corn-syrup>
 - 34 **Guzmán-Maldonado H**, Paredes-López O. Amylolytic enzymes and products derived from starch: a review. *Crit Rev Food Sci Nutr* 1995; **35**: 373-403 [PMID: 8573280 DOI: 10.1080/10408399509527706]
 - 35 **Xia Q**, Du Z, Lin D, Huo L, Qin L, Wang W, Qiang L, Yao Y, An Y. Review of contaminants in edible oil and analytical technologies. *Oil Crop Sci* 2021; **6**: 23-27 [DOI: 10.1016/j.oecsci.2021.02.001]
 - 36 **Khan K**, Khan H, Lu Y, Ihsanullah I, Nawab J, Khan S, Shah NS, Shamshad I, Maryam A. Evaluation of toxicological risk

- of foodstuffs contaminated with heavy metals in Swat, Pakistan. *Ecotoxicol Environ Saf* 2014; **108**: 224-232 [PMID: 25086826 DOI: 10.1016/j.ecoenv.2014.05.014]
- 37 **Wells EM**, Kopylev L, Nachman R, Radke EG, Segal D. Seafood, wine, rice, vegetables, and other food items associated with mercury biomarkers among seafood and non-seafood consumers: NHANES 2011-2012. *J Expo Sci Environ Epidemiol* 2020; **30**: 504-514 [PMID: 32015433 DOI: 10.1038/s41370-020-0206-6]
- 38 **Raehsler SL**, Choung RS, Marietta EV, Murray JA. Accumulation of Heavy Metals in People on a Gluten-Free Diet. *Clin Gastroenterol Hepatol* 2018; **16**: 244-251 [PMID: 28223206 DOI: 10.1016/j.cgh.2017.01.034]
- 39 **Vergeer L**, Franco-Arellano B, Tjong GB, Bernstein JT, L'Abbé MR. The Level of Processing, Nutritional Composition and Prices of Canadian Packaged Foods and Beverages with and without Gluten-Free Claims. *Nutrients* 2021; **13** [PMID: 33918418 DOI: 10.3390/nu13041183]
- 40 **Monteiro CA**, Cannon G, Levy RB, Moubarac JC, Louzada ML, Rauber F, Khandpur N, Cediel G, Neri D, Martinez-Steele E, Baraldi LG, Jaime PC. Ultra-processed foods: what they are and how to identify them. *Public Health Nutr* 2019; **22**: 936-941 [PMID: 30744710 DOI: 10.1017/S1368980018003762]
- 41 **United States Department of Agriculture**. Food availability (per capita) data system. [cited 3 November 2022]. Available from: <https://catalog.data.gov/dataset/food-availability-per-capita-data-system#:~:text=The%20ERS%20Food%20Availability%20%28Per%20Capita%29%20Data%20System,proxies%20for%20actual%20consumption%20at%20the%20national%20level>
- 42 **Mennella JA**, Li Y, Bittinger K, Friedman ES, Zhao C, Li H, Wu GD, Trabulsi JC. The Macronutrient Composition of Infant Formula Produces Differences in Gut Microbiota Maturation That Associate with Weight Gain Velocity and Weight Status. *Nutrients* 2022; **14** [PMID: 35334900 DOI: 10.3390/nu14061241]
- 43 **Martin CR**, Ling PR, Blackburn GL. Review of Infant Feeding: Key Features of Breast Milk and Infant Formula. *Nutrients* 2016; **8** [PMID: 27187450 DOI: 10.3390/nu8050279]
- 44 **US House of Representatives**. Baby foods are tainted with dangerous levels of arsenic, lead, cadmium, and mercury. [cited 4 February 2022]. Available from: <https://oversightdemocrats.house.gov/sites/democrats.oversight.house.gov/files/2021-02-04%20ECP%20Baby%20Food%20Staff%20Report.pdf>
- 45 **US House of Representatives**. New disclosures show dangerous levels of toxic metals in even more baby foods. [cited 29 September 2022]. Available from: <https://oversightdemocrats.house.gov/sites/democrats.oversight.house.gov/files/ECP%20Second%20Baby%20Food%20Report%209.29.21%20FINAL.pdf>
- 46 **Dabeka RW**, McKenzie AD. Survey of total mercury in infant formulae and oral electrolytes sold in Canada. *Food Addit Contam Part B Surveill* 2012; **5**: 65-69 [PMID: 24779697 DOI: 10.1080/19393210.2012.658087]
- 47 **Martins C**, Vasco E, Paixão E, Alvito P. Total mercury in infant food, occurrence and exposure assessment in Portugal. *Food Addit Contam Part B Surveill* 2013; **6**: 151-157 [PMID: 24779897 DOI: 10.1080/19393210.2013.775603]
- 48 **Gardener H**, Bowen J, Callan SP. Lead and cadmium contamination in a large sample of United States infant formulas and baby foods. *Sci Total Environ* 2019; **651**: 822-827 [PMID: 30253364 DOI: 10.1016/j.scitotenv.2018.09.026]
- 49 **Hassan MH**, Desoky T, Sakhr HM, Gabra RH, Bakri AH. Possible Metabolic Alterations among Autistic Male Children: Clinical and Biochemical Approaches. *J Mol Neurosci* 2019; **67**: 204-216 [PMID: 30600432 DOI: 10.1007/s12031-018-1225-9]
- 50 **Alexandrov PN**, Pogue AI, Lukiw WJ. Synergism in aluminum and mercury neurotoxicity. *Integr Food Nutr Metab* 2018; **5** [PMID: 29938114 DOI: 10.15761/IFNM.1000214]
- 51 **Alabdali A**, Al-Ayadhi L, El-Ansary A. A key role for an impaired detoxification mechanism in the etiology and severity of autism spectrum disorders. *Behav Brain Funct* 2014; **10**: 14 [PMID: 24776096 DOI: 10.1186/1744-9081-10-14]
- 52 **Li ZG**, Zhou FK, Yin AM, Gao YY, Jiang X, Liu SS, Zhang YY, Bo DD, Xie J, Jia QY, Feng JG, Feng C, Fan GQ. [Cellular damage of low-dose combined exposure to mercury, lead and cadmium on hippocampal neurons in rats]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2018; **52**: 976-982 [PMID: 30392313 DOI: 10.3760/cma.j.issn.0253-9624.2018.10.003]
- 53 **Mostafa GA**, Bjørklund G, Urbina MA, Al-Ayadhi LY. The levels of blood mercury and inflammatory-related neuropeptides in the serum are correlated in children with autism spectrum disorder. *Metab Brain Dis* 2016; **31**: 593-599 [PMID: 26738726 DOI: 10.1007/s11011-015-9784-8]
- 54 **Mahaffey KR**, Gartside PS, Glueck CJ. Blood lead levels and dietary calcium intake in 1- to 11-year-old children: the Second National Health and Nutrition Examination Survey, 1976 to 1980. *Pediatrics* 1986; **78**: 257-262 [PMID: 3488536]
- 55 **Gulson B**, Mizon K, Taylor A, Wu M. Dietary zinc, calcium and nickel are associated with lower childhood blood lead levels. *Environ Res* 2019; **168**: 439-444 [PMID: 30390566 DOI: 10.1016/j.envres.2018.10.029]
- 56 **Centers for Disease Control and Prevention**. Health effects of lead exposure. [cited 2 September 2022]. Available from: <https://www.cdc.gov/nceh/lead/prevention/health-effects.htm>
- 57 **Dufault R**, Schnoll R, Lukiw WJ, Leblanc B, Cornett C, Patrick L, Wallinga D, Gilbert SG, Crider R. Mercury exposure, nutritional deficiencies and metabolic disruptions may affect learning in children. *Behav Brain Funct* 2009; **5**: 44 [PMID: 19860886 DOI: 10.1186/1744-9081-5-44]
- 58 **Ward NI**, Soulsbury KA, Zettel VH, Colquhoun ID, Bunday S, Barnes B. The influence of the chemical additive tartrazine on the zinc status of hyperactive children- a double-blind placebo-controlled study. *J Nutr Env Med* 2009; **1**: 51-57 [DOI: 10.3109/13590849009003134]
- 59 **Ward NI**. Assessment of chemical factors in relation to child hyperactivity. *J Nutr Env Med* 2009; **7**: 333-342 [DOI: 10.1080/13590849762466]
- 60 **Bjørklund G**. The role of zinc and copper in autism spectrum disorders. *Acta Neurobiol Exp (Wars)* 2013; **73**: 225-236 [PMID: 23823984]
- 61 **Meguid NA**, Bjørklund G, Gebril OH, Doşa MD, Anwar M, Elsaied A, Gaber A, Chirumbolo S. The role of zinc supplementation on the metallothionein system in children with autism spectrum disorder. *Acta Neurol Belg* 2019; **119**: 577-583 [PMID: 31302864 DOI: 10.1007/s13760-019-01181-9]
- 62 **Maret W**. The function of zinc metallothionein: a link between cellular zinc and redox state. *J Nutr* 2000; **130**: 1455S-1458S [PMID: 10801959 DOI: 10.1093/jn/130.5.1455S]

- 63 **Coyle P**, Philcox JC, Carey LC, Rofe AM. Metallothionein: the multipurpose protein. *Cell Mol Life Sci* 2002; **59**: 627-647 [PMID: [10222471](#) DOI: [10.1007/s00018-002-8454-2](#)]
- 64 **Bonaventura P**, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. *Autoimmun Rev* 2015; **14**: 277-285 [PMID: [25462582](#) DOI: [10.1016/j.autrev.2014.11.008](#)]
- 65 **Milne DB**, Nielsen FH. The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *J Am Coll Nutr* 2000; **19**: 31-37 [PMID: [10682873](#) DOI: [10.1080/07315724.2000.10718911](#)]
- 66 **Medina-Díaz IM**, Ponce-Ruiz N, Ramírez-Chávez B, Rojas-García AE, Barrón-Vivanco BS, Elizondo G, Bernal-Hernández YY. Downregulation of human paraoxonase 1 (PON1) by organophosphate pesticides in HepG2 cells. *Environ Toxicol* 2017; **32**: 490-500 [PMID: [26948828](#) DOI: [10.1002/tox.22253](#)]
- 67 **Banhela N**, Naidoo P, Naidoo S. Association between pesticide exposure and paraoxonase-1 (PON1) polymorphisms, and neurobehavioural outcomes in children: a systematic review. *Syst Rev* 2020; **9**: 109 [PMID: [32386510](#) DOI: [10.1186/s13643-020-01330-9](#)]
- 68 **Costa LG**, Vitalone A, Cole TB, Furlong CE. Modulation of paraoxonase (PON1) activity. *Biochem Pharmacol* 2005; **69**: 541-550 [PMID: [15670573](#) DOI: [10.1016/j.bcp.2004.08.027](#)]
- 69 **Costa LG**, Giordano G, Furlong CE. Pharmacological and dietary modulators of paraoxonase 1 (PON1) activity and expression: the hunt goes on. *Biochem Pharmacol* 2011; **81**: 337-344 [PMID: [21093416](#) DOI: [10.1016/j.bcp.2010.11.008](#)]
- 70 **Zhou F**, Yin G, Gao Y, Liu D, Xie J, Ouyang L, Fan Y, Yu H, Zha Z, Wang K, Shao L, Feng C, Fan G. Toxicity assessment due to prenatal and lactational exposure to lead, cadmium and mercury mixtures. *Environ Int* 2019; **133**: 105192 [PMID: [31639605](#) DOI: [10.1016/j.envint.2019.105192](#)]
- 71 **Martin EM**, Fry RC. Environmental Influences on the Epigenome: Exposure- Associated DNA Methylation in Human Populations. *Annu Rev Public Health* 2018; **39**: 309-333 [PMID: [29328878](#) DOI: [10.1146/annurev-publhealth-040617-014629](#)]
- 72 **Chervona Y**, Costa M. The control of histone methylation and gene expression by oxidative stress, hypoxia, and metals. *Free Radic Biol Med* 2012; **53**: 1041-1047 [PMID: [22841757](#) DOI: [10.1016/j.freeradbiomed.2012.07.020](#)]
- 73 **Kloubert V**, Rink L. Zinc as a micronutrient and its preventive role of oxidative damage in cells. *Food Funct* 2015; **6**: 3195-3204 [PMID: [26286461](#) DOI: [10.1039/c5fo00630a](#)]
- 74 **Rahman MT**, De Ley M. Arsenic Induction of Metallothionein and Metallothionein Induction Against Arsenic Cytotoxicity. *Rev Environ Contam Toxicol* 2017; **240**: 151-168 [PMID: [27115674](#) DOI: [10.1007/398_2016_2](#)]
- 75 **Bozack AK**, Rifas-Shiman SL, Coull BA, Baccarelli AA, Wright RO, Amarasiwardena C, Gold DR, Oken E, Hivert MF, Cardenas A. Prenatal metal exposure, cord blood DNA methylation and persistence in childhood: an epigenome-wide association study of 12 metals. *Clin Epigenetics* 2021; **13**: 208 [PMID: [34798907](#) DOI: [10.1186/s13148-021-01198-z](#)]
- 76 **Neumann A**, Walton E, Alemany S, Cecil C, González JR, Jima DD, Lahti J, Tuominen ST, Barker ED, Binder E, Caramaschi D, Carracedo Á, Czamara D, Evandt J, Felix JF, Fuemmeler BF, Gutzkow KB, Hoyo C, Julvez J, Kajantie E, Laivuori H, Maguire R, Maitre L, Murphy SK, Murcia M, Villa PM, Sharp G, Sunyer J, Raikkönen K, Bakermans-Kranenburg M, Ijzendoorn MV, Guxens M, Relton CL, Tiemeier H. Association between DNA methylation and ADHD symptoms from birth to school age: a prospective meta-analysis. *Transl Psychiatry* 2020; **10**: 398 [PMID: [33184255](#) DOI: [10.1038/s41398-020-01058-z](#)]
- 77 **Cardenas A**, Rifas-Shiman SL, Agha G, Hivert MF, Litonjua AA, DeMeo DL, Lin X, Amarasiwardena CJ, Oken E, Gillman MW, Baccarelli AA. Persistent DNA methylation changes associated with prenatal mercury exposure and cognitive performance during childhood. *Sci Rep* 2017; **7**: 288 [PMID: [28325913](#) DOI: [10.1038/s41598-017-00384-5](#)]
- 78 **Cavalli G**, Heard E. Advances in epigenetics link genetics to the environment and disease. *Nature* 2019; **571**: 489-499 [PMID: [31341302](#) DOI: [10.1038/s41586-019-1411-0](#)]
- 79 **Samblas M**, Milagro FI, Martínez A. DNA methylation markers in obesity, metabolic syndrome, and weight loss. *Epigenetics* 2019; **14**: 421-444 [PMID: [30915894](#) DOI: [10.1080/15592294.2019.1595297](#)]
- 80 **McGinnis WR**. Oxidative stress in autism. *Altern Ther Health Med* 2004; **10**: 22-36; quiz 37, 92 [PMID: [15624347](#)]
- 81 **Manivasagam T**, Arunadevi S, Essa MM, SaravanaBabu C, Borah A, Thenmozhi AJ, Qoronfleh MW. Role of Oxidative Stress and Antioxidants in Autism. *Adv Neurobiol* 2020; **24**: 193-206 [PMID: [32006361](#) DOI: [10.1007/978-3-030-30402-7_7](#)]
- 82 **Li Y**, Pollock CA, Saad S. Aberrant DNA Methylation Mediates the Transgenerational Risk of Metabolic and Chronic Disease Due to Maternal Obesity and Overnutrition. *Genes (Basel)* 2021; **12** [PMID: [34828259](#) DOI: [10.3390/genes12111653](#)]
- 83 **Ando Y**, Yamada H, Munetsuna E, Yamazaki M, Kageyama I, Teshigawara A, Nouchi Y, Fujii R, Mizuno G, Sadamoto N, Ishikawa H, Suzuki K, Hashimoto S, Ohashi K. Maternal high-fructose corn syrup consumption causes insulin resistance and hyperlipidemia in offspring via DNA methylation of the Ppara promoter region. *J Nutr Biochem* 2022; **103**: 108951 [PMID: [35123000](#) DOI: [10.1016/j.jnutbio.2022.108951](#)]
- 84 **Dufault RJ**, Gilbert SG. Why does autism impact boys more often than girls? [cited 3 2022 November]. Available from: <https://blogs.scientificamerican.com/observations/why-does-autism-impact-boys-more-often-than-girls/>
- 85 **Vaiserman A**, Lushchak O. DNA methylation changes induced by prenatal toxic metal exposure: An overview of epidemiological evidence. *Environ Epigenet* 2021; **7**: dvab007 [PMID: [34631153](#) DOI: [10.1093/eeep/dvab007](#)]
- 86 **Alcorta A**, Porta A, Tárrega A, Alvarez MD, Vaquero MP. Foods for Plant-Based Diets: Challenges and Innovations. *Foods* 2021; **10** [PMID: [33535684](#) DOI: [10.3390/foods10020293](#)]
- 87 **David Hollar**. Ethical implications of epigenetics. Epigenetics, the environment, and children's health across lifespans. Switzerland: Springer, 2016: 327-334
- 88 **Song J**, Brown MK, Tan M, MacGregor GA, Webster J, Campbell NRC, Trieu K, Ni Mhurchu C, Cobb LK, He FJ. Impact of color-coded and warning nutrition labelling schemes: A systematic review and network meta-analysis. *PLoS Med* 2021; **18**: e1003765 [PMID: [34610024](#) DOI: [10.1371/journal.pmed.1003765](#)]

Clinical and Translational Research

Factors associated with subsequent surgery after septic arthritis of the knee in children

Jennifer Marie O'Donnell, Ernest Ekunseitan, Ishaan Swarup

Specialty type: Orthopedics**Provenance and peer review:**

Invited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0**P-Reviewer:** Carrozzo A; Muthu S, India**Received:** December 1, 2022**Peer-review started:** December 1, 2022**First decision:** December 13, 2022**Revised:** January 13, 2023**Accepted:** February 22, 2023**Article in press:** February 22, 2023**Published online:** March 9, 2023**Jennifer Marie O'Donnell**, Orthopaedic Surgery, University of California San Francisco, San Francisco, CA 94143, United States**Ernest Ekunseitan**, Medical School, University of California San Francisco, San Francisco, CA 94143, United States**Ishaan Swarup**, Pediatric Orthopaedic Surgery, UCSF Benioff Children's Hospital, Oakland, CA 94609, United States**Corresponding author:** Ishaan Swarup, MD, Assistant Professor, Pediatric Orthopaedic Surgery, UCSF Benioff Children's Hospital, 747 52nd Street, Oakland, CA 94609, United States. ishaan.swarup@ucsf.edu**Abstract****BACKGROUND**

Septic arthritis of the knee in children is a challenging problem. Surgical debridement is an established treatment, but there is a paucity of literature on long-term prognosis.

AIM

To determine the rates and factors associated with return to surgery (RTS) and readmission after index surgical debridement for septic arthritis of the knee in children.

METHODS

This is a retrospective cohort study that utilizes data from the Healthcare Cost and Utilization Project (HCUP). We included patients between ages 0 to 18 years that underwent surgical debridement for septic arthritis of the knee between 2005 and 2017. Demographic data included age, gender, race, hospital type and insurance type. Clinical data including index admission length of stay (LOS) and Charlson Comorbidity Index (CCI) were available from the HCUP database. Descriptive statistics were used to summarize the data and univariate and multivariate analyses were performed.

RESULTS

Nine-hundred thirty-two cases of pediatric septic knee were included. This cohort was 62.3% male, with mean age of 9.0 ($\pm$ 6.1) years. Approximately 46% of patients were white and approximately half had Medicaid insurance. Thirty-six

patients (3.6%) required RTS at a minimum of 2 year after index surgery, and 172 patients (18.5%) were readmitted at any point. The mean readmission LOS was 11.6(± 11.3) d. Higher CCI was associated with RTS ($P = 0.041$). There were no significant associations in age, gender, race, insurance type, or type of hospital to which patients presented. Multivariate analysis showed that both increased CCI ($P = 0.008$) and shorter LOS ($P = 0.019$) were predictive of RTS.

CONCLUSION

Septic arthritis of the knee is an important condition in children. The CCI was associated with RTS at a minimum of 2 years after index procedure. No association was found with age, gender, race, insurance type, or hospital type. Shorter LOS and CCI were associated with RTS in multivariate analysis. Overall, risk of subsequent surgery and readmission after pediatric septic knee arthritis is low, and CCI and shorter LOS are predictive of RTS.

Key Words: Septic arthritis; knee; Orthopaedic surgery; Infection; Osteomyelitis; Debridement

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Septic arthritis of the knee is an important condition in children. The Charlson Comorbidity Index and shorter length of stay during index admission were associated with return to surgery after index procedure. No association was found with age, gender, race, insurance type, or hospital type. Risk of subsequent surgery and readmission after pediatric septic arthritis of the knee is low; however, presence of comorbidities and shorter length of stay are predictive of subsequent surgery.

Citation: O'Donnell JM, Ekunseitan E, Swarup I. Factors associated with subsequent surgery after septic arthritis of the knee in children. *World J Clin Pediatr* 2023; 12(2): 38-44

URL: <https://www.wjgnet.com/2219-2808/full/v12/i2/38.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i2.38>

INTRODUCTION

Septic knee occurs in children at a rate between 5 and 12 per 100000[1,2]. This pathological invasion of the joint in children can place patients at risk for osteomyelitis, recurrent joint infection, and sepsis. Septic arthritis is often diagnosed clinically in pediatric patients, or can be diagnosed and treated based on arthrocentesis. Timely diagnosis and management is critical to decrease the risk of damage to articular cartilage and the joint[3]. Acute septic arthritis is typically of hematogenous origin in children. It is more common in boys and the most common causative agent is *Staphylococcus aureus*, with methicillin-resistant strains on the rise[4].

Treatment is typically comprised of antibiotics as well as surgical irrigation and debridement, either *via* arthroscopy or arthrotomy, which is typically determined by surgeon preference. Long-term sequelae of septic arthritis in children can include persistent infection, growth disturbance, chondrolysis, and degenerative arthritis[5]. However, it is important to note that complications such as symptomatic osteoarthritis develop slowly, and longer follow-up is required to detect all possible sequelae[6]. The rate of these sequelae has been cited at 10% among all patients with septic arthritis of the knee, and is increased when diagnosis and treatment are delayed[7]. To our knowledge, there are no studies investigating the need for subsequent surgery for these issues after septic arthritis of the knee.

This outcome has been similarly studied in septic arthritis of the hip in children[8-10]. Livingston *et al* [8] found that presence of left shift or higher C-reactive protein pre-operatively, higher post-operative temperature, and positive cultures were associated with increased risk for repeat surgery. As such, we hypothesize that similar preoperative risk factors may exist for recurrent septic arthritis of the knee.

The purpose of this study was to determine the incidence of patients that require any subsequent surgery after septic arthritis of the knee initially managed with irrigation and debridement. We also assess risk factors for subsequent surgery after septic arthritis of the knee. We hypothesized that in this database, demographic factors such as age, race, or ethnicity would have no effect on increased risk, and that clinical factors such as medical comorbidities would carry increased risk of subsequent surgery.

MATERIALS AND METHODS

Data collection

This study was reviewed by the Institutional Review Board and exempt as a database study. Data were collected from the Healthcare Cost and Utilization Project database from the states of California and Florida. Inclusion criteria were patients age 0 to 18 years, who underwent knee irrigation and debridement for septic arthritis from 2005 to 2017 and had at least two years of follow-up data.

Demographic data including age, sex, ethnicity, race, insurance, and state were collected for all patients. Clinical data included length of stay (LOS), type of hospital (pediatric, academic, county), and significant comorbidities. The Charlson Comorbidity Index (CCI) was utilized as a composite measure to capture the occurrence of major comorbidities[11-13]. The CCI is a validated tool and accounts for age and comorbidities such myocardial infarction, heart failure, liver or kidney disease, diabetes, and cancer [11]. Our primary outcome of interest was any surgical procedure after index irrigation and debridement of the knee, including those that occurred during the index or subsequent hospital admissions. Secondary outcomes included readmission and length of stay for re-operation.

Statistical analysis

Descriptive data are expressed as means $\pm$ standard deviation, or for categorical variables as percentage with counts. Differences among outcome groups and categorical variables were tested by chi-square test. Differences between continuous variables were analyzed using student's *t*-test. Pearson's correlation was used to analyze association between all studied parameters. The values $P < 0.05$ were considered statistically significant. Multivariate logistic regression analysis was then performed using any variables with $P < 0.10$ in univariate analysis, which was established *a priori*. Statistical analysis was done using Stata 17 (StataCorp LLC, College Station, TX, United States).

RESULTS

A total of 932 cases of septic arthritis of the knee were identified over the study period. Table 1 displays the demographic characteristics of this cohort. At the time of index admission for septic arthritis, the median age was 9.0 ± 6.1 years and 62% of patients were male. Approximately, 2% of patients were of Asian race, 26% were Hispanic, 22% were Black, 46% were white, and 3% identified as other race. Thirty percent of patients were seen at a county hospital, 13% were seen in an academic hospital, and 15% were seen in a children's hospital. Forty-nine percent of patients were state-insured and 41% were privately insured. The majority (58.5%) of admissions were emergent. The mean LOS for the index hospitalization was 9.3 ± 12.0 d, with a median of 6 d. The mean CCI of patients was 0.26 ± 0.73 , with a range from 0 to 8.

In total, 36 (3.9%) of these patients underwent subsequent surgery at a median of 11.5 d after index debridement (range 1-1641 d). Readmission was for a mean of 11.6 d (± 11.3 d). The most common readmission diagnosis was pyogenic arthritis, and the most common subsequent surgery code was knee arthroscopy. There were no significant differences in demographics, payor type or presenting hospital between patients that did or did not undergo a subsequent knee-related procedure. In univariate analysis, CCI at the time of initial treatment was significantly higher in the cohort who underwent subsequent surgery ($P = 0.041$). Shorter length of stay at the time of index admission trended towards significance as well and was therefore included in the subsequent multivariate analysis ($P = 0.066$). Multivariate analysis showed that both increased CCI ($P = 0.008$) and shorter LOS ($P = 0.019$) were predictive of subsequent surgery.

DISCUSSION

This retrospective database study demonstrated that in a population of 932 children who underwent initial surgical irrigation and debridement for septic arthritis of the knee, subsequent surgery was undertaken in 3.9% ($n = 39$) of them. Higher index CCI and shorter LOS were significantly associated with the group requiring repeat irrigation and debridement.

In the literature, it has been shown that in septic hip arthritis, risk factors for repeat debridement include methicillin-resistant *Staphylococcus aureus* infection, higher inflammatory markers and higher fevers. There are few similar studies that have looked at septic knee arthritis, and none have looked at the rates among a large patient population. We utilized a multi-state database to examine similar trends in septic knee arthritis in children. The current study shows that majority of patients with septic arthritis of the knee managed with surgical debridement do not require any subsequent surgery. However, baseline comorbidities and shorter LOS at the time of index admission may be associated with need for subsequent surgery.

Table 1 Cohort characteristics

Characteristics	Total	No return to surgery	Return to surgery	P value
<i>n</i>	932	896 (96.1)	36 (3.9)	
Age	8.96 6.07	8.90 6.09	10.47 5.53	0.129
Sex, % male	581 (62.3)	557 (62.2)	24 (66.7)	0.709
Race, %				0.366
Asian	19 (2.0)	17 (1.9)	2 (5.6)	
Black	185 (19.9)	181 (20.2)	4 (11.1)	
Hispanic	220 (23.6)	208 (23.2)	12 (33.3)	
White	382 (41.0)	367 (41.0)	15 (41.7)	
Native American	3 (0.3)	3 (0.3)	0 (0)	
Other	26 (2.8)	26 (2.9)	0 (0)	
County hospital, %	282 (30.3)	271 (30.3)	11 (30.6)	0.968
Academic hospital, %	120 (12.9)	113 (12.6)	7 (19.4)	0.230
Children's hospital, %	138 (15.0)	134 (15.1)	4 (11.4)	0.551
Insurance				0.716
Commercial	380 (40.8)	366 (40.9)	14 (38.9)	
Medicaid	460 (49.4)	444 (50.0)	16 (44.4)	
Other	67 (7.2)	62 (6.9)	5 (13.9)	
Self pay	19 (2.0)	18 (2.0)	1 (2.8)	
No charge	5 (0.5)	5 (0.6)	0 (0)	
Admission type				0.646
Elective	221 (23.8)	211 (24.7)	10 (27.8)	
Urgent	157 (16.9)	149 (16.7)	8 (22.2)	
Emergent	544 (58.5)	528 (58.9)	16 (44.4)	
State				0.268
CA	383 (41.1)	365 (40.7)	18 (50)	
FL	549 (58.9)	531 (59.3)	18 (50)	
Length of index stay	9.3 12.0	9.4 12.1	5.7 6.1	0.066
Charlson Comorbidity Index	0.26 0.73	0.25 0.73	0.5 0.81	0.041 ^a

^aSignificant.

The rate of subsequent surgery after index irrigation and debridement for septic arthritis of the knee is low. There may be several reasons for this finding. In cases of septic arthritis of the knee, joint aspiration is more readily accessible as a bedside procedure, and therefore an aspirate sample is obtained faster and treatment with antibiotics may be initiated sooner in the hospital course. The knee is also a larger joint without the tenuous vascularity as is noted in the hip. Most cases of septic arthritis of the knee are methicillin-sensitive *Staphylococcus aureus*, or other less virulent organisms such as *Kingella* which overall portend a more benign clinical course. Overall, these findings help to counsel patients that most will not require any subsequent surgery after initial irrigation and debridement.

The choice between arthrotomy and arthroscopy is actively studied in the literature[14]. One study suggests that arthrotomy was associated with reduced repeat surgeries and faster recovery[15]. However, additional research is needed. All these factors from microbiology to method of debridement can contribute to the success of the surgery in eradicating infection. One consequence of inadequate treatment is need for repeat surgery[16].

Comorbidities are an established risk factor for infections such as septic arthritis[17,18]. Additionally, greater comorbidities have been shown to contribute to poor outcomes after septic arthritis in adults [17]. The CCI has been used to quantify comorbid conditions in pediatric patients, and our study shows

that pediatric patients with comorbidities are at risk for requiring subsequent surgery after index irrigation and debridement. This information may be useful in counseling patients and families regarding the risk for subsequent surgery, and it may also help clinicians in determining postoperative management after index debridement.

Additionally, a shorter LOS was associated with a need for subsequent surgical management. A shorter LOS is likely associated with a shorter course of IV antibiotics and presumably less postoperative observation. Shorter courses of IV antibiotics have been associated with persistent infection and it is important to ensure appropriately clinical and laboratory improvement prior to transitioning to oral antibiotics for discharge[19]. This data is also helpful for healthcare systems to provide clinical pathways, which have been shown in previous studies to reduce the risk for readmission[20]. It should be noted, however, that our length of stay was long with mean of 9 d, and the standard deviation was wide.

This study found no significant differences across socioeconomic factors such as insurance type or hospital where patients were hospitalized. This is reassuring given the obvious disparities in healthcare; however, the number of subsequent surgeries in our cohort is low. Further study using data from more sources and including direct measures of patient socioeconomic status, such as household income, are needed to confirm this finding. Furthermore, sex and race were not significantly associated with subsequent surgery. However, it is important to note that the majority of our patients were male, which is consistent with the epidemiology of septic arthritis[17].

Limitations in this study include the retrospective nature of this database study, and the limited clinical data available. We did not have available data such as time to diagnosis, pre-operative inflammatory markers, microbiology results, or post-operative vital signs. Similarly, we are unable to determine the specific reasons or diagnosis codes for subsequent surgery such as growth disturbance or joint degeneration, or comorbidities such as osteomyelitis. Also, the data available are not able to determine with specificity between open and arthroscopic index procedures. We intend to study future cohorts with more clinical data available and explore the variables which best predict need for repeat surgeries in similar populations. Additionally, it is possible that some patients may have sought care elsewhere; however, this study utilized a large database and provides a baseline assessment of risk for subsequent surgery. Lastly, we only included patients that underwent a subsequent procedure and not all hospitalizations. It is likely that readmissions may be more common than the rate of subsequent surgery reported in this study; however, the goal of this study was to determine the rates of significant outcomes such as subsequent surgery after index septic arthritis of the knee.

Few patients require subsequent surgery after irrigation and debridement for septic arthritis of the knee. However, patients with comorbidities and shorter LOS at index admission are risk factors for subsequent surgery. Additional research is needed to determine the appropriate length of stay for patients with septic arthritis of the knee in order to optimize patient care and minimize the need for repeat surgery.

CONCLUSION

In conclusion, this retrospective database study demonstrated that in a population of 932 children who underwent initial surgical irrigation and debridement for septic arthritis of the knee, subsequent surgery was undertaken in 3.9% ($n = 39$) of them. Higher index CCI and shorter LOS were significantly associated with the group requiring repeat irrigation and debridement.

ARTICLE HIGHLIGHTS

Research background

Septic arthritis in children is a challenging clinical problem and carries with it many long-term sequelae. Repeat surgeries are sometimes necessary to eradicate infection. Understanding the rate of repeat irrigation and debridement in this population, and the risk factors associated, can help to focus clinical interventions and future studies.

Research motivation

Septic arthritis of the knee can be a serious clinical problem, and affects children and their families greatly. Understanding further the rate and risk of requiring multiple surgeries can help surgeons in counseling of these patients and their families.

Research objectives

To determine the rate of repeat irrigation and debridement in children who undergo surgical washout of the knee. Secondly, the aim is to highlight any significant risk factors associated with repeat surgery.

Research methods

This is a retrospective cohort study that utilizes data from the Healthcare Cost and Utilization Project (HCUP). We included patients between ages 0 to 18 years that underwent surgical debridement for septic arthritis of the knee between 2005 and 2017. Demographic data included age, gender, race, hospital type and insurance type. Clinical data including index admission length of stay and Charlson Comorbidity Index (CCI) were available from the HCUP database. Descriptive statistics were used to summarize this data. Univariate and multivariate analyses were performed with all variables with $P < 0.10$ on univariate analysis.

Research results

Nine-hundred thirty-two patients were included in this retrospective database study. In total, 36 (3.9%) of these patients underwent subsequent surgery after surgical irrigation and debridement for septic arthritis of the knee. In univariate analysis, CCI at the time of initial treatment was significantly higher in the cohort who underwent subsequent surgery ($P = 0.041$). Shorter length of stay at the time of index admission trended towards significance as well and was therefore included in the subsequent multivariate analysis ($P = 0.066$). Multivariate analysis showed that both increased CCI ($P = 0.008$) and shorter LOS ($P = 0.019$) were predictive of subsequent surgery.

Research conclusions

In conclusion, this retrospective database study demonstrated that in a population of 932 children who underwent initial surgical irrigation and debridement for septic arthritis of the knee, subsequent surgery was undertaken in 3.9% ($n = 39$) of them. Higher index CCI and shorter LOS were significantly associated with the group requiring repeat irrigation and debridement.

Research perspectives

Future research in this area should include prospective studies of septic arthritis of the knee in children, and can follow patients long-term for sequelae of disease. This study was limited as a retrospective database study to the clinical data available.

FOOTNOTES

Author contributions: O'Donnell JM, Ekunseitan E, and Swarup I all contributed to this work; O'Donnell JM and Swarup I designed the research study; O'Donnell JM and Ekunseitan E performed the research; O'Donnell JM analyzed the data; O'Donnell JM wrote the manuscript; Ekunseitan E and Swarup I edited and reviewed the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: This study was exempt by the local institutional review board.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

Data sharing statement: The authors will make available all data which are also part of a publicly available database.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United States

ORCID number: Jennifer Marie O'Donnell 0000-0002-9509-506X; Ishaan Swarup 0000-0003-3481-3408.

S-Editor: Chang KL

L-Editor: A

P-Editor: Chang KL

REFERENCES

- 1 Agarwal A, Aggarwal AN. Bone and Joint Infections in Children: Septic Arthritis. *Indian J Pediatr* 2016; **83**: 825-833 [PMID: 26189923 DOI: 10.1007/s12098-015-1816-1]
- 2 Pääkkönen M, Peltola H. Treatment of acute septic arthritis. *Pediatr Infect Dis J* 2013; **32**: 684-685 [PMID: 23439494 DOI: 10.1097/INF.0b013e31828e1721]
- 3 Obey MR, Minaie A, Schipper JA, Hosseinzadeh P. Pediatric Septic Arthritis of the Knee: Predictors of Septic Hip Do Not

- Apply. *J Pediatr Orthop* 2019; **39**: e769-e772 [PMID: [30950940](#) DOI: [10.1097/BPO.0000000000001377](#)]
- 4 **Gafur OA**, Copley LA, Hollmig ST, Browne RH, Thornton LA, Crawford SE. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. *J Pediatr Orthop* 2008; **28**: 777-785 [PMID: [18812907](#) DOI: [10.1097/BPO.0b013e318186eb4b](#)]
- 5 **Ilharreborde B**. Sequelae of pediatric osteoarticular infection. *Orthop Traumatol Surg Res* 2015; **101**: S129-S137 [PMID: [25553604](#) DOI: [10.1016/j.otsr.2014.07.029](#)]
- 6 **Pääkkönen M**. Septic arthritis in children: diagnosis and treatment. *Pediatric Health Med Ther* 2017; **8**: 65-68 [PMID: [29388627](#) DOI: [10.2147/PHMT.S115429](#)]
- 7 **Howard JB**, Highgenboten CL, Nelson JD. Residual effects of septic arthritis in infancy and childhood. *JAMA* 1976; **236**: 932-935 [PMID: [988890](#) DOI: [10.1001/JAMA.1976.03270090026021](#)]
- 8 **Livingston KS**, Kalish LA, Bae DS, Kim YJ, Shore BJ, Wash, Rinse, Repeat: Which Patients Undergo Serial Joint Irrigation in Pediatric Septic Hip Arthritis? *J Pediatr Orthop* 2019; **39**: e494-e499 [PMID: [30624342](#) DOI: [10.1097/BPO.0000000000001323](#)]
- 9 **Sabour AF**, Alluri RK, Heckmann N, Heidari KS, Rick Hatch GF 3rd, VandenBerg C. A nationwide analysis of failed irrigation and debridement for pediatric septic arthritis of the hip. *J Pediatr Orthop B* 2019; **28**: 470-475 [PMID: [30855548](#) DOI: [10.1097/BPB.0000000000000621](#)]
- 10 **Murphy RF**, Plumblee L, Barfield WB, Murphy JS, Fuerstenau N, Spence DD, Kelly DM, Dow MA, Mooney JF 3rd. Septic Arthritis of the Hip-Risk Factors Associated With Secondary Surgery. *J Am Acad Orthop Surg* 2019; **27**: 321-326 [PMID: [30520802](#) DOI: [10.5435/JAAOS-D-18-00058](#)]
- 11 **Charlson ME**, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373-383 [PMID: [3558716](#) DOI: [10.1016/0021-9681\(87\)90171-8](#)]
- 12 **D'Hoore W**, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. *Methods Inf Med* 1993; **32**: 382-387 [PMID: [8295545](#) DOI: [10.1055/s-0038-1634956](#)]
- 13 **Sundararajan V**, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004; **57**: 1288-1294 [PMID: [15617955](#) DOI: [10.1016/j.jclinepi.2004.03.012](#)]
- 14 **El-Sayed AM**. Treatment of early septic arthritis of the hip in children: comparison of results of open arthrotomy versus arthroscopic drainage. *J Child Orthop* 2008; **2**: 229-237 [PMID: [19308583](#) DOI: [10.1007/s11832-008-0094-0](#)]
- 15 **Johns B**, Loewenthal M, Ho E, Dewar D. Arthroscopic Versus Open Treatment for Acute Septic Arthritis of the Knee in Children. *Pediatr Infect Dis J* 2018; **37**: 413-418 [PMID: [28945678](#) DOI: [10.1097/INF.0000000000001795](#)]
- 16 **Stake S**, Scully R, Swenson S, Lee D, Lee R, Sparks A, Pandarinath R. Repeat irrigation & debridement for patients with acute septic knee arthritis: Incidence and risk factors. *J Clin Orthop Trauma* 2020; **11**: S177-S183 [PMID: [31992942](#) DOI: [10.1016/j.jcot.2019.12.006](#)]
- 17 **Okubo Y**, Nochioka K, Marcia T. Nationwide survey of pediatric septic arthritis in the United States. *J Orthop* 2017; **14**: 342-346 [PMID: [28706377](#) DOI: [10.1016/j.jor.2017.06.004](#)]
- 18 **Borzio R**, Mulchandani N, Pivec R, Kapadia BH, Leven D, Harwin SF, Urban WP. Predictors of Septic Arthritis in the Adult Population. *Orthopedics* 2016; **39**: e657-e663 [PMID: [27286047](#) DOI: [10.3928/01477447-20160606-05](#)]
- 19 **Swarup I**, Meza BC, Weltsch D, Jina AA, Lawrence JT, Baldwin KD. Septic Arthritis of the Knee in Children: A Critical Analysis Review. *JBJS Rev* 2020; **8**: e0069 [PMID: [32105243](#) DOI: [10.2106/JBJS.RVW.19.00069](#)]
- 20 **Spruiell MD**, Searns JB, Heare TC, Roberts JL, Wylie E, Pyle L, Donaldson N, Stewart JR, Heizer H, Reese J, Scott HF, Pearce K, Anderson CJ, Erickson M, Parker SK. Clinical Care Guideline for Improving Pediatric Acute Musculoskeletal Infection Outcomes. *J Pediatric Infect Dis Soc* 2017; **6**: e86-e93 [PMID: [28419275](#) DOI: [10.1093/jpids/pix014](#)]

Retrospective Cohort Study

Vaccination coverage in children with juvenile idiopathic arthritis, inflammatory bowel diseases, and healthy peers: Cross-sectional electronic survey data

Elizaveta Makarova, Aygul Khabirova, Natalia Volkova, Tatiana Gabrusskaya, Natalia Ulanova, Larisa Sakhno, Maria Revnova, Mikhail Kostik

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B, B, B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Chen K, China; Poddighe D, Kazakhstan

Received: December 4, 2022

Peer-review started: December 4, 2022

First decision: January 9, 2023

Revised: January 25, 2023

Accepted: February 13, 2023

Article in press: February 13, 2023

Published online: March 9, 2023



Elizaveta Makarova, Larisa Sakhno, Maria Revnova, Department of Polyclinic Pediatrics, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia

Aygul Khabirova, Mikhail Kostik, Department of Hospital Pediatrics, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia

Natalia Volkova, Tatiana Gabrusskaya, Natalia Ulanova, Department of Pediatric GI, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia

Corresponding author: Mikhail Kostik, MD, PhD, Full Professor, Professor, Department of Hospital Pediatrics, Saint-Petersburg State Pediatric Medical University, Lytovskaya 2, Saint-Petersburg 194100, Russia. kost-mikhail@yandex.ru

Abstract**BACKGROUND**

Patients with immune-mediated diseases, such as juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD) are at increased risk of developing infections, due to disease-related immune dysfunction and applying of immunosuppressive drugs.

AIM

To evaluate vaccine coverage in patients with IBD and JIA, and compare it with healthy children.

METHODS

In the cross-sectional study we included the data from a questionnaire survey of 190 Legal representatives of children with JIA ($n = 81$), IBD ($n = 51$), and healthy children (HC, $n = 58$). An electronic online questionnaire was created for the survey.

RESULTS

There were female predominance in JIA patients and younger onset age. Parents of JIA had higher education levels. Employment level and family status were similar in the three studied groups. Patients with JIA and IBD had lower vaccine coverage, without parental rejection of vaccinations in IBD, compare to JIA and

healthy controls. The main reason for incomplete vaccination was medical conditions in IBD and JIA. IBD patients had a lower rate of normal vaccine-associated reactions compared to JIA and HC. The encouraging role of physicians for vaccinations was the lowest in JIA patients. IBD patients had more possibilities to check antibodies before immune-suppressive therapy and had more supplementary vaccinations compared to JIA and HC.

CONCLUSION

JIA and IBD patients had lower vaccine coverage compared to HC. Physicians' encouragement of vaccination and the impossibility of discuss about future vaccinations and their outcomes seemed the main factors for patients with immune-mediated diseases, influencing vaccine coverage. Further investigations are required to understand the reasons for incomplete vaccinations and improve vaccine coverage in both groups, especially in rheumatic disease patients. The approaches that stimulate vaccination in healthy children are not always optimal in children with immune-mediated diseases. It is necessary to provide personalized vaccine-encouraging strategies for parents of chronically ill children with the following validation of these technics.

Key Words: Vaccines; Juvenile idiopathic arthritis; Inflammatory bowel diseases; Vaccine coverage; Immune-mediated diseases

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Juvenile idiopathic arthritis and inflammatory bowel disease patients had lower vaccine coverage compared to healthy children. Physician's encouraging to vaccination and impossibility to discuss about future vaccinations and their outcomes seemed the main factors for patients with immune-mediated diseases, influenced the vaccine coverage. Further investigations required to understand the reasons for incomplete vaccinations and improve the vaccine coverage in both groups, especially in rheumatic disease patients. The approaches that stimulate vaccination in healthy children are not always optimal in children with immune-mediated diseases. It is necessary to provide personalized vaccine-encouraging strategies for parents of chronically ill children with following validation of these technics.

Citation: Makarova E, Khabirova A, Volkova N, Gabrusskaya T, Ulanova N, Sakhno L, Revnova M, Kostik M. Vaccination coverage in children with juvenile idiopathic arthritis, inflammatory bowel diseases, and healthy peers: Cross-sectional electronic survey data. *World J Clin Pediatr* 2023; 12(2): 45-56

URL: <https://www.wjgnet.com/2219-2808/full/v12/i2/45.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i2.45>

INTRODUCTION

Patients with immune-mediated diseases, such as juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD), are at increased risk of developing infections, due to disease-related immune dysfunction and applying of immunosuppressive drugs[1,2]. Additional factors of increased infection risk include disease activity, malnutrition, surgical interventions, and concomitant chronic diseases, such as obesity, diabetes mellitus, atopic dermatitis, asthma, and others[3-5].

Biologic therapy with and without immune suppressors can reliably control inflammatory activity in many patients with immune-mediated diseases, including JIA and IBD. Tumor necrosis factor inhibitors - adalimumab and infliximab, with or without azathioprine, methotrexate, and sulfasalazine uses in IBD [6]. Etanercept, adalimumab, tocilizumab, abatacept, and tofacitinib with and without methotrexate applied in JIA[7]. Infections are the most common complications associated with biological treatment and immune suppressors. The main infectious, associated with immune-mediated diseases are pneumococcus, influenza, varicella-zoster virus, and measles[8-10]. Immune-compromised patients may have a more severe course of infections, requiring hospital admissions, using intravenous antibiotics and intravenous immunoglobulin lead to withdrawal of current therapy with following disease flare and non-achievement of the remission[11,12]. These above-mentioned factors may influence a child's overall health and long-term therapy outcomes[13].

Vaccination is a well-known and effective tool, which allows for reducing the frequency and severity of infectious episodes, and indirectly might reduce the risks of disease flare and failure to achieve remission, and significantly improve disease course and outcomes[14].

Several studies assessed reasons for low vaccine coverage from a medical point of view, but studies from a parental point of view are limited.

Our study aimed to assess the parental-related reasons for incomplete vaccination.

MATERIALS AND METHODS

Ethical statement

The study was approved by the Ethical Committee of the Saint-Petersburg State Pediatric Medical University (Protocol №3 from 01/03/2021). There were no violations of patients' rights according to the Declaration of Helsinki. The study was completely anonymous.

Study design and population

In the cross-sectional study, we included the data from questionnaire surveys of 190 Legal representatives of children, with JIA ($n = 81$), IBD ($n = 51$), and healthy children HC ($n = 58$). The electronic survey was disseminated through the parental social network for IBD and JIA in Saint-Petersburg and the North-West part of the Russian Federation from January 2022 to March 2022. The group of HC was collected with portable electronic devices in one of the city's schools and kindergartens with the exclusion of children with chronic diseases if it was reported in the survey. All parents of patients with IBD and JIA who were invited to participate responded to the survey. Initially, 58 out of 152 guardians of HC who had been asked to participate in the survey answered.

Survey

An electronic online questionnaire was created for the survey, containing 62 questions for parents of children with IBD, 55 questions for parents of children with JIA, and 37 questions for parents of healthy children. The majority of questions were identical for all three groups, some questions were equal for IBD and JIA and the remaining questions were disease-specific. The survey is in the [Supplementary material](#).

Data collection

We collected the following information: (1) Patient's demography: gender, type of disease, disease onset, age of inclusion; (2) Parental demography: gender of respondent, education, family status, and employment status; and (3) Information about vaccines: the coverage with obligatory and additional vaccines, reasons for incomplete vaccinations.

Statistical analysis

The sample size did not initially calculate. Descriptive statistics are reported in terms of medians and interquartile ranges for continuous variables and absolute frequencies and percentages for categorical variables. Missing data were not included in the analyses. We used a non-parametric statistic because all variables had non-normal distribution. To check whether the distribution was normal or not, we used the Kolmogorov-Smirnov test and distribution graphs. Pearson's χ^2 test or Fisher's exact test in the expected frequencies < 5 was used to compare the categorical variables. A comparison of two quantitative variables was carried out using the Mann-Whitney test. Bonferroni's correction test was applied to avoid multiple comparisons. The software Statistica (release 10.0, StatSoft Corporation, Tulsa, OK, United States) was used for data analysis, P value < 0.05 was considered to indicate a significant difference.

RESULTS

Patients and parental demography

A total of 190 individuals participated in the survey. The IBD group consisted of 51 patients, 39 (76%) with Crohn's disease and 12 (24%) with ulcerative colitis. The JIA group represented 81 parents, including systemic JIA ($n = 10$; 12.3%), RF positive or negative polyarthritis ($n = 23$; 28.4%), persistent or extended oligoarthritis ($n = 38$; 46.9%), enthesitis-related arthritis ($n = 3$; 3.7%), psoriatic ($n = 4$; 4.9%) and undifferentiated arthritis ($n = 3$; 3.7%). There was a female predominance in JIA patients ($n = 43$; 54% *vs* $n = 24$; 47% and $n = 28$; 49% for IBD and HC, respectively) and younger onset [4.7 (0.8; 16.0) *vs* 10.9 (1.0; 17.0) years for IBD] age and age of inclusion [7.8 (2.0; 18.0) years *vs* 13.6 (2.7; 17.0) and 11.3 (3.0; 17.0) for IBD and HC, respectively] in the present study. Mothers were the main survey respondents, with a lower part in JIA (88.2%) compared to IBD (96.1%) and HC (98.3%). Parents of JIA had higher education levels - 81.5% compared to 64% (IBD) and 77.6% (HC). Employment level and family status were similar in the three studied groups. Data are presented in [Table 1](#).

Russian national vaccination schedule and specific additional recommended vaccinations

The 2021 Russian national vaccination schedule included vaccinations against hepatitis B virus (HBV),

Table 1 Demographic characteristics of survey respondents

Parameters	Parents of IBD patients (n = 51)	Parents of JIA patients (n = 81)	Parents of HC (n = 58)	P value
Patients characteristics				
Age of inclusion in the study, years, Me (25%; 75%)	13.6 (2.7; 17.0)	7.8 (2.0; 18.0)	11.3 (3.0; 17.0)	0.00006
Gender, females, n (%)	24 (47)	43 (54)	28 (49)	0.0000001
The onset of the disease, years, Me (25%; 75%)	10.9 (1.0; 17.0)	4.7 (0.8; 16.0)	NA	0.0000001
Parental status				
Gender of representative, females, n (%)	49 (96.1)	71 (88.2)	57 (98.3)	0.022
Education level, n (%) -secondary school -higher education - academic degree	18 (36) 33 (64) 0 (0)	11 (13.6) 66 (81.5) 3 (4.9)	13 (22.4) 45 (77.6) 0 (0)	0.019
Level of employment, n (%) -working -self-employed - unemployed -receiving welfare support	32 (62.7) 5 (9.8) 8 (15.7) 6 (11.8)	48 (59) 8 (9.9) 12 (14.8) 13 (16.3)	37 (65) 11(18.5) 9 (16.5) 0 (0)	> 0.050
Family status, n (%) - Married - Divorced - Widow/widower - Single parent	43 (85.2) 4 (8.6) 1 (1.2) 2 (5)	66 (80.4) 9 (11.8) 3 (3.9) 3 (3.9)	46 (79.3) 11 (19.0) 1 (1.7) 0 (0)	0.327

IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.

tuberculosis, pneumococcus infection, poliomyelitis, diphtheria, tetanus, whooping cough, and measles - mumps - rubella (MMR)[21]. In addition, Haemophilus influenzae type B is recommended for all children from 3 mo (before 2021 it was voluntary and just for the risk group). Varicella-zoster virus (VZV) vaccination can be performed voluntarily, recommended for children after 1 year with negative VZV history. Influenza vaccination should be performed annually in children after 1 year. Vaccination against meningococcal, hepatitis A and tick-borne encephalitis are not recommended routinely for healthy children but can be performed voluntarily. Vaccinations against influenza (annually), pneumococcal, Haemophilus influenzae, Meningococcal, and hepatitis B infections are strongly recommended for IBD and JIA patients.

Assessment of vaccine coverage

Patients with JIA ($n = 65$; 79.9%) and IBD ($n = 42$; 82.3%) had lower vaccine coverage compared to HC ($n = 52$; 91.4%, $P = 0.320$). At least one episode of vaccine-associated reaction (low-grade fever, injection site reactions) was meant with a similar rate by parents in 40 (49.3%) JIA patients and 27 (46.6%) HC, and two times rarely in IBD ($n = 13$; 26.1, $P = 0.02$) patients. Fever after vaccination was reported by parents of JIA patients more frequently (33.3%) than by parents of IBD patients (21.6%) and HC (24.1%). Injections site reactions rate was the lowest in IBD children (3.9%) compare to JIA (16.1%) and HC (22.4%).

Reasons for incomplete vaccination

Temporary medical conditions (active stage of diseases, acute respiratory infections, high dose corticosteroids, and biologic therapy for live vaccines) were noted as the main reason for missing or delayed vaccinations in IBD ($n = 9$; 17.6%) and JIA patients ($n = 14$; 17.3%) with the same rate (Figure 1). No cases of parental rejection of vaccinations in IBD compared to JIA ($n = 2$; 2.5%) and HC ($n = 3$; 5.2%) were reported by respondents. A small proportion of JIA ($n = 6$; 7.4%) and IBD ($n = 5$; 10.9%) patients continue vaccinations after disease onset. Only a third part of immune-compromised patients: 23 (28.4%) of JIA and 16 (32%) of IBD patients' parents had the opportunity to discuss perspectives related to following vaccination with their attending physician. IBD patients ($n = 22$; 43.2%) had more frequent opportunities to measure levels of anti-vaccine antibodies before immune-suppressive therapy than JIA patients ($n = 24$; 29.6%). Among encouraging vaccination factors the role of attending physicians was the leading in IBD patients ($n = 42$; 84%), compared to JIA patients ($n = 56$; 69.1%) (Figure 2).

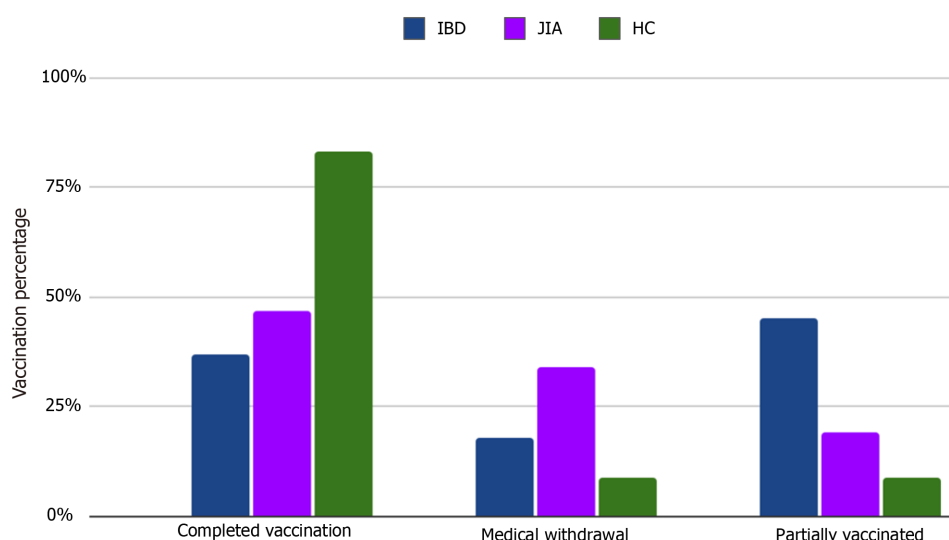
Patients with both immune-mediated diseases had a lower rate of supplementary vaccines, compared to HC, with an exception for the pneumococcal vaccine, which was more frequently used in IBD patients (data are in Table 2 and Figure 3).

According to parental opinion, lack of discussion about the safety of vaccines and future disease-related perspectives was the main factor, in the restraining of active vaccination. Vice versa, encouraging manner of attending physicians to vaccinate was meant by parents as a factor, that stimulated vaccination.

Table 2 Vaccine coverage of survey respondents

Parameters	Parents of IBD patients (n = 51)	Parents of JIA patients (n = 81)	Parents of HC (n = 58)	P value
Vaccine status				
Completed vaccination according to the national calendar, n (%)	42 (82.3)	65 (79.9)	52 (91.4)	0.320
Temporary medical contraindications for vaccination (postponed vaccination), n (%)	9 (17.6)	14 (17.3)	2 (3.4)	0.000001
Refused to be vaccinated, n (%)	0 (0)	2 (2.5)	3 (5.2)	0.00001
Vaccine-associated reactions: No reaction Fever Injection site reactions	38 (74.5) 11 (21.6) 2 (3.9)	41 (50.6) 27 (33.3) 13 (16.1)	31 (53.5) 14 (24.1) 13 (22.4)	0.020
Continued vaccination after diagnosis, n (%)	5 (10.9)	6 (7.4)	NA	0.505
Had an opportunity to discuss vaccinations with the attending physician, n (%)	16 (32)	23 (28.4)	NA	0.716
Control of anti-vaccine antibodies before immunosuppressive treatment, n (%)	22 (43.2)	24 (29.6)	NA	0.147
Factors encouraged vaccination, n (%) - Personal beliefs - Doctor's advice - Internet / Media - Parents' forums - Others	10 (20) 42 (84) 2 (4) 2 (4)	25 (30.8) 56 (69.1) 8 (9.9) 9.9 (12.3) 5 (6.4)	40 (70.9) 19 (34.5) 7 (12.7) 1 (1.8) 6 (10.9)	0.010
Additional vaccines, n (%), against - tick-borne encephalitis - influenza - meningococcus - pneumococcus - varicella	8 (9.8) 6 (11.7) 8 (16.0) 29 (56.8) 6 (12.7)	3 (3.7) 9 (11.1) 8 (9.8) 23 (29.4) 7 (6.2)	8 (14.5) 20 (35.1) 21 (36.8) 27 (48.9) 17 (30.2)	0.003 0.002 0.0000001 0.000004 0.000002

IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.



DOI: 10.5409/wjcp.v12.i2.45 Copyright ©The Author(s) 2023.

Figure 1 Vaccination coverage according to the National Preventive Immunization Calendar. IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.

DISCUSSION

In this study vaccine coverage and parental point of view on vaccination in patients with immune-mediated disease, (IBD and JIA) and HC were demonstrated.

Vaccine prophylaxis recommendations have been around for years, but the problem of low vaccination rates among these patients is still relevant. For children with rheumatic diseases, the major national and international medical societies, including the American College of Rheumatology and the European League of Associations for Rheumatology, as well as for children with IBD, including ECCO Guidelines, have recommended expanded vaccinations including pneumococcal, varicella-zoster, influenza and human papillomavirus (HPV) in addition to the common vaccines (hepatitis B, pertussis,

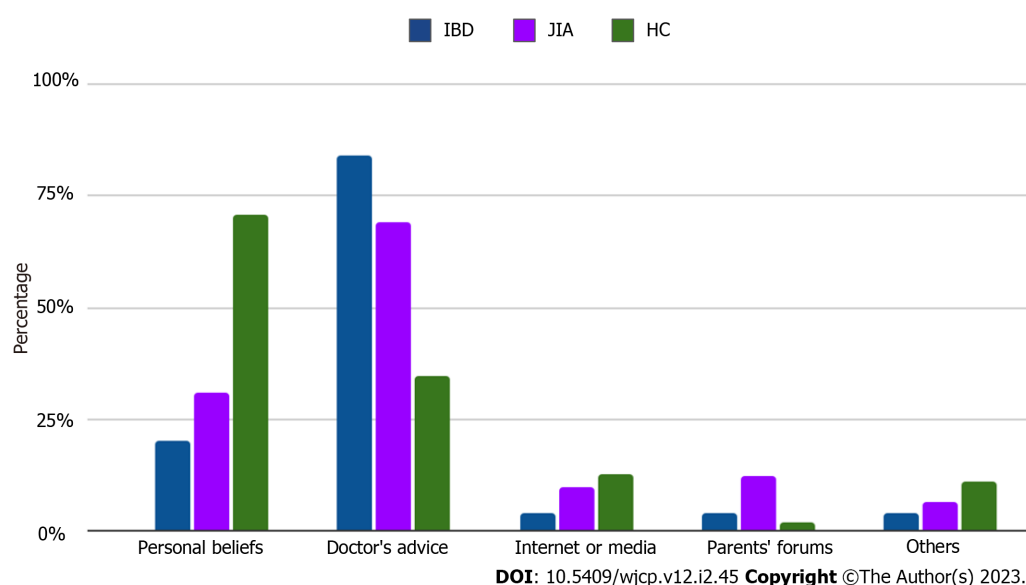


Figure 2 Sources influenced the parental decision on vaccination. IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.

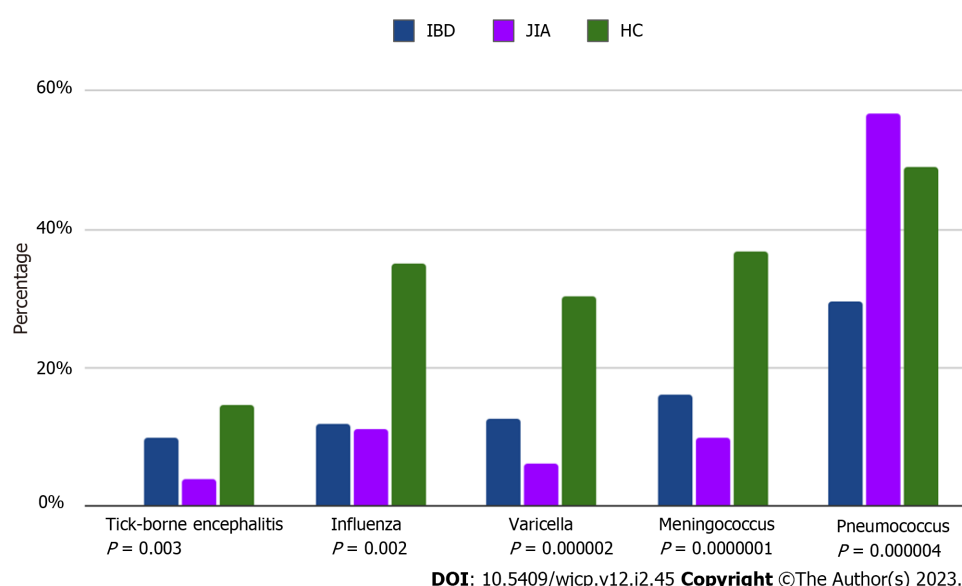


Figure 3 Vaccine coverage between the studied groups. IBD: Inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; HC: Healthy children.

diphtheria, tetanus, measles, rubella) [4,5,15]. Despite the existing international recommendations and consensus of the European communities of pediatric gastroenterologists and rheumatologists according to vaccination, current studies note a low level of awareness of the necessity and safety of vaccination among both types of physicians and parents, which translates into lower vaccine coverage in patients with both inflammatory bowel disease and juvenile idiopathic arthritis[16-19]. At the same time, it has been proven that maintaining appropriate vaccination status in these patients is critical for optimizing treatment outcomes. Vaccination recommendations for IBD and JIA patients are available, however, the implementation rate remains suboptimal[20,21]. In real practice, only 82.9% of gastroenterologists reported as "very important" to perform the vaccinations recommended by the guidelines in patients with IBD according to A Survey of the Italian Group for the Study of Inflammatory Bowel Disease[22].

Vaccine coverage and incomplete vaccination

The main previously published reasons for incomplete vaccination were the fear of physicians, as primary care or specialists in the efficacy and safety of vaccinations, and fears of parents about disease flares after vaccinations[18,19,25,26]. The fear and concerns of the physicians about the role of vaccines in the flares of pediatric rheumatic diseases might lead to vaccine delays or schedule interruption or

neglect of some "non-important vaccinations, according to their opinion"[25-27]. Due to the relevant issue of the effect of vaccination on the outcome of immune-mediated diseases, several large-scale cohort studies have been conducted, with no convincing evidence that the activity of immune-mediated diseases can be increased by vaccination[28,29]. The risk of infections, missing treatment, disease flare, and non-achievement of the remission usually are not mentioned as factors, associated with incomplete vaccination. Incomplete vaccination in JIA and pediatric rheumatic disease patients were reported in several previous studies[18,19,30,31,32]. From the medical point of view, the main predictors of incomplete vaccination were polyarticular and systemic JIA categories and immunosuppressive medications[30,31,33]. In our previous study, the younger JIA onset age was associated with a higher proportion of omitted vaccines similar to the study of Minden *et al*[18], but some authors reported that preschool children had a similar rate of vaccine coverage as healthy peers[30,32,33].

Usually, decreased vaccine coverage correlated with patients' age and teens had more omitted vaccines than preschools[18,30,32,33]. In our study, the proportion of patients, who received vaccination against pneumococcus was the highest in the IBD subgroup. Professional GI medical associations recommended using this vaccine to prevent respiratory infections, ensuring the treatment was uninterrupted and maintained remission. Many GI physicians follow this recommendation and encourage this vaccination. We hope that this can become a bridge to other vaccinations in patients with immune-mediated diseases.

The diphtheria vaccination coverage was lower in JIA and IBD patients[31,34]. The lower seroprotection was associated with an increased level of immunosuppression both in JIA and IBD children[31,35]. Booster revaccinations against diphtheria increased the proportions of subjects with seroprotection and were safe for JIA patients[31,34,36]. Canadian Association of Gastroenterology Clinical recommends vaccination against diphtheria for IBD patients[37].

Patients with JIA and IBD may have lower vaccine coverage (40%-75.8%) and seroprotection against hepatitis B (50%-60.7%) according to the data of several studies[35,38,39]. The vaccine against hepatitis B (HB) is recombinant and may be recommended for vaccination to all immune-compromised children because of its safety and efficacy[40,41,42]. The Japanese College of Rheumatology and the Japanese College of Hepatology considered anti-HB vaccination for unimmunized patients with JIA as soon as JIA has been under control for 3 mo[41,42].

Safety and efficacy of vaccines

Vaccines are considered to be effective and safe. There is no evidence that vaccines increase the risk of developing immune-mediated conditions or exacerbating the existing IBD or rheumatic diseases in children[43-45]. There are no contraindications for the administration of inactive or live vaccines in patients who are not receiving immunosuppressive treatment[15,16]. Despite the higher risk of live vaccines in immune-mediated diseases patients there was no strong correlation between the type of omitted vaccines (live or non-live) and disease activity[30,33]. Sometimes patients with pediatric rheumatic diseases might have omitted non-live vaccines[30,33]. Contemporary EULAR recommendations for children (2021) and adults (2019) with rheumatic diseases allow using live-attenuated vaccines, especially booster doses of MMR and varicella zoster virus in patients with low-grade immune suppression[5,15]. The protective role of vaccines in immune-compromised children was successfully demonstrated in several studies. Compared to healthy children, morbidity and mortality from influenza and streptococcus pneumonia-associated pneumonia are higher among patients with immune-mediated diseases. According to Tinsley A. 2013, patients with IBD who got influenza are more likely to be hospitalized and develop viral pneumonia, although this disease can be prevented by vaccination[46]. Vaccine coverage against pneumococcus was 5% in the Australian pediatric IBD cohort, 18.6% in 430 pediatric IBD patients, from a multicentre study, and 50.3% in JIA patients from Switzerland without differences irrespective of immune-suppressive therapy[33,47,48]. In the study of pneumococcal and anti-Hib vaccination of non-systemic and systemic JIA patients was shown the decreasing number of episodes of acute respiratory infections different etiology[49]. No differences in response related to treatment and disease activity stage were observed. The vaccination against both infections was safe and not associated with following short-term flares[49,50].

Immunization barriers

There are a lot of barriers between primary care physicians and specialists (rheumatologists, gastroenterologists) in the immunization process of patients with immune-mediated diseases. In a survey of 178 pediatric gastroenterologists conducted by Lester R, 2015, a different view on immunization of IBD patients among gastroenterologists was reported[15]. The main problem was the inability to coordinate patient follow-up for dispensary and immunoprophylaxis between gastroenterologists and pediatricians. Only 28% of GI physicians believed that only primary care physicians were responsible for immunizations. In contrast, in a survey of general pediatricians, only 29% were ready to prescribe vaccination to their patients with IBD[17]. General pediatricians avoid vaccinating patients with a pediatric rheumatic disease without specialists' confirmation. In a recent Greece study, it was shown that 50% of primary care physicians required rheumatologist approval for vaccination[25].

Similar to our data, patients themselves identified a lack of information and fear of side effects as the main reasons for low vaccination rates[51,52].

Practicing gastroenterologists checked the immunization status in 63.5% of cases at the time of diagnosis and in 44.4% before initiating immunosuppressive therapy, according to the survey of 657 gastroenterologists from North America, and only 9% checked serology to assess the protection of IBD children from vaccine-preventable diseases[17]. A relatively small number of our respondents had an opportunity to discuss vaccines and diseases course perspectives and check the serology against vaccines to vaccine-preventable diseases. This point should be improved.

The discrepancy of factors, encouraging vaccination, between IBD and JIA patients was observed. The urging role of attending physicians was lower in JIA patients compared to IBD, but the role of the parent's forum was higher. The sum of the role of internet/media and parental forums in vaccination coverage JIA patients was higher 22.2% compare to IBD - 8% ($P = 0.01$). It might explain the fact that a survey for JIA patients was disseminated through the parental forum where one of the manuscript co-authors (Mikhail K) delivered several lectures about the efficacy and safety of vaccinations in the last two years. This educational effort was very effective: the vaccine coverage for MMR and diphtheria in JIA patients was 42% and 50% respectively in 2018 and now vaccine coverage (complete vaccination) has raised to 79.9% in 2022[31].

How we can improve vaccine coverage?

The international guidelines on the management of opportunistic infections and vaccine prophylaxis in patients with IBD were updated in 2021[14]. Regular surveys of vaccine status in patients with inflammatory bowel disease have been recommended, as well as mandatory vaccination against common vaccines: tetanus, diphtheria, and poliomyelitis. In addition, each patient with inflammatory bowel disease should be considered for additional vaccination with the following five vaccines: Varicella-zoster vaccine, HPV, annual influenza (trivalent inactivated vaccine), pneumococcal polysaccharide vaccine, and hepatitis B vaccine for all HBV seronegative patients[4,5,16].

Professional communities should provide more information about the safety and efficacy of vaccination in immune-compromised children and encourage applying modern recommendations in their practical work and discussions with families. Education and vaccine access in clinics lead to the growth of influenza vaccine coverage from 47% to 75% (education) and 89.5% (plus vaccine access)[53]. It was shown that even a single specialized infectious disease consultation with patients can improve patients' knowledge of vaccination and influence their decision to vaccinate from initial coverage of 16.1% for pneumococcus to 85.7% after intervention[51]. Educational programs for IBD children and their parents increased the coverage for vaccines against diphtheria-tetanus-poliomyelitis (92% *vs* 100%) and *Haemophilus influenzae* (88% *vs* 98%), hepatitis B (52% *vs* 71%), pneumococcus (36% *vs* 57%), and meningococcus C (17% *vs* 41%) ($P < 0.05$)[38].

Physicians' encouragement of vaccination and the impossibility to discuss future vaccinations and their outcomes seemed the main positive and negative factors that influenced vaccine coverage in immune-mediated diseases patients. Individual vaccine schedules based on the evaluation of vaccine status and serial anti-vaccine antibody assessment should be a reliable tool for increasing trust in vaccines and persuading parents to continue vaccinations, especially omitted ones. It is strongly recommended to implement educational algorithms and programs for parents and children, provided by the attending physicians or other care-given providers about the safety and efficacy of vaccines in children with immune-mediated diseases.

Limitations

The main limitation of this study related to the self-reported nature of results, assessment of parental outcomes, and inability to compare parental data with official medical records related to vaccination. We cannot be sure of the proper meaning of complete vaccination and parental knowledge of the national vaccine schedule, which makes some bias in the study results. The small sample size and lack of validated surveys make some bias.

CONCLUSION

JIA and IBD patients had lower vaccine coverage compared to HC. Physicians' encouragement of vaccination and the impossibility of discuss about future vaccinations and their outcomes seemed the main factors for patients with immune-mediated diseases, influencing vaccine coverage. Further investigations are required to understand the reasons for incomplete vaccinations and improve vaccine coverage in both groups, especially in rheumatic disease patients. The approaches that stimulate vaccination in healthy children are not always optimal in children with immune-mediated diseases. It is necessary to provide personalized vaccine-encouraging strategies for parents of chronically ill children by following the validation of these techniques. Increasing immunization coverage and implementing advocacy events among special groups are required.

ARTICLE HIGHLIGHTS

Research background

Patients with immune-mediated diseases have incomplete vaccination.

Research motivation

There are no previous studies about parental view of the reasons of incomplete vaccination.

Research objectives

To evaluate the parental view about possible reasons of incomplete vaccination.

Research methods

An electronic survey for parents of immune-mediated disease patients and healthy controls was created and disseminated. The analysis of response was done.

Research results

Lower vaccine coverage in immune mediated patients was detected, compared to healthy controls. Medical conditions were the main medical reasons for incomplete vaccination in juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD). Less rate of vaccine-associated reactions was reported in IBD. Pediatric rheumatologists rarely explain the safety and benefits of vaccinations. Pediatric gastroenterology physicians frequently checked anti-vaccine antibodies and recommend more supplementary vaccines.

Research conclusions

Children with immune-mediated disease (IBD and JIA) have incomplete vaccination. The encouraging role of physicians and lack of discussion about the vaccines from physicians are factors, influencing completeness of the vaccination.

Research perspectives

Future studies on the effectiveness of educational programs supporting vaccinations may be planned.

FOOTNOTES

Author contributions: All authors were involved in the conception, drafting, and critical revision of the article, read and approved the final manuscript.

Institutional review board statement: The study was approved by the Ethical Committee of the Saint-Petersburg State Pediatric Medical University (Protocol №3 from 01/03/2021). There were no violations of patients' rights according to the Declaration of Helsinki. The study was completely anonymous.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Russia

ORCID number: Mikhail Kostik 0000-0002-1180-8086.

S-Editor: Wang LL

L-Editor: A

P-Editor: Wang LL

REFERENCES

- 1 Groot N, Heijstek MW, Wulfraat NM. Vaccinations in paediatric rheumatology: an update on current developments. *Curr Rheumatol Rep* 2015; **17**: 46 [PMID: 26025339 DOI: 10.1007/s11926-015-0519-y]
- 2 Nuti F, Civitelli F, Cucchiara S. Long-term safety of immunomodulators in pediatric inflammatory diseases. *Paediatr Drugs* 2014; **16**: 343-352 [PMID: 25047730 DOI: 10.1007/s40272-014-0084-2]
- 3 Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Viget N, Yazdanpanah Y, Eliakim R, Colombel JF; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 443-468 [PMID: 24613021 DOI: 10.1016/j.crohns.2013.12.013]
- 4 Kucharzik T, Ellul P, Greuter T, Rahier JF, Verstockt B, Abreu C, Albuquerque A, Allocca M, Esteve M, Farraye FA, Gordon H, Karmiris K, Kopylov U, Kirchgesner J, MacMahon E, Magro F, Maaser C, de Ridder L, Taxonera C, Toruner M, Tremblay L, Scharl M, Viget N, Zabana Y, Vavricka S. ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease. *J Crohns Colitis* 2021; **15**: 879-913 [PMID: 33730753 DOI: 10.1093/ecco-jcc/ijab052]
- 5 Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, Breedveld FC, D'Amelio R, Dougados M, Kapetanovic MC, van Laar JM, de Thurah A, Landewé RB, Molto A, Müller-Ladner U, Schreiber K, Smolar L, Walker J, Warnatz K, Wulfraat NM, Elkayam O. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020; **79**: 39-52 [PMID: 31413005 DOI: 10.1136/annrheumdis-2019-215882]
- 6 Hemperly A, Sandborn WJ, Vande Castele N. Clinical Pharmacology in Adult and Pediatric Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2018; **24**: 2527-2542 [PMID: 29788338 DOI: 10.1093/ibd/izy189]
- 7 Poddighe D, Romano M, Gattinara M, Gerloni V. Biologics for the Treatment of Juvenile Idiopathic Arthritis. *Curr Med Chem* 2018; **25**: 5860-5893 [PMID: 29788871 DOI: 10.2174/0929867325666180522085716]
- 8 Toussi SS, Pan N, Walters HM, Walsh TJ. Infections in children and adolescents with juvenile idiopathic arthritis and inflammatory bowel disease treated with tumor necrosis factor- α inhibitors: systematic review of the literature. *Clin Infect Dis* 2013; **57**: 1318-1330 [PMID: 23899685 DOI: 10.1093/cid/cit489]
- 9 Becker I, Horneff G. Risk of Serious Infection in Juvenile Idiopathic Arthritis Patients Associated With Tumor Necrosis Factor Inhibitors and Disease Activity in the German Biologics in Pediatric Rheumatology Registry. *Arthritis Care Res (Hoboken)* 2017; **69**: 552-560 [PMID: 27390133 DOI: 10.1002/acr.22961]
- 10 Nagy A, Mátrai P, Hegyi P, Alizadeh H, Bajor J, Czopf L, Gyöngyi Z, Kiss Z, Márta K, Simon M, Szilágyi ÁL, Veres G, Mosdósi B. The effects of TNF- α inhibitor therapy on the incidence of infection in JIA children: a meta-analysis. *Pediatr Rheumatol Online J* 2019; **17**: 4 [PMID: 30658717 DOI: 10.1186/s12969-019-0305-x]
- 11 Wakabayashi A, Ishiguro T, Takaku Y, Miyahara Y, Kagiya N, Takayanagi N. Clinical characteristics and prognostic factors of pneumonia in patients with and without rheumatoid arthritis. *PLoS One* 2018; **13**: e0201799 [PMID: 30075013 DOI: 10.1371/journal.pone.0201799]
- 12 Ardura MI, Toussi SS, Siegel JD, Lu Y, Bousvaros A, Crandall W. NASPGHAN Clinical Report: Surveillance, Diagnosis, and Prevention of Infectious Diseases in Pediatric Patients With Inflammatory Bowel Disease Receiving Tumor Necrosis Factor- α Inhibitors. *J Pediatr Gastroenterol Nutr* 2016; **63**: 130-155 [PMID: 27027903 DOI: 10.1097/MPG.0000000000001188]
- 13 Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr* 2015; **169**: 1053-1060 [PMID: 26414706 DOI: 10.1001/jamapediatrics.2015.1982]
- 14 Papp KA, Haraoui B, Kumar D, Marshall JK, Bissonnette R, Bitton A, Bressler B, Gooderham M, Ho V, Jamal S, Pope JE, Steinhart AH, Vinh DC, Wade J. Vaccination Guidelines for Patients with Immune-mediated Disorders Taking Immunosuppressive Therapies: Executive Summary. *J Rheumatol* 2019; **46**: 751-754 [PMID: 30709945 DOI: 10.3899/jrheum.180784]
- 15 Jansen MHA, Rondaan C, Legger GE, Minden K, Uziel Y, Toplak N, Maritsi D, van den Berg L, Berbers GAM, Bruijning P, Egert Y, Normand C, Bijl M, Foster HE, Koné-Paut I, Wouters C, Ravelli A, Elkayam O, Wulfraat NM, Heijstek MW. EULAR/PRES recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases: update 2021. *Ann Rheum Dis* 2023; **82**: 35-47 [PMID: 35725297 DOI: 10.1136/annrheumdis-2022-222574]
- 16 Esposito S, Antoniol G, Labate M, Passadore L, Alvisi P, Daccò V, Ghizzi C, Colombo C, Principi N. Vaccines in Children with Inflammatory Bowel Disease: Brief Review. *Vaccines (Basel)* 2021; **9** [PMID: 34064576 DOI: 10.3390/vaccines9050487]
- 17 Lester R, Lu Y, Tung J. Survey of Immunization Practices in Patients With Inflammatory Bowel Disease Among Pediatric Gastroenterologists. *J Pediatr Gastroenterol Nutr* 2015; **61**: 47-51 [PMID: 25611033 DOI: 10.1097/MPG.0000000000000730]
- 18 Minden K, Niewerth M, Borte M, Singendonk W, Haas JP. [Immunization in children and adolescents with rheumatic diseases]. *Z Rheumatol* 2007; **66**: 111-112, 114 [PMID: 17364157 DOI: 10.1007/s00393-007-0150-z]
- 19 Morin MP, Quach C, Fortin E, Chédeville G. Vaccination coverage in children with juvenile idiopathic arthritis followed at a paediatric tertiary care centre. *Rheumatology (Oxford)* 2012; **51**: 2046-2050 [PMID: 22864995 DOI: 10.1093/rheumatology/kes175]
- 20 Rollet-Cohen V, Mirete J, Dingulu G, Hofer F, Hofer M, Woerner A, Dommergues MA, Hentgen V. Suboptimal

- vaccination coverage of recommended vaccines among French children with recurrent autoinflammatory fever syndromes: a study from the Juvenile Inflammatory Rheumatism cohort. *Clin Rheumatol* 2021; **40**: 2855-2864 [PMID: [33439385](#) DOI: [10.1007/s10067-020-05553-y](#)]
- 21 **Benchimol EI**, Tse F, Carroll MW, deBruyn JC, McNeil SA, Pham-Huy A, Seow CH, Barrett LL, Bessissow T, Carman N, Melmed GY, Vanderkooi OG, Marshall JK, Jones JL. Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)-Part 1: Live Vaccines. *J Can Assoc Gastroenterol* 2021; **4**: e59-e71 [PMID: [34476338](#) DOI: [10.1093/jcag/gwab015](#)]
 - 22 **Macaluso FS**, Mazzola G, Ventimiglia M, Alvisi P, Renna S, Adamoli L, Galli M, Armuzzi A, Ardizzone S, Cascio A, Cottone M, Orlando A; on behalf of IG-IBD (Italian Group for the study of Inflammatory Bowel Disease). Physicians' Knowledge and Application of Immunization Strategies in Patients with Inflammatory Bowel Disease: A Survey of the Italian Group for the Study of Inflammatory Bowel Disease. *Digestion* 2020; **101**: 433-440 [PMID: [31167191](#) DOI: [10.1159/000500798](#)]
 - 23 The Order of the Ministry of Health of the Russian Federation from 06.12.2021 № 1122n "On approval of the national calendar of preventive vaccinations, calendar of preventive vaccinations for epidemic indications and the order of preventive vaccinations" (Registered 20.12.2021 № 66435)
 - 24 **Soon IS**, deBruyn JC, Wrobel I. Immunization history of children with inflammatory bowel disease. *Can J Gastroenterol* 2013; **27**: 213-216 [PMID: [23616959](#) DOI: [10.1155/2013/539524](#)]
 - 25 **Crawford NW**, Buttery JP. Adverse events following immunizations: fact and fiction. *Paediatr Child Health* 2013; **23**: 121-124 [DOI: [10.1016/j.paed.2012.06.004](#)]
 - 26 **Papailiou S**, Markade A, Eleftheriou I, Tsolia MN, Garoufi A, Maritsi DN. A National Survey Across Primary Care Pediatricians Regarding Immunization Views and Practices in Children With Rheumatic Diseases. *J Clin Rheumatol* 2021; **27**: e588-e590 [PMID: [31972735](#) DOI: [10.1097/RHU.0000000000001251](#)]
 - 27 **Hussain A**, Ali S, Ahmed M, Hussain S. The Anti-vaccination Movement: A Regression in Modern Medicine. *Cureus* 2018; **10**: e2919 [PMID: [30186724](#) DOI: [10.7759/cureus.2919](#)]
 - 28 **Rahier JF**, Papay P, Salleron J, Sebastian S, Marzo M, Peyrin-Biroulet L, Garcia-Sanchez V, Fries W, van Asseldonk DP, Farkas K, de Boer NK, Sipponen T, Ellul P, Louis E, Peake ST, Kopylov U, Maul J, Makhoul B, Fiorino G, Yazdanpanah Y, Chaparro M; European Crohn's and Colitis Organisation (ECCO). H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy. *Gut* 2011; **60**: 456-462 [PMID: [21270121](#) DOI: [10.1136/gut.2010.233981](#)]
 - 29 **Subesinghe S**, Rutherford AI, Ibrahim F, Harris H, Galloway J. A large two-centre study in to rates of influenza and pneumococcal vaccination and infection burden in rheumatoid arthritis in the UK. *BMC Musculoskelet Disord* 2016; **17**: 322 [PMID: [27491386](#) DOI: [10.1186/s12891-016-1187-4](#)]
 - 30 **Balažiová B**, Kuková Z, Mišíková D, Novosedlíková K, Dallos T. Real-life vaccination coverage in Slovak children with rheumatic diseases. *Front Pediatr* 2022; **10**: 956136 [PMID: [36034574](#) DOI: [10.3389/fped.2022.956136](#)]
 - 31 **Kostik MM**, Lubimova NA, Fridman IV, Goleva OV, Kharit SM. The vaccine coverage and vaccine immunity status and risk factors of non-protective levels of antibodies against vaccines in children with juvenile idiopathic arthritis: cross-sectional Russian tertiary Centre study. *Pediatr Rheumatol Online J* 2021; **19**: 108 [PMID: [34225748](#) DOI: [10.1186/s12969-021-00594-2](#)]
 - 32 **Bizjak M**, Blazina Š, Zajc Avramović M, Markelj G, Avčín T, Toplak N. Vaccination coverage in children with rheumatic diseases. *Clin Exp Rheumatol* 2020; **38**: 164-170 [PMID: [31577215](#)]
 - 33 **Welzel T**, Kuemmerle-Deschner J, Sluka C, Carlomagno R, Cannizzaro Schneider E, Kaiser D, Hofer M, Hentgen V, Woerner A. Vaccination completeness in children with rheumatic diseases: A longitudinal, observational multicenter cohort study in Switzerland. *Front Pediatr* 2022; **10**: 993811 [PMID: [36160778](#) DOI: [10.3389/fped.2022.993811](#)]
 - 34 **Heijstek MW**, van Gageldonk PG, Berbers GA, Wulffraat NM. Differences in persistence of measles, mumps, rubella, diphtheria and tetanus antibodies between children with rheumatic disease and healthy controls: a retrospective cross-sectional study. *Ann Rheum Dis* 2012; **71**: 948-954 [PMID: [22172491](#) DOI: [10.1136/annrheumdis-2011-200637](#)]
 - 35 **deBruyn JCC**, Soon IS, Fonseca K, Feng S, Purtzki M, Goedhart C, Kuhn S, Vanderkooi OG, Wrobel I. Serologic Status of Routine Childhood Vaccines, Cytomegalovirus, and Epstein-Barr Virus in Children With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2019; **25**: 1218-1226 [PMID: [30551205](#) DOI: [10.1093/ibd/izy366](#)]
 - 36 **Wanlapakorn N**, Maertens K, Thongmee T, Srimuan D, Thatsanathorn T, Van Damme P, Leuridan E, Poovorawan Y. Levels of antibodies specific to diphtheria toxoid, tetanus toxoid, and Haemophilus influenzae type b in healthy children born to Tdap-vaccinated mothers. *Vaccine* 2020; **38**: 6914-6921 [PMID: [32888740](#) DOI: [10.1016/j.vaccine.2020.08.058](#)]
 - 37 **Jones JL**, Tse F, Carroll MW, deBruyn JC, McNeil SA, Pham-Huy A, Seow CH, Barrett LL, Bessissow T, Carman N, Melmed GY, Vanderkooi OG, Marshall JK, Benchimol EI. Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)-Part 2: Inactivated Vaccines. *J Can Assoc Gastroenterol* 2021; **4**: e72-e91 [PMID: [34476339](#) DOI: [10.1093/jcag/gwab016](#)]
 - 38 **Fleurier A**, Pelatan C, Willot S, Ginies JL, Breton E, Bridoux L, Segura JF, Chaillou E, Jobert A, Darvot E, Cagnard B, Delaperrière N, Grimal I, Carre E, Wagner AC, Sylvestre E, Dabadie A. Vaccination coverage of children with inflammatory bowel disease after an awareness campaign on the risk of infection. *Dig Liver Dis* 2015; **47**: 460-464 [PMID: [25770456](#) DOI: [10.1016/j.dld.2015.02.009](#)]
 - 39 **Szczygielska I**, Hernik E, Kwiatkowska M, Rutkowska-Sak L, Kołodziejczyk B, Gazda A. Assessment of the level of vaccine-induced anti-HBs antibodies in children with inflammatory systemic connective tissue diseases treated with immunosuppression. *Reumatologia* 2015; **53**: 56-60 [PMID: [27407228](#) DOI: [10.5114/reum.2015.51503](#)]
 - 40 **Kasapcopur O**, Cullu F, Kamburoğlu-Goksel A, Cam H, Akdenizli E, Calýkan S, Sever L, Arýsoy N. Hepatitis B vaccination in children with juvenile idiopathic arthritis. *Ann Rheum Dis* 2004; **63**: 1128-1130 [PMID: [15308522](#) DOI: [10.1136/ard.2003.013201](#)]
 - 41 **Nerome Y**, Akaike H, Nonaka Y, Takezaki T, Kubota T, Yamato T, Yamasaki Y, Imanaka H, Kawano Y, Takei S. The safety and effectiveness of HBV vaccination in patients with juvenile idiopathic arthritis controlled by treatment. *Mod Rheumatol* 2016; **26**: 368-371 [PMID: [26471922](#) DOI: [10.3109/143](#)]

- 42 **Kobayashi I**, Mori M, Yamaguchi K, Ito S, Iwata N, Masunaga K, Shimojo N, Ariga T, Okada K, Takei S. Pediatric Rheumatology Association of Japan recommendation for vaccination in pediatric rheumatic diseases. *Mod Rheumatol* 2015; **25**: 335-343 [PMID: [25381726](#) DOI: [10.3109/14397595.2014.969916](#)]
- 43 **Uziel Y**, Moshe V, Onozo B, Kulcsár A, Tróbert-Sipos D, Akikusa JD, Salviato Pileggi G, Maritsi D, Kasapcopur O, Rodrigues M, Smerla R, Rigante D, Makay B, Atsali E, Wulffraat N, Toplak N; PRoS working party of Vaccination Study Group. Live attenuated MMR/V booster vaccines in children with rheumatic diseases on immunosuppressive therapy are safe: Multicenter, retrospective data collection. *Vaccine* 2020; **38**: 2198-2201 [PMID: [31987692](#) DOI: [10.1016/j.vaccine.2020.01.037](#)]
- 44 **Heijstek MW**, Kamphuis S, Armbrust W, Swart J, Gorter S, de Vries LD, Smits GP, van Gageldonk PG, Berbers GA, Wulffraat NM. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. *JAMA* 2013; **309**: 2449-2456 [PMID: [23780457](#) DOI: [10.1001/jama.2013.6768](#)]
- 45 **Alfayadh NM**, Gowdie PJ, Akikusa JD, Easton ML, Buttery JP. Vaccinations Do Not Increase Arthritis Flares in Juvenile Idiopathic Arthritis: A Study of the Relationship between Routine Childhood Vaccinations on the Australian Immunisation Schedule and Arthritis Activity in Children with Juvenile Idiopathic Arthritis. *Int J Rheumatol* 2020; **2020**: 1078914 [PMID: [32831849](#) DOI: [10.1155/2020/1078914](#)]
- 46 **Tinsley A**, Navabi S, Williams ED, Liu G, Kong L, Coates MD, Clarke K. Increased Risk of Influenza and Influenza-Related Complications Among 140,480 Patients With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2019; **25**: 369-376 [PMID: [30020478](#) DOI: [10.1093/ibd/izy243](#)]
- 47 **Martinelli M**, Giugliano FP, Strisciuglio C, Urbonas V, Serban DE, Banaszkiwicz A, Assa A, Hojsak I, Lerchova T, Navas-López VM, Romano C, Sladek M, Veres G, Aloï M, Kucinskiene R, Miele E. Vaccinations and Immunization Status in Pediatric Inflammatory Bowel Disease: A Multicenter Study From the Pediatric IBD Porto Group of the ESPGHAN. *Inflamm Bowel Dis* 2020; **26**: 1407-1414 [PMID: [31689349](#) DOI: [10.1093/ibd/izz264](#)]
- 48 **Crawford NW**, Catto-Smith AG, Oliver MR, Cameron DJ, Buttery JP. An Australian audit of vaccination status in children and adolescents with inflammatory bowel disease. *BMC Gastroenterol* 2011; **11**: 87 [PMID: [21798078](#) DOI: [10.1186/1471-230X-11-87](#)]
- 49 **Alexeeva EI**, Soloshenko MA, Dvoryakovskaya TM, Lomakina OL, Denisova RV, Isaeva KB, Karasyova AV. Efficacy and Safety of Immunization With Pneumococcal Polysaccharide Vaccine in Children With Juvenile Idiopathic Arthritis: Preliminary Results of a Prospective Open-Label Study. *Current Pediatrics* 2017; **16**: 142-147 [DOI: [10.15690/vsp.v16i2.1715](#)]
- 50 **Alexeeva EI**, Vankova DD, Dvoryakovskaya TM, Isaeva KB, Denisova RV, Mamutova AV, Chomakhidze AM, Radygina TV, Zubkova IV, Tkachenko NE, Fetisova AN, Lomakina OL, Orlova YO, Kurdup MK, Gautier MS, Krekhova EA, Shingarova MS, Galkina OP. Efficacy of Pneumococcal Polysaccharide Conjugate Vaccine (13-valent, Adsorbed) in Patients with Systemic Juvenile Idiopathic Arthritis Treated with Genetically Engineered Biologic Drugs (Tocilizumab or Canakinumab): Prospective Cohort Study. *Current Pediatrics* 2020; **19**: 190-199 [DOI: [10.15690/vsp.v19i3.2114](#)]
- 51 **Sitte J**, Frentiu E, Baumann C, Rousseau H, May T, Bronowicki JP, Peyrin-Biroulet L, Lopez A. Vaccination for influenza and pneumococcus in patients with gastrointestinal cancer or inflammatory bowel disease: A prospective cohort study of methods for improving coverage. *Aliment Pharmacol Ther* 2019; **49**: 84-90 [PMID: [30485467](#) DOI: [10.1111/apt.15057](#)]
- 52 **Melmed GY**, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, Frenck RW, Targan SR, Vasiliauskas EA. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. *Am J Gastroenterol* 2006; **101**: 1834-1840 [PMID: [16817843](#) DOI: [10.1111/j.1572-0241.2006.00646.x](#)]
- 53 **Huth K**, Benchimol EI, Aglipay M, Mack DR. Strategies to Improve Influenza Vaccination in Pediatric Inflammatory Bowel Disease Through Education and Access. *Inflamm Bowel Dis* 2015; **21**: 1761-1768 [PMID: [26199989](#) DOI: [10.1097/MIB.0000000000000425](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2023 June 9; 12(3): 57-161



MINIREVIEWS

- 57 COVID-19-induced liver injury in infants, children, and adolescents
Bitar R, Elghoudi AA, Rawat D, Azaz A, Miqdady M, Narchi H
- 68 Hirschsprung's disease associated enterocolitis: A comprehensive review
Gershon EM, Rodriguez L, Arbizu RA
- 77 Seronegative autoimmune hepatitis in childhood
Islek A, Tumgor G
- 86 Various aspects of hearing loss in newborns: A narrative review
Al-Ani RM
- 97 Emerging role of computed tomography coronary angiography in evaluation of children with Kawasaki disease
Singhal M, Paliana RK, Gupta P, Johnson N, Singh S

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 107 *IFIH1* and *DDX58* gene variants in pediatric rheumatic diseases
Raupov R, Suspitsin E, Belozarov K, Gabrusskaya T, Kostik M

Retrospective Study

- 115 Clinical characteristics of community-acquired pneumonia in children caused by mycoplasma pneumoniae with or without myocardial damage: A single-center retrospective study
Yusuf SO, Chen P

Observational Study

- 125 Psychiatric disorders and caregiver burden in children with transfusion dependent β -thalassaemia and their caregivers
Sahu S, Agrawal A, Shrivastava J, Tonk S
- 133 Evaluation of children and adults with post-COVID-19 persistent smell, taste and trigeminal chemosensory disorders: A hospital based study
Hamed SA, Kamal-Eldeen EB, Ahmed MAAR

Prospective Study

- 151 Prevalence of gastroesophageal reflux disease in children with extraesophageal manifestations using combined-video, multichannel intraluminal impedance-pH study
Eiamkulbutr S, Dumrisilp T, Sanpavat A, Sintusek P

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Tuna Kenar, MD, MSc, Assistant Professor, Department of Otolaryngology & Audiology, Private Denizli Cerrahi Hospital, Zeytinköy Ave. No:5 Pamukkale, Denizli, 20070, Türkiye. tuna.kenar@cerrahi.com.tr

AIMS AND SCOPE

The primary aim of the *World Journal of Clinical Pediatrics* (WJCP, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCP mainly publishes articles reporting research results and findings obtained in the field of pediatrics and covering a wide range of topics including anesthesiology, cardiology, endocrinology, gastroenterology, hematology, immunology, infections and infectious diseases, medical imaging, neonatology, nephrology, neurosurgery, nursing medicine, perinatology, pharmacology, respiratory medicine, and urology.

INDEXING/ABSTRACTING

The WJCP is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; **Production Department Director:** Xiang Li; **Editorial Office Director:** Yu-Jie Ma.

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Elena Daniela Serban, Surjit Singh, Consolato M Sergi, Toru Watanabe

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2219-2808/editorialboard.htm>

PUBLICATION DATE

June 9, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

COVID-19-induced liver injury in infants, children, and adolescents

Rana Bitar, Ahmed A Elghoudi, David Rawat, Amer Azaz, Mohamad Miqdady, Hassib Narchi

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Tudoran C, Romania; Wijaya JH, Indonesia

Received: September 27, 2022

Peer-review started: September 27, 2022

First decision: October 17, 2022

Revised: November 7, 2022

Accepted: March 17, 2023

Article in press: March 17, 2023

Published online: June 9, 2023



Rana Bitar, David Rawat, Amer Azaz, Mohamad Miqdady, Division of Pediatric Gastroenterology, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates

Rana Bitar, David Rawat, Amer Azaz, Mohamad Miqdady, College of Medicine and Health Sciences, Khalifa University, Abu Dhabi, United Arab Emirates

Ahmed A Elghoudi, Department of Pediatric, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates

Ahmed A Elghoudi, Hassib Narchi, Department of Pediatric, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

Corresponding author: Ahmed A Elghoudi, MBChB, MSc, Adjunct Associate Professor, Doctor, Department of Pediatric, Sheikh Khalifa Medical City, Al Karama Street, Al Khalidya, Abu Dhabi, United Arab Emirates. aelghoudi@seha.ae

Abstract

Coronavirus disease 2019 (COVID-19) typically presents with fever and respiratory symptoms in children. Most children develop an asymptomatic and mild illness, with a minority requiring specialist medical care. Gastrointestinal manifestations and liver injury can also occur in children following infection. The mechanisms of liver injury may include infection following direct viral hepatic tissue invasion, immune response, or medication effects. Affected children might develop mild liver dysfunction which has a benign course in most children with no pre-existing liver disease. However, the presence of non-alcoholic fatty liver disease or other pre-existing chronic liver disorders is associated with a higher risk of developing severe COVID-19 illness with poor outcomes. On the other hand, the presence of liver manifestations is associated with the severity of COVID-19 disease and is considered an independent prognostic factor. Respiratory, hemodynamic, and nutritional supportive therapies are the mainstay of management. Vaccination of children at increased risk of developing severe COVID-19 disease is indicated. This review describes the liver manifestations in children with COVID-19, detailing its epidemiology, basic mechanisms, clinical expression, management, and prognosis in those with and without pre-existing liver disease and also children who have had earlier liver transplantation.

Key Words: Child; COVID-19; Gastroenterology; Hepatic dysfunction; Infection; Liver diseases; SARS-CoV-2; Liver injury; Liver transplant

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Liver injury presenting with elevated levels of alanine aminotransferase and aspartate aminotransferase is common in children infected with the coronavirus disease 2019 (COVID-19) virus. The mechanism of liver injury is not fully understood and is likely secondary to the viral invasion of the liver, hepato-toxic medications, and the patient's own immune-mediated response. Liver injury in children is generally mild and resolves spontaneously but is usually seen in children with more severe illnesses. In addition, children with underlying non-alcoholic fatty liver disease or another chronic liver disease may have a higher risk of severe COVID-19 illness. Management of liver injury after COVID infection is supportive. Proactive vaccination may reduce the transmission of infection and the severity of the disease.

Citation: Bitar R, Elghoudi AA, Rawat D, Azaz A, Miqdady M, Narchi H. COVID-19-induced liver injury in infants, children, and adolescents. *World J Clin Pediatr* 2023; 12(3): 57-67

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/57.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.57>

INTRODUCTION

Coronavirus disease 2019 (COVID-19) typically presents with fever, weakness, myalgia, malaise, and pulmonary symptoms[1]. In addition, a significant percentage of those infected with the virus develop gut manifestations such as loss of appetite, colics, and loose stools[2]. Similarly, hepatic involvement has been reported in many studies[3,4]. Previous waves of the Middle East respiratory syndrome (MERS) have shown an association with elevated serum transaminases and bilirubin and concentrations with decreased serum albumin levels[5,6]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) shares up to 80% genomic sequence similarity with MERS and, consequently, hepatic injury is not an unexpected manifestation of COVID-19[7].

This review aims to describe liver injury in children with COVID-19, detailing its epidemiology, underlying mechanisms, clinical manifestations, management, and prognosis. We will also describe liver involvement in high-risk groups, including children with pre-existing liver disease.

EPIDEMIOLOGY

Acute liver injury in adults and children with SARS-CoV-2 infection is defined as an elevation in the serum concentration of aminotransferases (transaminases). The spectrum of liver injury ranges from asymptomatic elevated serum transaminase levels to severe liver injury, with reports of acute-on-chronic liver failure in patients with underlying liver disease. Usually, 14%-53% of adult patients develop mild to moderate elevation of liver enzymes[8,9].

Abnormal transaminase levels have also been linked to the severity of COVID-19[9-13]. Higher morbidity and mortality have been reported in those COVID-positive and altered liver function, with liver injury being an independent prognostic factor of COVID-19[14,15]. A review by Bende *et al*[15] of post-acute COVID-19 syndrome of 97 subjects demonstrated increased liver stiffness, viscosity, and steatosis in around one-third of the patients, worse in subjects with pulmonary injury compared to those without. COVID-19 in children and adolescents may be asymptomatic or cause only mild symptoms. These include fever, cough, upper respiratory tract symptoms, diarrhoea, nausea, and vomiting. In a multinational, multicentre cohort study, 22% of patients had gastrointestinal symptoms, of whom 7% had no respiratory symptoms[16]. In early pediatric reports, the rate of transaminase elevation was 14%-50%[12,17,18]. However, these data may not be representative because transaminase levels and liver function tests were only reported in a small proportion of patients. In a study involving 280 children ≤ 17 years of age with COVID-19, the elevation of serum transaminases was mild, with a prevalence of 29%, and predominantly children < 3 years of age[19]. Those with chronic liver diseases have developed more aggressive diseases with an increased risk of hepatic failure[20].

MECHANISMS OF LIVER INJURY

The causes of elevated liver transaminases in COVID-19 still need to be fully understood[21]. Some possible risk factors, illustrated in Figure 1, include:

Viral invasion of liver tissue

There is evidence that the virus infects the organ cells by exploiting the angiotensin-converting enzyme (ACE) 2 receptor, followed by intracellular replication. ACE2 receptors are found in the respiratory

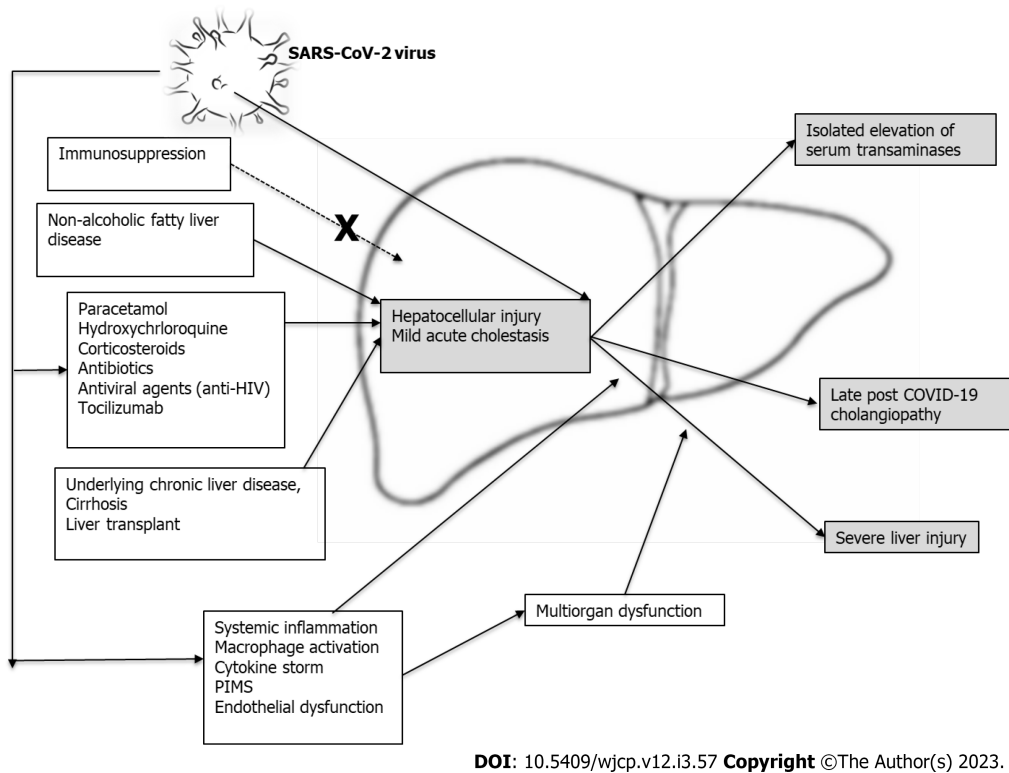


Figure 1 Mechanisms of liver injury in severe acute respiratory syndrome coronavirus 2 infections. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HIV: Human immunodeficiency virus.

tissues, gut, liver, kidney, and heart. However, compared to the viral load in the lungs of acutely infected children, the viral load in the hepatic cells was found to be low. Evidence of hepatic cell injury with a high level of serum transaminases has been found in > 70% of patients with severe COVID-19 disease[22,23]. Moreover, the virus has also been isolated from patients' stools, indicating that the infection spreads to the gastrointestinal tract and not exclusively the pulmonary cells[22,23]. This direct viral invasion of liver tissue and replication inside the hepatocytes can explain the resulting hepatic injury.

Medications

Another mechanism for liver injury associated with SARS-CoV-2 is the polypharmacy commonly used during COVID-19 illness. Antiviral drugs, antibiotics, and steroids used to treat moderate and severe COVID-19 may also cause liver toxicity in their own right[24,25]. Antipyretics, such as paracetamol, do not play a significant role in COVID-19 liver injury. Other drugs include chloroquine, isoniazid, antivirals, particularly anti-human immunodeficiency virus medications (lopinavir/ritonavir), and biological agents such as tocilizumab, which also be considered potential co-factors in the pathophysiology of liver injury in children with COVID-19[9,22,23]. In a study of 147 patients with COVID-19-induced liver injury treated as outpatients, the prevalence of hepatic injury was the same as in those with normal or impaired liver function. However, it was observed to be higher in those patients who received hospital care and with a higher rate of utilization of ritonavir[26].

The immune response

The resulting immune response is immature in infants and children with COVID-19 infection, and while it is mild in most patients, it can be severe. Hepatic injury caused by the SARS-CoV-2 virus in children is associated with systemic and local inflammatory responses of varying severity. During the acute stage of the infection, the immune system attempts to limit the reproduction of the virus through both immediate and delayed immune responses by producing specific antibodies against it. When exaggerated, this immune-mediated response can damage the hepatic tissue in children with more aggressive and prolonged disease[1]. The inflammatory markers such as cytokines, T helper 17 cells, cytotoxic DC8 T cells, interleukins 1, 2, and 6, serum ferritin, tumor necrosis factor, interferon, and other mediators[9], as well as C-reactive protein, are commonly elevated. In some patients, this may result in a "cytokine storm", leading to rapid clinical deterioration with multiple organ failure and endothelial dysfunction, further aggravating liver damage[2,26-32]. Endothelial dysfunction is associated with the stimulation of neutrophil extracellular traps through immunological mechanisms[19], causing the development of microthrombi in the lungs[33]. The liver is similarly affected, and hepatic damage may

be accelerated by a hypercoagulative disease state, which can involve other organs and tissues. Autopsy reports have confirmed the presence of hepatic sinusoidal congestion and micro thrombosis[20,27].

Acute liver injury is also a prominent feature of multi-system inflammatory diseases in children, occurring as a late complication of SARS-CoV-2 infection[34]. The exact mechanism still needs to be fully understood. Some researchers suggest an abnormal immune response to the SARS-CoV-2, similar to Kawasaki disease[35], or immunoglobulin G antibodies enhancement of monocytes and cytotoxic CD8+ T cells[8], with downregulation of neutrophil and lymphocyte functions[6,7]. The pediatric multi-system inflammatory syndrome temporally associated with COVID-19, also known as a multi-system inflammatory syndrome in children (MIS-C), is a persistent acute febrile illness progressing to multi-organ dysfunction, conferring over a 2-fold increased risk of elevated serum transaminases. Although affected children often have an underlying medical condition, such as obesity, immunocompromised state (including malignancy), or chronic liver disease (CLD)[36], it may also occur in previously healthy children and adolescents[37]. A few weeks after contracting SARS-CoV-2, affected children present with either a Kawasaki-like picture, shock, or macrophage activation syndrome, usually warranting admission to the pediatric intensive care unit (PICU). The clinical manifestations includes fever and multi-organ involvement, including gastrointestinal, cardiovascular, mucocutaneous, and neurological symptoms, with laboratory evidence of severe inflammatory activity and coagulopathy[38,39]. Although liver involvement is reported, it occurs as part of intense multi-organ involvement[24,25].

CLINICAL MANIFESTATIONS

Acute Manifestations

Liver injury in children infected with COVID-19 is suspected in the presence of elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels in 13% to 50% of patients[12,18,24,25,40]. AST levels > 50 UI/L are observed in 20%-50% of cases, and ALT levels > 45 UI/L in up to 35%[12,40]. Abnormal serum bilirubin levels may also occur but to a lesser extent than with transaminase. Raised alkaline phosphatase and gamma-glutamyl transferase levels are rarely observed. Liver injury is generally mild and resolves over time, with severe liver dysfunction being uncommon. Abnormal transaminase levels have also been linked to the severity of COVID-19, with liver injury occurring in 58.8% of patients with moderate and 66.7% of those with severe disease[10,11,41]. Other studies demonstrated elevated liver enzymes in 40%-60% of those with severe illness as compared to asymptomatic or patients with mild disease (18%-25%)[9,12,13]. In a meta-analysis and systematic review, significantly higher levels of aminotransferases and significantly lower albumin levels were more common in severe cases of COVID-19[42].

Severe acute liver injury

Severe acute liver injury, defined as serum ALT values five times above the upper limit of normal[9,36,43], is commonly associated with severe COVID-19 infection, shock, respiratory compromise, higher serum inflammatory markers, and longer overall length of stay in hospital[20]. However, acute liver failure (ALF) is rare and is more common in patients with severe illness and multi-organ dysfunction [20,22]. In one published case report, an early teenager died with acute fulminant hepatic failure secondary to COVID-19 infection. However, a similar child's life was saved with liver transplant (LT) [44,45].

Chronic manifestations

Post-COVID-19 cholangiopathy: This proliferative cholangiopathy is associated with lymphocytic portal and parenchymal infiltration, after excluding other possible causes such as adenovirus infection. It occurs at least several weeks after full recovery from asymptomatic or mild acute infection[40]. Two clinical patterns of presentations have been described: ALF in infants and acute hepatitis and cholestasis in older children. The group with hepatitis and cholestasis showed an excellent response to systemic steroids, while patients with ALF needed LT.

Secondary sclerosing cholangitis: Secondary sclerosing cholangitis (SSC) has been described in adults following COVID-19 as prolonged cholestasis with severe cholangiopathy. Unlike children, it occurs mainly in patients who have been through a complex and critical course of COVID-19 requiring admission to an intensive care unit (ICU), with a mean time of 118 d (range 138-319) between COVID-19 disease and the diagnosis of cholangiopathy. Compared to adults, ultrasound findings include strictures of intrahepatic bile ducts along with intraluminal sludging and casts formation[44,46]. Biliary duct dilatation, periportal and gallbladder wall oedema with thickening are more common in children.

Adult patients with post-COVID-19 cholangiopathy and SSC show progressive disease unresponsive to treatment with ursodiol therapy, with those most severely affected requiring LT. Corticosteroids, immunomodulators, or immunosuppressant therapies have not been studied in those patients.

Special considerations

Obesity and non-alcoholic fatty liver disease: In a meta-analysis of 285004 children infected with the novel virus, 9353 (3.3%) suffered from one or more comorbidities including obesity. Among 507 obese children, 64 had either severe COVID-19 or required ICU admission, with a calculated risk of severity of 2.87 (95%CI, 1.16-7.07)[46]. Obesity is thus the most common comorbidity reported in children with severe SARS-CoV-2 infection[20,47-50]. Although the proportion of patients with non-alcoholic fatty liver disease (NAFLD) in published obese cohorts remains unknown, children with NAFLD, especially those with obesity, should be considered a risk group for severe COVID-19[20].

Immunosuppressive therapy

The link between immune deficiency and severe gastrointestinal and liver involvement has not been proven[47,51,52]. Furthermore, some immunosuppressive medications even mitigate against severe COVID-19. These include calcineurin inhibitors, which potentially inhibit coronavirus replication[53]. European surveillance disproved any link between the use of calcineurin inhibitors and severe SARS-CoV-2 infections[54]. Moreover, drugs with antimetabolic activities such as mycophenolic acid have been reported, in laboratory studies, to interfere with the virus activity[55]. In addition, the regular use of immunosuppressants is not associated with a severe form of the disease[56,57]. In a study involving 180 children with an LT, 30 required non-ICU hospital admission (median 5 d) and three required ICU admission. However, none of them required inotropes or invasive ventilatory support[20]. Children on post-transplant immunosuppressive regimens have been shown to experience mild disease, similar to the general paediatric population[57-59].

MANAGEMENT

While liver involvement is commonly associated with COVID-19 infection in children, most children demonstrate mildly abnormal liver function, which usually normalises without any specific treatment [9].

Supportive therapy

Like most other viral illnesses with inflammatory liver involvement, the management of hepatic involvement with COVID-19 infection is supportive. It includes stabilisation of vital signs, fluid and electrolytes correction, and ensuring adequate liver oxygenation. Avoiding hypo-perfusion and hypoxia (especially in patients with respiratory distress) is essential. Liver recovery will likely be enhanced with the ongoing improvement of the systemic inflammatory status. Some patients might require poly-pharmacotherapy depending on the severity of their lung injury and the other organs involved. Avoidance of hepatotoxic medications is crucial. All specific virus-targeted therapies are still employed exclusively in clinical research trial settings[13].

Nutritional therapy

Nutrition is essential, especially in children with a prolonged critical illness. They are at higher risk of developing malnutrition, associated with increased morbidity and mortality. Hence, early oral or nasogastric tube feeding is recommended. It is preferred to parenteral nutrition, except in patients with severe gastrointestinal dysfunction. During the acute phase, the energy requirements do not need to exceed resting energy expenditure. Based on the tolerance and the patient's general condition, the European Society of Pediatric and Neonatal Intensive Care recommends a gradual increase toward the target caloric need. Enteral nutritional support must be maintained as long as required until adequate oral intake is reliably attained to support physical and nutritional rehabilitation[60,61].

Children with pre-existing CLD and LT recipients

Infected patients with underlying primary liver diseases and other metabolic liver diseases should continue to receive treatment for their underlying condition[9]. Elevated liver enzymes are not a reason to discontinue antiviral treatment as long as liver function is monitored[10]. Post-LT patients are advised to continue their immunosuppressants and modulator medications.

The COVID-19 pandemic has profoundly impacted transplantation worldwide, both donor's and recipients' viral transmission and healthcare resources[58]. There is no indication for delaying or interrupting oncological treatments, withdrawing immune suppression, or postponing any required treatments to those patients with liver-transplant[57].

PROGNOSIS

Mortality is higher in COVID-19 children with deranged hepatic function and the proportion of liver injury is directly related to the poor prognosis[14]. A literature review of 12 studies with a total of 6976

patients, whose laboratory tests were obtained at admission, showed high levels of transaminases and low albumin levels that were significantly more common in severe cases of COVID-19[42]. In a meta-analysis of 12 studies with a total of 5135 COVID-19 subjects with collected data on raised AST and outcomes, increased AST values were associated with three times higher risk of poor effects (pooled odds ratio: OR, 2.98; 95%CI, 2.35-3.77; $P < 0.00001$)[62]. Similarly, ten studies documented reported elevated ALT and outcomes, including 5091 patients, showed a marked increase in poor outcomes (pooled OR: 1.73; 95%CI: 1.32-2.27; $P < 0.0001$). Furthermore, a meta-analysis of four studies with a total sample size of 485 patients demonstrated that those with acute liver injury had higher odds of poor outcomes with a pooled OR of 1.68 (95%CI, 1.04-2.70; $P = 0.03$)[62].

Studies of COVID-19 outcomes among children with CLD are limited. Data from adult patients have reported mixed results and occasionally conflicting conclusions, making it difficult to determine a prognosis[63-65]. An earlier meta-analysis of 17 studies with a sample size of 8800 COVID-19 patients revealed that chronic liver disease did not significantly affect the outcomes (pooled OR, 0.96; 95%CI, 0.71-1.29; $P = 0.78$)[62]. A similar conclusion was also reached in a review where there were no major differences in COVID-19 severity and mortality between patients with liver disease and those without [66]. However, given the limitations of these studies, their results must be cautiously interpreted.

A more recent and comprehensive meta-analysis of 40 studies with 908032 participants concluded that CLD markedly affected clinical outcomes among COVID-19 patients[67]. For disease severity, the pooled OR was 2.44 with 95%CI of 1.89-3.16; for mortality, it was 2.35 (95%CI, 1.84-3.00). Subgroup analysis indicated that NAFLD, metabolic-associated fatty liver disease, and cirrhosis had the highest odd ratios of 5.6, 3.2, and 3.09 for COVID-19 severity. In other studies, cirrhosis was implicated as a significant risk factor for hospitalization, intensive care admission, and mortality. Mortality among cirrhotic patients was 32% compared to 8% among non-cirrhotic patients[68]. Other reports have also confirmed a higher risk of COVID-19 severity and mortality in CLD patients, up to four and two times, respectively, compared with those without CLD[62,69]. In children, a systematic review and meta-analysis inferred that those with COVID-19 have preserved effector and immunosuppressive components, and encountered a milder disease compared to adults[33].

Most children with MIS-C achieve full clinical recovery with a death rate of $< 1\%$. However, in those where the clinical course was severe and required intensive care interventions for ALF, the possibility of death was 11 times higher than in those without these complications[70].

PREVENTION

Preventative measures should be implemented for vulnerable patients at risk of exposure to SARS-CoV-2, as they may develop severe illness.

General public health measures

General measures for distancing, maintaining good hygiene and avoiding contamination with the virus are important for healthy children and the general public as well as for children with an underlying liver condition.

Vaccinations

Children suffering from CLD and/or LT are recommended to be administered the COVID-19 vaccination, which is generally safe in this group[71]. However, CLD among adults with non-cirrhotic compensated cirrhotic or decompensated cirrhotic was associated with lower rates of development of positive SARS-CoV-2 neutralizing antibodies compared with healthy individuals (77 vs 90 percent)[72]. Other studies suggested that patients with liver disease who received COVID-19 vaccination have a negligible risk of infection and COVID-19-associated mortality[73]. Likewise, children awaiting a LT also would need to be prioritized for receiving COVID-19 vaccine. The type of vaccine would depend on the active strain of the virus as well as the chance to choose from different vaccines as per the local infectious disease department recommendations and regardless of the time available prior to the transplant to allow the child to receive the 2 doses as in certain protocols[74]. Routine serology tests to check for the COVID-19 virus antibodies are not indicated[71].

CONCLUSION

The spectrum of liver injury in children with COVID-19 ranges from being asymptomatic with elevated serum transaminase levels to severe liver injury, with reports of acute-on-chronic liver failure in patients with underlying liver disease. The mechanism of liver injury is multifactorial. Most children demonstrate a mild self-resolving liver injury; the level of severity of the damage is linked to how severe the infection is with COVID-19 disease and is considered an independent prognostic factor. Treatment is supportive and LT is required only in very few patients. Children with underlying NAFLD and other

pre-existing chronic liver diseases carry a higher risk of developing severe COVID-19 illness and poor outcomes.

ACKNOWLEDGEMENTS

Thanks to Tasneem Abul Qasim, a senior librarian from the education department of SEHA, for her help and assistance with conducting the literature search.

FOOTNOTES

Author contributions: All the authors contributed equally to writing the manuscript and reviewing the final draft.

Conflict-of-interest statement: All authors have no conflicts of interest to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United Arab Emirates

ORCID number: Rana Bitar 0000-0002-2852-7707; Ahmed A Elghoudi 0000-0002-9078-6152; David Rawat 0000-0003-1788-8758; Amer Azaz 0000-0003-2303-0846; Mohamad Miqdady 0000-0001-9089-9424; Hassib Narchi 0000-0001-6258-2657.

S-Editor: Chang KL

L-Editor: A

P-Editor: Chang KL

REFERENCES

- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]
- Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020; **115**: 766-773 [PMID: 32287140 DOI: 10.14309/ajg.0000000000000620]
- Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. *J Hepatol* 2020; **73**: 1231-1240 [PMID: 32553666 DOI: 10.1016/j.jhep.2020.06.006]
- Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int* 2021; **41**: 20-32 [PMID: 33190346 DOI: 10.1111/liv.14730]
- Yang Z, Xu M, Yi JQ, Jia WD. Clinical characteristics and mechanism of liver damage in patients with severe acute respiratory syndrome. *Hepatobiliary Pancreat Dis Int* 2005; **4**: 60-63 [PMID: 15730921]
- Song JE, Kang MK, Lee YR, Lee CH, Park JG, Kweon YO, Tak WY, Park SY, Jang SY, Hwang JS, Jang BK, Jang WY, Suh JI, Chung WJ, Kim BS; Daegu-Gyeongbuk Liver Study Group (DGLSG). Multicenter Analysis of Clinical Features and Prognosis of COVID-19 Patients with Hepatic Impairment. *Gut Liver* 2021; **15**: 606-615 [PMID: 33782216 DOI: 10.5009/gnl20267]
- Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). *J Gen Intern Med* 2020; **35**: 1545-1549 [PMID: 32133578 DOI: 10.1007/s11606-020-05762-w]
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cockingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]
- Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]
- Huang W, Li C, Wang Z, Wang H, Zhou N, Jiang J, Ni L, Zhang XA, Wang DW. Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. *Sci China Life Sci* 2020; **63**: 1678-1687 [PMID: 32567003 DOI: 10.1007/s11427-020-1733-4]
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P,

- Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
- 12 Parri N, Lenge M, Buonsenso D; Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in Pediatric Emergency Departments in Italy. *N Engl J Med* 2020; **383**: 187-190 [PMID: 32356945 DOI: 10.1056/NEJMc2007617]
- 13 Calitri C, Fumi I, Ignaccolo MG, Banino E, Benetti S, Lupica MM, Fantone F, Pace M, Garofalo F. Gastrointestinal involvement in paediatric COVID-19 - from pathogenesis to clinical management: A comprehensive review. *World J Gastroenterol* 2021; **27**: 3303-3316 [PMID: 34163113 DOI: 10.3748/wjg.v27.i23.3303]
- 14 Chen LY, Chu HK, Bai T, Tu SJ, Wei Y, Li ZL, Hu LL, Zhu R, Zhang L, Han CQ, Xiao L, He Q, Song J, Liu WH, Zhu QJ, Chen H, Yang L, Hou XH. Liver damage at admission is an independent prognostic factor for COVID-19. *J Dig Dis* 2020; **21**: 512-518 [PMID: 32713118 DOI: 10.1111/1751-2980.12925]
- 15 Bende F, Tudoran C, Sporea I, Fofiu R, Bâldea V, Cotrău R, Popescu A, Sirli R, Ungureanu BS, Tudoran M. A Multidisciplinary Approach to Evaluate the Presence of Hepatic and Cardiac Abnormalities in Patients with Post-Acute COVID-19 Syndrome-A Pilot Study. *J Clin Med* 2021; **10** [PMID: 34204032 DOI: 10.3390/jcm10112507]
- 16 Göttinger F, Santiago-García B, Noguera-Julian A, Lanasa M, Lancelli L, Calò Carducci FI, Gabrovská N, Velizarova S, Prunk P, Osterman V, Krivec U, Lo Vecchio A, Shingadia D, Soriano-Arandes A, Melendo S, Lanari M, Pierantoni L, Wagner N, L'Huillier AG, Heining U, Ritz N, Bandi S, Krajcar N, Roglić S, Santos M, Christiaens C, Creuven M, Buonsenso D, Welch SB, Bogyi M, Brinkmann F, Tebruegge M; ptbnet COVID-19 Study Group. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health* 2020; **4**: 653-661 [PMID: 32593339 DOI: 10.1016/S2352-4642(20)30177-2]
- 17 Mansourian M, Ghandi Y, Habibi D, Mehrabi S. COVID-19 infection in children: A systematic review and meta-analysis of clinical features and laboratory findings. *Arch Pediatr* 2021; **28**: 242-248 [PMID: 33483192 DOI: 10.1016/j.arcped.2020.12.008]
- 18 Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, Zhang W, Wang Y, Bao S, Li Y, Wu C, Liu H, Liu D, Shao J, Peng X, Yang Y, Liu Z, Xiang Y, Zhang F, Silva RM, Pinkerton KE, Shen K, Xiao H, Xu S, Wong GWK; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 Infection in Children. *N Engl J Med* 2020; **382**: 1663-1665 [PMID: 32187458 DOI: 10.1056/NEJMc2005073]
- 19 Zhou YH, Zheng KI, Targher G, Byrne CD, Zheng MH. Abnormal liver enzymes in children and infants with COVID-19: A narrative review of case-series studies. *Pediatr Obes* 2020; **15**: e12723 [PMID: 32875680 DOI: 10.1111/ijpo.12723]
- 20 Nicastro E, Ebel NH, Kehar M, Czubkowski P, Ng VL, Michaels MG, Lobritto SJ, Martinez M, Indolfi G. The Impact of Severe Acute Respiratory Syndrome Coronavirus Type 2 on Children With Liver Diseases: A Joint European Society for Pediatric Gastroenterology, Hepatology and Nutrition and Society of Pediatric Liver Transplantation Position Paper. *J Pediatr Gastroenterol Nutr* 2022; **74**: 159-170 [PMID: 34694269 DOI: 10.1097/MPG.0000000000003339]
- 21 Anirvan P, Bharali P, Gogoi M, Thuluvath PJ, Singh SP, Satapathy SK. Liver injury in COVID-19: The hepatic aspect of the respiratory syndrome - what we know so far. *World J Hepatol* 2020; **12**: 1182-1197 [PMID: 33442447 DOI: 10.4254/wjh.v12.i12.1182]
- 22 Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol* 2020; **5**: 335-337 [PMID: 32087098 DOI: 10.1016/S2468-1253(20)30048-0]
- 23 Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, Lang C, Xiao Q, Xiao K, Yi Z, Qiang M, Xiang J, Zhang B, Chen Y. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). Cold Spring Harbor Laboratory 2020 [DOI: 10.1101/2020.02.10.20021832]
- 24 Ahmed J, Rizwan T, Malik F, Akhter R, Malik M, Ahmad J, Khan AW, Chaudhary MA, Usman MS. COVID-19 and Liver Injury: A Systematic Review and Meta-Analysis. *Cureus* 2020; **12**: e9424 [PMID: 32864250 DOI: 10.7759/cureus.9424]
- 25 Ali N, Hossain K. Liver injury in severe COVID-19 infection: current insights and challenges. *Expert Rev Gastroenterol Hepatol* 2020; **14**: 879-884 [PMID: 32649840 DOI: 10.1080/17474124.2020.1794812]
- 26 Li J, Fan JG. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. *J Clin Transl Hepatol* 2020; **8**: 13-17 [PMID: 32274341 DOI: 10.14218/JCTH.2020.00019]
- 27 Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, Zhang XJ, Cai J, Lin L, Ouyang S, Wang X, Yang C, Cheng X, Liu W, Li H, Xie J, Wu B, Luo H, Xiao F, Chen J, Tao L, Cheng G, She ZG, Zhou J, Wang H, Lin J, Luo P, Fu S, Ye P, Xiao B, Mao W, Liu L, Yan Y, Chen G, Huang X, Zhang BH, Yuan Y. Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China. *Hepatology* 2020; **72**: 389-398 [PMID: 32359177 DOI: 10.1002/hep.31301]
- 28 Li Y, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *J Med Virol* 2020; **92**: 1491-1494 [PMID: 32369204 DOI: 10.1002/jmv.25973]
- 29 Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front Immunol* 2020; **11**: 1708 [PMID: 32754163 DOI: 10.3389/fimmu.2020.01708]
- 30 Wang J, Lu Z, Jin M, Wang Y, Tian K, Xiao J, Cai Y, Zhang X, Chen T, Yao Z, Yang C, Deng R, Zhong Q, Deng X, Chen X, Yang XP, Wei G, Wang Z, Tian J, Chen XP. Clinical characteristics and risk factors of COVID-19 patients with chronic hepatitis B: a multi-center retrospective cohort study. *Front Med* 2022; **16**: 111-125 [PMID: 34387851 DOI: 10.1007/s11684-021-0854-5]
- 31 Wang M, Yan W, Qi W, Wu D, Zhu L, Li W, Wang X, Ma K, Ni M, Xu D, Wang H, Chen G, Yu H, Ding H, Xing M, Han M, Luo X, Chen T, Guo W, Xi D, Ning Q. Clinical characteristics and risk factors of liver injury in COVID-19: a retrospective cohort study from Wuhan, China. *Hepatol Int* 2020; **14**: 723-732 [PMID: 33026573 DOI: 10.1007/s12072-020-10075-5]
- 32 Debes JD, Anugwom CM, Aby ES. Systematic analysis of acute liver injury during SARS-CoV-2 infection. *Dig Liver Dis* 2020; **52**: 953-955 [PMID: 32487506 DOI: 10.1016/j.dld.2020.05.006]
- 33 Di Giorgio A, Hartleif S, Warner S, Kelly D. COVID-19 in Children With Liver Disease. *Front Pediatr* 2021; **9**: 616381 [PMID: 33777864 DOI: 10.3389/fped.2021.616381]

- 34 **Carter MJ**, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, Acors S, Graham C, Timms E, Kenny J, Neil S, Malim MH, Tibby SM, Shankar-Hari M. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med* 2020; **26**: 1701-1707 [PMID: [32812012](#) DOI: [10.1038/s41591-020-1054-6](#)]
- 35 **Lee PY**, Day-Lewis M, Henderson LA, Friedman KG, Lo J, Roberts JE, Lo MS, Platt CD, Chou J, Hoyt KJ, Baker AL, Banzon TM, Chang MH, Cohen E, de Ferranti SD, Dionne A, Habiballah S, Halyabar O, Hausmann JS, Hazen MM, Janssen E, Meidan E, Nelson RW, Nguyen AA, Sundel RP, Dedeoglu F, Nigrovic PA, Newburger JW, Son MBF. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. *J Clin Invest* 2020; **130**: 5942-5950 [PMID: [32701511](#) DOI: [10.1172/JCI141113](#)]
- 36 **Perez A**, Cantor A, Rudolph B, Miller J, Kogan-Liberman D, Gao Q, Da Silva B, Margolis KG, Ovchinsky N, Martinez M. Liver involvement in children with SARS-CoV-2 infection: Two distinct clinical phenotypes caused by the same virus. *Liver Int* 2021; **41**: 2068-2075 [PMID: [33826804](#) DOI: [10.1111/liv.14887](#)]
- 37 **Cavalcanti A**, Islabão A, Magalhães C, Veloso S, Lopes M, do Prado R, Aquilante B, Terrazas AM, Rezende MF, Clemente G, Terreri MT. Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): a Brazilian cohort. *Adv Rheumatol* 2022; **62**: 6 [PMID: [35189972](#) DOI: [10.1186/s42358-022-00237-4](#)]
- 38 **Whittaker E**, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, Ramnarayan P, Fraisse A, Miller O, Davies P, Kucera F, Brierley J, McDougall M, Carter M, Tremoulet A, Shimizu C, Herberg J, Burns JC, Lyall H, Levin M; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA* 2020; **324**: 259-269 [PMID: [32511692](#) DOI: [10.1001/jama.2020.10369](#)]
- 39 **Jenke A**, Steinmetz M. Paediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS) - a German single centre real-life evaluation of the Swiss and UK consensus statements. *Cardiol Young* 2022; 1-5 [PMID: [35546290](#) DOI: [10.1017/S1047951122001251](#)]
- 40 **Chiappini E**, Licari A, Motisi MA, Manti S, Marseglia GL, Galli L, Lionetti P. Gastrointestinal involvement in children with SARS-CoV-2 infection: An overview for the pediatrician. *Pediatr Allergy Immunol* 2020; **31** Suppl 26: 92-95 [PMID: [33236437](#) DOI: [10.1111/pai.13373](#)]
- 41 **Fan H**, Cai J, Tian A, Li Y, Yuan H, Jiang Z, Yu Y, Ruan L, Hu P, Yue M, Chen N, Li J, Zhu C. Comparison of Liver Biomarkers in 288 COVID-19 Patients: A Mono-Centric Study in the Early Phase of Pandemic. *Front Med (Lausanne)* 2020; **7**: 584888 [PMID: [33521010](#) DOI: [10.3389/fmed.2020.584888](#)]
- 42 **Abdulla S**, Hussain A, Azim D, Abdullah EH, Elawamy H, Nasim S, Kumar S, Naveed H. COVID-19-Induced Hepatic Injury: A Systematic Review and Meta-Analysis. *Cureus* 2020; **12**: e10923 [PMID: [33194489](#) DOI: [10.7759/cureus.10923](#)]
- 43 **Phipps MM**, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020; **72**: 807-817 [PMID: [32473607](#) DOI: [10.1002/hep.31404](#)]
- 44 **Haji Esmail Memar E**, Mamishi S, Sharifzadeh Ekbatani M, Alimadadi H, Yaghmaei B, Chegini V, Janani S, Mahmoudi S. Fulminant hepatic failure: A rare and devastating manifestation of Coronavirus disease 2019 in an 11-year-old boy. *Arch Pediatr* 2020; **27**: 502-505 [PMID: [33069564](#) DOI: [10.1016/j.arcped.2020.09.009](#)]
- 45 **Yohanathan L**, Campioli CC, Mousa OY, Watt K, Friedman DZP, Shah V, Ramkissoon R, Hines AS, Kamath PS, Razonable RR, Badley AD, DeMartino ES, Joyner MJ, Graham R, Vergidis P, Simonetto DA, Sanchez W, Taner T, Heimbach JK, Beam E, Leise MD. Liver transplantation for acute liver failure in a SARS-CoV-2 PCR-positive patient. *Am J Transplant* 2021; **21**: 2890-2894 [PMID: [33792185](#) DOI: [10.1111/ajt.16582](#)]
- 46 **Tsankov BK**, Allaire JM, Irvine MA, Lopez AA, Sauvé LJ, Vallance BA, Jacobson K. Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis. *Int J Infect Dis* 2021; **103**: 246-256 [PMID: [33227520](#) DOI: [10.1016/j.ijid.2020.11.163](#)]
- 47 **Kehar M**, Ebel NH, Ng VL, Baquero JER, Leung DH, Slowik V, Ovchinsky N, Shah AA, Arnon R, Miloh T, Gupta N, Mohammad S, Kogan-Liberman D, Squires JE, Sanchez MC, Hildreth A, Book L, Chu C, Alrabadi L, Azzam R, Chepuri B, Elisofon S, Falik R, Gallagher L, Kader H, Mogul D, Mujawar Q, Namjoshi SS, Valentino PL, Vitola B, Waheed N, Zheng MH, Lobritto S, Martinez M. Severe Acute Respiratory Syndrome Coronavirus-2 Infection in Children With Liver Transplant and Native Liver Disease: An International Observational Registry Study. *J Pediatr Gastroenterol Nutr* 2021; **72**: 807-814 [PMID: [33605666](#) DOI: [10.1097/MPG.0000000000003077](#)]
- 48 **Gao F**, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, Chen YP, Targher G, Byrne CD, George J, Zheng MH. Obesity Is a Risk Factor for Greater COVID-19 Severity. *Diabetes Care* 2020; **43**: e72-e74 [PMID: [32409499](#) DOI: [10.2337/dc20-0682](#)]
- 49 **Zachariah P**, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A, Banker SL, Giordano M, Manice CS, Diamond R, Sewell TB, Schweickert AJ, Babineau JR, Carter RC, Fenster DB, Orange JS, McCann TA, Kernie SG, Saiman L; Columbia Pediatric COVID-19 Management Group. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. *JAMA Pediatr* 2020; **174**: e202430 [PMID: [32492092](#) DOI: [10.1001/jamapediatrics.2020.2430](#)]
- 50 **Korakas E**, Ikonomidis I, Kousathana F, Balampanis K, Kountouri A, Raptis A, Palaodimou L, Kokkinos A, Lambadiari V. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. *Am J Physiol Endocrinol Metab* 2020; **319**: E105-E109 [PMID: [32459524](#) DOI: [10.1152/ajpendo.00198.2020](#)]
- 51 **Kates OS**, Haydel BM, Florman SS, Rana MM, Chaudhry ZS, Ramesh MS, Safa K, Kotton CN, Blumberg EA, Besharatian BD, Tanna SD, Ison MG, Malinis M, Azar MM, Rakita RM, Morilla JA, Majeed A, Sait AS, Spaggiari M, Hemmige V, Mehta SA, Neumann H, Badami A, Goldman JD, Lala A, Hemmersbach-Miller M, McCort ME, Bajrovic V, Ortiz-Bautista C, Friedman-Moraco R, Sehgal S, Lease ED, Fisher CE, Limaye AP; UW COVID-19 SOT Study Team. Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study. *Clin Infect Dis* 2021; **73**: e4090-e4099 [PMID: [32766815](#) DOI: [10.1093/cid/ciaa1097](#)]
- 52 **Webb GJ**, Marjot T, Cook JA, Aloman C, Armstrong MJ, Brenner EJ, Catana MA, Cargill T, Dhanasekaran R, Garcia-

- Juárez I, Hagström H, Kennedy JM, Marshall A, Masson S, Mercer CJ, Perumalswami PV, Ruiz I, Thaker S, Ufere NN, Barnes E, Barritt AS 4th, Moon AM. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. *Lancet Gastroenterol Hepatol* 2020; **5**: 1008-1016 [PMID: 32866433 DOI: 10.1016/S2468-1253(20)30271-5]
- 53 **Carbajo-Lozoya J**, Müller MA, Kallies S, Thiel V, Drosten C, von Brunn A. Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506. *Virus Res* 2012; **165**: 112-117 [PMID: 22349148 DOI: 10.1016/j.virusres.2012.02.002]
- 54 **Belli LS**, Fondevila C, Cortesi PA, Conti S, Karam V, Adam R, Coilly A, Ericzon BG, Loinaz C, Cuervas-Mons V, Zambelli M, Llado L, Diaz-Fontenla F, Invernizzi F, Patrono D, Faitot F, Bhooori S, Pirenne J, Perricone G, Magini G, Castells L, Detry O, Cruchaga PM, Colmenero J, Berrevoet F, Rodriguez G, Ysebaert D, Radenne S, Metselaar H, Morelli C, De Carlis LG, Polak WG, Duvoux C; ELITA-ELTR COVID-19 Registry. Protective Role of Tacrolimus, Deleterious Role of Age and Comorbidities in Liver Transplant Recipients With Covid-19: Results From the ELITA/ELTR Multi-center European Study. *Gastroenterology* 2021; **160**: 1151-1163.e3 [PMID: 33307029 DOI: 10.1053/j.gastro.2020.11.045]
- 55 **Schoot TS**, Kerckhoffs APM, Hilbrands LB, van Marum RJ. Immunosuppressive Drugs and COVID-19: A Review. *Front Pharmacol* 2020; **11**: 1333 [PMID: 32982743 DOI: 10.3389/fphar.2020.01333]
- 56 **Nicastro E**, Di Giorgio A, Zambelli M, Ginammi M, Bravi M, Stroppa P, Casotti V, Palladino R, Colledan M, D'Antiga L. Impact of the Severe Acute Respiratory Syndrome Coronavirus 2 Outbreak on Pediatric Liver Transplant Recipients in Lombardy, Northern Italy. *Liver Transpl* 2020; **26**: 1359-1362 [PMID: 32614988 DOI: 10.1002/lt.25840]
- 57 **D'Antiga L**. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl* 2020; **26**: 832-834 [PMID: 32196933 DOI: 10.1002/lt.25756]
- 58 **Donà J**, Torres Canizales J, Benetti E, Cananzi M, De Corti F, Calore E, Hierro L, Ramos Boluda E, Melgosa Hijosa M, García Guereta L, Pérez Martínez A, Barrios M, Costa Reis P, Teixeira A, Lopes MF, Kaliciński P, Branchereau S, Boyer O, Debray D, Sciveres M, Wennberg L, Fischler B, Barany P, Baker A, Baumann U, Schwerk N, Nicastro E, Candusso M, Toporski J, Sokal E, Stephenne X, Lindemans C, Miglinas M, Rascon J, Jara P; ERN TransplantChild. Pediatric transplantation in Europe during the COVID-19 pandemic: Early impact on activity and healthcare. *Clin Transplant* 2020; **34**: e14063 [PMID: 32786120 DOI: 10.1111/ctr.14063]
- 59 **Nikoupour H**, Kazemi K, Arasteh P, Ghazimoghadam S, Eghlimi H, Dara N, Gholami S, Nikeghbalian S. Pediatric liver transplantation and COVID-19: a case report. *BMC Surg* 2020; **20**: 224 [PMID: 33023552 DOI: 10.1186/s12893-020-00878-6]
- 60 **Oba J**, Carvalho WB, Silva CA, Delgado AF. Gastrointestinal manifestations and nutritional therapy during COVID-19 pandemic: a practical guide for pediatricians. *Einstein (Sao Paulo)* 2020; **18**: eRW5774 [PMID: 32667418 DOI: 10.31744/einstein_journal/2020rw5774]
- 61 **Tume LN**, Valla FV, Joosten K, Jotterand Chaparro C, Latten L, Marino LV, Macleod I, Moullet C, Pathan N, Rooze S, van Rosmalen J, Verbruggen SCAT. Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) metabolism, endocrine and nutrition section position statement and clinical recommendations. *Intensive Care Med* 2020; **46**: 411-425 [PMID: 32077997 DOI: 10.1007/s00134-019-05922-5]
- 62 **Sharma A**, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, Honganur NS, Akbar A, Deol A, Francis B, Patel S, Mehta D, Jaiswal R, Singh J, Patel U, Malik P. Liver disease and outcomes among COVID-19 hospitalized patients - A systematic review and meta-analysis. *Ann Hepatol* 2021; **21**: 100273 [PMID: 33075578 DOI: 10.1016/j.aohp.2020.10.001]
- 63 **Bajaj JS**, Garcia-Tsao G, Biggins SW, Kamath PS, Wong F, McGeorge S, Shaw J, Pearson M, Chew M, Fagan A, de la Rosa Rodríguez R, Worthington J, Olofson A, Weir V, Trisolini C, Dwyer S, Reddy KR. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. *Gut* 2021; **70**: 531-536 [PMID: 32660964 DOI: 10.1136/gutjnl-2020-322118]
- 64 **Frager SZ**, Szymanski J, Schwartz JM, Massoumi HS, Kinkhabwala M, Wolkoff AW. Hepatic Predictors of Mortality in Severe Acute Respiratory Syndrome Coronavirus 2: Role of Initial Aspartate Aminotransferase/Alanine Aminotransferase and Preexisting Cirrhosis. *Hepatol Commun* 2021; **5**: 424-433 [PMID: 33681677 DOI: 10.1002/hep4.1648]
- 65 . Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1295 [PMID: 32234718 DOI: 10.1136/bmj.m1295]
- 66 **Lippi G**, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. *Eur J Gastroenterol Hepatol* 2021; **33**: 114-115 [PMID: 32282549 DOI: 10.1097/MEG.0000000000001742]
- 67 **Nagarajan R**, Krishnamoorthy Y, Rajaa S, Hariharan VS. COVID-19 Severity and Mortality Among Chronic Liver Disease Patients: A Systematic Review and Meta-Analysis. *Prev Chronic Dis* 2022; **19**: E53 [PMID: 36007255 DOI: 10.5888/pcd19.210228]
- 68 **Marjot T**, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: 33035628 DOI: 10.1016/j.jhep.2020.09.024]
- 69 **Wu ZH**, Yang DL. A meta-analysis of the impact of COVID-19 on liver dysfunction. *Eur J Med Res* 2020; **25**: 54 [PMID: 33148326 DOI: 10.1186/s40001-020-00454-x]
- 70 **Center for Disease Control and Prevention**. Center for Preparedness and Response: Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19), Clinician Outreach and Communication (Coca) Webinar. [cited 19 May 2020]. Available from: https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp?deliveryName=USCDC_1052-DM28623
- 71 **Fix OK**, Blumberg EA, Chang KM, Chu J, Chung RT, Goacher EK, Hameed B, Kaul DR, Kulik LM, Kwok RM, McGuire BM, Mulligan DC, Price JC, Reau NS, Reddy KR, Reynolds A, Rosen HR, Russo MW, Schilsky ML, Verna EC, Ward JW, Fontana RJ; AASLD COVID-19 Vaccine Working Group. American Association for the Study of Liver

- Diseases Expert Panel Consensus Statement: Vaccines to Prevent Coronavirus Disease 2019 Infection in Patients With Liver Disease. *Hepatology* 2021; **74**: 1049-1064 [PMID: [33577086](#) DOI: [10.1002/hep.31751](#)]
- 72 **Ai J**, Wang J, Liu D, Xiang H, Guo Y, Lv J, Zhang Q, Li J, Zhang X, Li Q, Liang J, Guo X, Feng Y, Liu L, Qin W, Wang X, Rao W, Tian Q, Zhang Y, Xie F, Jiang S, Yan Y, Qiu Y, Wu H, Hou Z, Zhang N, Zhang A, Ji J, Yang J, Huang J, Zhao Z, Gu Y, Bian L, Zhang Z, Zou S, Ji H, Ge G, Du X, Hou A, Zhu Y, Cong Q, Xu J, Zu H, Wang Y, Yan Z, Yan X, Bian Ba Y, Ci Q, Zhang L, Yang S, Gao X, Zhong L, He S, Liu C, Huang Y, Liu Y, Xu D, Zhu Q, Xu X, Lv M, Zhang W, Qi X. Safety and Immunogenicity of SARS-CoV-2 Vaccines in Patients With Chronic Liver Diseases (CHESS-NMCID 2101): A Multicenter Study. *Clin Gastroenterol Hepatol* 2022; **20**: 1516-1524.e2 [PMID: [34942370](#) DOI: [10.1016/j.cgh.2021.12.022](#)]
- 73 **Bondarev VN**, Lakotkina EA, Gorvat NA. [Some data on the incidence of allergic reactions and the course of vaccinal process in healthy children and in those with reactivity changes]. *Pediatrics* 1971; **50**: 15-17 [PMID: [4254978](#) DOI: [10.1001/jamainternmed.2021.4325](#)]
- 74 **Polack FP**, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**: 2603-2615 [PMID: [33301246](#) DOI: [10.1056/NEJMoa2034577](#)]



Hirschsprung's disease associated enterocolitis: A comprehensive review

Eric M Gershon, Leonel Rodriguez, Ricardo A Arbizu

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Lourencao P, Brazil; Sergi CM, Canada

Received: December 29, 2022

Peer-review started: December 29, 2022

First decision: January 31, 2023

Revised: February 9, 2023

Accepted: March 21, 2023

Article in press: March 21, 2023

Published online: June 9, 2023



Eric M Gershon, Leonel Rodriguez, Ricardo A Arbizu, Section of Pediatric Gastroenterology, Yale University School of Medicine, New Haven, CT 06520, United States

Corresponding author: Ricardo A Arbizu, MD, MS, Assistant Professor, Section of Pediatric Gastroenterology, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06520, United States. ricardo.arbizu@yale.edu

Abstract

Hirschsprung's disease (HSCR) is a congenital disorder characterized by failure of the neural crest cells to migrate and populate the distal bowel during gestation affecting different lengths of intestine leading to a distal functional obstruction. Surgical treatment is needed to correct HSCR once the diagnosis is confirmed by demonstrating the absence of ganglion cells or aganglionosis of the affected bowel segment. Hirschsprung's disease associated enterocolitis (HAEC) is an inflammatory complication associated with HSCR that can present either in the pre- or postoperative period and associated with increased morbidity and mortality. The pathogenesis of HAEC remains poorly understood, but intestinal dysmotility, dysbiosis and impaired mucosal defense and intestinal barrier function appear to play a significant role. There is no clear definition for HAEC, but the diagnosis is primarily clinical, and treatment is guided based on severity. Here, we aim to provide a comprehensive review of the clinical presentation, etiology, pathophysiology, and current therapeutic options for HAEC.

Key Words: Hirschsprung's; Enterocolitis; Pathogenesis; Microbiome; Dysbiosis; Dysmotility; Treatment

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Hirschsprung's disease associated enterocolitis (HAEC) is an inflammatory complication of Hirschsprung's disease (HSCR) with variable degrees of severity. It is important for pediatric providers to be aware of the signs and symptoms of HAEC as it can affect patients before or after corrective surgery. The pathogenesis of HAEC is multifactorial and previous and ongoing studies continue to improve our knowledge of this potentially fatal complication of HSCR and will ultimately allow clinicians to provide personalized care for these patients. In the meantime, current preventive measures and treatment guidelines have helped decrease the morbidity and mortality associated with HAEC.

Citation: Gershon EM, Rodriguez L, Arbizu RA. Hirschsprung's disease associated enterocolitis: A comprehensive review. *World J Clin Pediatr* 2023; 12(3): 68-76

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/68.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.68>

INTRODUCTION

Hirschsprung's Disease (HSCR) is an intestinal motor disorder caused by failure of neural crest cells (precursors of intestinal ganglion cells) to migrate completely during intestinal development. The aganglionic segment of bowel with impaired relaxation leads to a functional obstruction and symptoms [1]. In healthy children, craniocaudal migration of neural crest cells commence at 4 wk gestation and finishes at 7 wk, but the true etiology of this failure of migration in HSCR is unknown. However, theories include premature differentiation of neural crest cells leading to lack of further migration and local ganglion cell destruction [1].

The incidence of HSCR ranges from 1 in 3500 to 5000 live births [2] and has a male predominance with a male to female ratio of 4:1 [3]. The extent of aganglionosis varies from short-segment disease comprising the recto-sigmoid (75%-80% of cases), to total colonic aganglionosis (5%-7% of cases). Ten to 15% of cases, referred to as long-segment disease, display aganglionosis proximal to the sigmoid colon [4]. Common presentations of HSCR vary depending on several factors, mainly the length of the affected colonic segment. These include symptoms and signs of neonatal distal intestinal obstruction: Abdominal distension, bilious vomiting, failure to pass meconium and explosive stools [4]. Screening modalities for HSCR include contrast enema (demonstrating a dilated colon, transition zone, or abnormal recto-sigmoid ratio), and anorectal manometry (to assess for the presence of a recto-anal inhibitory reflex) and when abnormal, a suction or full thickness rectal biopsy confirms the diagnosis by demonstrating absence of ganglion cells (aganglionosis) [4]. Treatment for HSCR is primarily limited to surgical resection of affected segment, or pull-through procedure, where innervated bowel is reconnected to the anus while attempting to preserve anal sphincter function [4]. Although most patients have normal quality of life and bowel function after surgery, some will have ongoing obstructive symptoms [5] like abdominal distension, chronic constipation, and intestinal inflammation or Hirschsprung's disease associated enterocolitis (HAEC) which is considered one of the most fatal complications in patients with HSCR. In this review, we will discuss the clinical presentation, etiology, pathophysiology, and current therapeutic options for HAEC (Figure 1) and discuss the future directions for the evaluation and management of this condition that is still encountered in patients with HSCR.

HIRSCHSPRUNG'S DISEASE ASSOCIATED ENTEROCOLITIS

HAEC is a severe and potentially lethal complication of HSCR. HAEC can have a variable clinical presentation but is classically manifested as fever, lethargy, abdominal distention, foul-smelling and explosive diarrhea [6]. This condition can occur both pre- and postoperatively with varying reported incidence. Preoperative incidence is estimated between 6%-60% while the postoperative incidence is estimated between 25-42% [6]. Mortality associated with HAEC ranges between 5%-50%, with higher prevalence in the neonatal period prior to definitive surgical correction [7]. Nevertheless, mortality rates have continued to decline to less than 1% due to advances in surgical technique and medical care [3]. HAEC has also been reported as the presenting symptom of HSCR in up to 25% of infants [8]. HAEC can also present with bowel perforation in the neonatal period documented as occurring in 3%-6% of HSCR patients [9-11]. In a retrospective analysis of complications in patients awaiting definitive surgical correction for HSCR, bowel perforation was noted as the most common complication (7% of total patients analyzed) [12]. Theories for perforation as a presentation in HSCR include increased luminal pressure, transmural inflammation and vascular accidents leading to ischemia and subsequently perforation. Zhu *et al* [13] performed a retrospective review looking at risk factors for perforated HSCR in neonates. They noted that most perforations occurred at the proximal ganglionic bowel (71%) as opposed to the transition zone or aganglionic bowel and that perforation was more common with

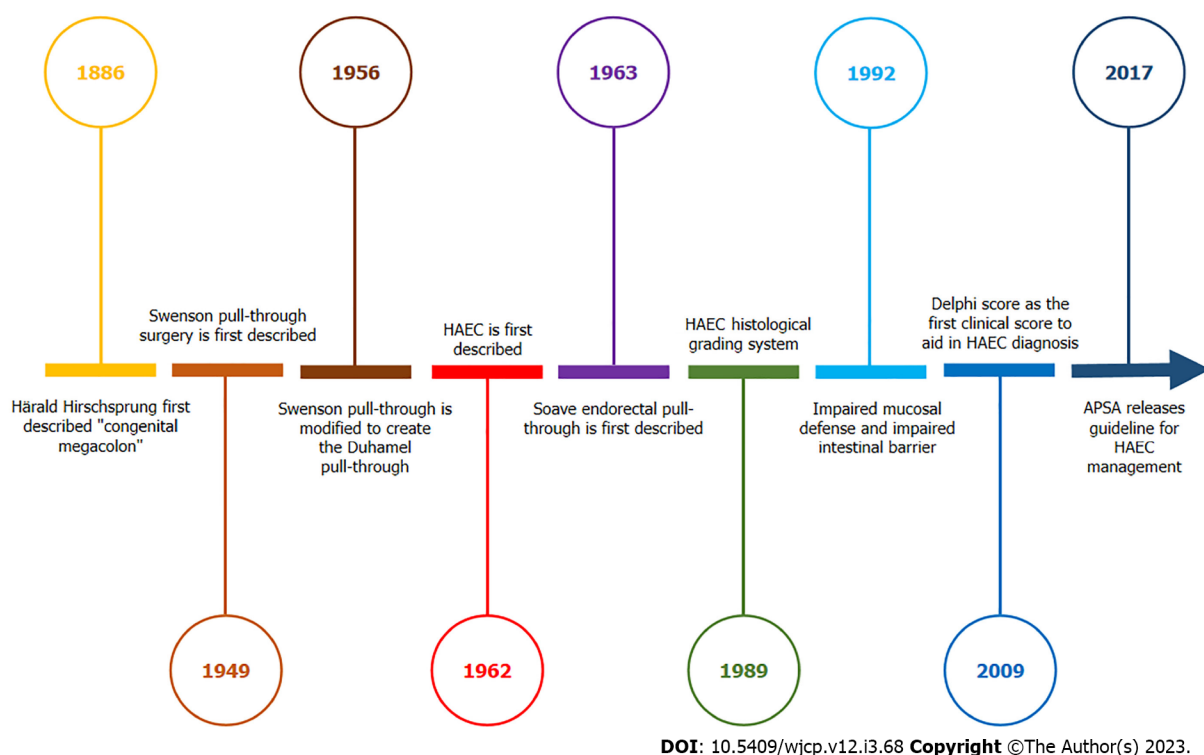


Figure 1 Timeline graphic illustrating pivotal definitions, surgical treatment, and management guideline for Hirschsprung's disease associated enterocolitis. HAEC: Hirschsprung's disease associated enterocolitis.

higher grade inflammation of the bowel wall. They demonstrated that laboratory studies and bowel histopathologic changes in patients with perforated HSCR were similar to those found in HAEC, thus illustrating a potential association between the two.

The variety of presenting symptomatology of HAEC leads to difficulty in making the diagnosis and there is no standardized definition of HAEC. However, several groups have tried to establish a scoring system to standardize the diagnosis. Notably in 2009, an expert panel used the Delphi method to achieve a consensus of 18 items present in patient history, physical exam, laboratory and imaging findings to aid in the diagnosis of HAEC[14]. A score of 10 or more indicated a diagnosis of HAEC, with equal weight given to all factors other than diarrhea with explosive stool, diarrhea with foul-smelling stool, explosive discharge of stool on rectal exam, and distended abdomen which were weighted more heavily in support of the diagnosis. These criteria, while expansive, had limited validation and have been used more in research studies rather than in clinical practice[15]. In 2018, Frykman *et al*[16] performed a multicenter retrospective review to optimize the sensitivity and specificity of the Delphi score. In this study, they found that lowering the score threshold for diagnosis from 10 to 4 optimized sensitivity and specificity (83.7% and 98.6%, respectively). Most recently, Lewit *et al*[15] performed a multicenter data collection and used multivariate analysis to create a new scoring system limited to fever, bloody diarrhea, leukocytosis, obstipation, distention, and dilated loops of bowel in x-ray. This score seemed to outperform both the Delphi and Frykman scores due to its higher sensitivity. Finally, while not including a scoring system, the American Pediatric Surgery Association (APSA) released its guidelines in 2017 to aid in the diagnosis of this variably presenting complication of HSCR. This system places patient presentations into three categories (possible, definite, and severe) based off patient history, physical exam, and imaging studies. The goal of this system was to create an easily used yet clinically relevant grade to help provide consistency in therapy[17].

Histopathology

In 1989, Teitelbaum *et al*[18] described a grading system based on the histological intestinal mucosal changes found in HAEC. They included factors such as intestinal crypt dilation, cryptitis, mucin retention, crypt abscess, mucosal ulceration, and necrosis and proposed a classification system of 5 grades with increasing severity of disease, with grade 0 being normal mucosa and grade 5 being the most severe. They reported a significant correlation between clinically apparent HAEC and histopathologic scores of grade 3 and above. This grading system has persisted and is still used for both clinical and research purposes.

Predisposing risk factors for HAEC

There are several known risk factors for developing HAEC and can be subdivided into preoperative and postoperative. Commonly reported preoperative risk factors include a family history of HSCR, long-segment disease, trisomy 21, presence of associated congenital anomalies, and delay in diagnosis of HSCR[19]. Engum *et al*[20] reported a series of 20 infants and children with history of HSCR and found that the incidence of HAEC was more than double in patients with family history of HSCR (35% *vs* 16%). The reason for this increased risk is thought to be secondary to heritable factors. Trisomy 21 is one of the best-established clinical risk factors conveying a risk as high as 54% of HAEC[19,21] and hypothesized to be due to an intrinsically decreased humoral and cytotoxic T-cell function present in infants with this syndrome[22]. Long-segment disease has also shown to confer larger risk of HAEC, thought to be secondary to increased stasis of luminal contents[19]. Several reports have demonstrated an increased rate of HAEC, as high as 56%, in patients with long-segment disease[23,24]. Finally, delay in diagnosis in the newborn period also seems to be a significant risk factor for HAEC. Lee *et al*[25] performed a retrospective review of 51 newborns diagnosed with HSCR and found a preoperative incidence of 63% of HAEC in patients diagnosed after 7 days of life compared to 12% in those diagnosed before 7 days. They also noted a significant increase in morbidity after HAEC in the late diagnosis group including increased risk of developing postoperative adhesive bowel obstruction and failure to thrive.

Postoperative risk factors for HAEC can be subdivided into histopathologic and mechanical. Histologically, the presence of a segment of aganglionic bowel after definitive surgery is a risk factor for HAEC. This can be seen if there is residual disease after surgery, if an area of bowel becomes aganglionic due to degenerative changes in the bowel after surgery, if a skip area was present where an unknown proximal portion of bowel was also aganglionic, or if the transition zone between normal and aganglionic bowel is not entirely resected[26]. Mechanical predisposing risk factors include bowel torsion proximal to the anastomosis site and formation of an anastomotic stricture or cuff stenosis on the pulled-through segment of normal bowel. Overall, the common premise uniting these risk factors for postoperative HAEC are mechanisms that affect the motility or produce a functional obstruction of the pulled-through bowel. Other clinical risk factors that have been investigated during the postoperative period include a history of preoperative episodes of HAEC and definitive surgery before age of 6 mo[27,28]. Additionally, socioeconomic risk factors for the development of HAEC have been identified. In a study of 100 children awaiting surgical correction for HSCR, the authors found that patients that used public transportation for clinic visits, had one or more missed appointments, had any reported safety concerns, had parents or guardians who were not married, lived with people other than their immediate family, or had mothers who reported drug use or lack of prenatal care were found to have a higher likelihood of developing HAEC[29].

Pathophysiology

The exact mechanism underlying HAEC remains unknown. However, there has been significant progress in our understanding of the pathogenesis of this disorder and studies underscore the potential role of the following pathways:

Intestinal dysmotility: Impaired intestinal motility affecting the aganglionic segment was one of the earliest described mechanisms causing HAEC. However, ongoing dilation of the proximal ganglionated bowel leading to fecal stasis, bacterial translocation and ischemia was later proposed as a cause for HAEC. Nevertheless, HAEC still develops after surgical correction or in the presence of a diverting ostomy in some patients suggestive of an intrinsic defect at the level of the enteric nervous system leading to dysmotility. Several HSCR mouse model studies have demonstrated a decrease in neuronal cell density at the level of the proximal ganglionated bowel[30] and alteration in the balance of local cholinergic and nitrergic neurons[31], with overrepresentation of the latter which are involved in intestinal relaxation. These findings were later corroborated in a human study and most importantly, demonstrated a possible correlation with clinical outcomes[32]. In contrary, a retrospective study in humans concluded that in HSCR patients with a low mucosal nerve fiber innervation grade in the distal aganglionic bowel have a higher risk of developing HAEC[33]. Similarly, a prospective study also demonstrated that lack of cholinergic innervation in the distal colon of HSCR patients was associated with increased risk of postoperative HAEC[34].

Impaired mucosal defense and intestinal barrier function: One of the initial studies implicating impaired mucosal defense in HSCR evaluated the role of secretory immunoglobulin A (sIgA). The authors found that the transfer of sIgA across the gastrointestinal wall is impaired in patients with HSCR (despite increased sIgA levels in the lamina propria plasma cells) and decreased in those with HAEC[35]. Other studies have suggested that the production and transport of intestinal mucins may be abnormal in HSCR and may have a potential role in the pathogenesis of HAEC[36,37]. Of these, MUC-2 is the predominant mucin expressed in humans and *in vitro* studies have demonstrated that it can prevent bacterial translocation across the intestinal wall[38]. A study that analyzed stool samples in humans found that the protein expression of MUC-2 was significantly decreased in patients with HSCR when compared to controls and absent in those with clinical features of HAEC[39]. Interestingly, studies

in a HSCR mouse model demonstrated an increase in goblet cell proliferation and differentiation in areas of aganglionosis, and subsequent altered surface mucus properties prior to the development of inflammation in the distal colon epithelium in HAEC[40]. Other studies of the caudal type homeobox gene-1 and -2 (CDX-1 and CDX-2) that control proliferation and differentiation of intestinal mucosal cells[41], intracellular adhesion molecule-1 (ICAM-1) a cell surface adhesion glycoprotein involved in leukocyte recruitment[42], and caveolin-1 involved in inflammation and intestinal epithelial barrier function[43], have shown altered gene expression in the colonic mucosal epithelium of patients with HAEC.

Dysbiosis: Emerging techniques, like next generation sequencing, have provided novel insight of the human intestinal microbiota, both in health and disease. Animal and human studies have demonstrated that the microbiota composition and diversity are different between controls, HSCR and HAEC. However, most are limited to a small number of samples or differences in technique that demonstrate variation in results. Nevertheless, it seems evident that dysbiosis is part of the pathogenesis in HAEC. A study by Frykman *et al*[44] evaluated the intestinal microbiota in fecal samples of HSCR patients with and without HAEC. By using DNA sequencing they demonstrated that not only the bacterial, but also the fungal composition was different in children with HAEC compared to those without HAEC. The authors found modest reductions in Firmicutes and Verrucomicrobia and increases in Bacteroidetes and Proteobacteria. Varieties of fungi were also observed. Specifically, *Candida* was increased and *Malassezia* and *Saccharomyces* were reduced[44]. Li *et al*[45] collected fecal samples from the proximal and distal colon during routine or emergency surgery in patients with HSCR, prior history of HAEC, and active HAEC and found a predominance of Bacteroidetes in the first group and of Proteobacteria the latter groups. Interestingly, these changes persisted in patients with HAEC and the microbiota composition was different between the proximal and distal colon sites in HSCR patients, but not in those with a prior history or active HAEC. More recently, Parker *et al*[46] demonstrated longitudinal changes in the intestinal microbiota from fecal samples of HSCR patients with active enterocolitis and demonstrated composition similarity in patients that achieved remission (also enrichment with *Blautia*), while patients with recurrent HAEC demonstrated ongoing substantial variability in their microbiota composition. We have demonstrated that the microbiota composition and diversity is different between patients with and without a history of postoperative HAEC by 16S rDNA sequencing of colon tissue samples. Specifically, we reported an increased relative abundance of the phyla Bacteroidetes, Firmicutes and Cyanobacteria in HAEC patients and Fusobacteria, Actinobacteria and Proteobacteria in HSCR patients and an increased relative abundance of the genera *Dolosigranulum*, *Roseouria* and *Streptococcus* in HAEC patients and *Propionibacterium* and *Delftia* in HSCR patients[47]. These findings highlight that changes in the intestinal microbiota composition and diversity can be seen both in the intestinal lumen and the bowel wall in HSCR patients with and without HAEC.

Treatment

There are several treatment modalities utilized in the care of patients with HAEC. The HAEC severity grading system described by the APSA provides recommendations for management based on grade of severity (Table 1)[17]. Grade 1, or possible HAEC, can be managed in the outpatient setting with oral antibiotics (metronidazole), oral hydration and potential use of rectal irrigations. Rectal irrigations are meant to wash out retained stool to help relieve any obstruction that is present. They are typically given 2-4 times per day using large bore rubber catheters until the effluent is clear[19]. Grade 2 (definite HAEC) requires inpatient management where the patient is usually kept Nil Per Os (NPO) and treated with intravenous (IV) antibiotics (metronidazole) with consideration of broad-spectrum antibiotic coverage, and rectal irrigations. Patients should have stool tests to rule out potential infections that could be involved and cause a similar presenting symptomatology (*Clostridioides difficile*, *Salmonella*, *Shigella*, *Rotavirus*)[19]. Grade 3 management is largely similar to grade 2. However, these patients are quite ill, often requiring intensive care unit level care, nasogastric decompression, and may need surgical management such as proximal bowel diversion. Several studies have shown that use of this standardized algorithm or other similar tools to guide management decreases length of stay, use of IV antibiotics, and readmission[48,49].

Another treatment option for HAEC is the use of Botulinum toxin injection (BTI) to the internal anal sphincter (IAS). In patients with HSCR, due to the absence of the recto-anal inhibitory reflex, the IAS does not relax upon rectal distension with stool or gas leading to continued distal bowel obstruction after surgical correction and potentially increasing the risk of HAEC. Botulinum toxin prevents the presynaptic release of acetylcholine producing a state of temporary local denervation with subsequent decrease of the resting anal pressure, potentially relieving the distal functional obstruction. In 2021, Svetanoff *et al*[50] performed a retrospective study looking at BTI in the setting of HAEC and found a statistically significant increase in the time between readmission in patients with recurrent HAEC. BTI has also been shown to decrease the duration of IV antibiotics and length of stay in patients with HAEC [51]. However, most studies assessing the utility of BTI in HAEC are retrospective and underpowered. Roorda *et al*[52] performed a meta-analysis of the evidence for BTI in HSCR and specifically looked at effectiveness in HAEC. They included 3 studies involving 52 patients which showed reduction of

Table 1 Hirschsprung's disease associated enterocolitis severity score and management[17]

APSA category	Symptom	Radiography	Treatment	Additional measures
Grade 1 (Possible HAEC)	Anorexia, diarrhea, mild abdominal distension	Normal, or mild signs of ileus	Oral hydration; Oral metronidazole	Rectal irrigations
Grade 2 (Definite HAEC)	One or more of the following: Explosive diarrhea; Fever, tachycardia, or lethargy; Moderate abdominal distension and/or tenderness; Explosive gas/stool on rectal examination;	May include: Signs of ileus (air fluid levels, dilated bowel loops); Distension of the proximal colon w/rectosigmoid cutoff	Clear liquids or NPO; IV hydration; Metronidazole (PO or IV); Broad spectrum antibiotic coverage; Rectal irrigations	NGT decompression
Grade 3 (Severe HAEC)	Grade II symptoms plus: Obstipation; Poor perfusion; Hypotension; Altered mental status; Marked abdominal distension; Signs of peritonitis	Signs of Grade II PLUS possible: Pneumatosis intestinalis; Pneumoperitoneum (rare)	NPO; Metronidazole (IV) + broad spectrum antibiotics (IV ampicillin + gentamicin, IV piperacillin/tazobactam); Rectal irrigations	NGT decompression; Possible surgical intervention

APSA: American Pediatric Surgery Association; HAEC: Hirschsprung's disease associated enterocolitis; IV: Intravenous; NGT: Nasogastric tube; NPO: Nothing by mouth; PO: Per oral.

enterocolitis in an average of 58% of patients, however the effect was not statistically significant. Further studies are needed to truly evaluate the use of BTI for active HAEC. Additionally, others have evaluated the use of BTI as a preventative measure for postoperative obstructive symptoms and HAEC. After other causes of obstruction are ruled out, BTI into the internal and external sphincter can serve as a therapeutic intervention and may reduce the incidence of obstructive symptoms and HAEC[51]. Other studies have suggested there may be a decrease in hospitalizations for patients with recurrent HAEC. Chumpitazi *et al*[53] performed a retrospective review looking at BTI use in patients with surgically repaired HSCR and IAS achalasia. They demonstrated a potential decrease in hospitalizations per year in their HAEC subgroup; however, the long-term response to the injections varied and children with IAS achalasia seemed to respond better than HAEC patients. They also noted that initial short-term improvement in symptoms after first BTI was useful in predicting favorable long-term outcomes.

Other postoperative preventive measures include the daily use of rectal irrigations, anal dilations, and rectal tube placement. A systematic review and meta-analysis demonstrated that the use of rectal irrigations after pull-through surgery significantly reduced the incidence of postoperative HAEC[54]. However, this same study concluded that the potential role of routine anal dilations in preventing postoperative HAEC remains unclear. A randomized trial demonstrated that the temporary use of a rectal catheter for 5 days after surgery reduced the postoperative incidence of HAEC in the first 30 days [55].

In terms of operative management for HAEC, there does appear to be a role for intestinal diverting ostomy in severe cases. Several features which may warrant consideration of diversion include delayed presentation for HSCR, presence of multiple risk factors for HAEC, or multiple concomitant comorbid conditions including sepsis, trisomy 21, and Bardet- Biedl Syndrome[19]. Prior to corrective pull-through, diversion can be considered in the decompensating neonate with long-segment disease given that they have higher failure rates of rectal washouts[56]. In these rare cases, a leveling colostomy is performed with intraoperative frozen section histology which is essential to ensure the colostomy is created just proximal to the transition zone[57]. While diversion may not entirely resolve HAEC, it does improve the patient's clinical status and quality of life.

CONCLUSION

There are several aspects of HAEC care that still require further study. Notably, improvement in both diagnostic strategies and standardization of care is needed across institutions. Promising areas of research include intestinal microbiota analysis which may help to personalize therapy, stem cell administration to restore the motor function to the remaining portions of bowel, and therapies aimed at altering colonic mucus barrier properties could be explored towards preventing the onset of enterocolitis in HSCR. This along with advances in our understanding of the pathophysiology itself will allow us to better care for HSCR patients suffering from recurrent HAEC.

FOOTNOTES

Author contributions: Gerson EM, Rodriguez L and Arbizu RA contributed equally with initial manuscript draft and final approval; Arbizu RA performed concept design, revisions, and final approval.

Conflict-of-interest statement: The authors have nothing to disclose and have no potential conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United States

ORCID number: Eric M Gershon 0000-0002-4268-6456; Leonel Rodriguez 0000-0002-7128-6048; Ricardo A Arbizu 0000-0003-1118-5066.

S-Editor: Ma YJ

L-Editor: A

P-Editor: Ma YJ

REFERENCES

- 1 Langer JC. Hirschsprung disease. *Curr Opin Pediatr* 2013; **25**: 368-374 [PMID: 23615177 DOI: 10.1097/MOP.0b013e328360c2a0]
- 2 Karim A, Tang CS, Tam PK. The Emerging Genetic Landscape of Hirschsprung Disease and Its Potential Clinical Applications. *Front Pediatr* 2021; **9**: 638093 [PMID: 34422713 DOI: 10.3389/fped.2021.638093]
- 3 Suita S, Taguchi T, Ieiri S, Nakatsuji T. Hirschsprung's disease in Japan: analysis of 3852 patients based on a nationwide survey in 30 years. *J Pediatr Surg* 2005; **40**: 197-201; discussion 201 [PMID: 15868585 DOI: 10.1016/j.jpedsurg.2004.09.052]
- 4 Das K, Mohanty S. Hirschsprung Disease - Current Diagnosis and Management. *Indian J Pediatr* 2017; **84**: 618-623 [PMID: 28600660 DOI: 10.1007/s12098-017-2371-8]
- 5 Oltean I, Hayawi L, Larocca V, Bijelić V, Beveridge E, Kaur M, Grandpierre V, Kanyinda J, Nasr A. Quality of life outcomes in children after surgery for Hirschsprung disease and anorectal malformations: a systematic review and meta-analysis. *World J Pediatr Surg* 2022; **5**: e000447 [PMID: 36474732 DOI: 10.1136/wjps-2022-000447]
- 6 Puri P, SpringerLink (Online service). Hirschsprung's Disease and Allied Disorders. Available from: <https://yale.idm.oclc.org/Login?URL=https://doi.org/10.1007/978-3-030-15647-3>
- 7 Pini Prato A, Rossi V, Avanzini S, Mattioli G, Disma N, Jasonni V. Hirschsprung's disease: what about mortality? *Pediatr Surg Int* 2011; **27**: 473-478 [PMID: 21253751 DOI: 10.1007/s00383-010-2848-2]
- 8 Gosain A. Established and emerging concepts in Hirschsprung's-associated enterocolitis. *Pediatr Surg Int* 2016; **32**: 313-320 [PMID: 26783087 DOI: 10.1007/s00383-016-3862-9]
- 9 Swenson O, Sherman JO, Fisher JH. Diagnosis of congenital megacolon: an analysis of 501 patients. *J Pediatr Surg* 1973; **8**: 587-594 [PMID: 4752993 DOI: 10.1016/0022-3468(73)90395-3]
- 10 Newman B, Nussbaum A, Kirkpatrick JA Jr. Bowel perforation in Hirschsprung's disease. *AJR Am J Roentgenol* 1987; **148**: 1195-1197 [PMID: 3495146 DOI: 10.2214/ajr.148.6.1195]
- 11 Singh S, Rawat J, Wakhlu A, Kureel SN, Pandey A. Six-year retrospective analysis of colonic perforation in neonates and infants: single centre experience. *Afr J Paediatr Surg* 2012; **9**: 102-105 [PMID: 22878755 DOI: 10.4103/0189-6725.99391]
- 12 Beltman L, Labib H, Oosterlaan J, van Heurn E, Derikx J. Risk factors for complications in patients with Hirschsprung disease while awaiting surgery: Beware of bowel perforation. *J Pediatr Surg* 2022; **57**: 561-568 [PMID: 35354528 DOI: 10.1016/j.jpedsurg.2022.02.022]
- 13 Zhu T, Zhang G, Meng X, Yang J, Niu Y, He Y, Yang H, Xiong X, Feng J. Enterocolitis Is a Risk Factor for Bowel Perforation in Neonates With Hirschsprung's Disease: A Retrospective Multicenter Study. *Front Pediatr* 2022; **10**: 807607 [PMID: 35198516 DOI: 10.3389/fped.2022.807607]
- 14 Pastor AC, Osman F, Teitelbaum DH, Caty MG, Langer JC. Development of a standardized definition for Hirschsprung's-associated enterocolitis: a Delphi analysis. *J Pediatr Surg* 2009; **44**: 251-256 [PMID: 19159752 DOI: 10.1016/j.jpedsurg.2008.10.052]
- 15 Lewit RA, Veras LV, Cowles RA, Fowler K, King S, Lapidus-Krol E, Langer JC, Park CJ, Youssef F, Vavilov S, Gosain A. Reducing Underdiagnosis of Hirschsprung-Associated Enterocolitis: A Novel Scoring System. *J Surg Res* 2021; **261**: 253-260 [PMID: 33460971 DOI: 10.1016/j.jss.2020.12.030]
- 16 Frykman PK, Kim S, Wester T, Nordenskjöld A, Kawaguchi A, Hui TT, Teitelbaum DH, Granström AL, Rogatko A; HAEC Collaborative Research Group (HCRG). Critical evaluation of the Hirschsprung-associated enterocolitis (HAEC) score: A multicenter study of 116 children with Hirschsprung disease. *J Pediatr Surg* 2018; **53**: 708-717 [PMID: 28760457 DOI: 10.1016/j.jpedsurg.2017.07.009]
- 17 Gosain A, Frykman PK, Cowles RA, Horton J, Levitt M, Rothstein DH, Langer JC, Goldstein AM; American Pediatric Surgical Association Hirschsprung Disease Interest Group. Guidelines for the diagnosis and management of Hirschsprung-

- associated enterocolitis. *Pediatr Surg Int* 2017; **33**: 517-521 [PMID: 28154902 DOI: 10.1007/s00383-017-4065-8]
- 18 **Teitelbaum DH**, Caniano DA, Qualman SJ. The pathophysiology of Hirschsprung's-associated enterocolitis: importance of histologic correlates. *J Pediatr Surg* 1989; **24**: 1271-1277 [PMID: 2593059 DOI: 10.1016/s0022-3468(89)80566-4]
 - 19 **Frykman PK**, Short SS. Hirschsprung-associated enterocolitis: prevention and therapy. *Semin Pediatr Surg* 2012; **21**: 328-335 [PMID: 22985838 DOI: 10.1053/j.sempedsurg.2012.07.007]
 - 20 **Engum SA**, Petrites M, Rescorla FJ, Grosfeld JL, Morrison AM, Engles D. Familial Hirschsprung's disease: 20 cases in 12 kindreds. *J Pediatr Surg* 1993; **28**: 1286-1290 [PMID: 8263688 DOI: 10.1016/s0022-3468(05)80314-8]
 - 21 **Morabito A**, Lall A, Gull S, Mohee A, Bianchi A. The impact of Down's syndrome on the immediate and long-term outcomes of children with Hirschsprung's disease. *Pediatr Surg Int* 2006; **22**: 179-181 [PMID: 16362310 DOI: 10.1007/s00383-005-1617-0]
 - 22 **Nair MP**, Schwartz SA. Association of decreased T-cell-mediated natural cytotoxicity and interferon production in Down's syndrome. *Clin Immunol Immunopathol* 1984; **33**: 412-424 [PMID: 6209046 DOI: 10.1016/0090-1229(84)90312-x]
 - 23 **Elhalaby EA**, Coran AG, Blane CE, Hirschl RB, Teitelbaum DH. Enterocolitis associated with Hirschsprung's disease: a clinical-radiological characterization based on 168 patients. *J Pediatr Surg* 1995; **30**: 76-83 [PMID: 7722836 DOI: 10.1016/0022-3468(95)90615-0]
 - 24 **Reding R**, de Ville de Goyet J, Gosseye S, Clapuyt P, Sokal E, Buts JP, Gibbs P, Otte JB. Hirschsprung's disease: a 20-year experience. *J Pediatr Surg* 1997; **32**: 1221-1225 [PMID: 9269974 DOI: 10.1016/s0022-3468(97)90686-2]
 - 25 **Lee CC**, Lien R, Chiang MC, Yang PH, Chu SM, Fu JH, Lai JY. Clinical impacts of delayed diagnosis of Hirschsprung's disease in newborn infants. *Pediatr Neonatol* 2012; **53**: 133-137 [PMID: 22503261 DOI: 10.1016/j.pedneo.2012.01.011]
 - 26 **Kapur RP**, Smith C, Ambartsumyan L. Postoperative Pullthrough Obstruction in Hirschsprung Disease: Etiologies and Diagnosis. *Pediatr Dev Pathol* 2020; **23**: 40-59 [PMID: 31752599 DOI: 10.1177/1093526619890735]
 - 27 **Taylor MA**, Bucher BT, Reeder RW, Avansino JR, Durham M, Calkins CM, Wood RJ, Levitt MA, Drake K, Rollins MD. Comparison of Hirschsprung Disease Characteristics between Those with a History of Postoperative Enterocolitis and Those without: Results from the Pediatric Colorectal and Pelvic Learning Consortium. *Eur J Pediatr Surg* 2021; **31**: 207-213 [PMID: 32947626 DOI: 10.1055/s-0040-1716876]
 - 28 **Hagens J**, Reinshagen K, Tomuschat C. Prevalence of Hirschsprung-associated enterocolitis in patients with Hirschsprung disease. *Pediatr Surg Int* 2022; **38**: 3-24 [PMID: 34595554 DOI: 10.1007/s00383-021-05020-y]
 - 29 **Knaus ME**, Pendola G, Srinivas S, Wood RJ, Halaweish I. Social determinants of health and Hirschsprung-associated enterocolitis. *J Pediatr Surg* 2022 [PMID: 36371352 DOI: 10.1016/j.jpedsurg.2022.09.039]
 - 30 **Zaitoun I**, Erickson CS, Barlow AJ, Klein TR, Heneghan AF, Pierre JF, Epstein ML, Gosain A. Altered neuronal density and neurotransmitter expression in the ganglionated region of Ednr^b null mice: implications for Hirschsprung's disease. *Neurogastroenterol Motil* 2013; **25**: e233-e244 [PMID: 23360229 DOI: 10.1111/nmo.12083]
 - 31 **Cheng LS**, Schwartz DM, Hotta R, Graham HK, Goldstein AM. Bowel dysfunction following pullthrough surgery is associated with an overabundance of nitergic neurons in Hirschsprung disease. *J Pediatr Surg* 2016; **51**: 1834-1838 [PMID: 27570241 DOI: 10.1016/j.jpedsurg.2016.08.001]
 - 32 **Brooks LA**, Fowler KL, Veras LV, Fu M, Gosain A. Resection margin histology may predict intermediate-term outcomes in children with rectosigmoid Hirschsprung disease. *Pediatr Surg Int* 2020; **36**: 875-882 [PMID: 32504125 DOI: 10.1007/s00383-020-04689-x]
 - 33 **Moesch M**, Usemann J, Bruder E, Romero P, Schwab C, Niesler B, Tapia-Laliena MA, Khasanov R, Nisar T; Study Group NIG Retro, Holland-Cunz S, Keck S. Associations of Mucosal Nerve Fiber Innervation Density with Hirschsprung-Associated Enterocolitis: A Retrospective Three-Center Cohort Study. *Eur J Pediatr Surg* 2022 [PMID: 35777734 DOI: 10.1055/a-1889-6355]
 - 34 **Keck S**, Galati-Fournier V, Kym U, Moesch M, Usemann J, Müller I, Subotic U, Tharakan SJ, Krebs T, Stathopoulos E, Schmittenbecher P, Cholewa D, Romero P, Reingruber B, Bruder E; Group NS, Holland-Cunz S. Lack of Mucosal Cholinergic Innervation Is Associated With Increased Risk of Enterocolitis in Hirschsprung's Disease. *Cell Mol Gastroenterol Hepatol* 2021; **12**: 507-545 [PMID: 33741501 DOI: 10.1016/j.jcmgh.2021.03.004]
 - 35 **Imamura A**, Puri P, O'Briain DS, Reen DJ. Mucosal immune defence mechanisms in enterocolitis complicating Hirschsprung's disease. *Gut* 1992; **33**: 801-806 [PMID: 1624163]
 - 36 **Aslam A**, Spicer RD, Corfield AP. Children with Hirschsprung's disease have an abnormal colonic mucus defensive barrier independent of the bowel innervation status. *J Pediatr Surg* 1997; **32**: 1206-1210 [PMID: 9269971 DOI: 10.1016/s0022-3468(97)90683-7]
 - 37 **Yildiz HM**, Carlson TL, Goldstein AM, Carrier RL. Mucus Barriers to Microparticles and Microbes are Altered in Hirschsprung's Disease. *Macromol Biosci* 2015; **15**: 712-718 [PMID: 25644515 DOI: 10.1002/mabi.201400473]
 - 38 **Gork AS**, Usui N, Ceriati E, Drongowski RA, Epstein MD, Coran AG, Harmon CM. The effect of mucin on bacterial translocation in I-407 fetal and Caco-2 adult enterocyte cultured cell lines. *Pediatr Surg Int* 1999; **15**: 155-159 [PMID: 10370012 DOI: 10.1007/s003830050544]
 - 39 **Mattar AF**, Coran AG, Teitelbaum DH. MUC-2 mucin production in Hirschsprung's disease: possible association with enterocolitis development. *J Pediatr Surg* 2003; **38**: 417-21; discussion 417 [PMID: 12632359 DOI: 10.1053/jpsu.2003.50071]
 - 40 **Thiagarajah JR**, Yildiz H, Carlson T, Thomas AR, Steiger C, Pieretti A, Zukerberg LR, Carrier RL, Goldstein AM. Altered goblet cell differentiation and surface mucus properties in Hirschsprung disease. *PLoS One* 2014; **9**: e99944 [PMID: 24945437 DOI: 10.1371/journal.pone.0099944]
 - 41 **Lui VC**, Li L, Sham MH, Tam PK. CDX-1 and CDX-2 are expressed in human colonic mucosa and are down-regulated in patients with Hirschsprung's disease associated enterocolitis. *Biochim Biophys Acta* 2001; **1537**: 89-100 [PMID: 11566252 DOI: 10.1016/s0925-4439(01)00056-4]
 - 42 **Kobayashi H**, Hirakawa H, Puri P. Overexpression of intercellular adhesion molecule-1 (ICAM-1) and MHC class II antigen on hypertrophic nerve trunks suggests an immunopathologic response in Hirschsprung's disease. *J Pediatr Surg* 1995; **30**: 1680-1683 [PMID: 8749923 DOI: 10.1016/0022-3468(95)90451-4]

- 43 Nakamura H, O'Donnell AM, Tomuschat C, Coyle D, Puri P. Altered expression of caveolin-1 in the colon of patients with Hirschsprung's disease. *Pediatr Surg Int* 2019; **35**: 929-934 [PMID: 31256294 DOI: 10.1007/s00383-019-04505-1]
- 44 Frykman PK, Nordenskjöld A, Kawaguchi A, Hui TT, Granström AL, Cheng Z, Tang J, Underhill DM, Iliev I, Funari VA, Wester T; HAEC Collaborative Research Group (HCRG). Characterization of Bacterial and Fungal Microbiome in Children with Hirschsprung Disease with and without a History of Enterocolitis: A Multicenter Study. *PLoS One* 2015; **10**: e0124172 [PMID: 25909773 DOI: 10.1371/journal.pone.0124172]
- 45 Li Y, Poroyko V, Yan Z, Pan L, Feng Y, Zhao P, Xie Z, Hong L. Characterization of Intestinal Microbiomes of Hirschsprung's Disease Patients with or without Enterocolitis Using Illumina-MiSeq High-Throughput Sequencing. *PLoS One* 2016; **11**: e0162079 [PMID: 27603009 DOI: 10.1371/journal.pone.0162079]
- 46 Parker KD, Mueller JL, Westfal M, Goldstein AM, Ward NL. A pilot study characterizing longitudinal changes in fecal microbiota of patients with Hirschsprung-associated enterocolitis. *Pediatr Surg Int* 2022; **38**: 1541-1553 [PMID: 35951092 DOI: 10.1007/s00383-022-05191-2]
- 47 Arbizu RA, Collins D, Wilson RC, Alekseyenko AV. Evidence for Differentiation of Colon Tissue Microbiota in Patients with and without Postoperative Hirschsprung's Associated Enterocolitis: A Pilot Study. *Pediatr Gastroenterol Hepatol Nutr* 2021; **24**: 30-37 [PMID: 33505891 DOI: 10.5223/pghn.2021.24.1.30]
- 48 Wall N, Kastenber Z, Zobell S, Mammen L, Rollins MD. Use of an enterocolitis triage and treatment protocol in children with Hirschsprung disease reduces hospital admissions. *J Pediatr Surg* 2020; **55**: 2371-2374 [PMID: 32553451 DOI: 10.1016/j.jpedsurg.2020.05.004]
- 49 Svetanoff WJ, Dekonenko C, Osuchukwu O, Oyetunji TA, Aguayo P, Fraser JD, Juang D, Snyder CL, Hendrickson R, Peter SS, Rentea RM. Inpatient management of Hirschsprung's associated enterocolitis treatment: the benefits of standardized care. *Pediatr Surg Int* 2020; **36**: 1413-1421 [PMID: 33001257 DOI: 10.1007/s00383-020-04747-4]
- 50 Svetanoff WJ, Lopez J, Aguayo P, Hendrickson RJ, Oyetunji TA, Rentea RM. The impact of botulinum injection for hospitalized children with Hirschsprung-associated enterocolitis. *Pediatr Surg Int* 2021; **37**: 1467-1472 [PMID: 34309717 DOI: 10.1007/s00383-021-04966-3]
- 51 Svetanoff WJ, Lim-Beutal IIP, Wood RJ, Levitt MA, Rentea RM. The utilization of botulinum toxin for Hirschsprung disease. *Semin Pediatr Surg* 2022; **31**: 151161 [PMID: 35690464 DOI: 10.1016/j.sempedsurg.2022.151161]
- 52 Roorda D, Abeln ZA, Oosterlaan J, van Heurn LW, Derikx JP. Botulinum toxin injections after surgery for Hirschsprung disease: Systematic review and meta-analysis. *World J Gastroenterol* 2019; **25**: 3268-3280 [PMID: 31333317 DOI: 10.3748/wjg.v25.i25.3268]
- 53 Chumtazi BP, Fishman SJ, Nurko S. Long-term clinical outcome after botulinum toxin injection in children with nonrelaxing internal anal sphincter. *Am J Gastroenterol* 2009; **104**: 976-983 [PMID: 19259081 DOI: 10.1038/ajg.2008.110]
- 54 Soh HJ, Nataraja RM, Pacilli M. Prevention and management of recurrent postoperative Hirschsprung's disease obstructive symptoms and enterocolitis: Systematic review and meta-analysis. *J Pediatr Surg* 2018; **53**: 2423-2429 [PMID: 30236605 DOI: 10.1016/j.jpedsurg.2018.08.024]
- 55 Zhang X, Li L, Li SL, Li SX, Wang XY, Tang ST. Primary laparoscopic endorectal pull-through procedure with or without a postoperative rectal tube for hirschsprung disease: a multicenter perspective study. *J Pediatr Surg* 2020; **55**: 381-386 [PMID: 31296328 DOI: 10.1016/j.jpedsurg.2019.06.013]
- 56 Lewit RA, Kuruvilla KP, Fu M, Gosain A. Current understanding of Hirschsprung-associated enterocolitis: Pathogenesis, diagnosis and treatment. *Semin Pediatr Surg* 2022; **31**: 151162 [PMID: 35690459 DOI: 10.1016/j.sempedsurg.2022.151162]
- 57 Demehri FR, Halaweish IF, Coran AG, Teitelbaum DH. Hirschsprung-associated enterocolitis: pathogenesis, treatment and prevention. *Pediatr Surg Int* 2013; **29**: 873-881 [PMID: 23913261 DOI: 10.1007/s00383-013-3353-1]

Seronegative autoimmune hepatitis in childhood

Ali Islek, Gokhan Tumgor

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ng HY, China; Wu X, China; Yu F, China

Received: January 28, 2023

Peer-review started: January 28, 2023

First decision: April 2, 2023

Revised: April 26, 2023

Accepted: May 8, 2023

Article in press: May 8, 2023

Published online: June 9, 2023



Ali Islek, Gokhan Tumgor, Department of Pediatric Gastroenterology, Cukurova University School of Medicine, Adana 01320, Turkey

Corresponding author: Ali Islek, MD, Associate Professor, Department of Pediatric Gastroenterology, Cukurova University School of Medicine, Sarıcam, Adana 01320, Turkey. islekali@hotmail.com

Abstract

Comprehensive guidelines on seropositive autoimmune hepatitis have been published for both adults and children, although these guidelines comprise only limited knowledge about seronegative autoimmune hepatitis. Autoimmune hepatitis presents as an acute or chronic progressive disease and poor outcomes are inevitable if left untreated. The absence of autoantibody positivity, hypergammaglobulinemia and lack of comprehensive algorithms makes seronegative autoimmune hepatitis a mysterious disease. In general, seronegative autoimmune hepatitis often presents with acute hepatitis, and its treatment and prognosis similar to seropositive autoimmune hepatitis. The present review focuses on the known characteristics of seronegative autoimmune hepatitis in childhood, and those of which current knowledge is vague.

Key Words: Seronegative autoimmune hepatitis; Autoantibody negative; Lymphocytopenia; Aplastic anemia

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Seronegative autoimmune hepatitis is a diagnostic dilemma. The absence of autoantibodies and hypergammaglobulinemia which is not uncommon in seronegative autoimmune hepatitis complicates the diagnosis. Seronegative autoimmune hepatitis often presents with acute hepatitis, and its treatment and prognosis similar to seropositive autoimmune hepatitis. This review discusses whether seronegativity is only a matter of laboratory issue or if it implies an entity with different pathogenesis, clinical features, treatment algorithms, and prognosis.

Citation: Islek A, Tumgor G. Seronegative autoimmune hepatitis in childhood. *World J Clin Pediatr* 2023; 12(3): 77-85

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/77.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.77>

INTRODUCTION

The diagnosis of autoimmune hepatitis is based on the ruling out of other causes of liver damage with the presence of non-organ specific autoantibodies and specific histological findings. The value of autoantibodies cannot be denied in the diagnosis and subtyping of autoimmune hepatitis and in the follow-up of disease activity. Failure to diagnose may increase mortality in children presenting for the first time with acute hepatic failure or cirrhosis will be inevitable in children due to progressive disease course if not treated. Autoimmune hepatitis is a progressive inflammatory disease that responds well to immunosuppressive therapy and is diagnosed with histologically interface hepatitis, serologically presence of non-organ-specific autoantibodies, and biochemically elevated transaminase and immunoglobulin G (IgG) levels[1,2]. The term seronegativity refers to the condition in which no autoantibodies are detected, but other features partially or completely support the diagnosis of autoimmune hepatitis, although the term seronegative autoimmune hepatitis has not been widely accepted. It is not known whether seronegativity is only a matter of laboratory issue or if it implies an entity with different pathogenesis, clinical features, treatment algorithms, and prognosis. We present here a discussion of the aspects of seronegative cases that are already known or those that require further elucidation.

EPIDEMIOLOGY

Autoimmune hepatitis can present in childhood or adulthood. Different incidence and prevalence rates have been reported for autoimmune hepatitis from different countries, with reported incidences in the range of 0.23-0.4 cases/100.000 people and prevalence in the range of 2.4-9 cases/100.000 people. Differences in the incidence and prevalence in the same ethnic origins but in different geographic regions suggest that factors other than genetic predisposition play a role in disease development. Autoimmune hepatitis is more commonly observed in females than in males[3]. There is a lack of detailed information about the prevalence of seronegative autoimmune hepatitis in which conventional autoantibodies are not detected. Seronegative autoimmune hepatitis account for 5%-20% of all autoimmune hepatitis, and on top of the uncertainties regarding which patients should be considered seronegative-it is no secret that some seronegative cases are classified as cryptogenic hepatitis-there is also a possibility of false-negative results in autoantibodies[4]. In our series of 54 patients, 27.7% (15/54) were identified as seronegative autoimmune hepatitis at the time of diagnosis, and a significant proportion (60%) of the cases were female, as is the case with type-1 autoimmune hepatitis. The average age at presentation was 5.69 years in those with seronegative autoimmune hepatitis. The mean age at presentation was 11 years in patients with type-1 autoimmune hepatitis and 5.1 years in those with type-2 autoimmune hepatitis[5].

PATHOGENESIS

The liver cells become damaged in cases of autoimmune hepatitis as a result of the joint effects of cellular and humoral immunity. It is suggested that damage develops in the target organ with the loss of immunity control that is triggered by a virus in individuals with a genetic predisposition. The loss of immune tolerance to hepatocyte antigens (these antigens are considered to be asialoglycoprotein receptors, liver cytosolic antigens, and soluble liver antigens) due to the compromised functioning of regulatory T cells (Tregs) results in the activation of the CD4 and CD8 T-cells, which release such proinflammatory cytokines such as interferon- γ and tumor necrosis factor- α [6]. A recent study suggested a decrease in Tregs in the peripheral blood of patients with untreated seropositive autoimmune hepatitis, together with increased Treg/T-cell and Treg/B-cell ratios identified on liver biopsy, and this finding was associated with the migration of these cells to the center of inflammation [7]. Proinflammatory cytokines initiate hepatocyte damage and result in the immune activation and proliferation of macrophages, B and T-cells, and natural killer cells. B-cells subsequently transform into plasma cells, which produce the antibodies that serve as the diagnostic instruments in autoimmune hepatitis[6]. The antibodies and target antigens described in seropositive autoimmune hepatitis are listed in Table 1.

T-cells serve as the trigger in the initiation of autoimmune hepatitis and mediate the activation of humoral immunity[8]. Autoantibodies are currently used in the diagnosis of autoimmune hepatitis, and for the determination of the subtype and the assessment of remission. Anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (ASMA) are detected in type-1 autoimmune hepatitis, and anti-liver-kidney microsomal antibody (LKM) and/or liver cytosol type-1 antibody (LC-1) in type-2 autoimmune hepatitis. ANA and ASMA are positive in approximately half of the patients with autoimmune hepatitis, while ANA alone is positive in 10%-15% and ASMA alone in 30%-35% of patients. Both anti-LKM and anti-LC-1 are positive in approximately half of the patients with type-2 autoimmune hepatitis. A positive anti-LC-1 alone is reported in 10% of patients with type-2 autoimmune hepatitis. A positive anti-soluble liver antigen/liver-pancreas antigen (anti-SLA) reported

Table 1 The antibodies and target antigens in autoimmune hepatitis

Antibody	Target antigen
ANA	Single-stranded/ double-stranded DNA, ribonucleoproteins
ASMA	Filamentous actin, vimentin, desmin
LKM	Cytochrome P450 2D6 (CYP2D6)
anti-SLA	UGA serine transfer RNA associated protein
LC-1	Formiminotransferase cyclo-deaminase
pANCA	Nuclear lamina proteins
ASGP-R	Asialoglycoprotein receptor

ANA: Anti-nuclear antibody; ASMA: Anti-smooth muscle antibody; LKM: liver-kidney microsomal antibody; LC-1: Liver cytosol type-1 antibody; SLA: Anti-soluble liver antigen/liver–pancreas antigen; ASGP-R: Asialoglycoprotein receptor; pANCA: Perinuclear anti-neutrophil cytoplasmic antibody.

in both types of autoimmune hepatitis, being positive in approximately one-fifth of those with type-1 and half of those with type-2 autoimmune hepatitis. A positive anti-SLA alone is reported in less than 10% of all patients[9]. Serum concentrations of anti-LKM, anti-LC-1, and ASMA have been identified as indicators of disease severity. In other words, hepatocyte necrosis can be severe, and the disease may progress rapidly to cirrhosis[2,9]. This raises the question: “Is the pathogenesis of seronegative autoimmune hepatitis different, and does it have a milder disease course?” Under normal circumstances, T cells initiate the immune cascade in seropositive autoimmune hepatitis, while the inflammatory events continue with B cells (Figure 1). Activated B cells, which are switched to plasma cells with the stimulation of T cells, release autoantibodies and cytokines/chemokines, cause autoantibody-mediated activation of complement and macrophage/dendritic cells and continue to contribute to inflammation with antigen presentation to T cells, while on the other hand suppress Treg and B cells' anti-inflammatory effects[10-12]. There is a lack of comprehensive data on the contribution of autoantibodies to cell damage in seronegative autoimmune hepatitis. The presence of plasma cells in the liver biopsies of patients with seronegative autoimmune hepatitis suggests that similar physiopathological mechanisms are involved in the pathogenesis of seronegative autoimmune hepatitis. Perhaps a defect in differentiation and maturation of B cells could impair antibody production, but its effects on T cell regulation were preserved. There is, however, a lack of evidence supporting this theory in seronegative patients.

There may also be a case of pseudo-seronegativity. This may be attributed to several reasons for this. Firstly, the autoantibody tests may not have been performed as recommended. The International Autoimmune Hepatitis Group has determined a threshold of $\geq 1:40$ for autoantibodies to be detected by an indirect immunofluorescence method by diluting the serum in adults[13]. The recommended autoantibody threshold levels in children are lower than those determined for adults, with a titer of 1:20 for ANA and ASMA and a titer of 1:10 for anti-LKM being considered significant[14]. In adults, thresholds for all antibodies are $\geq 1:40$. False-negative results may be obtained if standard high dilutions are used in the laboratory designated for adult patients. This problem can be overcome by communicating with the laboratory personnel for testing serum in low dilutions or it may be beneficial to test such autoantibodies using an enzyme-linked immunosorbent assay (ELISA), even if its validity has not been fully demonstrated. Secondly, previous studies have suggested that the commonly used immunofluorescence tests may initially produce false-negative results due to an intense antigen-antibody reaction in patients presenting with acute hepatic failure and acute hepatitis[8,15]. This theory is supported by the observation of seroconversion during the disease course in some patients who were initially seronegative. Furthermore, immunosuppressive agents such as corticosteroids and azathioprine may lead to conversion from seronegative to seropositive with the elimination of the effect of unknown factors. It is currently unknown when, and in what titers will the autoantibodies be positive due to limited data. In an earlier study by the present authors, the majority of patients with seronegative autoimmune hepatitis had an acute presentation (13 out of 15 patients), and the autoantibody tests turned positive in half of the patients (7 of the 15 patients) during follow-up, with a median time to seroconversion of 28 d (18–51 d)[5]. Thirdly, antibodies other than ANA, ASMA, and anti-LKM such as anti-SLA and anti-LC-1, tested by ELISA or immunoblotting methods and cannot be studied in many centers, can be checked[16]. The investigation of these autoantibodies and novel antibodies that are yet to be discovered can reduce the number of cases labeled as seronegative autoimmune hepatitis when conventional antibodies are negative.

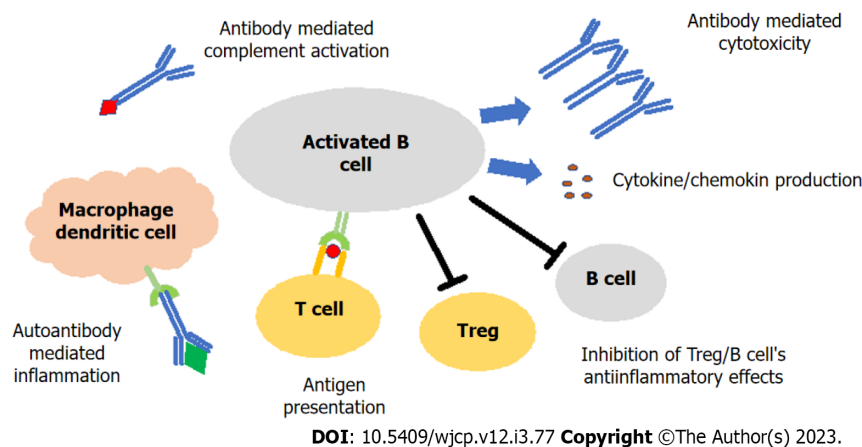


Figure 1 B cell role in the pathogenesis of autoimmune hepatitis. T cells allow B cells to switch to antibody-producing plasma cells. Autoreactive B cells release autoantibody and cytokine/chemokines. B cells continue to contribute to inflammation by presenting antigen to T cells and cause autoantibody-mediated activation of macrophage/dendritic cells, while suppressing the anti-inflammatory effects of Treg and B cells. Treg: Regulatory T cell.

PATHOLOGY

A liver biopsy is essential for the establishment of a diagnosis of autoimmune hepatitis. The anticipated primary histological finding is lymphoplasmacytic infiltration in portal areas extending to the lobule center, in other words, interface hepatitis. That said, interface hepatitis can also be observed in other liver diseases, such as acute and chronic viral hepatitis, drug-induced liver disease, and Wilson's disease. Other histological findings include portal lymphoplasmacytic infiltration, rosette formation, emperipolesis, central perivenulitis, and portal-to-portal or portal-to-central fibrosis. Centrilobular necrosis and multilobular collapse can be observed in acute presentations. Interface hepatitis may not be obvious in cirrhotic patients and those receiving immunosuppressive therapy. It has been stated that the presence of central perivenulitis and hyaline droplets in Kupffer cells may be an important diagnostic finding in the absence of interface hepatitis[1,6].

Studies of adult patients have suggested that a histopathological finding specific to seronegative autoimmune hepatitis is lacking, although there have been contradictory statements on whether the severity of histopathological findings differs from that observed in seropositive autoimmune hepatitis. Previous studies have reported that advanced histological-stage cirrhosis is more common in seronegative patients than in seropositive patients[17]. Despite the limited data on pediatric patients, we commonly encounter centrilobular necrosis in patients with seronegative autoimmune hepatitis in our practice due to the frequency of acute presentation.

In one study, CD8 T-cell-dominant infiltration was identified in the liver biopsies of a small number of pediatric patients with seronegative autoimmune hepatitis and aplastic anemia[18]. In a study of 33 patients in whom the authors described the underlying disease as "acute hepatic failure with an unknown cause", including eight patients who had hepatitis-associated aplastic anemia (HAAA), CD8 T-cell infiltration was identified in the livers of the majority of cases. The patients diagnosed with "acute hepatic failure with an unknown cause" actually fully meet the definition of seronegative autoimmune hepatitis. The authors state, however, that CD8 T-cell infiltration presented to various degrees in a small number of patients with autoimmune hepatitis, although further research is needed in this regard[19].

CLINICAL FINDINGS

Seropositive autoimmune hepatitis can be discovered incidentally with asymptomatic transaminase elevation but can also be diagnosed after presentation with a severe clinical course. The presentation may vary between different regions but is generally as follows: Approximately one-third of patients present with fatigue, nausea, abdominal pain, and jaundice, as in acute viral hepatitis (acute presentation), while the other third presents with such symptoms of chronic hepatitis as lack of appetite, weight loss, amenorrhea, and intermittent jaundice. Less than one-fifth presents with the symptoms of cirrhosis and its complications, such as ascites, abdominal distention, splenomegaly, and variceal hemorrhage. Type-1 autoimmune hepatitis is often observed in adolescence, while type-2 autoimmune hepatitis is mostly encountered in young children. Patients with type-2 autoimmune hepatitis commonly present with acute hepatitis or acute hepatic failure[1]. The data derived from adult patients suggests that acute presentations are uncommon in seronegative autoimmune hepatitis[20]. There are no detailed clinical findings related seronegative autoimmune hepatitis in children. In a study of 38 pediatric patients with seronegative autoimmune hepatitis, three-quarters presented with acute

symptoms[16]. In our previous study, 13 of 15 patients who were considered to have seronegative autoimmune hepatitis presented with acute hepatitis[5]. There is another terminology called HAAA in the literature[21]. Aplastic anemia develops within a couple of weeks or months after the onset of hepatitis, while it rarely develops after one year. Patients can be recognized at the acute hepatitis stage with symptoms such as vomiting and jaundice but can also be diagnosed after the development of aplastic anemia. HAAA, is thought to develop as a result of autoimmunity, triggered by an unknown factor, although a virus is suspected. Although HAAA can be diagnosed at any age, including adulthood, reports in literature focus mostly on pediatric cases, and most are case reports or small case series[22]. The prevalence of HAAA was found to be 5% in a multicenter European study of 3916 adult patients with aplastic anemia[23]. While previous studies have described the histopathological findings of the liver as lobular inflammations as in viral hepatitis[24], some have described features of autoimmune hepatitis and termed it as seronegative autoimmune hepatitis with the absence of autoantibodies[25]. The confusing situation for the diagnosis of autoimmune hepatitis is the spontaneous normalization of transaminases without any treatment. Our clinical experience suggests that transaminase elevation is no longer observed once aplastic anemia has developed. Autoimmune hepatitis in fact has a chronic disease course that is characterized by fluctuations. In our previous study, aplastic anemia developed in two patients with seronegative autoimmune hepatitis who presented with cholestatic hepatitis, despite dramatic improvement in hypertransaminasemia and direct bilirubinemia after corticosteroid treatment[5]. Furthermore, hepatitis did not recur within two years of the discontinuation of immunosuppressive therapy.

DIAGNOSIS

As is the case with seropositive autoimmune hepatitis, there is no pathognomonic finding of seronegative autoimmune hepatitis, so it is important to rule out other conditions such as viral hepatitis, alpha-1 antitrypsin deficiency, metabolic conditions such as Wilson's disease, and drug-induced liver injury. Hypergammaglobulinemia is one of the vital criteria for a diagnosis of seropositive autoimmune hepatitis[4]. Alongside the absence of autoantibodies, hypergammaglobulinemia which is not uncommon in seronegative autoimmune hepatitis, further complicates diagnosis. While serum IgG levels may be within normal ranges for age in seronegative cases, a decrease from baseline may be observed with treatment[12,25]. Patients diagnosed in the hepatitis stage who subsequently develop aplastic anemia are often found to have lymphocytopenia before the development of aplastic anemia. It has been found that the CD4 T-cell count is decreased in these patients[18]. If a patient is found to have isolated persistent lymphocytopenia without stigmas of a viral infection, the patient will most likely develop aplastic anemia in the future. Finally, it is essential to identify any histopathological liver features specific to autoimmune hepatitis to confirm a diagnosis of seronegative autoimmune hepatitis, although some histopathological findings can be observed also in other liver diseases.

Simplified diagnostic criteria is used for research purposes in autoimmune hepatitis but may also be used in cases that pose diagnostic challenges[4]. This scoring system has been found to have a sensitivity of 77% and a false-negative rate of 17%, and these false-negative cases are indeed seronegative cases[26]. In cases where conventional antibodies negative with an immunofluorescence assay, repeat tests with other techniques such as ELISA or immunoblotting and investigations of other autoantibodies may aid the diagnosis of autoimmune hepatitis. Monitoring treatment response seems to be the best option to avoid the consequences of delayed diagnosis. The algorithm followed in our clinic for the treatment of seronegative patients is presented in Figure 2.

TREATMENT

Delays in treatment can lead to disease progression in patients with autoimmune hepatitis, while timely treatment can prevent such severe complications as cirrhosis. The treatment of seronegative autoimmune hepatitis involves immunosuppressive therapy, as in seropositive autoimmune hepatitis. The goal of treatment in seropositive autoimmune hepatitis is to normalize transaminase and IgG levels, to turn autoantibodies negative and to provide improvement to histological inflammation. Clinical and biochemical improvement is expected immediately after treatment[4]. Even if IgG level by age is within normal range a decrease within the normal range is often expected with treatment and can be regarded as a marker of biochemical response. Repeat autoantibody tests should be carried out to observe if they turn positive during treatment. Patients who develop aplastic anemia often have lymphocytopenia initially, but in those without lymphocytopenia, it should be evaluated whether lymphocytopenia develops during treatment, even if transaminase levels decrease with immunosuppressants[5,16,25]. Aplastic anemia may develop even in the early period during corticosteroid induction therapy. You can begin the treatment with corticosteroid (prednisone or prednisolone) and continue with low-dose corticosteroid or corticosteroid plus azathioprine or azathioprine monotherapy. The main challenge in the treatment of seronegative patients is the timing of the switch to such second-line therapies as

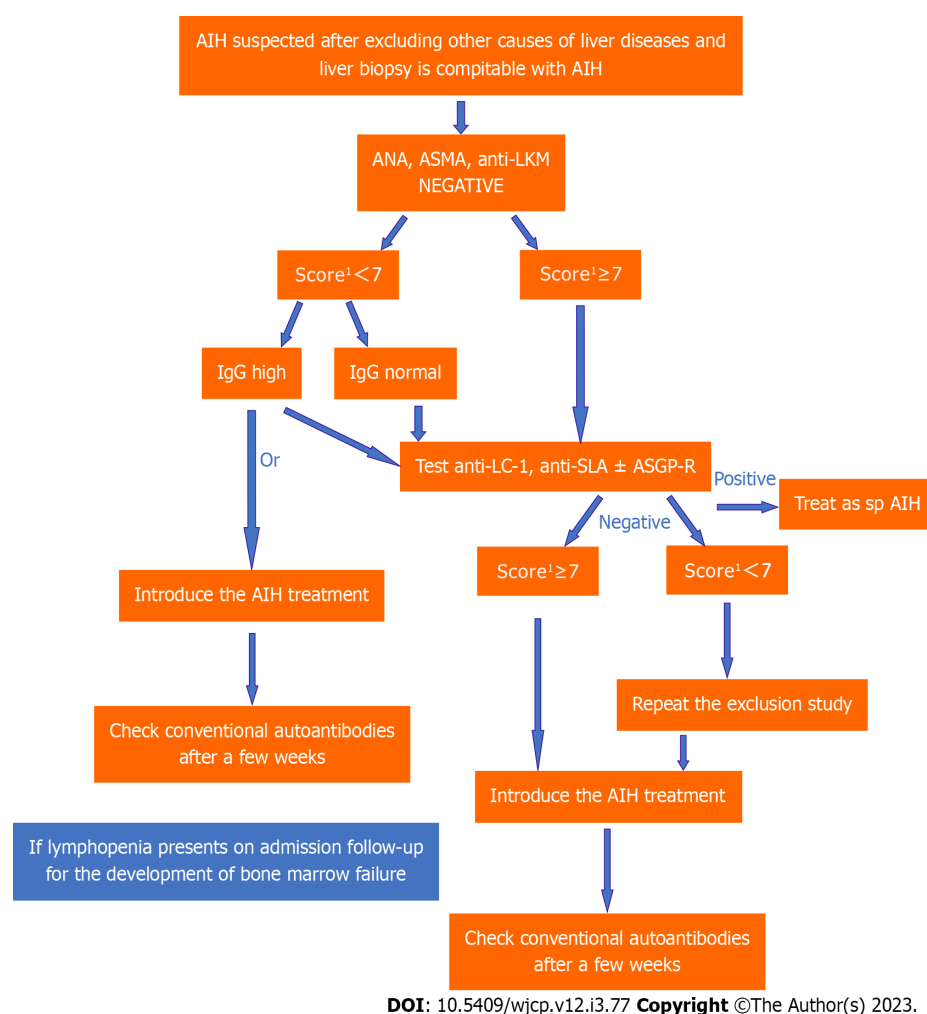


Figure 2 Algorithm for the diagnosis of seronegative autoimmune hepatitis. ¹Proposed scoring criteria for the diagnosis of juvenile autoimmune liver disease by ESPGHAN 2018 (10). AIH: Autoimmune hepatitis; ANA: Anti-nuclear antibody; ASMA: Anti-smooth muscle antibody; LKM: liver-kidney microsomal antibody; IgG: Immunoglobulin G; LC-1: Liver cytosol type-1 antibody; SLA: Anti-soluble liver antigen/liver-pancreas antigen; ASGP-R: Asialoglycoprotein receptor.

mycophenolate mofetil or calcineurin inhibitors when the patient fails to respond to first-line therapies. In such cases, we recommend re-assessing differential diagnoses, including metabolic disorders, and re-checking autoantibody status before initiating second-line therapies. Current literature on adult patients suggests that the treatment response in seronegative patients is similar to that of seropositive patients [11], although there is a paucity of such data on pediatric cases. Based on our experience and available pediatric data [5,16,18,25], we consider that the response to treatment is not different from seropositive patients. The cessation of therapy may be considered if biochemical and histological remission is observed following two years of therapy in patients with type-1 autoimmune hepatitis, although this is not recommended in patients with type-2 autoimmune hepatitis due to the high relapse rates. It is unclear whether treatment can be discontinued in patients with seronegative autoimmune hepatitis. Although a previous study [25] reported the successful cessation of treatment in pediatric seronegative patients, we made no such attempt at cessation due to the unpredictability of the outcomes, as in our practice, young seronegative children exhibited acute severe clinical presentations similar to that of patients with type-2 autoimmune hepatitis.

The benefits of corticosteroid therapy are arguable, even in patients with seropositive autoimmune hepatitis who present with acute hepatic failure. Survival without transplantation is possible in patients treated with corticosteroid, although an increased risk of sepsis and mortality has been reported [1]. The appropriate approach to patients presenting with acute hepatic failure and unresponsive to corticosteroid therapy—if steroid therapy has been attempted—and in those with decompensated cirrhosis is liver transplantation.

PROGNOSIS

Despite the limited data related to pediatric patients, prognosis is generally good in patients with

Table 2 The differences between seropositive and seronegative autoimmune hepatitis

Seropositive individuals	Seronegative individuals
High IgG	Normal IgG (may be high)
Presents with an acute or chronic course of disease	Generally, presents with acute manifestations
Does not show bone marrow abnormality	Lymphopenia may accompany (generally initially) and bone marrow failure may develop
Autoantibodies are detectable on admission	Autoantibody positivity may develop after immunosuppressive therapy
Disease onset is usually in the second decade for type 1 AIH and at any age in the first decade for type 2	Disease onset is similar to type 2 AIH (may be at any age)
Treatment response is generally good	Treatment response is generally good
Immunosuppressant withdrawal possible (Recurrence rate is higher in type 2 AIH than type 1)	Immunosuppressant withdrawal possible (Recurrence rate is unknown)

IgG: Immunoglobulin G; AIH: Autoimmune hepatitis.

seronegative autoimmune hepatitis. In a study of 38 seronegative patients, Maggiore *et al*[25] reported that all were still alive after 4-17 years. Among the study participants, one presented with acute hepatic failure underwent liver transplantation, while four patients with aplastic anemia underwent bone marrow transplantations. The median time to the cessation of immunosuppressive therapy in 20 out of the 38 cases was 4 years (1-6 years), and nine in whom the immunosuppressive therapy was stopped had aplastic anemia[25]. One adult study reported a high risk of developing hepatitis in the transplanted livers of patients with seronegative autoimmune hepatitis[20], although there is a lack of long-term data that would allow us to speculate on the situation in children. The differences between seropositive and seronegative autoimmune hepatitis are summarized in Table 2.

CONCLUSION

While seronegative autoimmune hepatitis is not a rare entity, little is known about its diagnosis and treatment. However, based on this limited literature and our experience, we can summarize seronegative autoimmune hepatitis as follows. Since autoantibody positivity at low dilutions in immunofluorescence is sufficient for a diagnosis of autoimmune hepatitis in children, it should be ensured that the laboratory conditions are arranged for opportunity to test autoantibodies in low dilutions, or other non-conventional autoantibodies should be studied. The presence of lymphopenia points to the development of bone marrow failure in the future. Treatment should not be delayed after other causes have been ruled out in patients with liver biopsy features consistent with autoimmune hepatitis to prevent the development of complications. The treatment of seronegative autoimmune hepatitis is similar to seropositive autoimmune hepatitis and the authors believe that the prognosis is good in seronegative autoimmune hepatitis.

FOOTNOTES

Author contributions: Islek A substantially contributed to the conception and design of the paper and the acquisition, analysis and interpretation of the data; Islek A and Tumgor G drafted the article and made critical revisions related to the intellectual content of the manuscript and approved the final version of the article to be published.

Conflict-of-interest statement: There was no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Turkey

ORCID number: Ali Islek 0000-0001-6172-7797; Gokhan Tumgor 0000-0002-3919-002X.

S-Editor: Fan JR

L-Editor: A

P-Editor: Ju JL

REFERENCES

- Kerkar N, Mack CL. Autoimmune hepatitis in children. In: Suchy FJ, Sokol RJ, Balistreri WF, Bezerra JA, Mack CL, Shneider BL. *Liver Disease in Children*, 5th ed. Cambridge, UK: Cambridge University Press, 2021: 321-332
- Sebode M, Weiler-Normann C, Liwinski T, Schramm C. Autoantibodies in Autoimmune Liver Disease-Clinical and Diagnostic Relevance. *Front Immunol* 2018; **9**: 609 [PMID: 29636752 DOI: 10.3389/fimmu.2018.00609]
- Palle SK, Naik KB, McCracken CE, Kolachala VL, Romero R, Gupta NA. Racial disparities in presentation and outcomes of paediatric autoimmune hepatitis. *Liver Int* 2019; **39**: 976-984 [PMID: 30802337 DOI: 10.1111/liv.14081]
- Mieli-Vergani G, Vergani D, Czaja AJ, Manns MP, Krawitt EL, Vierling JM, Lohse AW, Montano-Loza AJ. Autoimmune hepatitis. *Nat Rev Dis Primers* 2018; **4**: 18017 [PMID: 29644994 DOI: 10.1038/nrdp.2018.17]
- Islek A, Keskin H. Seronegative autoimmune hepatitis in children: a single-center experience. *Acta Gastroenterol Belg* 2021; **84**: 305-310 [PMID: 34217180 DOI: 10.51821/84.2.305]
- Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmune hepatitis. *Cell Mol Immunol* 2022; **19**: 158-176 [PMID: 34580437 DOI: 10.1038/s41423-021-00768-8]
- Diestelhorst J, Junge N, Schlue J, Falk CS, Manns MP, Baumann U, Jaeckel E, Taubert R. Pediatric autoimmune hepatitis shows a disproportionate decline of regulatory T cells in the liver and of IL-2 in the blood of patients undergoing therapy. *PLoS One* 2017; **12**: e0181107 [PMID: 28700730 DOI: 10.1371/journal.pone.0181107]
- Assis DN. Immunopathogenesis of Autoimmune Hepatitis. *Clin Liver Dis (Hoboken)* 2020; **15**: 129-132 [PMID: 32257125 DOI: 10.1002/cld.873]
- Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Serology in autoimmune hepatitis: A clinical-practice approach. *Eur J Intern Med* 2018; **48**: 35-43 [PMID: 29056396 DOI: 10.1016/j.ejim.2017.10.006]
- Mieli-Vergani G, Vergani D, Baumann U, Czubkowski P, Debray D, Dezsofi A, Fischler B, Gupte G, Hierro L, Indolfi G, Jahnel J, Smets F, Verkade HJ, Hadžić N. Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement. *J Pediatr Gastroenterol Nutr* 2018; **66**: 345-360 [PMID: 29356770 DOI: 10.1097/MPG.0000000000001801]
- Narkewicz MR, Horslen S, Belle SH, Rudnick DA, Ng VL, Rosenthal P, Romero R, Loomes KM, Zhang S, Hardison RM, Squires RH; Pediatric Acute Liver Failure Study Group. Prevalence and Significance of Autoantibodies in Children With Acute Liver Failure. *J Pediatr Gastroenterol Nutr* 2017; **64**: 210-217 [PMID: 27496798 DOI: 10.1097/MPG.0000000000001363]
- Taylor SA, Assis DN, Mack CL. The Contribution of B Cells in Autoimmune Liver Diseases. *Semin Liver Dis* 2019; **39**: 422-431 [PMID: 31226726 DOI: 10.1055/s-0039-1688751]
- Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR, McFarlane I, Dienes HP, Lohse AW; International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008; **48**: 169-176 [PMID: 18537184 DOI: 10.1002/hep.22322]
- Khedr MA, Salem TA, Boghdadi GM, Elharoun AS, El-Shahaway AA, Atallah HR, Sira MM. Seronegative autoimmune hepatitis in children : A real diagnostic challenge. *Wien Klin Wochenschr* 2022; **134**: 195-201 [PMID: 34283299 DOI: 10.1007/s00508-021-01907-x]
- Bhumi SA, Wu GY. Seronegative Autoimmune Hepatitis. *J Clin Transl Hepatol* 2023; **11**: 459-465 [PMID: 36643052 DOI: 10.14218/JCTH.2022.00235]
- Czaja AJ. Autoantibody-negative autoimmune hepatitis. *Dig Dis Sci* 2012; **57**: 610-624 [PMID: 22187100 DOI: 10.1007/s10620-011-2017-z]
- Kumari N, Kathuria R, Srivastav A, Krishnani N, Poddar U, Yachha SK. Significance of histopathological features in differentiating autoimmune liver disease from nonautoimmune chronic liver disease in children. *Eur J Gastroenterol Hepatol* 2013; **25**: 333-337 [PMID: 23085577 DOI: 10.1097/MEG.0b013e32835a68a1]
- Kemme S, Stahl M, Brigham D, Lovell MA, Nakano T, Feldman AG, Mack C. Outcomes of Severe Seronegative Hepatitis-associated Aplastic Anemia: A Pediatric Case Series. *J Pediatr Gastroenterol Nutr* 2021; **72**: 194-201 [PMID: 32925550 DOI: 10.1097/MPG.0000000000002940]
- Chapin CA, Burn T, Meijome T, Loomes KM, Melin-Aldana H, Kreiger PA, Whittington PF, Behrens EM, Alonso EM. Indeterminate pediatric acute liver failure is uniquely characterized by a CD103(+) CD8(+) T-cell infiltrate. *Hepatology* 2018; **68**: 1087-1100 [PMID: 29603342 DOI: 10.1002/hep.29901]
- Donaghy L, Barry FJ, Hunter JG, Stableforth W, Murray IA, Palmer J, Bendall RP, Elsharkawy AM, Dalton HR. Clinical and laboratory features and natural history of seronegative hepatitis in a nontransplant centre. *Eur J Gastroenterol Hepatol* 2013; **25**: 1159-1164 [PMID: 23652914 DOI: 10.1097/MEG.0b013e3283610484]
- Patel KR, Bertuch A, Sasa GS, Himes RW, Wu H. Features of Hepatitis in Hepatitis-associated Aplastic Anemia: Clinical and Histopathologic Study. *J Pediatr Gastroenterol Nutr* 2017; **64**: e7-e12 [PMID: 28030425 DOI: 10.1097/MPG.0000000000001271]
- Gonnot M, Neumann F, Huet F, Maudinas R, Leblanc T, Lacaille F. Hepatitis-associated Aplastic Anemia. *J Pediatr Gastroenterol Nutr* 2022; **75**: 553-555 [PMID: 36070526 DOI: 10.1097/MPG.0000000000003603]
- Locasciulli A, Bacigalupo A, Bruno B, Montante B, Marsh J, Tichelli A, Socié G, Passweg J; Severe Aplastic Anemia Working Party of the European Blood and Marrow Transplant Group (SAA-WP, EBMT). Hepatitis-associated aplastic anaemia: epidemiology and treatment results obtained in Europe. A report of The EBMT aplastic anaemia working party.

- Br J Haematol* 2010; **149**: 890-895 [PMID: 20456352 DOI: 10.1111/j.1365-2141.2010.08194.x]
- 24 **Gonzalez-Casas R**, Garcia-Buey L, Jones EA, Gisbert JP, Moreno-Otero R. Systematic review: hepatitis-associated aplastic anaemia--a syndrome associated with abnormal immunological function. *Aliment Pharmacol Ther* 2009; **30**: 436-443 [PMID: 19508613 DOI: 10.1111/j.1365-2036.2009.04060.x]
 - 25 **Maggiore G**, Socie G, Sciveres M, Roque-Afonso AM, Nastasio S, Johanet C, Gottrand F, Fournier-Favre S, Jacquemin E, Bernard O. Seronegative autoimmune hepatitis in children: Spectrum of disorders. *Dig Liver Dis* 2016; **48**: 785-791 [PMID: 27079745 DOI: 10.1016/j.dld.2016.03.015]
 - 26 **Arcos-Machancoses JV**, Molera Busoms C, Julio Tatis E, Bovo MV, Martín de Carpi J. Accuracy of the Simplified Criteria for Autoimmune Hepatitis in Children: Systematic Review and Decision Analysis. *J Clin Exp Hepatol* 2019; **9**: 147-155 [PMID: 31024195 DOI: 10.1016/j.jceh.2018.10.006]

Various aspects of hearing loss in newborns: A narrative review

Raid M Al-Ani

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Lee KS, South Korea;
Mirsalehi M, Iran; Redaelli de Zinis
LO, Italy

Received: February 8, 2023

Peer-review started: February 8, 2023

First decision: April 20, 2023

Revised: April 22, 2023

Accepted: May 22, 2023

Article in press: May 22, 2023

Published online: June 9, 2023



Raid M Al-Ani, Department of Surgery/Otolaryngology, University of Anbar, College of Medicine, Ramadi 31001, Anbar, Iraq

Corresponding author: Raid M Al-Ani, MBChB, Academic Editor, Consultant Physician-Scientist, Full Professor, Researcher, Science Editor, Department of Surgery/Otolaryngology, University of Anbar, College of Medicine, Al-Andulus, Ramadi 31001, Anbar, Iraq.
med.raed.alani2003@uoanbar.edu.iq

Abstract

Hearing loss is considered the most common birth defect. The estimated prevalence of moderate and severe hearing loss in a normal newborn is 0.1%-0.3%, while the prevalence is 2%-4% in newborns admitted to the newborn intensive care unit. Neonatal hearing loss can be congenital (syndromic or non-syndromic) or acquired such as ototoxicity. In addition, the types of hearing loss can be conductive, sensorineural, or mixed. Hearing is vital for the acquisition of language and learning. Therefore, early detection and prompt treatment are of utmost importance in preventing the unwanted sequel of hearing loss. The hearing screening program is mandatory in many nations, especially for high-risk newborns. An automated auditory brainstem response test is used as a screening tool in newborns admitted to the newborn intensive care unit. Moreover, genetic testing and screening for cytomegalovirus in newborns are essential in identifying the cause of hearing loss, particularly, mild and delayed onset types of hearing loss. We aimed to update the knowledge on the various aspects of hearing loss in newborns with regard to the epidemiology, risk factors, causes, screening program, investigations, and different modalities of treatment.

Key Words: Newborns; Hearing loss; Deafness; Sensorineural hearing loss; Congenital hearing loss; Universal hearing screening program in newborns

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Hearing loss in newborns is a common problem worldwide. Hearing is responsible for the acquisition of language, speech, cognition, and learning. Deaf individuals have a great negative impact on public health and the economic state. Early detection and prompt intervention lead to better outcomes. The universal hearing screening program, genetic testing, and cytomegalovirus detection are useful tools for the early detection of hearing loss in newborns. Rehabilitation of deaf infants with hearing aids or cochlear implants, gene therapy, and treatment of cytomegalovirus infection are satisfactory methods of treatment. However, researchers are focused on resolving the ambiguities regarding the diagnosis and treatment of hearing loss.

Citation: Al-Ani RM. Various aspects of hearing loss in newborns: A narrative review. *World J Clin Pediatr* 2023; 12(3): 86-96

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/86.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.86>

INTRODUCTION

Hearing loss is the most common sensory deficit and one of the most common congenital abnormalities [1,2]. It affects 432 million adults and 34 million children across the globe (<https://www.who.int/en/news-room/fact-sheets/detail/deafness-and-hearing-loss>). It was estimated that the prevalence of bilateral moderate to severe hearing loss ranged from 1-3/1000 normal newborns and 2-4/1000 in high-risk group newborns[3,4].

Hearing loss in newborns can be caused by a genetic factor in 50% of cases, while acquired hearing loss is related to many causes in the prenatal, natal, and postnatal periods[5]. Hearing is essential for the acquisition of speech, language, and learning development[6]. Therefore, hearing loss particularly of bilateral severe to profound severity harms the development of newborns and results in them living with a significant handicap if not detected and treated early[7].

Early detection of hearing loss and prompt intervention are of utmost importance to minimize the negative impact of hearing loss and at the same time to maximize healthy development of the auditory pathway during the critical period of neural growth. Hence, the Joint Committee on Infant Hearing (JCIH) recommends that all newborns must be screened for hearing and the diagnosis should be established by the age of three months of life, and deaf infants treated at the age of six months[8]. Of course, timely fitting of hearing aids or cochlear implants is useful for deaf children[9].

The diagnosis of hearing loss depends on the doctor or family's suspicion and cannot diagnose all cases of significant hearing impairment. Besides, hearing screening of high-risk newborns (such as a family history of congenital hearing loss) can detect approximately 50% of cases with significant hearing loss. Therefore, it is essential to perform universal hearing screening of all newborns[3].

Otoacoustic emissions as well as auditory brainstem response tests are the usual screening tools for hearing screening in newborns. However, Universal Newborn Hearing Screening is not able to detect mild or delayed onset hearing loss in newborns, in addition, the cause of hearing loss cannot be identified using this program[10]. Therefore, nowadays genetic testing of hearing loss is a useful adjunct to the Universal Newborn Hearing Screening in the early identification of a significant number of newborns with hearing loss[10].

Owing to the importance of hearing and early detection and treatment of hearing loss in newborns, we conducted this comprehensive review to update and summarize the various aspects of hearing loss in newborns (a critical period of human life).

ANATOMY OF THE EAR AND AUDITORY PATHWAY

The hearing pathway consists of the peripheral (structural) and the central component (sensorineural). These differ in their function and timeline development. The peripheral part consists of the external, middle, and internal ear. The functions of the external and middle ear are to collect and conduct the sound waves into the Organ of Corti of the inner ear. Then, these mechanical waves are converted into electrical energy which is transmitted through the auditory nerve fibers to the auditory cortex[11]. This cortex is tonotopically arranged in areas 22, 41, and 42 of the temporal lobe[12].

The labyrinth or inner ear starts to form at the 4th gestational week and is completely developed in the 20th gestational week[11-13]. Also, the auditory cortex is fully developed at the 20th gestational week[14].

The cochlea and temporal lobe are the most important sensitive parts of the auditory pathway. There are many deleterious conditions affecting these components including, for example, prenatal and postnatal infection, postnatal antibiotic, and noise exposure in the newborn intensive care unit[15]. This deleterious effect starts from full development of the neurosensory component at the 20th week of

intrauterine life until the 5th month of extra-uterine life[11].

The auditory pathway can transmit sound waves to the developing brain of the fetus during the period from the 25th to the 29th gestational week. The uterus acts as a protective barrier from deleterious factors to fetal development and protects the auditory pathway from high-intensity sounds[12,16]. However, the developing fetus can recognize various sounds (both attenuated and distorted sounds), particularly the mother's speech[17]. Furthermore, intrauterine sound stimulation helps the tonotopic development of the inner ear hair cells and auditory higher center[18]. The cortical auditory center continues to develop due to surrounding sound stimuli in the neonatal period. Therefore, this period is considered the time of the continuous auditory development process to fetal life[11]. This is supported by evidence from a study that compared vision and hearing development. Sight develops only in extra-uterine life, while hearing develops during the last 10th to 12th gestational weeks as well as after birth [11].

NEWBORN LIFE

The neonatal period is defined as the first 28 d of life[19]. The transition from intrauterine life (fetus) to extra-uterine life (newborn) is a complex process. This process is affected by certain factors, including gestational age, the health of the mother and chronic medical problems, placenta state, congenital anomalies, and care level in the delivery room. Despite the majority of infants passing this stage smoothly, around 10% need adequate resuscitation in the newborn intensive care unit to pass this process[20].

Actually, in many nations, there is a lack of contact between the mothers and their newborns and the health services with around 50% of deliveries across the globe occurring in the home without proper postnatal care[21]. This factor might harm the general health of newborns, in general, and hearing development, in particular.

The maturation of the auditory pathway might be affected by many factors including prematurity, admission to the intensive care baby unit, gestational age, and the gender of the newborn[22,23]. Therefore, great care is necessary during this critical period of life to prevent any preventable causes of hearing loss or to reduce the effect of hearing impairment by early detection of hearing loss and prompt intervention.

EPIDEMIOLOGY

Hearing loss is the 4th leading cause of handicap worldwide[24]. Hearing loss of more than 40 dB in the better ear can be considered disabling for adulthood (≥ 15 years), while, in children (0-14 years), a deficit of > 30 dB in the better ear has a disabling effect[25].

There was an increment in the number with disabling hearing loss across the globe from 42 million in 1985 to 360 million in 2010[26]. This included 7.5 million children less than 5 years old. At present, there are 466 million individuals with disabling hearing loss across the globe (<https://www.who.int/en/news-room/fact-sheets/detail/deafness-and-hearing-loss>). Of note, the actual number is more than the reported number with an expected continuous rising with time. This might be due to increased life span of people[27,28]. It is expected that 630 million individuals will have disabling hearing loss by the year 2030 and approximately 900 million by 2050 if no counter-measures are taken[29].

There is no gender predilection for hearing loss in newborns. However, there is a geographical variation concerning the prevalence of hearing loss. The highest prevalence was seen in Asia Pacific, South Asia, and Sub-Saharan Africa[30].

CAUSES

There are two main reasons for congenital hearing loss in newborns; genetic and environmental. According to recent investigations in developed countries, 80% of the causes are genetic, while the remaining 20% of cases are acquired or due to environmental reasons[31].

There are three reasons for genetic hearing loss; (1) Non-syndromic and syndromic; (2) Autosomal dominant/recessive/X-linked; and (3) Mitochondrial inheritance patterns[32].

The classification of syndromic and non-syndromic hearing loss depends on whether other systemic manifestations are associated with hearing loss. It is very important to diagnose syndromic hearing loss early and this depends on clinical assessment and molecular diagnostic tools. The advantages of early diagnosis include; predicting the progress of hearing impairment, looking for other systemic abnormalities, and guidance of treatment. Otolaryngologists are the first physicians to deal with children with syndromic hearing impairment and cooperate with other specialties for prompt management[33].

The non-syndromic and autosomal recessive cases outnumber the cases of syndromic and autosomal dominant cases. This means that congenital hearing loss can occur with a negative family history of hearing loss or without systemic abnormalities, which might be an unexpected aspect of the family[32]. Several investigations studied adding genetic testing to the current universal newborn hearing screening. However, only 1.4% of newborns who passed the hearing screening had a positive genetic screening test[10,34]. DFNB1 is the most prevalent form of congenital hearing loss in developed countries. DFNB1 results from mutations in the gap junction protein beta 2 (GJB2) gene[35]. GJB2 is expressed between the supporting cells and spiral ligament, stria vascularis, and spiral limbus of the cochlea. It is included in the potassium recycling mechanism, that hair cells utilize to produce an action potential to external sound waves[36]. Hence, GJB2 gene mutations are considered a cause of sensorineural hearing loss (SNHL). The common causes of hereditary hearing loss are shown in Table 1 [37,38].

Although the environmental causes of hearing loss in newborns are relatively low in number, great attention should be paid to prevent the significant sequel of hearing loss in the individual, family, and population. Another issue should be mentioned here, that is infections (such as cytomegalovirus infection) might lead to delayed onset hearing loss[39].

Generally, the causes of hearing loss are divided into three groups; prenatal, natal, and postnatal causes. In the prenatal period, TORCH infections include toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus, herpes simplex infections are groups of congenital infections and caused by *Toxoplasma gondii*, *Treponema pallidum*, *Hepatitis B virus*, *Rubella virus*, *cytomegalovirus*, and *herpes virus simplex* (HSV) viruses, respectively. If these infections occur in the first trimester, the severity of the infection is worse[40]. These infections cause different congenital anomalies and SNHL is one of them. In the era of coronavirus disease 2019 (COVID-19), the maternal-fetal transmission of severe acute respiratory syndrome coronavirus 2 could occur and harm the fetal ear[41]. Maternal smoking may have a deleterious effect on the inner ear of the fetus[42]. A pregnant woman with cardiovascular diseases, diabetes mellitus, ototoxic drugs such as aminoglycoside antibiotics, loop diuretics, and immunosuppressive drugs, and other conditions might have teratogenic effects on the well-being of the developing fetus including development of the ear[43].

During parturition, many factors might affect the hearing of newborns such as vertical transmission of infection from the mother to the fetus, birth asphyxia (Apgar score ≤ 6 at 5 min), meconium aspiration, and trauma[44].

In the neonatal period, several causes lead to hearing impairment including, but not limited to, prematurity, low birth weight, severe hyperbilirubinemia, ototoxic drugs like aminoglycosides, bacterial meningitis, respiratory distress, assisted ventilation > 5 d after delivery, long stay in the newborn intensive care unit (more than 5 d), and head trauma or intracranial hemorrhage[44].

TYPES AND SEVERITY OF HEARING LOSS

Hearing loss is a difficulty in hearing. Many classifications of hearing loss depend on the laterality of the hearing loss (unilateral or bilateral), symmetry (symmetrical or asymmetrical), affected frequencies (low, moderate, or high), involved site of the auditory pathway (conductive, sensorineural, or mixed), and the onset of hearing loss (congenital or acquired)[45].

In conductive hearing loss, the lesion involves the conductive hearing pathway, namely the external and middle ear, such as stenosis or atresia of the external ear, otitis media with effusion, or dislocation of ossicles. In SNHL, there is an abnormality in the cochlea, or auditory nerve fibers, or in the auditory cortex, or a combination of them. The majority of congenital cases of hearing loss are due to genetic causes, as seen in the United States and other developed nations (around 80%). Other causes of hearing loss include, but are not limited to, prenatal and postnatal infections, noise exposure, hyperbilirubinemia, and hypoxia[31].

Regarding severity, hearing loss is divided according to the degree of hearing loss into slight (where the hearing loss of 16-25 dB), mild (26-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90 dB), and profound (> 90 dB)[45].

EVALUATION OF HEARING IN NEWBORNS

Currently, three screening programs are useful in detecting the majority of causes of hearing loss in newborns[39].

Newborn hearing screening program

In the past, hearing screening in the infant was performed by distraction or other behavioral tests[46]. These tests are usually performed in high-risk groups of hearing loss in newborns or depend on parental concern for their infants.

Table 1 Common causes of hereditary hearing loss

Type	Mode of inheritance	Gene or syndrome	Type of deafness	Laterality	Severity of deafness	Systemic disorders
Non-syndromic	Autosomal dominant	WFS1	Mostly SNHL	Uni- or bilateral	Variables	No
		TECTA	Mostly SNHL	Uni- or bilateral	Variables	No
		COCH	Mostly SNHL	Uni- or bilateral	Variables	No
		KNCQ4	Mostly SNHL	Uni- or bilateral	Variables	No
	Autosomal recessive	GJB2	Mostly SNHL	Uni- or bilateral	Variables	No
		SLC26A4	Mostly SNHL	Uni- or bilateral	Variables	No
		MYO15A	Mostly SNHL	Uni- or bilateral	Variables	No
		OTOF	Mostly SNHL	Uni- or bilateral	Variables	No
		CDH23	Mostly SNHL	Uni- or bilateral	Variables	No
		TMC1	Mostly SNHL	Uni- or bilateral	Variables	No
Syndromic	Autosomal dominant	Neurofibromatosis 2	High frequency SNHL	Bilateral	Mild to profound	Facial nerve paresis or paralysis; Tinnitus; Vertigo
		Branchio-oto-renal syndrome	Mixed (50%), Conductive (30), SNHL (20%)	Bilateral	Severe and progressive	Otological problems (<i>e.g.</i> cochlear dysplasia), Branchial anomalies <i>e.g.</i> lateral cervical fistulae, Renal such as agenesis
		Treacher Collins	Conductive; Sensorineural or mixed hearing loss less common	Unilateral or bilateral	Various severities	Craniofacial abnormalities such as hypoplastic facial bones and external auditory canal atresia
		Stickler syndrome	Conductive; SNHL; Mixed	Unilateral or bilateral	Various severities	Ophthalmological such as vitreous anomaly. Joint hypermobility; Craniofacial anomalies such as hypertelorism
		Waardenburg syndrome				Dystopia canthorum, heterochromia iridium, white forelock, synophrys, broad nasal root, hypoplasia of, the alae nasi, patent metopic suture line, and a square jaw
	Autosomal recessive	Pendred syndrome	SNHL			Goiter and a partial defect in iodide organification
		Jervell and Lange-Nielsen syndrome	SNHL		Severe to profound	Marked prolongation of the QT interval, and multiple syncopal attacks induced by exercise or emotion
		Usher syndrome	SNHL	Bilateral	Various severities	Vestibular dysfunction, retinitis pigmentosa
		Refsum disease	SNHL		Severe and progressive	Peripheral polyneuropathy; Cerebellar ataxia; Retinitis pigmentosa; Ichthyosis
	X-linked dominant	Alport syndrome	SNHL	Bilateral	Progressive	Hemorrhagic nephritis; Vision changes
	Mitochondrial	MELAS	SNHL	Bilateral	Progressive	Short stature; Nausea; Migraines; Seizures; Alternating hemiparesis; Hemianopia; Cortical blindness
		MERRF				Myoclonic epilepsy; Ataxia; Dementia; Optic atrophy; Short stature; Neuropathy

SNHL: Sensorineural hearing loss.

In 1982, the Joint Committee on Infant Hearing of the United States recommended that detection of hearing loss should be screened in newborns. This early identification has a crucial role in achieving an optimum outcome of rehabilitation[47]. Despite the benefit of early detection of hearing loss in newborns and early infantile life having been recognized for 80 years, the real efforts on a country level to detect congenital hearing loss were started at the beginning of the last decade of the 20th century[48]. Currently, the national universal newborn hearing screening program was practiced in all developed countries and some developing nations[32,45,49]. Unfortunately, Iraq is one of the developing countries that still have not practiced this vital program[50]. A recent large global survey reported that 38% of the world's neonates and infants had no or minimal hearing screening and 33% screened approximately 85% of newborns[51].

As a rule of thumb, a screening test for hearing should have the following characteristics; cheap, easy to learn and apply by screeners, quick to administer, not invasive, high compliance, and high specificity and sensitivity. There are two screening tests used in the newborn hearing screening program; otoacoustic emission (records responses from the outer hair cells of the cochlea) and automated auditory brainstem response (measures response to sound based on the neural transmission of a signal from the cochlea to the brainstem) or a combination of both screening tests[31]. Owing to the high validity of the tests, they are accepted across the globe. These screening tests give either pass or fail, the latter indicates the possibility of hearing loss in the screened newborn who requires a referral for further audiological evaluation to detect the type, severity, and configuration of hearing loss[31].

If the above-mentioned step is unable to detect the cause of hearing loss, genetic testing, radiological evaluation, laboratory tests, and consultation from other specialists are necessary depending on the case under the evaluation process[52].

Application of the universal hearing screening program in newborns is cost-effective[53].

Genetic testing

Genetic screening is an adjuvant to Universal Newborn Hearing Screening as the latter fails to identify syndromic hearing loss, risk factors for aminoglycoside-related hearing loss, auditory neuropathy, mild hearing loss, and delayed-onset hearing loss[10,45].

There are 124 identified genes implicated in non-syndromic congenital SNHL (<https://hereditary-hearingloss.org>).

There are three main technologies for genetic testing: Direct sequencing, Microarrays, and Next-generation sequencing. Direct sequencing can identify the exact order of nucleotide bases in an examined gene or the part of interest[54]. Sanger Sequencing is the most widely used technique of direct sequencing. The benefits of this technique are its ability to detect the vast majority of mutations (including novel mutations) present in a sequence, and it is the most accurate method. The drawbacks are as follows; costly, time-consuming, and labor-intensive. Therefore, this technique is used mainly in the identification of novel mutations or to confirm the results of other experimental screening methods [10].

Microarrays or mutation chips can be used for screening multiple mutations at one time. Microarrays are easily adjusted according to a specific population depending on the frequencies of the gene mutations. The benefits of this method over direct sequencing are low cost and speed as multiple genes can be screened at the same time. However, this technique cannot determine novel mutations as the direct sequencing method can. Despite the many mutations that can be screened simultaneously, this technique is limited by increasing the mutations without a significant increment in the time and cost [54]. At present, there are 15-300 mutations in 4-31 common hearing loss-related genes[55].

Next-generation sequencing or high-throughput sequencing techniques or massively parallel sequencing is now available and able to test all hearing loss-related genes in children with congenital hearing loss[37].

Cytomegalovirus testing

Congenital cytomegalovirus infection is considered the main non-hereditary reason for hearing loss at birth, the estimated incidence is approximately 10% of all causes of congenital hearing loss and 15%-20% in all children with hearing loss[56]. Approximately 6% of newborns who fail the hearing screening tested positive for cytomegalovirus[57].

Newborns with cytomegalovirus infection are divided into asymptomatic (90%) and symptomatic (10%). The most common symptomatic conditions are premature delivery, intrauterine growth restriction, and dysfunction of multiple organs. Approximately 50% of symptomatic newborns can develop SNHL[58]. Unilateral hearing loss is mostly seen among asymptomatic newborns with cytomegalovirus infection which is detected during screening. Owing to the high possibility of late occurrence of hearing loss in childhood, therefore, long-term follow-up of those children with cytomegalovirus infection is of utmost importance to detect late-onset hearing loss[59].

It is not necessary to test all neonates for cytomegalovirus because the test is not useful or cost-effective, as the majority of the infected neonates are asymptomatic. The correct timing of testing for congenital cytomegalovirus is either during pregnancy or during the first 21 d of neonatal life[60]. There are two methods for testing cytomegalovirus in the fetus; culture and polymerase chain reaction (PCR) testing of the amniotic fluid through amniocentesis[61]. Amniocentesis is not recommended for routine

screening testing as there is a 0.49% risk of demise in the fetus. The best samples used for the detection of cytomegalovirus by PCR are saliva or urine because they have sensitivities and specificities reaching 100%[58]. In newborns, detection of IgM antibodies against cytomegalovirus is not recommended as only 70% of those with positive cytomegalovirus infection can be detected using this serological test. There is limited value of cytomegalovirus detection using PCR of dried blood spots due to low sensitivity (28.3%)[62].

A recent study adopted a comprehensive hearing screening of newborns which comprised hearing screening, genetic testing, and cytomegalovirus testing[45]. The benefits of this program include; detection of the causes of hearing loss in newborns who were not detected on the routine hearing screening program, providing the etiological pattern of the hearing loss, reducing the number of children that might be lost to follow-up, and reducing the cost by decreasing the cases that need later testing.

Table 2 shows certain studies from various countries using the above-mentioned investigations in the diagnosis of neonatal hearing loss.

TREATMENT

Successful treatment depends on early detection of hearing loss in newborns as well as prompt intervention. The main treatment modalities are discussed below.

Hearing aid and cochlear implant

A multidisciplinary team is necessary for audiological, educational, and medical management. The team consists of an otolaryngologist, audiologist, pediatrician, specialist in genetics, and others[39]. The main factors that affect the development of language in a deaf infant are early detection and intervention[63]. It is critical to start intervention in a deaf infant at the age of 6 mo for better acquisition of language. At this age, the infant gets similar results to normal-hearing infants[64].

There are two options for the rehabilitation of hearing-impaired infants; hearing aids and cochlear implants. The hearing aid is the treatment of choice for mild-to-moderate congenital SNHL, while those with severe-to-profound SNHL can benefit from cochlear implants[65].

Gene therapy

Due to the developments in genetic sequencing technology in the last several years, there have been significant advancements in the molecular and biochemical pathways concerning the treatment of congenital hearing loss[66]. Following the first clinical approval protocol of human gene therapy by the Food and Drug Administration in 1990[67], there has been a significant increase in the acceptance of human gene therapy as a treatment option for different clinical problems including hearing loss.

There are four methods of human gene therapy; gene suppression, cell replacement, gene replacement, and targeted gene editing[68]. The application of these methods in cases of hearing loss faces difficulty in their administration to the inner ear as it is not an easily accessible structure and is covered by a strong bony labyrinth. Besides, most treated cases of hearing loss are severe and associated with irreversible destruction of the hair cells (outer and inner). However, many hearing loss-related genes have been successfully treated with curative gene therapy in an animal model[39].

Novel gene therapy in humans to prevent or restore SNHL is still under investigation[68].

Treatment of cytomegalovirus infection

The recommended treatment for symptomatic cytomegalovirus infection is either parenteral use of ganciclovir or oral valganciclovir. The triphosphate derivative of ganciclovir can inhibit cytomegalovirus DNA replication[69]. A previous clinical trial in 2003 reported that there was preservation of hearing in infants at 6 mo and one year following treatment with ganciclovir for symptomatic cytomegalovirus infection for those infants who received treatment during the neonatal period. The study also reported that 63% of the infants (29/46 treated group) had grade 3 or 4 neutropenia following antiviral treatment with ganciclovir[70].

Recently, three randomized controlled clinical trials studied the efficacy of valganciclovir antiviral therapy on the severity and course of cytomegalovirus-related SNHL[39].

CONCLUSION

Hearing is vital for speech, language, cognition, and learning. Hearing loss is the most common sensory abnormality. Hearing loss harms the person, family, and community. Early identification and intervention of hearing loss in newborns can result in an excellent outcome. Early detection of hearing loss in newborns can be accomplished by the hearing screening program, genetic testing, and cytomegalovirus infection testing. The rule of 1, 3, and 6 should be applied to hearing loss in newborns and

Table 2 Studies from various nations using different tools to diagnose hearing loss in newborns

Authors	Country	Year	Sample size	Study method	Data type	Diagnostic tool	Predictor(s)
Malesci <i>et al</i> [7]	Italy	2022	318878	Longitudinal retrospective study	Newborns	UNHS	UNHS is feasible and effective
Chu <i>et al</i> [34]	Taiwan	2015	15345	Retrospective study	Newborns	UNHS; Genetic testing	A genetic profile of the connexin genes and SLC26A4 gene among infants with hearing impairment detected by a UNHS program in Taiwan
Durante <i>et al</i> [42]	Brazil	2021	105	Comparative study	Newborns	Transient-evoked otoacoustic emissions and distortion product otoacoustic emissions	The impact of smoking exposure could be analyzed through transient-evoked otoacoustic emissions in newborns.
Bielecki <i>et al</i> [44]	Poland	2011	5282	Comparative study	Newborns	UNHS	Most common risk factors for hearing loss; Ototoxic drugs; Premature birth; Low birth weight; Intensive care in excess of 7 d
Pitathawatchai <i>et al</i> [53]	Thailand	2023	126	A decision analytical model with a 78-year time horizon	Newborns	UNHS; TNHS	Both tools are cost-effective
Rawlinson <i>et al</i> [57]	Australia	2018	1669	Cohort study	Newborns, Infants	UNHS; CMV testing	Congenital CMV (5.9%) in infants with permanent hearing loss and who did not pass the UNHS
Boppana <i>et al</i> [62]	United States	2010	20448	Comparative study	Newborns	CMV testing	Saliva rapid culture had low sensitivity in comparison with CMV testing with DBS real-time PCR

UNHS: Universal newborn hearing screening; TNHS: Targeted newborn hearing screening; CMV: Cytomegalovirus; PCR: Polymerase chain reaction.

infants. Number 1 means that the assessment of hearing should be started at the first month, number 3, accomplish the diagnosis at three months, and number 6, intervention should be started at 6 mo of life. Rehabilitation of deaf infants with hearing aids or cochlear implantation, gene therapy, and antiviral therapy for cytomegalovirus infection are recommended treatment modalities for hearing loss. Further investigations are necessary to solve the many ambiguities concerning hearing loss in newborns.

FOOTNOTES

Author contributions: Al-Ani RM is responsible for the design of the study and writing the manuscript; Al-Ani RM has read and approved the final draft of the article.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Iraq

ORCID number: Raid M Al-Ani 0000-0003-4263-9630.

S-Editor: Li L

L-Editor: Webster JR

P-Editor: Li L

REFERENCES

- 1 Sheffield AM, Smith RJH. The Epidemiology of Deafness. *Cold Spring Harb Perspect Med* 2019; **9** [PMID: 30249598 DOI: 10.1101/cshperspect.a033258]

- 2 **van Beeck Calkoen EA**, Engel MSD, van de Kamp JM, Yntema HG, Goverts ST, Mulder MF, Merkus P, Hensen EF. The etiological evaluation of sensorineural hearing loss in children. *Eur J Pediatr* 2019; **178**: 1195-1205 [PMID: [31152317](#) DOI: [10.1007/s00431-019-03379-8](#)]
- 3 **Erenberg A**, Lemons J, Sia C, Trunkel D, Ziring P. Newborn and infant hearing loss: detection and intervention. American Academy of Pediatrics. Task Force on Newborn and Infant Hearing, 1998- 1999. *Pediatrics* 1999; **103**: 527-530 [PMID: [9925859](#) DOI: [10.1542/peds.103.2.527](#)]
- 4 **Mehl AL**, Thomson V. Newborn hearing screening: the great omission. *Pediatrics* 1998; **101**: E4 [PMID: [9417168](#) DOI: [10.1542/peds.101.1.e4](#)]
- 5 **Wroblewska-Seniuk KE**, Dabrowski P, Szyfter W, Mazela J. Universal newborn hearing screening: methods and results, obstacles, and benefits. *Pediatr Res* 2017; **81**: 415-422 [PMID: [27861465](#) DOI: [10.1038/pr.2016.250](#)]
- 6 **Jasper KM**, Jamshidi A, Reilly BK. Pediatric otolaryngology, molecular diagnosis of hereditary hearing loss: next-generation sequencing approach. *Curr Opin Otolaryngol Head Neck Surg* 2015; **23**: 480-484 [PMID: [26488533](#) DOI: [10.1097/MOO.0000000000000208](#)]
- 7 **Malesci R**, Del Vecchio V, Bruzzese D, Burattini E, Auletta G, Errichiello M, Fetoni AR, Franzè A, Laria C, Toscano F, Caso A, Marciano E. Performance and characteristics of the Newborn Hearing Screening Program in Campania region (Italy) between 2013 and 2019. *Eur Arch Otorhinolaryngol* 2022; **279**: 1221-1231 [PMID: [33768315](#) DOI: [10.1007/s00405-021-06748-y](#)]
- 8 **Joint Committee on Infant Hearing**: American Academy of Audiology; American Academy of Pediatrics; American Speech-Language-Hearing Association; Directors of Speech and Hearing Programs in State Health and Welfare Agencies. Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. Joint Committee on Infant Hearing, American Academy of Audiology, American Academy of Pediatrics, American Speech-Language-Hearing Association, and Directors of Speech and Hearing Programs in State Health and Welfare Agencies. *Pediatrics* 2000; **106**: 798-817 [PMID: [11015525](#) DOI: [10.1542/peds.106.4.798](#)]
- 9 **Khoza-shangase a**, kanji a. Early detection and intervention in audiology - An african perspective. South Africa: Wits University Press, 2021: 117
- 10 **D'Aguillo C**, Bressler S, Yan D, Mittal R, Fifer R, Blanton SH, Liu X. Genetic screening as an adjunct to universal newborn hearing screening: literature review and implications for non-congenital pre-lingual hearing loss. *Int J Audiol* 2019; **58**: 834-850 [PMID: [31264897](#) DOI: [10.1080/14992027.2019.1632499](#)]
- 11 **Graven SN**, Browne JV. Auditory development in the fetus and infant. *Newborn infant Nurs. Rev* 2008; **8**: 187-193 [DOI: [10.1053/j.nainr.2008.10.010](#)]
- 12 **Urbanec J**, Kremláček J, Chládková K, Skálová S. The Development and Neurophysiological Assessment of Newborn Auditory Cognition: A Review of Findings and Their Application. *Acta Medica (Hradec Kralove)* 2022; **65**: 1-7 [PMID: [35793502](#) DOI: [10.14712/18059694.2022.9](#)]
- 13 **Mehta K**, Watkin P, Baldwin M, Marriage J, Mahon M, Vickers D. Role of Cortical Auditory Evoked Potentials in Reducing the Age at Hearing Aid Fitting in Children With Hearing Loss Identified by Newborn Hearing Screening. *Trends Hear* 2017; **21**: 2331216517744094 [PMID: [29205100](#) DOI: [10.1177/2331216517744094](#)]
- 14 **Joos K**, Gilles A, Van de Heyning P, De Ridder D, Vanneste S. From sensation to percept: the neural signature of auditory event-related potentials. *Neurosci Biobehav Rev* 2014; **42**: 148-156 [PMID: [24589492](#) DOI: [10.1016/j.neubiorev.2014.02.009](#)]
- 15 **Savenko IV**, Garbaruk ES, Krasovskaya EA. Changes in auditory function in premature children: A prospective cohort study. *Int J Pediatr Otorhinolaryngol* 2020; **139**: 110456 [PMID: [33096380](#) DOI: [10.1016/j.ijporl.2020.110456](#)]
- 16 **Thiede A**, Virtala P, Ala-Kurikka I, Partanen E, Huutilainen M, Mikkola K, Leppänen PHT, Kujala T. An extensive pattern of atypical neural speech-sound discrimination in newborns at risk of dyslexia. *Clin Neurophysiol* 2019; **130**: 634-646 [PMID: [30870799](#) DOI: [10.1016/j.clinph.2019.01.019](#)]
- 17 **Chládková K**, Paillereau N. The what and when of universal perception: A review of early speech sound acquisition. *Lang. Learn* 2020; **70**: 1136-1182 [DOI: [10.1111/Lang.12422](#)]
- 18 **Lahav A**, Skoe E. An acoustic gap between the NICU and womb: a potential risk for compromised neuroplasticity of the auditory system in preterm infants. *Front Neurosci* 2014; **8**: 381 [PMID: [25538543](#) DOI: [10.3389/fnins.2014.00381](#)]
- 19 **Centeno-Tablante E**, Medina-Rivera M, Finkelstein JL, Rayco-Solon P, Garcia-Casal MN, Rogers L, Ghezzi-Kopel K, Ridwan P, Peña-Rosas JP, Mehta S. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review. *Ann N Y Acad Sci* 2021; **1484**: 32-54 [PMID: [32860259](#) DOI: [10.1111/nyas.14477](#)]
- 20 **Swanson JR**, Sinkin RA. Transition from fetus to newborn. *Pediatr Clin North Am* 2015; **62**: 329-343 [PMID: [25836701](#) DOI: [10.1016/j.pcl.2014.11.002](#)]
- 21 **World Health Organization (WHO)**. Newborn and infant hearing screening: Current issues and guiding principles for action. Switzerland: WHO Libr. Cat, 2010
- 22 **Stipdonk LW**, Weisglas-Kuperus N, Franken MC, Nasserinejad K, Dudink J, Goedegebure A. Auditory brainstem maturation in normal-hearing infants born preterm: a meta-analysis. *Dev Med Child Neurol* 2016; **58**: 1009-1015 [PMID: [27168415](#) DOI: [10.1111/dmcn.13151](#)]
- 23 **Antinmaa J**, Lapinleimu H, Salonen J, Stolt S, Kaljonen A, Jääskeläinen S. Neonatal brainstem auditory function associates with early receptive language development in preterm children. *Acta Paediatr* 2020; **109**: 1387-1393 [PMID: [31833585](#) DOI: [10.1111/apa.15136](#)]
- 24 **World Health Organization**. Addressing the rising prevalence of hearing loss. Switzerland: World Health Organization, 2018
- 25 **Neumann K**, Chadha S, Tavartkiladze G, Bu X, White KR. Newborn and Infant Hearing Screening Facing Globally Growing Numbers of People Suffering from Disabling Hearing Loss. *Int J Neonatal Screen* 2019; **5**: 7 [PMID: [33072967](#) DOI: [10.3390/ijns5010007](#)]
- 26 **Tucci DL**, Wilson BS, O'Donoghue GM. The Growing-and Now Alarming-Burden of Hearing Loss Worldwide. *Otol Neurotol* 2017; **38**: 1387-1388 [PMID: [29065094](#) DOI: [10.1097/MAO.0000000000001593](#)]
- 27 **GBD 2015 Disease and Injury Incidence and Prevalence Collaborators**. Global, regional, and national incidence,

- prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1545-1602 [PMID: 27733282 DOI: 10.1016/S0140-6736(16)31678-6]
- 28 **Wilson BS**, Tucci DL, Merson MH, O'Donoghue GM. Global hearing health care: new findings and perspectives. *Lancet* 2017; **390**: 2503-2515 [PMID: 28705460 DOI: 10.1016/S0140-6736(17)31073-5]
 - 29 **Chadha S**, Cieza A, Krug E. Global hearing health: future directions. *Bull World Health Organ* 2018; **96**: 146 [PMID: 29531409 DOI: 10.2471/BLT.18.209767]
 - 30 **Stevens G**, Flaxman S, Brunskill E, Mascarenhas M, Mathers CD, Finucane M; Global Burden of Disease Hearing Loss Expert Group. Global and regional hearing impairment prevalence: an analysis of 42 studies in 29 countries. *Eur J Public Health* 2013; **23**: 146-152 [PMID: 22197756 DOI: 10.1093/eurpub/ckr176]
 - 31 **Shave S**, Botti C, Kwong K. Congenital Sensorineural Hearing Loss. *Pediatr Clin North Am* 2022; **69**: 221-234 [PMID: 35337535 DOI: 10.1016/j.pcl.2021.12.006]
 - 32 **Choe G**, Park SK, Kim BJ. Hearing loss in neonates and infants. *Clin Exp Pediatr* 2023 [PMID: 36634668 DOI: 10.3345/cep.2022.01011]
 - 33 **Liu M**, Zhang T. [A review of diagnosis and treatment of syndromic hearing loss]. *Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2021; **35**: 285-288 [PMID: 33794621 DOI: 10.13201/j.issn.2096-7993.2021.03.022]
 - 34 **Chu CW**, Chen YJ, Lee YH, Jaung SJ, Lee FP, Huang HM. Government-funded universal newborn hearing screening and genetic analyses of deafness predisposing genes in Taiwan. *Int J Pediatr Otorhinolaryngol* 2015; **79**: 584-590 [PMID: 25724631 DOI: 10.1016/j.ijporl.2015.01.033]
 - 35 **Kelsell DP**, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, Mueller RF, Leigh IM. Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997; **387**: 80-83 [PMID: 9139825 DOI: 10.1038/387080a0]
 - 36 **Kikuchi T**, Adams JC, Paul DL, Kimura RS. Gap junction systems in the rat vestibular labyrinth: immunohistochemical and ultrastructural analysis. *Acta Otolaryngol* 1994; **114**: 520-528 [PMID: 7825434 DOI: 10.3109/00016489409126097]
 - 37 **Chang KW**. Genetics of Hearing Loss--Nonsyndromic. *Otolaryngol Clin North Am* 2015; **48**: 1063-1072 [PMID: 26275501 DOI: 10.1016/j.otc.2015.06.005]
 - 38 **Gettelfinger JD**, Dahl JP. Syndromic Hearing Loss: A Brief Review of Common Presentations and Genetics. *J Pediatr Genet* 2018; **7**: 1-8 [PMID: 29441214 DOI: 10.1055/s-0037-1617454]
 - 39 **Thorpe RK**, Smith RJH. Future directions for screening and treatment in congenital hearing loss. *Precis Clin Med* 2020; **3**: 175-186 [PMID: 33209510 DOI: 10.1093/pccmedi/pbaa025]
 - 40 **Jaana A**, Rajnik M. TORCH Complex. 2022 Oct 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan- [PMID: 32809363]
 - 41 **Mazur-Bialy AI**, Kołomańska-Bogucka D, Tim S, Oplawski M. Pregnancy and Childbirth in the COVID-19 Era-The Course of Disease and Maternal-Fetal Transmission. *J Clin Med* 2020; **9** [PMID: 33233369 DOI: 10.3390/jcm9113749]
 - 42 **Durante AS**, Nascimento CMD, Lopes C. Otoacoustic emissions in neonates exposed to smoke during pregnancy. *Braz J Otorhinolaryngol* 2021; **87**: 193-199 [PMID: 31611072 DOI: 10.1016/j.bjorl.2019.08.001]
 - 43 **Boulay H**, Mazaud-Guittot S, Supervielle J, Chemouny JM, Dardier V, Lacroix A, Dion L, Vigneau C. Maternal, foetal and child consequences of immunosuppressive drugs during pregnancy in women with organ transplant: a review. *Clin Kidney J* 2021; **14**: 1871-1878 [PMID: 34345409 DOI: 10.1093/ckj/sfab049]
 - 44 **Bielecki I**, Horbulewicz A, Wolan T. Risk factors associated with hearing loss in infants: an analysis of 5282 referred neonates. *Int J Pediatr Otorhinolaryngol* 2011; **75**: 925-930 [PMID: 21571377 DOI: 10.1016/j.ijporl.2011.04.007]
 - 45 **Shearer AE**, Shen J, Amr S, Morton CC, Smith RJ; Newborn Hearing Screening Working Group of the National Coordinating Center for the Regional Genetics Networks. A proposal for comprehensive newborn hearing screening to improve identification of deaf and hard-of-hearing children. *Genet Med* 2019; **21**: 2614-2630 [PMID: 31171844 DOI: 10.1038/s41436-019-0563-5]
 - 46 **Stewart-Brown S**, Haslum MN. Screening for hearing loss in childhood: a study of national practice. *Br Med J (Clin Res Ed)* 1987; **294**: 1386-1388 [PMID: 3109668 DOI: 10.1136/bmj.294.6584.1386]
 - 47 **Bonfils P**, François M, Aidan D, Avan P, Parat S, Boissinot C, Narcy P. [Deafness in the neonatal period: basis for screening]. *Arch Pediatr* 1995; **2**: 685-691 [PMID: 7663662 DOI: 10.1016/0929-693X(96)81228-0]
 - 48 **Deng X**, Gaffney M, Grosse SD. Early Hearing Detection and Intervention in the United States: Achievements and Challenges in the 21(st) Century. *China CDC Wkly* 2020; **2**: 378-382 [PMID: 32774988 DOI: 10.46234/ccdcw2020.097]
 - 49 **Abdussalaam II**, Abdullateef A, Wahab, NO. Universal Newborn Hearing Screening Programme in Malaysia and Nigeria: A Comparative Analysis. In: Taukeni SG. Epidemiological Research Applications for Public Health Measurement and Intervention. IGI Global, 2021: 101-110 [DOI: 10.4018/978-1-7998-4414-3.ch007]
 - 50 **Al-Ani RM**, Mohsin TM, Hassan ZM, Al-Dulaimy HI. Importance of ophthalmological examination in children with congenital sensorineural hearing loss. *Saudi Med J* 2009; **30**: 1197-1201 [PMID: 19750267]
 - 51 **Neumann K**, Mathmann P, Chadha S, Euler HA, White KR. Newborn Hearing Screening Benefits Children, but Global Disparities Persist. *J Clin Med* 2022; **11** [PMID: 35012010 DOI: 10.3390/jcm11010271]
 - 52 **Liming BJ**, Carter J, Cheng A, Choo D, Curotta J, Carvalho D, Germiller JA, Hone S, Kenna MA, Loundon N, Preciado D, Schilder A, Reilly BJ, Roman S, Strychowsky J, Triglia JM, Young N, Smith RJ. International Pediatric Otolaryngology Group (IPOG) consensus recommendations: Hearing loss in the pediatric patient. *Int J Pediatr Otorhinolaryngol* 2016; **90**: 251-258 [PMID: 27729144 DOI: 10.1016/j.ijporl.2016.09.016]
 - 53 **Pitathawatchai P**, Chaichulee S, Wannaro W, Pongprawat P. Cost-effectiveness analysis on implementing newborn hearing screening programmes in a low- to middle-income country. *Int J Audiol* 2023; **62**: 79-88 [PMID: 35075981 DOI: 10.1080/14992027.2021.2014072]
 - 54 **Linden Phillips L**, Bitner-Glindzicz M, Lench N, Steel KP, Langford C, Dawson SJ, Davis A, Simpson S, Packer C. The future role of genetic screening to detect newborns at risk of childhood-onset hearing loss. *Int J Audiol* 2013; **52**: 124-133 [PMID: 23131088 DOI: 10.3109/14992027.2012.733424]
 - 55 **D'Aguillo C**, Liu, XZ, Angeli, SI. Advances in the clinical application of genetic screening in hereditary hearing loss. Hugo Rodríguez, 2020: 216. Dec 2020. [cited 3 May 2023]. Available from: http://aaofp.org.ar/manual_12.pdf#page=216

- 56 **Grosse SD**, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment. *J Clin Virol* 2008; **41**: 57-62 [PMID: [17959414](#) DOI: [10.1016/j.jcv.2007.09.004](#)]
- 57 **Rawlinson WD**, Palasanthiran P, Hall B, Al Yazidi L, Cannon MJ, Cottier C, van Zuylen WJ, Wilkinson M. Neonates with congenital Cytomegalovirus and hearing loss identified via the universal newborn hearing screening program. *J Clin Virol* 2018; **102**: 110-115 [PMID: [29571077](#) DOI: [10.1016/j.jcv.2018.03.006](#)]
- 58 **Marsico C**, Kimberlin DW. Congenital Cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment. *Ital J Pediatr* 2017; **43**: 38 [PMID: [28416012](#) DOI: [10.1186/s13052-017-0358-8](#)]
- 59 **Puhakka L**, Lappalainen M, Lönnqvist T, Nieminen T, Boppa S, Saxen H, Niemensivu R. Hearing outcome in congenitally CMV infected children in Finland - Results from follow-up after three years age. *Int J Pediatr Otorhinolaryngol* 2022; **156**: 111099 [PMID: [35276528](#) DOI: [10.1016/j.ijporl.2022.111099](#)]
- 60 **Lazzarotto T**, Guerra B, Lanari M, Gabrielli L, Landini MP. New advances in the diagnosis of congenital cytomegalovirus infection. *J Clin Virol* 2008; **41**: 192-197 [PMID: [18054840](#) DOI: [10.1016/j.jcv.2007.10.015](#)]
- 61 **Bonalumi S**, Trapanese A, Santamaria A, D'Emidio L, Mobili L. Cytomegalovirus infection in pregnancy: review of the literature. *J Prenat Med* 2011; **5**: 1-8 [PMID: [22439067](#)]
- 62 **Boppa SB**, Ross SA, Novak Z, Shimamura M, Tolan RW Jr, Palmer AL, Ahmed A, Michaels MG, Sánchez PJ, Bernstein DI, Britt WJ, Fowler KB; National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) Study. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA* 2010; **303**: 1375-1382 [PMID: [20388893](#) DOI: [10.1001/jama.2010.423](#)]
- 63 **Levitt H**, McGarr N, Geffner D. Development of language and communication skills in hearing-impaired children. Introduction. *ASHA Monogr* 1987; 1-8 [PMID: [3509663](#)]
- 64 **Yoshinaga-Itano C**, Sedey AL, Coulter DK, Mehl AL. Language of early- and later-identified children with hearing loss. *Pediatrics* 1998; **102**: 1161-1171 [PMID: [9794949](#) DOI: [10.1542/peds.102.5.1161](#)]
- 65 **Renauld JM**, Basch ML. Congenital Deafness and Recent Advances Towards Restoring Hearing Loss. *Curr Protoc* 2021; **1**: e76 [PMID: [33780161](#) DOI: [10.1002/cpz1.76](#)]
- 66 **Stamatiou GA**, Stankovic KM. A comprehensive network and pathway analysis of human deafness genes. *Otol Neurotol* 2013; **34**: 961-970 [PMID: [23770690](#) DOI: [10.1097/MAO.0b013e3182898272](#)]
- 67 **Rosenberg SA**, Aebersold P, Cornetta K, Kasid A, Morgan RA, Moen R, Karson EM, Lotze MT, Yang JC, Topalian SL. Gene transfer into humans--immunotherapy of patients with advanced melanoma, using tumor-infiltrating lymphocytes modified by retroviral gene transduction. *N Engl J Med* 1990; **323**: 570-578 [PMID: [2381442](#) DOI: [10.1056/NEJM199008303230904](#)]
- 68 **Omichi R**, Shibata SB, Morton CC, Smith RJH. Gene therapy for hearing loss. *Hum Mol Genet* 2019; **28**: R65-R79 [PMID: [31227837](#) DOI: [10.1093/hmg/ddz129](#)]
- 69 **Matthews T**, Boehme R. Antiviral activity and mechanism of action of ganciclovir. *Rev Infect Dis* 1988; **10** Suppl 3: S490-S494 [PMID: [2847285](#) DOI: [10.1093/clinids/10.Supplement_3.S490](#)]
- 70 **Kimberlin DW**, Lin CY, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Pass RF, Kiell JM, Soong SJ, Whitley RJ; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003; **143**: 16-25 [PMID: [12915819](#) DOI: [10.1016/S0022-3476\(03\)00192-6](#)]



Emerging role of computed tomography coronary angiography in evaluation of children with Kawasaki disease

Manphool Singhal, Rakesh Kumar Pilania, Pankaj Gupta, Nameirakpam Johnson, Surjit Singh

Specialty type: Rheumatology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Dauey K, Kazakhstan; Rigante D, Italy

Received: March 4, 2023

Peer-review started: March 4, 2023

First decision: April 13, 2023

Revised: May 8, 2023

Accepted: May 22, 2023

Article in press: May 22, 2023

Published online: June 9, 2023



Manphool Singhal, Pankaj Gupta, Departments of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, Chandigarh, India

Rakesh Kumar Pilania, Nameirakpam Johnson, Surjit Singh, Pediatric Allergy Immunology Unit, Department of Paediatrics, Advanced Pediatrics Center, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, Chandigarh, India

Corresponding author: Manphool Singhal, MBBS, MD, DNB, FSCCT, FSCMR, Professor, Departments of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Madhya Marg, Sector 12, Chandigarh 160012, Chandigarh, India.

drmsinghal74@gmail.com

Abstract

Coronary artery abnormalities are the most important complications in children with Kawasaki disease (KD). Two-dimensional transthoracic echocardiography currently is the standard of care for initial evaluation and follow-up of children with KD. However, it has inherent limitations with regard to evaluation of mid and distal coronary arteries and, left circumflex artery and the poor acoustic window in older children often makes evaluation difficult in this age group. Catheter angiography (CA) is invasive, has high radiation exposure and fails to demonstrate abnormalities beyond lumen. The limitations of echocardiography and CA necessitate the use of an imaging modality that overcomes these problems. In recent years advances in computed tomography technology have enabled explicit evaluation of coronary arteries along their entire course including major branches with optimal and acceptable radiation exposure in children. Computed tomography coronary angiography (CTCA) can be performed during acute as well as convalescent phases of KD. It is likely that CTCA may soon be considered the reference standard imaging modality for evaluation of coronary arteries in children with KD.

Key Words: Coronary artery abnormalities; Computed tomography coronary angiography; 2D-echocardiography; Kawasaki disease; Imaging modality; Acquired heart disease

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In recent years advances in computed tomography technology have enabled explicit evaluation of coronary arteries along their entire course including major branches with optimal and acceptable radiation exposure in children. Computed tomography coronary angiography (CTCA) can be performed during acute as well as convalescent phases of Kawasaki disease (KD). It is likely that CTCA may soon be considered the gold standard imaging modality for evaluation of coronary arteries in children with KD.

Citation: Singhal M, Pilania RK, Gupta P, Johnson N, Singh S. Emerging role of computed tomography coronary angiography in evaluation of children with Kawasaki disease. *World J Clin Pediatr* 2023; 12(3): 97-106

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/97.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.97>

INTRODUCTION

Kawasaki disease (KD) is the most common vasculitis in children with a special predilection for coronary arteries. Coronary artery abnormalities (CAAs) are usually proportional to the extent of inflammation and without appropriate treatment, up to a quarter of patients with KD can develop CAAs. With early diagnosis and prompt institution of therapy, the incidence of CAAs is less than 5%, however there may be non-responsiveness to standard intravenous immunoglobulin therapy posing risk of developing severe CAAs[1-3]. CAAs can be assessed by several imaging techniques. 2D-echocardiography is the preferred imaging modality for coronary arteries evaluation both during the acute phase as well as during convalescence[4]. However, there has been increasing interest about other evolving modalities that can address the limitations of echocardiography[4,5]. In this context, we have discussed the role of computed tomography coronary angiography (CTCA) for detection of CAAs in KD and compared its performance with other available modalities. Current guidelines on use of CTCA have also been discussed along with the proposed use of CTCA in management of children with KD.

CORONARY ARTERY ABNORMALITIES IN KD AND NEED OF IMAGING

Coronary artery abnormalities (CAA) are the dreaded complications of KD requiring prompt and accurate diagnosis. In the acute phase of illness, typical CAAs include dilatation and aneurysm formation. These may resolve, remodel or persist during convalescence or may be complicated by thrombosis and steno-occlusive lesions mandating long term surveillance[6-10]. Concerns have also been raised that KD may act as a risk factor for premature atherosclerosis[11]. Precise imaging is required for assessment of these complications.

2D-echocardiography is the standard imaging modality for coronary arteries at presentation and during follow-up[12]. However, it has several limitations and these preclude its use in certain circumstances[12,13].

Other imaging techniques that have been used for coronary artery evaluation include catheter angiography (CA), CTCA and magnetic resonance coronary angiography (MRCA).

CA is an invasive procedure with uncontrolled radiation exposure[12], whereas MR angiography is technically difficult and very few centers have requisite expertise[4]. With the availability of modern CT scanners there is increasing interest in CTCA as an imaging modality of KD. It is non-invasive, has optimized sub-millisievert radiation exposure and has the potential to address all the limitations of CA and echocardiography[14-19]. Moreover CTCA has an ability to detect the earliest changes of atherosclerosis[20,21]. In this scenario CTCA seems promising and its incorporation into the management algorithm of KD should be considered. In this review we have discussed the emerging role of CTCA in evaluation of children with KD for detection of CAAs.

CTCA IN KD: NEEDS AND CHALLENGES

Transthoracic echocardiography is the presently standard of care for KD. However, it has several limitations. CA is invasive, has significant radiation exposure and cannot be repeated frequently.

After the advent of 64-Slice CT platforms, CTCA has become feasible. Radiation associated with CTCA is the biggest challenge as such radiation exposure has been linked to malignancies in children [22,23]. The older platforms also had sub-optimal image quality due to inherent high heart rates in children[14,24]. In recent years, however, CT technology has undergone a remarkable progress enabling the radiologist to acquire high resolution coronary artery images with acceptable radiation exposure and at any heart rate. This was possible due to higher slice CT (128, 256 and 320 slice) platforms and

dual source (DS) CT scanners[14-18]. DSCT has superior diagnostic performance as compared to single-source CT in the evaluation of coronary arteries and this gives an advantage of scanning in children who otherwise have inherent high heart rates and obviates the need of large doses of beta-blockers[17, 18].

As a result, CTCA is now being increasingly used for evaluation of children with KD and CAAs. It provides information about coronary arteries and the major branches with exquisite details of luminal caliber and intramural changes. Moreover, it can be repeated on follow-up as it is non-invasive. CTCA is especially useful in older children and adolescents who often have a poor acoustic window for echocardiography.

CTCA: CALCIUM SCORING AND LUMINOGRAPHY

CT calcium scoring is a technique that identifies calcium deposition in coronary arteries without the need of intravenous contrast (Figure 1). Calcium deposition in coronary arteries is a strong predictor of previous coronary artery involvement in patients with KD. Kahn *et al*[21] reported coronary artery calcium scoring using a low radiation dose CT protocol on 70 patients with KD at median of 14.8 years' follow-up and showed that coronary calcification was not present in patients with KD and normal coronaries during acute phase of disease. Ten out of 14 subjects with CAAs in acute phase had coronary calcification. A subsequent study from the same group of investigators affirmed that calcium deposition was not seen in patients with KD who did not develop CAAs during acute phase of disease[25]. The authors have shown that calcium scoring by CT is also a useful tool for identification of unidentified CAAs in patients with remote history of KD. It was also noted that sensitivity and specificity of calcium scoring to identify presence of CAAs is highest when scans were performed after more than 10 years of follow-up. Whether the degree of calcification has prognostic value in patients with KD is still conjectural. Zero calcium score in patients with remote history of KD is reassuring if performed at least 10 years after the initial illness.

Angiography or luminography is acquisition of data after injection of intra-venous contrast for evaluation of CAA. Acquisition of data should preferably be done with low radiation protocols and following strategies should be employed to reduce the radiation exposure:

Lower kilovoltage (kVp) for acquisition: kVp below 80 is appropriate - this reduces radiation exposure up to 70%[26-28].

Prospective ECG triggering: In this technique data acquisition is regulated by ECG signal and the X-ray tube current is either switched off or markedly lowered according to phase of R-R interval. This allows reduction of radiation exposure up to 90% as compared to retrospective ECG-gating, where X-ray exposure is given continuously[29-31]. Duan *et al*[17] and Kim *et al*[32] reported mean effective dose of 0.36 ± 0.06 mSv and 0.6 ± 0.5 mSv respectively on DSCT. Even in our experience the radiation had always been below 1 mSv[18].

(ECG)-controlled tube current modulation: With this technology up to 50% reduction in radiation exposure is achievable[32,33].

High pitch: Pitch in CT refers to area coverage with overlap and has inverse relationship with radiation exposure. With DSCT higher pitch (up to 3.4) there is further reduction in radiation exposure[34-36].

Iterative image reconstruction method: This is a newer development that allows to reconstruct data post-acquisition with high resolution images even at low radiation parameters (lower kilovoltage and tube current values)[36,37].

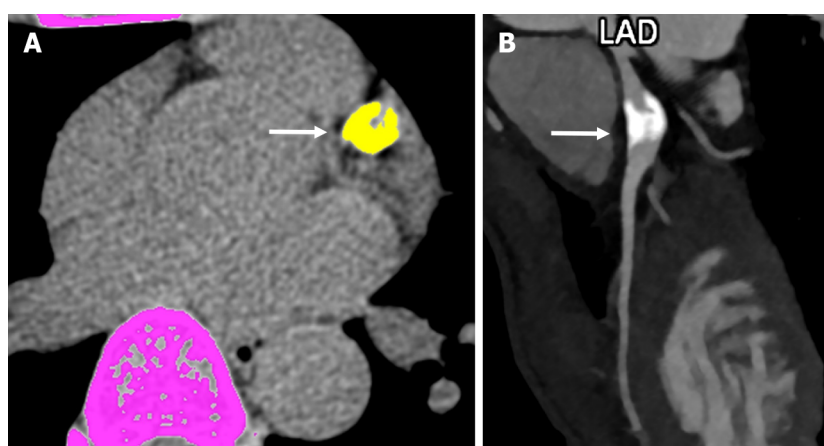
Using the dose saving strategies discussed above, radiation exposure can be brought down significantly below 1 mSv level[18,36].

CTCA: STRENGTH AND ADVANTAGES

CTCA with the current technologies of radiation optimization and fast scanning has capability to image the entire course of all coronary arteries especially left circumflex coronary artery which is difficult to evaluate on 2D-echocardiography (Figure 2). CTCA also allows to detect CAAs in middle and distal segments of coronary arteries[38]. These are usually missed on echocardiography (Figure 3). It also precisely identifies location and morphology of aneurysms (Figure 4) and thrombo-occlusive lesions (Figures 5 and 6). Mural abnormalities (calcifications, plaque, and adherent thrombus to luminal wall) are also well characterized on CTCA (Figures 1, 5 and 6).

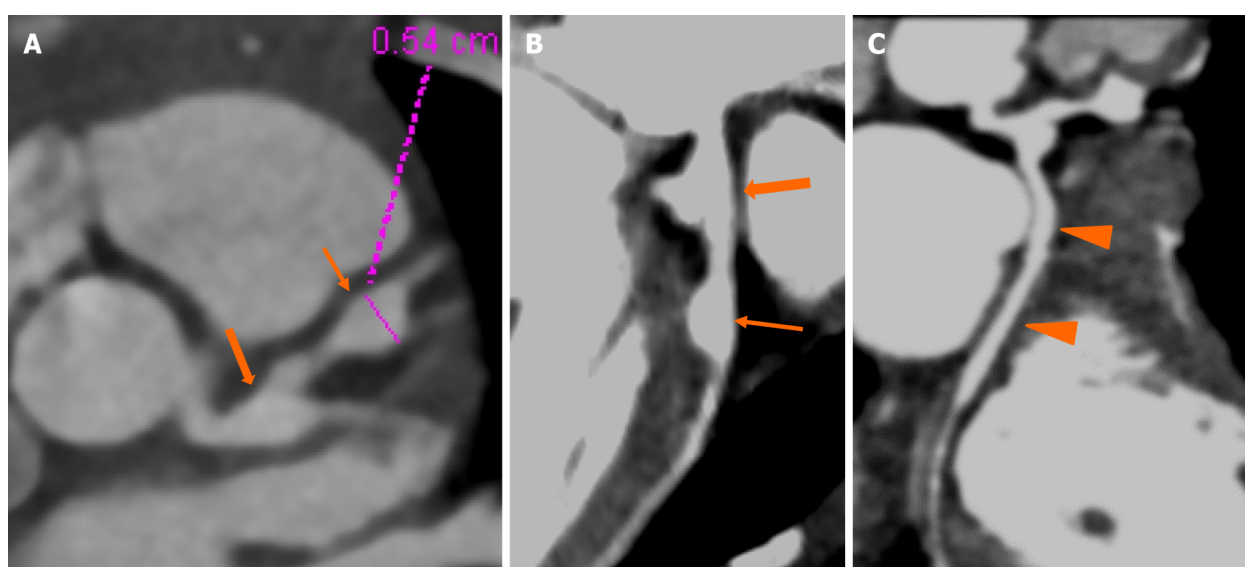
LIMITATIONS OF CTCA

CTCA has few limitations as it may not be available at all the centers, need of sedation in infants and



DOI: 10.5409/wjcp.v12.i3.97 Copyright ©The Author(s) 2023.

Figure 1 Computed tomography derived calcium score and role of angiography in convalescent phase of Kawasaki disease. A: Computed tomography (CT) derived calcium scoring in a 19 years male patient on follow-up with history of Kawasaki disease in childhood shows a thickly calcified lesion in the proximal course of left anterior descending coronary artery (color marked as yellow with an arrow (calcium score was 910); B: Subsequent CT coronary angiographic curved reformat image shows calcified aneurysm (arrow). LAD: Left anterior descending.



DOI: 10.5409/wjcp.v12.i3.97 Copyright ©The Author(s) 2023.

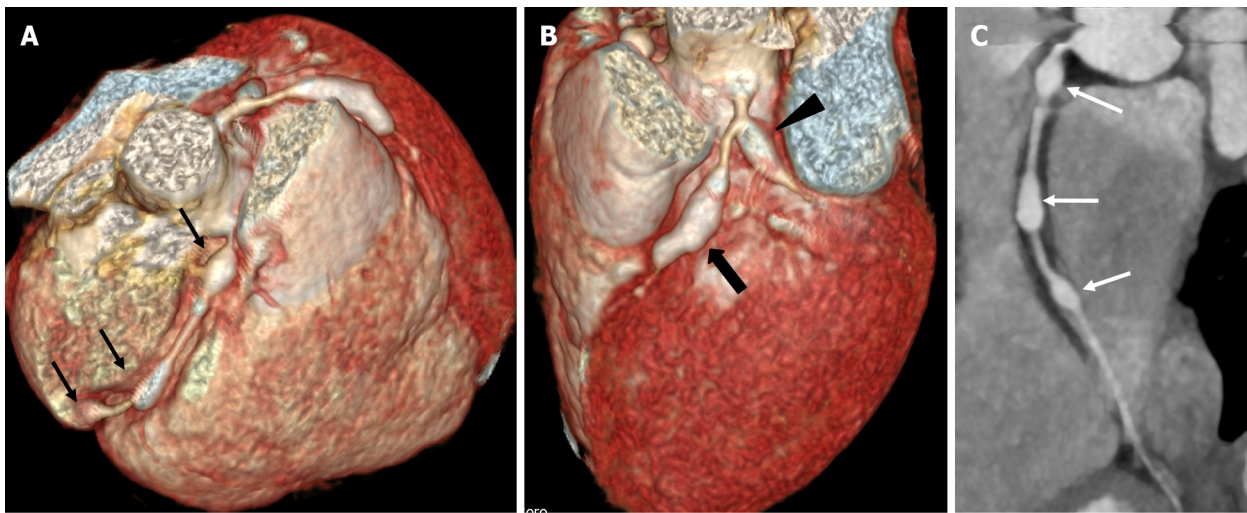
Figure 2 Computed tomography coronary angiography images showing its strength to evaluate coronary artery abnormalities in left circumflex artery. A: 3 years male child at presentation shows fusiform aneurysm at bifurcation of left main coronary artery [left main coronary artery (LMCA)- thick arrows in A and B] with extension into ostio-proximal segment of left anterior descending (LAD). Note a skip fusiform aneurysm in proximal LAD (thin arrow in b). C: Proximal and mid segments of left circumflex (LCX) are dilated (arrow heads in C). Echo demonstrated LMCA and LAD aneurysms however cannot evaluate LCX due to its orientation and course.

young children, portability and radiation exposure. However, these are minor considering the advantages derived and moreover advanced CT scanners with radiation optimization are now finding space in large centers. Sedation if so, needed in infants and young children is of short duration and general anesthesia is not required in our experience[38-40].

CTCA: COMPARISON WITH OTHER IMAGING MODALITIES

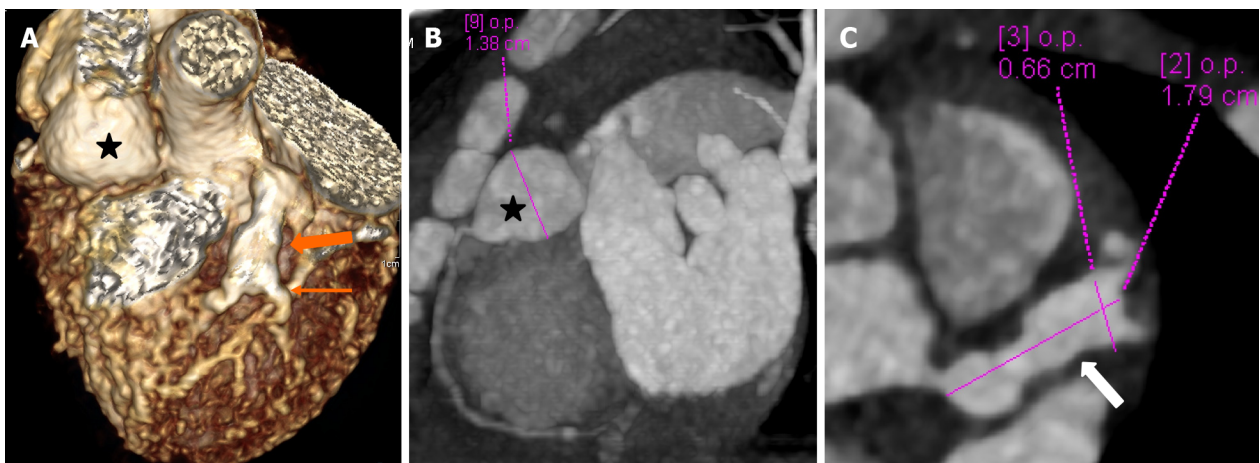
2D-echocardiography

It is known that CAAs in patients with KD can involve all segments of main coronary arteries. 2D-echocardiography remains the imaging modality of choice of evaluation of CAAs in patients with KD because of its inherent advantages – it is easily available, is inexpensive and can be repeated as often as required. However, it has only a limited role in evaluation of middle and distal coronary arteries and



DOI: 10.5409/wjcp.v12.i3.97 Copyright ©The Author(s) 2023.

Figure 3 Computed tomography coronary angiography images showing its ability to evaluate mid and distal segments of coronary arteries. Computed tomography coronary angiography (A and B: Volume rendered images; C: Curved reformatted image of RCA) of 4 years male at presentation demonstrate skip fusiform aneurysms in RCA (Thin arrows in A and C) and fusiform aneurysms in proximal LAD (thick arrow in B) and proximal left circumflex (arrow head in B). Fusiform aneurysm in mid and distal RCA could not be visualized on transthoracic echocardiography.



DOI: 10.5409/wjcp.v12.i3.97 Copyright ©The Author(s) 2023.

Figure 4 Panel of computed tomography coronary angiography images showing its ability to precisely identify location and morphology of aneurysms with extension into side branches. Computed tomography coronary angiography (A: Volume rendered image; B: Curved reformatted image and C-axial image) of 4 years female child in acute phase (presentation) demonstrate giant sacular aneurysm in proximal resonance coronary angiography (asterisk in A and B). Fusiform aneurysm is seen in proximal left anterior descending (thick arrow in A) with extension into diagonal-1 branch (thin arrow in A).

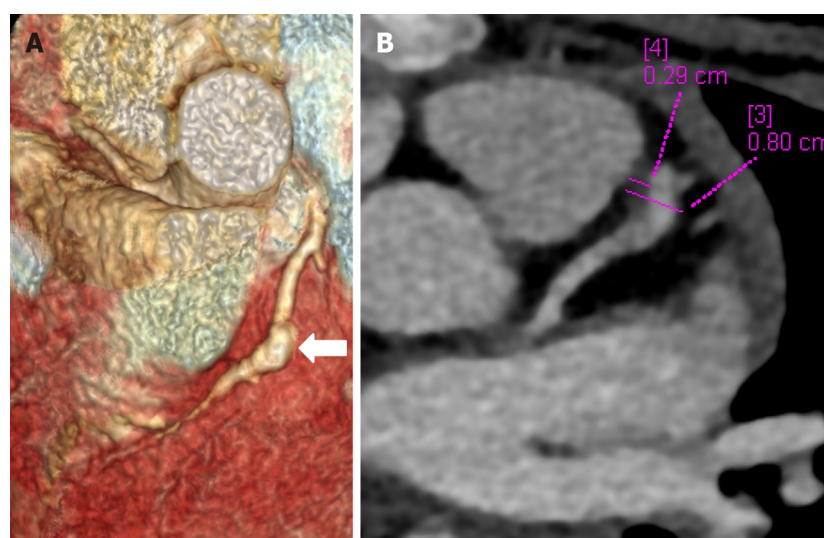
the left circumflex coronary artery[41]. CTCA provides an ideal method for evaluation of all segments of coronary arteries[38,42-45]. Several investigators have reported a good correlation between echocardiography and CTCA for the size of the aneurysms.

MRCA

It is still under evaluation for assessment of CAAs in children with KD. MRCA has lower spatial (related to image accuracy that measure fineness of image) and temporal (scanning speed) resolution and poorer image quality compared to CTCA[46,47]. Moreover, MRCA takes long scan time and often requires sedation in young children[32]. Steno-occlusive lesions are better delineated on CTCA compared to MRCA[32]. MRCA, however, is better for evaluation of coronary arteries with heavy intramural calcifications (leading to blooming artefact on CT), assessment of myocardial perfusion and viability, and serial follow-up of thrombotic aneurysms[48].

CA

It is the gold standard for evaluation of coronary artery lumen, but is of limited value for assessment of mural abnormalities (thickening, plaque and calcifications) and intramural thrombi. Moreover, it is an



DOI: 10.5409/wjcp.v12.i3.97 Copyright ©The Author(s) 2023.

Figure 5 Computed tomography coronary angiography images depicting complications in coronary artery abnormalities (thrombus).

Computed tomography coronary angiography [(A: Volume rendered image; B: Axial image in plane of left anterior descending (LAD))] during follow up at shows a giant fusiform aneurysm in mid segment of LAD (thick arrow in A) with a hypodense plaque like tissue attached to the anterior wall (B) suggestive of thrombus. Child was having chest pain and ECHO at presentation and during the current episode was reported as normal; ECHO fails to elicit coronary artery abnormalities and its complication of thrombus in the aneurysm.

invasive procedure with inordinate radiation exposure. CTCA with CA has been shown to have excellent agreement for measurement of size of aneurysms[49].

CTCA: WHEN TO ADVISE?

Current guidelines and the way forward

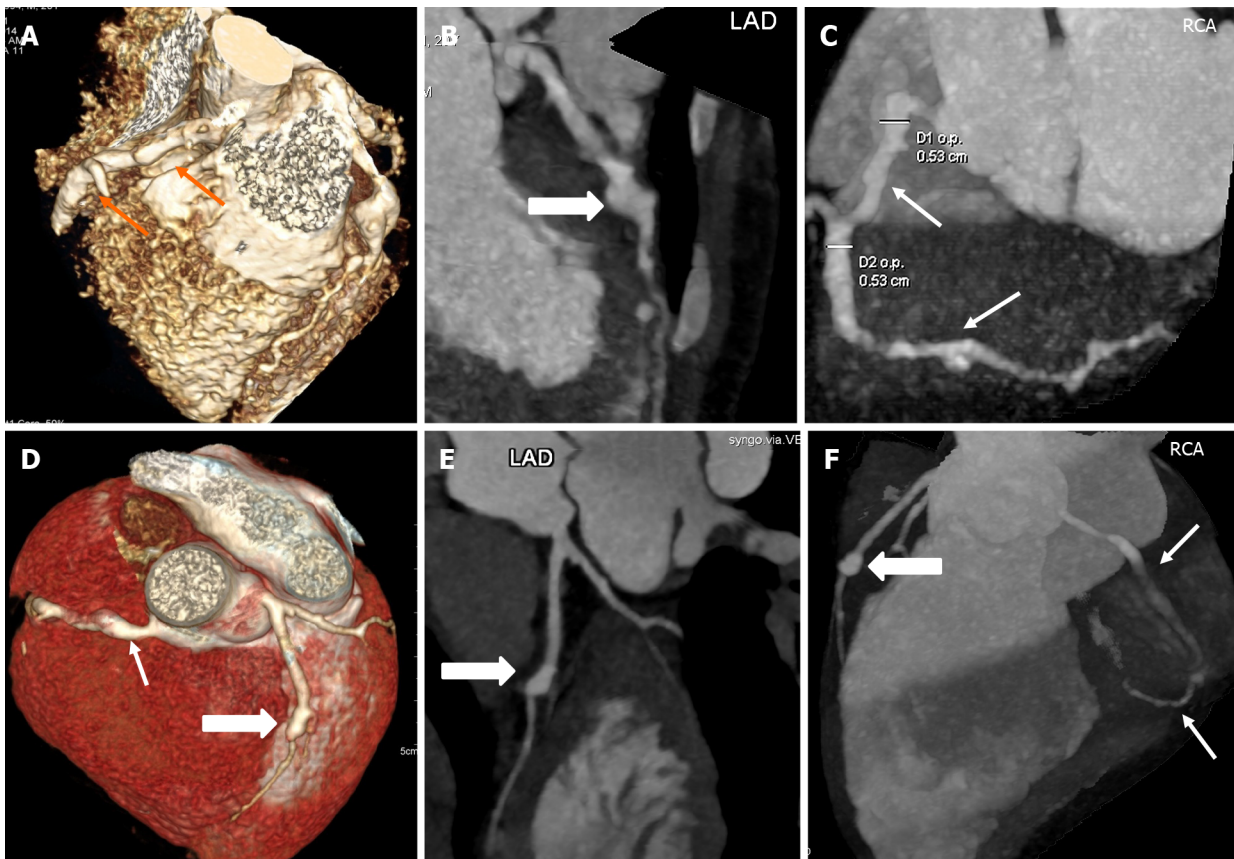
The American Heart Association Guidelines 2017 have recommended use of CTCA in following circumstances during follow-up when 2D-echocardiography becomes limiting[50]: (1) Due to poor acoustic window in older children; (2) Poor sensitivity to detect complications like thrombosis, stenosis; (3) Inability to detect distal abnormalities; and (4) For detection of mural abnormalities or calcification; However, based on our clinical experience over 25 years we suggest that CTCA may be considered under the following circumstances: As a baseline additional investigation in acute phase in children having significant CAAs on 2D-echocardiography for confirmation of echocardiography findings, detection of distal CAAs and for follow-up[38]. When the initial 2D-echocardiography examination in acute phase is equivocal or sub-optimal, Apparently normal 2D-echocardiography examination in acute phase with a stormy clinical course, On follow-up assessment of CAAs to document resolution or complications (*e.g.*, thrombosis, stenosis), Long term surveillance for detection of mural abnormalities and dystrophic calcifications. At the present time there is no consensus amongst experts on the timing and frequency of carrying out CTCA during follow up of children with KD.

Recent advances in CTCA in KD

Cardiac single-photon emission computed tomography (SPECT) and CT hybrid imaging has been recently described for accurate demonstration of ischemic regions of the myocardium. Abe *et al*[51] have performed SPECT/CT in 17 patients with KD in chronic phase of disease and showed that this fusion imaging was capable of accurately evaluating myocardial ischemia/infarction as cardiovascular sequelae of KD and delineating the affected coronary arteries.

CONCLUSION

State of the art CT platforms now allow CTCA with high resolution images at sub-millisievert radiation exposure. CTCA has the ability to detect CAAs along the entire course of coronary arteries and delineates mural abnormalities, which otherwise are missed on current standard of care 2D-echocardiography. CTCA can be performed during acute as well as convalescent phases of KD. It is likely that CTCA may soon be considered the imaging modality of choice for evaluation of coronary arteries in children with KD and multi-centric studies focused on use of CTCA is desirable to formulate guidelines.



DOI: 10.5409/wjcp.v12.i3.97 Copyright ©The Author(s) 2023.

Figure 6 Computed tomography coronary angiography images showing its role in follow-up imaging and its role in assessment of complications. Computed tomography coronary angiography (CTCA) at presentation in 1 year male (top row A-C) shows a giant complex aneurysm in mid segment of left anterior descending (LAD) (thick arrow in A and B) with multiple segmental aneurysms along the entire course of resonance coronary angiography (RCA). Follow-up CTCA after 3 years of presentation shows remodelling of LAD aneurysm (now becomes fusiform with mural calcification and severe stenosis its distal aspect (thick arrows D-F), also note resolution of aneurysmal dilatations of RCA (lower row D-F).

FOOTNOTES

Author contributions: Singhal M and Pilia RK contributed equally and shared the first authorship. Singhal M and Pilia RK designed the research, written first draft, review of literature, editing of manuscript and critical revision of manuscript at all stages; Gupta P and Johnson N contributed in literature review and editing of the manuscript; Singh S review of literature, editing of manuscript, critical revision of manuscript at all stages. Singhal M and Pilia RK are joint first authors.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: India

ORCID number: Manphool Singhal 0000-0002-1311-7203; Rakesh Kumar Pilia 0000-0002-9015-1704; Pankaj Gupta 0000-0003-3914-3757; Nameirakpam Johnson 0000-0002-9016-7722; Surjit Singh 0000-0002-8738-4582.

S-Editor: Ma YJ

L-Editor: A

P-Editor: Ma YJ

REFERENCES

- 1 **Kato H.** [Natural history of Kawasaki disease vasculitis]. *Nihon Rinsho* 2014; **72**: 1530-1535 [PMID: [25518398](#)]
- 2 **Kato H,** Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Eto G, Yamakawa R. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation* 1996; **94**: 1379-1385 [PMID: [8822996](#) DOI: [10.1161/01.cir.94.6.1379](#)]
- 3 **Rigante D,** Andreozzi L, Fastiggi M, Bracci B, Natale MF, Esposito S. Critical Overview of the Risk Scoring Systems to Predict Non-Responsiveness to Intravenous Immunoglobulin in Kawasaki Syndrome. *Int J Mol Sci* 2016; **17**: 278 [PMID: [26927060](#) DOI: [10.3390/ijms17030278](#)]
- 4 **Newburger JW,** Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA; Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease; Council on Cardiovascular Disease in the Young; American Heart Association; American Academy of Pediatrics. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004; **110**: 2747-2771 [PMID: [15505111](#) DOI: [10.1161/01.CIR.0000145143.19711.78](#)]
- 5 **Dajani AS,** Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M, Takahashi M, Bierman FZ, Karchmer AW, Wilson W. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993; **87**: 1776-1780 [PMID: [8491037](#) DOI: [10.1161/01.cir.87.5.1776](#)]
- 6 **Suzuki A,** Kamiya T, Arakaki Y, Kinoshita Y, Kimura K. Fate of coronary arterial aneurysms in Kawasaki disease. *Am J Cardiol* 1994; **74**: 822-824 [PMID: [7942561](#) DOI: [10.1016/0002-9149\(94\)90446-4](#)]
- 7 **Suzuki A,** Kamiya T, Ono Y, Kinoshita Y, Kawamura S, Kimura K. Clinical significance of morphologic classification of coronary arterial segmental stenosis due to Kawasaki disease. *Am J Cardiol* 1993; **71**: 1169-1173 [PMID: [8480642](#) DOI: [10.1016/0002-9149\(93\)90641-o](#)]
- 8 **Suzuki A,** Kamiya T, Ono Y, Kohata T, Kimura K, Takamiya M. Follow-up study of coronary artery lesions due to Kawasaki disease by serial selective coronary arteriography in 200 patients. *Heart Vessels* 1987; **3**: 159-165 [PMID: [3440782](#) DOI: [10.1007/BF02058793](#)]
- 9 **Pilania RK,** Jindal AK, Bhattarai D, Naganur SH, Singh S. Cardiovascular Involvement in Kawasaki Disease Is Much More Than Mere Coronary Arteritis. *Front Pediatr* 2020; **8**: 526969 [PMID: [33072669](#) DOI: [10.3389/fped.2020.526969](#)]
- 10 **Pilania RK,** Bhattarai D, Singh S. Controversies in diagnosis and management of Kawasaki disease. *World J Clin Pediatr* 2018; **7**: 27-35 [PMID: [29456929](#) DOI: [10.5409/wjcp.v7.i1.27](#)]
- 11 **Takahashi K,** Oharaseki T, Naoe S. Pathological study of postcoronary arteritis in adolescents and young adults: with reference to the relationship between sequelae of Kawasaki disease and atherosclerosis. *Pediatr Cardiol* 2001; **22**: 138-142 [PMID: [11178671](#) DOI: [10.1007/s002460010180](#)]
- 12 **Sokmen G,** Tuncer C, Sokmen A, Suner A. Clinical and angiographic features of large left main coronary artery aneurysms. *Int J Cardiol* 2008; **123**: 79-83 [PMID: [17407794](#) DOI: [10.1016/j.ijcard.2007.01.054](#)]
- 13 **Sato Y,** Kato M, Inoue F, Fukui T, Imazeki T, Mitsui M, Matsumoto N, Takahashi M, Karasawa K, Ayusawa M, Kanamaru H, Harada K, Kanmatsuse K. Detection of coronary artery aneurysms, stenoses and occlusions by multislice spiral computed tomography in adolescents with kawasaki disease. *Circ J* 2003; **67**: 427-430 [PMID: [12736482](#) DOI: [10.1253/circj.67.427](#)]
- 14 **Mizuno N,** Funabashi N, Imada M, Tsunoo T, Endo M, Komuro I. Utility of 256-slice cone beam tomography for real four-dimensional volumetric analysis without electrocardiogram gated acquisition. *Int J Cardiol* 2007; **120**: 262-267 [PMID: [17084925](#) DOI: [10.1016/j.ijcard.2006.07.219](#)]
- 15 **de Graaf FR,** Schuijf JD, van Velzen JE, Kroft LJ, de Roos A, Reiber JH, Boersma E, Schalijs MJ, Spanó F, Jukema JW, van der Wall EE, Bax JJ. Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography in the non-invasive evaluation of significant coronary artery disease. *Eur Heart J* 2010; **31**: 1908-1915 [PMID: [20047991](#) DOI: [10.1093/eurheartj/ehp571](#)]
- 16 **Pasricha SS,** Nandurkar D, Seneviratne SK, Cameron JD, Crossett M, Schneider-Kolsky ME, Troupis JM. Image quality of coronary 320-MDCT in patients with atrial fibrillation: initial experience. *AJR Am J Roentgenol* 2009; **193**: 1514-1521 [PMID: [19933642](#) DOI: [10.2214/AJR.09.2319](#)]
- 17 **Duan Y,** Wang X, Cheng Z, Wu D, Wu L. Application of prospective ECG-triggered dual-source CT coronary angiography for infants and children with coronary artery aneurysms due to Kawasaki disease. *Br J Radiol* 2012; **85**: e1190-e1197 [PMID: [22932064](#) DOI: [10.1259/bjr/18174517](#)]
- 18 **Singhal M,** Singh S, Gupta P, Sharma A, Khandelwal N, Burns JC. Computed Tomography Coronary Angiography for Evaluation of Children With Kawasaki Disease. *Curr Probl Diagn Radiol* 2018; **47**: 238-244 [PMID: [29203262](#) DOI: [10.1067/j.cpradiol.2017.09.013](#)]
- 19 **Tsuda E,** Singhal M. Role of imaging studies in Kawasaki disease. *Int J Rheum Dis* 2018; **21**: 56-63 [PMID: [29115035](#) DOI: [10.1111/1756-185X.13210](#)]
- 20 **Thangathurai J,** Kalashnikova M, Takahashi M, Shinbane JS. Coronary Artery Aneurysm in Kawasaki Disease: Coronary CT Angiography through the Lens of Pathophysiology and Differential Diagnosis. *Radiol Cardiothorac Imaging* 2021; **3**: e200550 [PMID: [34778780](#) DOI: [10.1148/ryct.2021200550](#)]
- 21 **Kahn AM,** Budoff MJ, Daniels LB, Jimenez-Fernandez S, Cox AS, Gordon JB, Burns JC. Calcium scoring in patients with a history of Kawasaki disease. *JACC Cardiovasc Imaging* 2012; **5**: 264-272 [PMID: [22421171](#) DOI: [10.1016/j.jcmg.2011.12.010](#)]
- 22 **Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation,** Nuclear and Radiation Studies Board, Division on Earth and Life Studies, National Research Council of the National Academies. Available from: <https://nap.nationalacademies.org/catalog/11340/health-risks-from-exposure-to-low-levels-of-ionizing-radiation>
- 23 **Brenner DJ,** Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 2007; **357**: 2277-

- 2284 [PMID: [18046031](#) DOI: [10.1056/NEJMra072149](#)]
- 24 **Peng Y**, Zeng J, Du Z, Sun G, Guo H. Usefulness of 64-slice MDCT for follow-up of young children with coronary artery aneurysm due to Kawasaki disease: initial experience. *Eur J Radiol* 2009; **69**: 500-509 [PMID: [18164157](#) DOI: [10.1016/j.ejrad.2007.11.024](#)]
 - 25 **Kahn AM**, Budoff MJ, Daniels LB, Oyamada J, Gordon JB, Burns JC. Usefulness of Calcium Scoring as a Screening Examination in Patients With a History of Kawasaki Disease. *Am J Cardiol* 2017; **119**: 967-971 [PMID: [28193446](#) DOI: [10.1016/j.amjcard.2016.11.055](#)]
 - 26 **Leschka S**, Stolzmann P, Schmid FT, Scheffel H, Stinn B, Marincek B, Alkadhi H, Wildermuth S. Low kilovoltage cardiac dual-source CT: attenuation, noise, and radiation dose. *Eur Radiol* 2008; **18**: 1809-1817 [PMID: [18392829](#) DOI: [10.1007/s00330-008-0966-1](#)]
 - 27 **Pfleiderer T**, Rudofsky L, Ropers D, Bachmann S, Marwan M, Daniel WG, Achenbach S. Image quality in a low radiation exposure protocol for retrospectively ECG-gated coronary CT angiography. *AJR Am J Roentgenol* 2009; **192**: 1045-1050 [PMID: [19304712](#) DOI: [10.2214/AJR.08.1025](#)]
 - 28 **Sun Z**, Choo GH, Ng KH. Coronary CT angiography: current status and continuing challenges. *Br J Radiol* 2012; **85**: 495-510 [PMID: [22253353](#) DOI: [10.1259/bjr/15296170](#)]
 - 29 **Scheffel H**, Alkadhi H, Leschka S, Plass A, Desbiolles L, Guber I, Krauss T, Gruenfelder J, Genoni M, Luescher TF, Marincek B, Stolzmann P. Low-dose CT coronary angiography in the step-and-shoot mode: diagnostic performance. *Heart* 2008; **94**: 1132-1137 [PMID: [18519548](#) DOI: [10.1136/hrt.2008.149971](#)]
 - 30 **Husmann L**, Valenta I, Gaemperli O, Adda O, Treyer V, Wyss CA, Veit-Haibach P, Tatsugami F, von Schulthess GK, Kaufmann PA. Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating. *Eur Heart J* 2008; **29**: 191-197 [PMID: [18089704](#) DOI: [10.1093/eurheartj/ehm613](#)]
 - 31 **Shuman WP**, Branch KR, May JM, Mitsumori LM, Lockhart DW, Dubinsky TJ, Warren BH, Caldwell JH. Prospective versus retrospective ECG gating for 64-detector CT of the coronary arteries: comparison of image quality and patient radiation dose. *Radiology* 2008; **248**: 431-437 [PMID: [18552312](#) DOI: [10.1148/radiol.2482072192](#)]
 - 32 **Kim JW**, Goo HW. Coronary artery abnormalities in Kawasaki disease: comparison between CT and MR coronary angiography. *Acta Radiol* 2013; **54**: 156-163 [PMID: [23482350](#) DOI: [10.1258/ar.2012.120484](#)]
 - 33 **Lee TY**, Chhem RK. Impact of new technologies on dose reduction in CT. *Eur J Radiol* 2010; **76**: 28-35 [PMID: [20643522](#) DOI: [10.1016/j.ejrad.2010.06.036](#)]
 - 34 **Ertel D**, Lell MM, Harig F, Flohr T, Schmidt B, Kalender WA. Cardiac spiral dual-source CT with high pitch: a feasibility study. *Eur Radiol* 2009; **19**: 2357-2362 [PMID: [19565245](#) DOI: [10.1007/s00330-009-1503-6](#)]
 - 35 **Gosling O**, Loader R, Venables P, Roobottom C, Rowles N, Bellenger N, Morgan-Hughes A. A comparison of radiation doses between state-of-the-art multislice CT coronary angiography with iterative reconstruction, multislice CT coronary angiography with standard filtered back-projection and invasive diagnostic coronary angiography. *Heart* 2010; **96**: 922-926 [PMID: [20538667](#) DOI: [10.1136/hrt.2010.195909](#)]
 - 36 **Hausleiter J**, Meyer T, Hadamitzky M, Huber E, Zankl M, Martinoff S, Kastrati A, Schömig A. Radiation dose estimates from cardiac multislice computed tomography in daily practice: impact of different scanning protocols on effective dose estimates. *Circulation* 2006; **113**: 1305-1310 [PMID: [16520411](#) DOI: [10.1161/CIRCULATIONAHA.105.602490](#)]
 - 37 **Weustink AC**, Neefjes LA, Kyrzopoulos S, van Straten M, Neoh Eu R, Meijboom WB, van Mieghem CA, Capuano E, Dijkshoorn ML, Cademartiri F, Boersma E, de Feyter PJ, Krestin GP, Mollet NR. Impact of heart rate frequency and variability on radiation exposure, image quality, and diagnostic performance in dual-source spiral CT coronary angiography. *Radiology* 2009; **253**: 672-680 [PMID: [19864512](#) DOI: [10.1148/radiol.2533090358](#)]
 - 38 **Singhal M**, Pilania RK, Jindal AK, Gupta A, Sharma A, Guleria S, Johnson N, Maralakunte M, Vignesh P, Suri D, Sandhu MS, Singh S. Distal coronary artery abnormalities in Kawasaki disease: experience on CT coronary angiography in 176 children. *Rheumatology (Oxford)* 2023; **62**: 815-823 [PMID: [35394488](#) DOI: [10.1093/rheumatology/keac217](#)]
 - 39 **Dusad S**, Singhal M, Pilania RK, Suri D, Singh S. CT Coronary Angiography Studies After a Mean Follow-up of 3.8 Years in Children With Kawasaki Disease and Spontaneous Defervescence. *Front Pediatr* 2020; **8**: 274 [PMID: [32548085](#) DOI: [10.3389/fped.2020.00274](#)]
 - 40 **van Stijn D**, Planken RN, Groenink M, Streekstra GJ, Kuipers TW, Kuipers IM. Coronary artery assessment in Kawasaki disease with dual-source CT angiography to uncover vascular pathology. *Eur Radiol* 2020; **30**: 432-441 [PMID: [31428828](#) DOI: [10.1007/s00330-019-06367-6](#)]
 - 41 **Yu Y**, Sun K, Wang R, Li Y, Xue H, Yu L, Chen S, Xi L. Comparison study of echocardiography and dual-source CT in diagnosis of coronary artery aneurysm due to Kawasaki disease: coronary artery disease. *Echocardiography* 2011; **28**: 1025-1034 [PMID: [21854436](#) DOI: [10.1111/j.1540-8175.2011.01486.x](#)]
 - 42 **Arnold R**, Ley S, Ley-Zaporozhan J, Eichhorn J, Schenk JP, Ulmer H, Kauczor HU. Visualization of coronary arteries in patients after childhood Kawasaki syndrome: value of multidetector CT and MR imaging in comparison to conventional coronary catheterization. *Pediatr Radiol* 2007; **37**: 998-1006 [PMID: [17768616](#) DOI: [10.1007/s00247-007-0566-2](#)]
 - 43 **Chu WC**, Mok GC, Lam WW, Yam MC, Sung RY. Assessment of coronary artery aneurysms in paediatric patients with Kawasaki disease by multidetector row CT angiography: feasibility and comparison with 2D echocardiography. *Pediatr Radiol* 2006; **36**: 1148-1153 [PMID: [16912893](#) DOI: [10.1007/s00247-006-0281-4](#)]
 - 44 **Xing Y**, Wang H, Yu X, Chen R, Hou Y. Assessment of coronary artery lesions in children with Kawasaki disease: evaluation of MSCT in comparison with 2-D echocardiography. *Pediatr Radiol* 2009; **39**: 1209-1215 [PMID: [19669746](#) DOI: [10.1007/s00247-009-1364-9](#)]
 - 45 **Jrad M**, Ben Salem F, Barhoumi C, Lassoued F, Frikha W, Boukriba S, Mizouni H. The Role of Computed Tomography Coronary Angiography in Kawasaki Disease: Comparison with Transthoracic Echocardiography in a 25-Case Retrospective Study. *Pediatr Cardiol* 2019; **40**: 265-275 [PMID: [30600370](#) DOI: [10.1007/s00246-018-2044-z](#)]
 - 46 **Schuijff JD**, Bax JJ, Shaw LJ, de Roos A, Lamb HJ, van der Wall EE, Wijns W. Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography. *Am Heart J* 2006; **151**: 404-411 [PMID: [16442907](#) DOI: [10.1016/j.ahj.2005.03.022](#)]
 - 47 **Bluemke DA**, Achenbach S, Budoff M, Gerber TC, Gersh B, Hillis LD, Hundley WG, Manning WJ, Printz BF, Stuber M,

Woodard PK. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the american heart association committee on cardiovascular imaging and intervention of the council on cardiovascular radiology and intervention, and the councils on clinical cardiology and cardiovascular disease in the young. *Circulation* 2008; **118**: 586-606 [PMID: [18586979](#) DOI: [10.1161/CIRCULATIONAHA.108.189695](#)]

- 48 **Zhang S**, Levin DC, Halpern EJ, Fischman D, Savage M, Walinsky P. Accuracy of MDCT in assessing the degree of stenosis caused by calcified coronary artery plaques. *AJR Am J Roentgenol* 2008; **191**: 1676-1683 [PMID: [19020235](#) DOI: [10.2214/AJR.07.4026](#)]
- 49 **Tsujii N**, Tsuda E, Kanzaki S, Kurosaki K. Measurements of Coronary Artery Aneurysms Due to Kawasaki Disease by Dual-Source Computed Tomography (DSCT). *Pediatr Cardiol* 2016; **37**: 442-447 [PMID: [26515298](#) DOI: [10.1007/s00246-015-1297-z](#)]
- 50 **McCordle BW**, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017; **135**: e927-e999 [PMID: [28356445](#) DOI: [10.1161/CIR.0000000000000484](#)]
- 51 **Abe M**, Fukazawa R, Ogawa S, Watanabe M, Fukushima Y, Kiriya T, Hayashi H, Itoh Y. Usefulness of Single Photon Emission Computed Tomography/Computed Tomography Fusion-Hybrid Imaging to Evaluate Coronary Artery Disorders in Patients with a History of Kawasaki Disease. *J Nippon Med Sch* 2016; **83**: 71-80 [PMID: [27180792](#) DOI: [10.1272/jnms.83.71](#)]

Retrospective Cohort Study

IFIH1 and DDX58 gene variants in pediatric rheumatic diseases

Rinat Raupov, Evgeny Suspitsin, Konstantin Belozarov, Tatiana Gabrusskaya, Mikhail Kostik

Specialty type: Pediatrics**Provenance and peer review:**

Invited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Dauey K, Kazakhstan; Gastañaga-Holguera T, Spain; Tanaka H, Japan**Received:** December 30, 2022**Peer-review started:** December 30, 2022**First decision:** January 20, 2023**Revised:** February 3, 2023**Accepted:** April 24, 2023**Article in press:** April 24, 2023**Published online:** June 9, 2023**Rinat Raupov, Konstantin Belozarov, Mikhail Kostik**, Department of Pediatrics, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia**Evgeny Suspitsin**, Department of Genetics, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia**Tatiana Gabrusskaya**, Department of Gastrointestinal Diseases, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg 194100, Russia**Corresponding author:** Mikhail Kostik, MD, PhD, Professor, Department of Pediatrics, Saint-Petersburg State Pediatric Medical University, Lytovskaya 2, Saint-Petersburg 194100, Russia. kost-mikhail@yandex.ru**Abstract****BACKGROUND**

The *IFIH1* gene codes the MDA5 protein and the *DDX58* gene codes the RIG-I receptor. Both proteins are parts of the interferon (IFN) I signaling pathway and are responsible for antiviral defense and innate immune response. *IFIH1* and *DDX58* polymorphisms are associated with a spectrum of autoimmune diseases. Rare gain-of-function *IFIH1* mutations have been found in Singleton-Merten and Aicardi-Goutières syndrome, while *DDX58* mutation can cause atypical Singleton-Merten syndrome.

AIM

To characterize children with pediatric rheumatic diseases (PRD) carrying *DDX58* or *IFIH1* variants.

METHODS

Clinical exome sequencing was performed on 92 children with different PRD. *IFIH1* and *DDX58* variants have been detected in 14 children. IFN-I score has been analyzed and the clinical characteristics of patients have been studied.

RESULTS

A total of seven patients with systemic lupus erythematosus (SLE) ($n = 2$), myelodysplastic syndrome with SLE features at the onset of the disease ($n = 1$), mixed connective tissue disease (MCTD) ($n = 1$), undifferentiated systemic autoimmune-inflammatory disease (uSAID) ($n = 3$) have 5 different variants of the *DDX58* gene. A common non-pathogenic variant p.D580E has been found in five children. A rare variant of uncertain significance (VUS) p.N354S was found in one patient with uSAID, a rare likely non-pathogenic variant p.E37K in one patient with

uSAID, and a rare likely pathogenic variant p.Cys864fs in a patient with SLE. Elevated IFN-I score was detected in 6 of 7 patients with *DDX58* variants. Seven patients had six different *IFIH1* variants. They were presented with uSAID ($n = 2$), juvenile dermatomyositis (JDM) ($n = 1$), SLE-like disease ($n = 1$), Periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome ($n = 1$), and systemic onset juvenile idiopathic arthritis ($n = 1$). Three patients have VUS p.E627X, one patient has benign variant p.I923V. Rare VUS p.R595H was detected in the JDM patient. Another rare VUS p.L679Ifs*2 and previously not reported variant p.V599Ffs*5 were detected in the patient with uSAID. One patient with uSAID has rare VUS p.T520A. All patients had elevated IFN-I scores.

CONCLUSION

Rare compound-heterozygous *IFIH1* variant (p.L679Ifs*2 and p.V599Ffs*5), heterozygous *IFIH1* variant (p.T520A) and heterozygous *DDX58* variant (p.Cys864fs) are probably disease causative for uSAID and SLE. The majority of patients with different *DDX58* and *IFIH1* variants had hyperactivation of the IFN I signaling pathway.

Key Words: *IFIH1*; *DDX58*; Undifferentiated systemic autoinflammatory disease; Systemic lupus erythematosus; Interferon-I score

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Interferon (IFN) I signaling pathway is the important part of innate immune system and antiviral defense. It's known that defects in the components of IFN I signaling system can leads to its hyperactivation. This pathogenetic phenomenon is considered as one of the most important in the pathogenesis of immune-mediated diseases, such as systemic lupus erythematosus, dermatomyositis, systemic autoinflammatory diseases. From database containing 92 patients with different rheumatic diseases, whom clinical exome sequencing was performed we selected 14 children (10 girls and 4 boys): 7 patients had *DDX58* and 7 had *IFIH1* gene variants. The majority of patient with different *DDX58* and *IFIH1* variants had hyperactivation of IFN I signaling pathway.

Citation: Raupov R, Suspitsin E, Belozerov K, Gabrusskaya T, Kostik M. *IFIH1* and *DDX58* gene variants in pediatric rheumatic diseases. *World J Clin Pediatr* 2023; 12(3): 107-114

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/107.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.107>

INTRODUCTION

The *DDX58* gene encodes the RIG-I receptor (retinoic acid-induced protein I), which is responsible for the virus's ribonucleic acid (RNA) recognition[1]. RIG-1 interacts with short-stranded RNA (ssRNA) of viruses that lead to mitochondrial antiviral-signaling protein (MAVS) activation, which in turn leads to the expression of interferon (IFN)-regulated genes and the secretion of type I IFNs. The *IFIH1* gene encodes a cytoplasmic receptor that senses double-stranded RNA viral products to activate type I IFN signaling through the MAVS adaptor molecule. This can inhibit virus replication and modulate cellular immune responses. *IFIH1* may also help recognize and limit the replication of ssRNA viruses[2].

IFN I signaling pathway is an important part of the innate immune system and antiviral defense[3]. It's known that defects in the components of the IFN I signaling system can lead to its hyperactivation. This pathogenetic phenomenon is considered one of the most important in the pathogenesis of immune-mediated diseases, such as systemic lupus erythematosus (SLE), dermatomyositis (DM), and systemic autoinflammatory diseases (SAID)[4]. The roles of *DDX58* and *IFIH1* gene variants in the pathogenesis of immune-mediated diseases are not fully studied. Our study aimed to describe children with different rheumatic diseases who have variants in *DDX58* or *IFIH1* genes.

MATERIALS AND METHODS

From a database containing 92 patients with different rheumatic diseases, for whom clinical exome sequencing was performed we selected 14 children (10 girls and 4 boys) having the variants of *DDX58* or *IFIH1* genes. They have the following diagnosis: SAID ($n = 6$), SLE ($n = 5$), juvenile DM (JDM) ($n = 1$), systemic onset juvenile idiopathic arthritis ($n = 1$), mixed connective tissue disease ($n = 1$).

IFN-I score was measured in the majority of patients. Real-time polymerase chain reaction with previous reverse transcription of RNA was used for IFN-I score assessment. Amplification was carried out using hybridization probes (TaqMan probes); changes in gene expression were evaluated by the ratio of signals “studied gene/referee gene”; the value of the IFN-I score corresponds to the median relative expression of 5 genes studied (*IFI44L*, *IFI44*, *IFIT3*, *LY6E*, *MX1*). The IFN-I score value of ≥ 2.0 was taken as a cut-off, indicating increased transcription of IFN-I-regulated genes *i.e.*, the presence of an IFN signature.

RESULTS

Five different variants of the *DDX58* gene were found in 7/14 patients included in the study, among which the p.D580E variant was found in 4 patients. One patient had 2 different variants of *DDX58*, including p.D580E. The variant p.D580E is a frequent polymorphism [minor allele frequency (MAF): 0.11]. Two patients had likely non-pathogenic variants *DDX58* according to American College of Medical Genetics (ACMG) (p.S144F and p.E37K). A rare variant of uncertain significance (VUS) of the *DDX58* (p.N354S) gene was detected in one patient. Only one patient with SLE had a likely pathogenic variant of the *DDX58* gene - p.Cys864fs. Patients had the following distribution according to the diagnosis: SLE ($n = 2$), myelodysplastic syndrome with SLE features at the onset of the disease ($n = 1$), mixed connective tissue disease ($n = 1$), undifferentiated SAID (uSAID) ($n = 3$). IFN-I score was evaluated in 6/7 patients with *DDX58* variants. IFN-I score was higher by 4 or more times compared to reference values in 5 patients, whereas in one patient IFN-I score was slightly increased - 2.13 UE/mL (normal value is less than 2.0 UE/mL). **Table 1** shows variants of the *DDX58* genes and the values of the IFN-I scores. Brief clinical characteristics of patients with rare *DDX58* variants will be presented below.

Patient's description

Patient 1 (**Table 1**) is 12-year-old the boy developed fever, abdominal pain, diarrhea, livedo reticularis, and edema of the 4th proximal interphalangeal (PIP) joint of the left hand and 3rd PIP joint of the right hand. *Shigella spp.* was detected and he was treated with antibiotics. Abdominal symptoms and fever resolved, but he had periodic fever episodes and livedo reticularis. Blood tests showed elevated inflammatory markers. We ruled out autoimmune diseases, inflammatory bowel disease. Genetic testing was performed and VUS in the *DDX58* gene (p.N354S) was detected. The patient was treated with short-course corticosteroids. Fever, livedo reticularis, and laboratory inflammation resolved.

Patient 2 (**Table 1**) is a 7-year-old boy who has had 7 episodes of exudative pericarditis for one year preceding our hospital admission. He required pericardiocentesis twice. Pericardial effusion usually was accompanied by systemic inflammation (leukocytosis, increased C-reactive protein) and has been resolved on treatment with corticosteroids. Infectious, oncologic, and autoimmune diseases have been excluded. Multigene-targeted sequencing revealed a pathogenic mutation in the *JAK1* gene and likely a non-pathogenic variant of the *DDX58* gene (p.E37K). Colchicine and canakinumab were initiated, however, due to four following flares during the year of treatment, he was switched to tocilizumab.

Patient 3 (**Table 2**) is a 16-year-old girl with SLE. Clinical manifestations in the disease onset included fever, lymphadenopathy, pancytopenia, and minimal proteinuria (0.2 g/d) were noted. The malar rash, stomatitis, and polyserositis (by computed tomography) were developed. She had positive ANA, anti-dsDNA antibodies, and hypocomplementemia. She's been treated with corticosteroids (IV, oral), hydroxychloroquine, and rituximab. Disease remission was achieved and corticosteroids were stopped. IFN-I score was increased 10 times than the normal value (21.0 UE, normal value less than 2.0 UE), and following multigene targeted sequencing revealed two variants in the *DDX58* gene (p.Cys864fs, p.D580E). A rare variant of p.C864Ffs*9 was inherited from a healthy mother. There is no information about the pathogenicity of this variant in the ClinVar database. Variant *DDX58* p.D580E refers to frequent benign variants of the gene.

Different variants in the *IFIH1* gene were found in 7/14 patients (**Table 2**). All patients had elevated IFN scores. Three patients had the p.E627X variant. This variant has conflicting interpretations of pathogenicity according to ClinVar and uncertain significance according to ACMG. One patient with systemic onset juvenile idiopathic arthritis had a benign p.I923V variant, and one patient with JDM had a rare (MAF 0.0001) likely benign coding sequence variant p.R595H.

Patient 1 (**Table 2**) had compound-heterozygous variants in the *IFIH1* gene (p.L679Ifs*2 and p.V599Ffs*5) that can contribute to disease development. She is 17-year-old girl with undifferentiated interferonopathy. Her clinical manifestations included fever, systemic inflammation, panniculitis, sialadenitis, nodular rash, hepatitis, migraine headaches, and growth failure. Treatment with corticosteroids, azathioprine, and mycophenolate mofetil was ineffective. The application of tofacitinib partially controlled her disease (no fever flares and rash) and allowed her to taper corticosteroids to 0.15 mg/kg.

Patient 2 (**Table 2**) is 16-year-old girl with fever, pancytopenia, petechial rash, hepatomegaly, lower extremities edema, inflammation, and hyperferritinemia. She initially was treated with IV corticosteroids and cyclosporine A. Then she developed panniculitis nodules in the back, the abdomen, and the lower extremities, and muscle weakness. Pancytopenia and inflammation had recurred. Biopsy of

Table 1 *DDX58* variants in children with immune-mediated diseases

No.	<i>DDX58</i> variant	MAF	ClinVar	ACMG	IFN-I score (n.v. 0-1.9 UE/L)	Diagnosis
1	c.1061A>G (p.N354S)	0.0001	VUS	VUS	2.13	uSAID
2	c.109G>A (p.E37K)	0.000008	Not reported	Likely non-pathogenic	N/A	uSAID
3	c.2587_2590dup (p.Cys864fs)	0.0006	Not reported	Likely pathogenic	21.0	SLE
4	c.1740T>A (p.D580E)	0.11	Non-pathogenic	Non-pathogenic		
	c.431C>T (p.S144F)	0.0277	Non-pathogenic	Likely non-pathogenic	13.31	MCTD
	c.T1740A (p.D580E)	0.11	Non-pathogenic	Non-pathogenic	8.5	SLE and MDS
6	c.1740T>A (p.D580E)	0.11	Non-pathogenic	Non-pathogenic	24.35	SLE
7	c.1740T>A (p.D580E)	0.11	Non-pathogenic	Non-pathogenic	18.93	uSAID

ACMG: The American College of Medical Genetics; GnomAD: The Genome Aggregation Database; MAF: Minor allele frequency; MCTD: Mixed connective tissue disease; MDS: Myelodysplastic syndrome; n.v.: Normal value; SLE: Systemic lupus erythematosus; uSAID: Undifferentiated systemic autoinflammatory disease; VUS: A variant of uncertain significance; N/A: Not applicable.

Table 2 *IFIH1* variants in children with immune-mediated diseases

No.	<i>IFIH1</i> variant	MAF	ClinVar	ACMG	IFN-score (n.v. 0-1.9 UE/L)	Diagnosis
1	c.2035_2036del (p.L679Ifs*2)	0.0001	VUS	VUS	5.4	uSAID
	c.1795delG (p.V599Ffs*5)		Not reported	Not reported		
2	c.1558A>G (p.T520A)	0.0002	CIP	VUS	5.52	uSAID
3	c.1784G>A (p.R595H)	0.0001	Likely benign	VUS	29.0	JDM
4	c.1879G>T (p.E627X)	0.003	CIP	VUS	20.2	SLE-like disease
5	c.1879G>T (p.E627X)	0.003	CIP	VUS	11.3	SLE
6	c.1879G>T (p.E627X)	0.003	CIP	VUS	2.95	PFAPA
7	c.A2767G (p.I923V)	0.0126	Benign/likely benign	Benign	10.0	soJIA

ACMG: The American College of Medical Genetics; CIP: Conflicting interpretations of pathogenicity; GnomAD: The Genome Aggregation Database; JDM: Juvenile dermatomyositis; MAF: Minor allele frequency; n.v.: Normal value; PFAPA: Periodic fever with aphthous stomatitis, pharyngitis, and adenitis; SLE: Systemic lupus erythematosus; soJIA: Systemic onset juvenile idiopathic arthritis; uSAID: Undifferentiated systemic autoinflammatory disease; VUS: A variant of uncertain significance.

nodules revealed adipocytes and xanthoma cells infiltrating by lymphocytes. Electromyography detected axonal-demyelinating polyneuropathy of motor and sensory nerve fibers of the upper and lower extremities. Further treatment with different medications, including cyclosporine A, etanercept, tocilizumab, tofacitinib, and anakinra showed partial efficacy. It's unknown does her heterozygous variant p.T520A lead to disease manifestations or not. Functional tests are necessary to prove its pathogenicity.

DISCUSSION

Studies of the *DDX58* gene in patients with rheumatic diseases are mostly limited to the evaluation of *DDX58* polymorphisms as one of the factors of susceptibility to viral diseases. It is known that some *DDX58* gene variants can lead to atypical Singleton-Merton syndrome, which was first described in 2015 in family members who had glaucoma, aortic calcification, and skeletal abnormalities[5]. Subsequently, the *DDX58* gene variants were studied in 100 patients with congenital glaucoma, and in one family with congenital glaucoma, dental abnormalities, and skeletal dysplasia, variant c.803G>T (p.Cys268Phe) was found. The functional tests confirmed the pathogenicity of this gene variant. Hyperactivation of the type

I IFN signaling system was observed in all the above-mentioned patients[5]. Two families with the Singleton-Merten syndrome having glaucoma, psoriasis-like rashes, calcifications of the joints, and aorta had *DDX58* gene variants[6].

In the study of 15 patients with IIM 5/5 patients with DM had an increased expression of *DDX58*, which was associated with excessive secretion of IFN-beta[7]. All patients with *DDX58* variants had high levels of IFN-I scores in our study. The association between *DDX58* p.D580E polymorphism and SLE has not been confirmed in the study of 344 patients with SLE and 641 healthy persons[8]. Three of our patients with SLE had the same *DDX58* polymorphic variant which is unlikely to have any causal role.

A novel *DDX58* pathogenic variant R109C has been recently identified in five unrelated families with lupus nephritis. Transcriptome analysis revealed an increased IFN signature in patient monocytes. One patient was effectively treated with baricitinib[9]. Gain-of-function *IFIH1* gene variants lead to an inadequate perception of both own and viral nucleic acids and contribute to the hyperactivation of the IFN-I type[10]. Currently, less than 100 *IFIH1* mutations are known.

It was recently shown that some *IFIH1* polymorphisms are associated with a spectrum of autoimmune diseases[11]. Rare *IFIH1* variants have been found in Aicardi- Goutières syndrome-7, Singleton-Merten syndrome, and MDA-5 immunodeficiency. All these diseases are characterized by IFN signaling upregulation[12]. In our group of patients with the *IFIH1* variant, hyperactivation of the IFN-I signaling pathway was also observed, but it is unclear whether it was caused by *IFIH1* defects.

In our opinion, two patients with uSAID have probably causative *IFIH1* variants (compound-heterozygous p.L679Ifs*2, p.V599Ffs*5, and heterozygous p.T520A). Functional tests are pending. Almlöf *et al* [13] detected two heterozygous missense *IFIH1* variants (p.Arg77Trp and p.Arg374Cys) with high potential to contribute to SLE. *IFIH1* gene variant p.E627X found in our patients showed a significant association with decreased risk of type 1 diabetes[14].

Combined exome sequencing, transcriptomic analysis, and *in vitro* functional tests have been analyzed to identify genetic variants causing predisposition to severe courses of common respiratory viral infections. Pathogen-restricted immunodeficiency due to loss-of-function variants in *IFIH1* (p.Glu627Ter, p.Leu509_Glu547del, and p.Ile872Ter) have been detected. They result in defective innate recognition of RNA viruses, preventing the activation of an efficient antiviral IFN response[15].

Homozygous nonsense mutation, c.2665A>T (p.Lys889*) in the *IFIH1* gene was identified in a patient with microcephaly, severe psychomotor retardation, seizures, cataracts, and recurrent episodes of prolonged and severe chest infections. The results of the western blot analysis of protein from cultured fibroblasts of the patient indicated the absence of wild-type MDA5/*IFIH1*, compatible with nonsense-mediated decay[16].

It is not fully understood whether influence detected variants *IFIH1* and *DDX58* on the severity and activity of rheumatic diseases. The patients with rare pathogenic or likely pathogenic variants have had clinical features of interferonopathy (fever, livedo, nodular rash, panniculitis). It seems that patients with *IFIH1* and *DDX58* variants may be considered candidates for agents blocking the IFN-I signaling pathway (IFN-I receptor antibodies, JAK inhibitors) especially when standard treatment is ineffective.

We believe that the results of our study allow us to consider some patients with rheumatic diseases with unusual manifestations or resistance to standard treatment as patients with monogenic disorders, in which other pathogenic signaling pathways are involved and another type of treatment can be assumed. This information added to the discussion.

Genetic testing is becoming an increasingly accessible and widely used method in clinical practice. Careful assessment of clinical signs and family history, selection of patients with unusual clinical manifestations, and paying more attention to patients who do not respond to standard treatment protocols should alert the doctor about possible genetic disorders. Evaluation of the activity of the IFN type I signaling pathway may be an additional criterion when selecting patients for genetic testing. However, the results of the IFN-I score analysis remain contradictory in several studies, a high concentration can be observed both in classical autoimmune (SLE, DM) and in rare forms of auto-inflammatory diseases[17]. Sönmez *et al*[18] proposed preliminary classification criteria for type I interferonopathy, which were developed based on the analysis of a small group of patients. Assessing the sensitivity of these criteria is difficult due to the rare occurrence of these conditions. The development of international registries of both patients with interferonopathies and with genetic variants is promising for the development of diagnostic tools.

Future perspectives are associated with the wider use of genetic testing in patients with seemingly classic rheumatic diseases. The creation of new drugs or clinical trials of existing drugs, but to new indications (*e.g.*, JAK inhibitors in DM and SLE, IFN-I receptor antibodies for DM), seem promising. The limitations of our study are related to a very small number of patients, and the heterogeneity of the selected group of patients. The results are preliminary. Without functional studies, it is very difficult to judge the actual pathogenicity of these variants.

CONCLUSION

The majority of patients with *DDX58* and *IFI1* variants had hyperactivation of the IFN I signaling pathway. Thus, the use of RNA-based IFN-I score seems to help select candidates for further genetic analysis. This study extends the existing data on the spectrum of *DDX58* and *IFIH1*-associated phenotypes. Further studies and collection of patients with *IFIH1* and *DDX58* variants are needed.

ARTICLE HIGHLIGHTS

Research background

The *IFIH1* gene and the *DDX58* gene both are involved in the interferon (IFN) type I signaling pathway. Monogenic diseases with the features of systemic rheumatic diseases were described in patients with these genetic variants. Rheumatic disease patients with IFN type I hyperactivation may have these variants.

Research motivation

Patients with rheumatic diseases with unusual manifestations (clinical features of interferonopathy) or resistant to standard treatment may have molecular variants in genes, regulating IFN I type pathway.

Research objectives

To describe children with different rheumatic diseases who have variants in *DDX58* or *IFIH1* genes.

Research methods

Clinical exome sequencing was performed 92 patients with different rheumatic diseases, and 14 children (10 girls and 4 boys) with *DDX58* or *IFIH1* genes were selected. They have the following diagnosis: Systemic autoinflammatory disease ($n = 6$), systemic lupus erythematosus ($n = 5$), juvenile dermatomyositis ($n = 1$), systemic onset juvenile idiopathic arthritis ($n = 1$), mixed connective tissue disease ($n = 1$). Real-time polymerase chain reaction with previous reverse transcription of RNA was used for IFN-I score assessment.

Research results

All patients had elevated IFN-I scores. Variants in both genes were described in the studied population.

Research conclusions

Patients with *DDX58* and *IFI1* variants had hyperactivation of the IFN I signaling pathway. The RNA-based IFN-I score is a good tool to select candidates for further genetic analysis.

Research perspectives

Research perspectives are more on molecular tests in rheumatic diseases, more functional studies confirming the role of genetic variants, and an assessment of the efficacy and safety of drugs on new indications.

FOOTNOTES

Author contributions: All authors contributed to the manuscript revision, read, and approved the submitted version.

Institutional review board statement: The Ethic Committee of Saint-Petersburg Sate Pediatric Medical University approved the study (protocol # 1/3 or 11.01.2021).

Informed consent statement: Written consent of legal representatives for inclusion of the data and using of the pictures was obtained.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-

NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/Licenses/by-nc/4.0/>

Country/Territory of origin: Russia

ORCID number: Mikhail Kostik 0000-0002-1180-8086.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Zhang XD

REFERENCES

1. Zevini A, OLAGNIE D, HISCOTT J. Crosstalk between Cytoplasmic RIG-I and STING Sensing Pathways. *Trends Immunol* 2017; **38**: 194-205 [PMID: 28073693 DOI: 10.1016/j.it.2016.12.004]
2. Lamborn IT, Jing H, Zhang Y, Drutman SB, Abbott JK, Munir S, Bade S, Murdock HM, Santos CP, Brock LG, Masutani E, Fordjour EY, McElwee JJ, Hughes JD, Nichols DP, Belkadi A, Oler AJ, Happel CS, Matthews HF, Abel L, Collins PL, Subbarao K, Gelfand EW, Ciancanelli MJ, Casanova JL, Su HC. Recurrent rhinovirus infections in a child with inherited MDA5 deficiency. *J Exp Med* 2017; **214**: 1949-1972 [PMID: 28606988 DOI: 10.1084/jem.20161759]
3. Wang HY, Hu HJ, Zhang KJ. Overview of Interferon: Characteristics, signaling and anti-cancer effect. *Arch Biotechnol Biomed* 2017; **1**: 001-016 [DOI: 10.29328/journal.hjb.1001001]
4. Jiang J, Zhao M, Chang C, Wu H, Lu Q. Type I Interferons in the Pathogenesis and Treatment of Autoimmune Diseases. *Clin Rev Allergy Immunol* 2020; **59**: 248-272 [PMID: 32557263 DOI: 10.1007/s12016-020-08798-2]
5. Jang MA, Kim EK, Now H, Nguyen NT, Kim WJ, Yoo JY, Lee J, Jeong YM, Kim CH, Kim OH, Sohn S, Nam SH, Hong Y, Lee YS, Chang SA, Jang SY, Kim JW, Lee MS, Lim SY, Sung KS, Park KT, Kim BJ, Lee JH, Kim DK, Kee C, Ki CS. Mutations in DDX58, which encodes RIG-I, cause atypical Singleton-Merten syndrome. *Am J Hum Genet* 2015; **96**: 266-274 [PMID: 25620203 DOI: 10.1016/j.ajhg.2014.11.019]
6. Prasov L, Bohnsack BL, El Husny AS, Tsoi LC, Guan B, Kahlenberg JM, Almeida E, Wang H, Cowen EW, De Jesus AA, Jani P, Billi AC, Moroi SE, Wasikowski R, Almeida I, Almeida LN, Kok F, Garnai SJ, Mian SI, Chen MY, Warner BM, Ferreira CR, Goldbach-Mansky R, Hur S, Brooks BP, Richards JE, Hufnagel RB, Gudjonsson JE. DDX58(RIG-I)-related disease is associated with tissue-specific interferon pathway activation. *J Med Genet* 2022; **59**: 294-304 [PMID: 33495304 DOI: 10.1136/jmedgenet-2020-107447]
7. Suárez-Calvet X, Gallardo E, Nogales-Gadea G, Querol L, Navas M, Díaz-Manera J, Rojas-García R, Illa I. Altered RIG-I/DDX58-mediated innate immunity in dermatomyositis. *J Pathol* 2014; **233**: 258-268 [PMID: 24604766 DOI: 10.1002/path.4346]
8. Enevold C, Kjaer L, Nielsen CH, Voss A, Jacobsen RS, Hermansen ML, Redder L, Oturai AB, Jensen PE, Bendtzen K, Jacobsen S. Genetic polymorphisms of dsRNA ligating pattern recognition receptors TLR3, MDA5, and RIG-I. Association with systemic lupus erythematosus and clinical phenotypes. *Rheumatol Int* 2014; **34**: 1401-1408 [PMID: 24719229 DOI: 10.1007/s00296-014-3012-4]
9. Peng J, Wang Y, Han X, Zhang C, Chen X, Jin Y, Yang Z, An Y, Zhang J, Liu Z, Chen Y, Gao E, Zhang Y, Xu F, Zheng C, Zhou Q. Clinical Implications of a New DDX58 Pathogenic Variant That Causes Lupus Nephritis due to RIG-I Hyperactivation. *J Am Soc Nephrol* 2023; **34**: 258-272 [PMID: 36261300 DOI: 10.1681/ASN.2022040477]
10. Crow YJ, Manel N. Aicardi-Goutières syndrome and the type I interferonopathies. *Nat Rev Immunol* 2015; **15**: 429-440 [PMID: 26052098 DOI: 10.1038/nri3850]
11. Zervou MI, Andreou AC, Eliopoulos EE, Goulielmos GN. Functional significance of the rare rs35667974 IFIH1 gene polymorphism, associated with multiple autoimmune diseases, using a structural biological approach. *Autoimmunity* 2022; **55**: 455-461 [PMID: 35918839 DOI: 10.1080/08916934.2022.2103799]
12. Rice GI, Park S, Gavazzi F, Adang LA, Ayuk LA, Van Eyck L, Seabra L, Barrea C, Battini R, Belot A, Berg S, Billette de Villemeur T, Bley AE, Blumkin L, Boespflug-Tanguy O, Briggs TA, Brimble E, Dale RC, Darin N, Debray FG, De Giorgis V, Denecke J, Doummar D, Drake AF, Hagelsrum G, Eleftheriou D, Estienne M, Fazzi E, Feillet F, Galli J, Hartog N, Harvengt J, Heron B, Heron D, Kelly DA, Lev D, Levrat V, Livingston JH, Marti I, Mignot C, Mochel F, Nougues MC, Oppermann I, Pérez-Dueñas B, Popp B, Rodero MP, Rodriguez D, Saletti V, Sharpe C, Tonduti D, Vadlamani G, Van Haren K, Tomas Vila M, Vogt J, Wassmer E, Wiedemann A, Wilson CJ, Zerem A, Zweier C, Zuberi SM, Orcesi S, Vanderver AL, Hur S, Crow YJ. Genetic and phenotypic spectrum associated with IFIH1 gain-of-function. *Hum Mutat* 2020; **41**: 837-849 [PMID: 31898846 DOI: 10.1002/humu.23975]
13. Almlöf JC, Nystedt S, Leonard D, Eloranta ML, Grosso G, Sjöwall C, Bengtsson AA, Jönsen A, Gunnarsson I, Svenungsson E, Rönnblom L, Sandling JK, Syvänen AC. Whole-genome sequencing identifies complex contributions to genetic risk by variants in genes causing monogenic systemic lupus erythematosus. *Hum Genet* 2019; **138**: 141-150 [PMID: 30707351 DOI: 10.1007/s00439-018-01966-7]
14. Chistiakov DA, Voronova NV, Savost'Anov KV, Turakulov RI. Loss-of-function mutations E6 27X and I923V of IFIH1 are associated with lower poly(I:C)-induced interferon- β production in peripheral blood mononuclear cells of type 1 diabetes patients. *Hum Immunol* 2010; **71**: 1128-1134 [PMID: 20736039 DOI: 10.1016/j.humimm.2010.08.005]
15. Asgari S, Schlapbach LJ, Anchisi S, Hammer C, Bartha I, Junier T, Mottet-Osman G, Posfay-Barbe KM, Longchamp D, Stocker M, Cordey S, Kaiser L, Riedel T, Kenna T, Long D, Schibler A, Telenti A, Tapparel C, McLaren PJ, Garcin D, Fellay J. Severe viral respiratory infections in children with IFIH1 loss-of-function mutations. *Proc Natl Acad Sci U S A*

- 2017; **114**: 8342-8347 [PMID: [28716935](#) DOI: [10.1073/pnas.1704259114](#)]
- 16 **Zaki M**, Thoenes M, Kawalia A, Nürnberg P, Kaiser R, Heller R, Bolz HJ. Recurrent and Prolonged Infections in a Child with a Homozygous IFIH1 Nonsense Mutation. *Front Genet* 2017; **8**: 130 [PMID: [29018476](#) DOI: [10.3389/fgene.2017.00130](#)]
- 17 **Chasset F**, Dayer JM, Chizzolini C. Type I Interferons in Systemic Autoimmune Diseases: Distinguishing Between Afferent and Efferent Functions for Precision Medicine and Individualized Treatment. *Front Pharmacol* 2021; **12**: 633821 [PMID: [33986670](#) DOI: [10.3389/fphar.2021.633821](#)]
- 18 **Sönmez HE**, Karaaslan C, de Jesus AA, Batu ED, Anlar B, Sözeri B, Bilginer Y, Karaguzel D, Cagdas Ayvaz D, Tezcan I, Goldbach-Mansky R, Ozen S. A clinical score to guide in decision making for monogenic type I IFNopathies. *Pediatr Res* 2020; **87**: 745-752 [PMID: [31641281](#) DOI: [10.1038/s41390-019-0614-2](#)]



Retrospective Study

Clinical characteristics of community-acquired pneumonia in children caused by mycoplasma pneumoniae with or without myocardial damage: A single-center retrospective study

Shukri Omar Yusuf, Peng Chen

Specialty type: Pediatrics

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Moshref RH, Saudi Arabia

Received: December 3, 2022

Peer-review started: December 3, 2022

First decision: February 21, 2023

Revised: March 8, 2023

Accepted: March 30, 2023

Article in press: March 30, 2023

Published online: June 9, 2023



Shukri Omar Yusuf, Peng Chen, Department of Pediatrics, The Second Hospital of Jilin University, Changchun 130041, Jilin Province, China

Corresponding author: Peng Chen, Doctor, Chief Physician, Department of Pediatrics, The Second Hospital of Jilin University, Yatai Street, Changchun 130041, Jilin Province, China. c_p@jlu.edu.cn

Abstract

BACKGROUND

Mycoplasma pneumoniae (MP) is a prevalent pathogen that causes respiratory infections in children and adolescents.

AIM

To assess the differences in the clinical features of MP-associated community-acquired pneumonia (CAP) in children who presented with mild or severe mycoplasma pneumoniae pneumonia (MPP); to identify the incidence of myocardial damage between the two groups.

METHODS

This work is a retrospective study. We identified children between 2 mo and 16 years of age with clinical and radiological findings consistent with CAP. We admitted patients to the inpatient department of the Second Hospital of Jilin University, Changchun, China, from January 2019 to December 2019.

RESULTS

A total of 409 hospitalized patients were diagnosed with MPP. Among them were 214 (52.3%) males and 195 (47.7%) females. The duration of fever and cough was the longest in severe MPP cases. Similarly, plasma levels of highly sensitive C-reactive protein ($t = -2.834$, $P < 0.05$), alanine transaminase ($t = -2.511$, $P < 0.05$), aspartate aminotransferase ($t = -2.939$, $P < 0.05$), and lactate dehydrogenase (LDH) ($t = -2.939$, $P < 0.05$) were all elevated in severe MPP cases compared with mild MPP cases, and these elevations were statistically significant ($P < 0.05$). Conversely, the neutrophil percentage was significantly lower in severe MPP cases than in mild MPP cases. The incidence of myocardial damage was significantly higher in severe MPP cases than in mild MPP cases ($\chi^2 = 157.078$, $P < 0.05$).

CONCLUSION

Mycoplasma pneumoniae is the main cause of CAP. The incidence of myocardial damage was higher and statistically significant in severe MPP cases than in mild MPP cases.

Key Words: Community-acquired pneumonia; *Mycoplasma pneumoniae*; Mild mycoplasma pneumoniae pneumonia; Severe mycoplasma pneumoniae pneumonia; Myocardial damage

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Our study highlighted which clinical parameters should be focused on to differentiate between mild and severe mycoplasma pneumoniae pneumonia (MPP), which is crucial for pediatricians as it would enable us to make a quick diagnosis and consequently prompt treatment in case of severe MPP. We found that the duration of fever and cough was longer in the severe MPP group than in the mild MPP group. Similarly, the high sensitivity C-reactive protein levels, procalcitonin, alanine transaminase, aspartate aminotransferase, and lactate dehydrogenase were significantly higher in the severe MPP cohort than in the mild MPP group. Paradoxically, the neutrophil count was significantly higher in the mild MPP group than in the severe MPP group. More importantly, the incidence of myocardial damage was significantly higher in the severe MPP group than in mild MPP cases. However, it is unknown whether there is a causal link between severe MPP and myocardial damage; therefore, to ascertain this hypothesis, future research is recommended.

Citation: Yusuf SO, Chen P. Clinical characteristics of community-acquired pneumonia in children caused by mycoplasma pneumoniae with or without myocardial damage: A single-center retrospective study. *World J Clin Pediatr* 2023; 12(3): 115-124

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/115.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.115>

INTRODUCTION

Community-acquired pneumonia (CAP) is a pulmonary infection (parenchyma or pleura) acquired outside the hospital[1]. CAP is a significant cause of inpatient hospitalization and mortality in children. The annual incidence of CAP requiring hospitalization is over 20 million[2]. In 2015, data from Asia showed that 15% of all fatalities in children under five years of age were caused by pneumonia, with an estimated 922000 children in this age group dying[3]. Similarly, global mortality is estimated at 14%, ranging from 2% of those treated as outpatients to 37% of those admitted to intensive care units (ICUs) [4].

In China, the incidence density of pneumonia in children under five years of age is 0.06 to 0.27% per year. According to a systematic review of data from the China Mortality Surveillance System from 2001 to 2015, the mortality rate for children under the age of five was 153.2 per 100000 live births[5]. Multiple microorganisms drive the pathophysiology of CAP. Classical typical pneumonia is caused by bacteria, while atypical pneumonia is caused by atypical pathogens, such as *Mycoplasma pneumoniae* (MP), *Legionella pneumoniae*, and *Chlamydia pneumoniae*. These three pathogens combined are responsible for 21% to 28% of adult CAP worldwide[6]. MP is one of the most common pathogens causing respiratory illness in adolescents and children, accounting for up to 40% of CAP in children above five years of age[7].

Mycoplasma is a small cell wall-deficient prokaryote. Microbes are cell-free and malleable organisms that can grow and proliferate in a cell-free environment[8].

According to the mycoplasma pneumoniae pneumonia (MPP) diagnostic criteria of CAP in children, MP patients are classified as mild mycoplasma pneumoniae pneumonia (MMPP) and severe mycoplasma pneumoniae pneumonia (SMPP) (revised in 2013). Typical clinical symptoms, such as cough and fever, radiological findings, elevated inflammatory markers, and the detection of serum specificity MP-IgM antibody are the diagnostic criteria of MMPP.

SMPP is defined as MPP with protracted fevers, worsening clinical symptoms, and persistent radiological features following a week-long routine of macrolide antibiotic therapy[9]. Similarly, SMPP is defined as a fever (> 38.5°C), persistent cough for more than two weeks, CRP > 40 mg/L, radiological features showing consolidation in two or more pulmonary lobes, and extrapulmonary complications were the criteria to diagnose SMPP as per the algorithm of community-acquired pneumonia in children [10,11].

Consensus on the definition of SMPP is lacking because it can affect any part of the body, including the musculoskeletal system, neurological system, hematological system, and skin[12]. However, MP infection most severely affects the respiratory system; hence, respiratory and metabolic acid-base disturbances may indirectly indicate severe disease. Therefore, prompt and effective treatment is recommended[13]. Moreover, immune evasion by specific pathogens *via* the transmission of host-derived lipid membranes can lead to uninhibited proliferation, resulting in overt clinical symptoms and a worsening disease course[14].

MP is contagious and can be transmitted through aerosols from coughing and sneezing, causing acute upper and lower respiratory tract inflammation[15]. These respiratory pathogens are ubiquitous on environmental surfaces, and mucous membrane contact with these contaminated surfaces aids in disease transmission. The propensity for children to play with toys and have poor hand hygiene make children a high-risk and susceptible group in daycare and school settings[16]. MP infection also causes nonrespiratory symptoms, including myocarditis, arthritis, and thrombosis, in newborns. If left untreated, multiple organ failures may ensue[17]. Acute myocardial injury in people hospitalized with community-acquired pneumonia (CAP) is caused by many different factors. These factors include type-2 myocardial infarction with or without prior coronary artery disease (CAD) due to an imbalance between demand and supply and non-CAD myocardial damage caused by toxins, direct myocardial infection, inflammatory mediators, and stress-induced cardiomyopathy[18]. MP-induced myocarditis is usually confirmed *via* an electrocardiogram (ECG), which shows conduction arrhythmias and myocardial atrioventricular block. Chest pain can be a sign of myocarditis or pericarditis and has been linked to anti-cardiolipin antibodies[19].

Although uncommon, the prevalence of myocarditis in children with MP ranges from 1% to 8%, and the prevalence rate is slightly higher in adults than in children[20]. Mycoplasma-associated carditis (myo- or pericarditis) is a rare condition that has affected 1%-5% of patients since Pönkä's study in 1979. However, individuals with mycoplasma carditis seem to be older on average. This study supports Pönkä's conclusion that the mean age was 32. This recurring finding is not fully understood. However, it may be related to the increased rates of mycoplasma infection in older persons appearing as pneumonia, which is more common in patients with carditis[21].

This study aims to assess the differences in the clinical characteristics of children diagnosed with CAP caused by MP and to further identify the cohort of patients who developed MP-induced myocardial damage and those without heart failure.

MATERIALS AND METHODS

Study population

This study was a single-center retrospective study. We identified children between 2 mo and 16 years of age with clinical and radiological findings consistent with CAP admitted to the inpatient department of the Second Hospital of Jilin University, Changchun, China, from January 2019 to December 2019. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of The Second Hospital of Jilin University (In 2022, research review No. 073).

Inclusion criteria were as follows

(1) Age between 2 mo and 16 years old; (2) Children admitted to the inpatient pediatric department of the Second Hospital of Jilin University in 2019 with diagnosed MPP; (3) Radiological findings, such as interstitial infiltration, linear opacities, patchy infiltration, segmental or lobar consolidation, reticulonodular infiltrate, or pleural effusion; and (4) Diagnosed with MP by serology with an immunoglobulin M (IgM) titer of > 1.1 considered positive. MP-IgM was identified by enzyme-linked immunosorbent assay (ELISA) as serum MP antibodies.

The exclusion criteria were as follows

(1) Children aged less than two months and greater than 16 years old; (2) Children with chronic respiratory tract infection or other pulmonary illness; (3) Community-acquired pneumonia caused by other species, such as chlamydia pneumonia; and (4) Concomitant other pathogenic infections

Data collection

Clinical data were collected uniformly from the Second Hospital of Jilin University pediatrics inpatient department database. Based on the following symptoms, all patients were diagnosed with CAP: Cough, tachypnea, chest retractions, fever, wheezing, crackles or reduced breath sounds, and radiological abnormalities with pulmonary fever, wheezing, or infiltrates. IgM titer (> 1.1), age, gender, white blood cell (WBC) count, lymphocyte percentage, neutrophil percentage, C-reactive protein (CRP), high-sensitivity C-reactive protein, procalcitonin, alanine transaminase (ALT), aspartate aminotransferase (AST), creatine phosphokinase and lactate dehydrogenase (LDH) were obtained from the patient chart. Fever ($> 38.5^{\circ}\text{C}$), persistent cough for more than two weeks, CRP $> 40\text{ mg/L}$, and intra- and extrapul-

monary complications were the criteria to diagnose SMPP per the algorithm of community-acquired pneumonia in children. White blood cell (WBC) count > 15000 cells/mL or < 5500 cells/mL for children < 5 years old and WBC count > 11000 cells/mL or < 3000 cells/mL for children ≥ 5 years old were considered abnormal. Fever (> 38.5°C), persistent cough for more than two weeks, CRP > 40 mg/L, and intra- and extrapulmonary complications were the criteria to diagnose SMPP per the algorithm of community-acquired pneumonia in children. According to myocardial damage, an ECG was performed to check for different heart conditions. We also performed blood tests to check for proteins associated with heart damage, such as troponin.

Data analysis

The data were populated in Microsoft Excel 2016. Categorical data and comparisons among these two groups between mild and severe MPP were analyzed using the chi-squared or Fisher's exact tests. An independent t test was used to compare the differences between continuous variables. Statistical analyses were performed using IBM SPSS statistics 26, and statistical significance was set at a *P* value of < 0.05. The results are presented as the mean ± SD for numerical variables.

RESULTS

Sociodemographics

In our study, 409 children with CAP were included, among whom 214 (52.3%) were males and 195 (47.7%) were females. MP infection was more prevalent in males than females (Table 1). Among the mild MPP cases, 232 patients were < 5 years old, accounting for 77.6% of patients: 67 patients were ≥ 5 years old, accounting for 22.4% of patients. In severe cases, 85 patients were < 5 years old, accounting for 77.3% old, while 25 patients were ≥ 5 years, accounting for 22.7% of patients, as shown (Table 2 and Figure 1).

The seasonal distribution of MP infection: The seasonal distribution of hospitalized children with mild MPP (102/299, 34.10%) and severe MPP indicated that 41/110 children (37.30%) were diagnosed during winter. In comparison, mild MPP (80/299, 26.80%) and severe MPP (28/110, 25.50%) patients were diagnosed during the spring. Moreover, 28/299 (9.40%) patients with mild MPP and 28/110 (10.00%) patients with severe MPP were diagnosed during summer, whereas 89/299 (29.80%) patients with mild MPP and 30/110 (27.3%) patients with severe MPP were diagnosed during autumn. These results indicated that the prevalence rate of M pneumonia in hospitalized children was highest in winter (Table 3).

According to Pearson's chi-square test, a significant difference was not detected between seasons according to severe MPP cases and mild MPP cases ($\chi^2 = 0.487$, $P > 0.05$).

Clinical characteristics

Clinical symptoms of children in both groups were compared head-to-head. In our study, the incidences of mild and severe MPP cases did not differ by sex or age ($t = 0.54$, $P > 0.05$, $t = 0.69$, $P > 0.05$, respectively) (Table 4). Common clinical symptoms included phlegm (31/409, 7.6%), hoarseness (22/409, 5.3%), rhinorrhea (12/409, 3%), diarrhea (9/409, 2.2%), vomiting (7/409, 1.7%), and rash (7/409, 1.7%). These symptoms, signs, or physical findings did not significantly differ between mild and severe MPP.

However, auscultated respiratory sounds significantly differed between severe and mild MPP cases in our study ($\chi^2 = 11.915$, $P < 0.05$) (Table 5).

Similarly, myocardial damage significantly differed between mild and severe MPP cases ($\chi^2 = 157.078$, $P < 0.05$). Specifically, the incidence of myocardial damage was higher in severe MPP cases than in mild MPP cases (Table 5).

Independent t test samples showed that the duration of fever was significantly different between severe and mild MPP ($t = -2.72$, $P < 0.05$). The duration of cough was also significantly longer in severe MPP cases than in mild MPP cases ($t = -5.103$, $P < 0.05$). Conversely, the neutrophil percentage was significantly higher in mild MPP cases than in severe MPP cases ($t = 2.113$, $P < 0.05$) (Table 4).

High sensitivity C-reactive protein was significantly higher in severe MPP cases than in mild MPP cases ($t = -2.834$, $P < 0.05$). Both ALT and AST were significantly higher in severe MPP cases than in mild MPP cases ($t = -2.511$, $P < 0.05$ and $t = -2.939$, $P < 0.05$, respectively). Lactate dehydrogenase (LDH) was also significantly higher in severe MPP cases than in mild MPP cases ($t = -2.939$, $P < 0.05$). The remaining variables did not significantly differ ($P > 0.05$) between severe and mild MPP (Table 4).

DISCUSSION

This work is the first study to discuss the relationship between *Mycoplasma pneumoniae* pneumonia and myocardial damage in children. We investigated the clinical and laboratory characteristics of

Table 1 Gender distribution

Gender	Frequency	Percentage
Female	195	47.68
Male	214	52.32
Total	409	100.00

Table 2 Age distribution of community-acquired pneumonia in hospitalized children with mycoplasma pneumoniae pneumonia categorized as mild and severe, n (%)

Age group	Total	Mild MPP	Severe MPP
< 5 yr	317	232 (77.6)	85 (77.3)
≥ 5 yr	92	67 (22.4)	25 (22.7)
Total	409	299	110

MPP: Mycoplasma pneumoniae pneumonia.

Table 3 Seasonality of mycoplasma pneumoniae pneumonia, n (%)

Season	Mild MPP	Severe MPP
Winter	102 (34.10)	41 (37.30)
Spring	80 (26.80)	28 (25.50)
Summer	28 (9.40)	11 (10.00)
Autumn	89 (29.80)	30 (27.30)

MPP: Mycoplasma pneumoniae pneumonia.

children with CAP caused by MP and compared them with those with mild MPP and severe MPP. Our study showed that MP was the leading cause of CAP in hospitalized children in Changchun, China, in 2019.

CAP is a nonhospital-acquired illness of the lower respiratory tract[22]. MP is one of the most common infections in children with CAP. MPP is usually self-limiting and is adequately treated with macrolides. Conversely, severe MPP is common and may result in problems such as pleural effusion, atelectasis, and lung consolidation[23]. In recent years, an upsurge in the number of refractory, severe, and even deadly MPP cases has been reported[24]. The pathogen MP, discovered in the 1940s, causes a wide range of clinical symptoms with a unique seasonal pattern; it is most active in the fall/early winter, with favorable peak rates of 3% to 4% between September and January[25]. MP is a benign, self-limiting disease; however, missed early detection opportunities, clinical misdiagnosis, and drug resistance often lead to poor outcomes[26].

Following the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, comprehensive testing and positivity rates of MP plummeted compared to previous years[27]. A national multicenter prospective survey of all-age patients (52.2% were aged 18 years) with acute respiratory tract infections in China between 2009 and 2019 revealed a peak in the positivity rate of MP in 2011 and a gradual upward trend in the positivity rate of MP from 2015 to 2019 (the majority being pediatric patients)[28]. MP is contagious and can be transmitted through aerosols from coughing and sneezing, causing acute upper and lower respiratory tract inflammation. The positivity rate for MP was low during 2020, which coincided with the COVID-19 era, suggesting that the implementation of nationwide countermeasures, such as strict face mask-wearing and population quarantine measures, may have also effectively prevented the concurrent spread of MP[29]. Our data showed that the rate of MP in hospitalized children was higher in winter than in autumn, which corroborated previously published data[30]. Conversely, a study from Serbia reported that the highest number of MP infections was recorded in the fall (33.3%), and this rate was higher than that in winter (29.2%)[31]. Similar studies on the seasonality of MP infection from Shanghai, China, showed a peak in spring that declined precipitously until the following summer[29]. However, some studies from Italy and Tunisia found no seasonal correlation in MP infection[31]. In our research, we found that children < 5 years of age were likely to have more severe MPP than mild MPP, accounting for 77.3% of cases. This finding was similar to data from a study

Table 4 Clinical characteristics and laboratory investigations of hospitalized children with community-acquired pneumonia caused by mycoplasma pneumonia were compared between the severe and mild case groups

Parameters	Mild MPP (n = 299)	Severe MPP (n = 110)	Z	P value
Gender	1.48 ± 0.501	1.45 ± 0.500	0.54	0.58
Age (yr)	3.59 ± 2.63	3.40 ± 2.16	0.69	0.49
Fever (°C)	38.73 ± 0.86	38.71 ± 0.83	0.163	0.87
Duration of fever	4.27 ± 3.37	5.76 ± 5.39	-2.72	0.007
Duration of cough	5.98 ± 6.9	11.4 ± 10.33	-5.103	< 0.001
WBC (10 ⁹ /L)	8.98 ± 4.77	9.34 ± 4.23	-0.691	0.49
Lymphocyte (%)	35.87 ± 14.04	38.93 ± 18.29	-1.59	0.114
Neutrophil (%)	54.48 ± 15.46	49.98 ± 20.28	2.113	0.036
Neutrophil to lymphocyte ratio	2.06 ± 1.702	2.046 ± 2.20	0.078	0.938
CRP (mg/L)	12.59 ± 19.24	10.48 ± 17.82	1	0.318
hsCRP (mg/L)	6.1 ± 5.84	8.35 ± 7.5	-2.834	0.005
PCT (ng/mL)	0.42 ± 0.93	0.76 ± 3.15	-1.097	0.27
Alanine transaminase (U/L)	15.95 ± 8.42	24.97 ± 37.32	-2.511	0.013
Aspartate aminotransferase (U/L)	32.25 ± 20.31	41.37 ± 30.11	-2.939	0.004
Creatine kinase (U/L)	97.3 ± 110.38	101.4 ± 83	-0.354	0.724
Lactate dehydrogenase (U/L)	286.55 ± 69.12	317.55 ± 93.77	-3.633	< 0.001

CRP: C-reactive protein; hsCRP: C-reactive protein; PCT: Procalcitonin; WBC: White blood cell.

Table 5 Auscultatory and myocardial damage findings among the mild and severe mycoplasma pneumoniae pneumonia cases, n (%)

Parameters		Mild MPP	Severe MPP	χ^2	P value
1 Auscultation	Crackles	37 (12.40)	23 (20.90)	11.915	0.008
	Normal	141 (47.20)	35 (31.80)		
	Wet rales	7 (2.30)	7 (6.40)		
	Wheezing	114 (38.10)	45 (40.90)		
2 Myocardial damage	Yes	0 (0.0)	52 (47.30)	157.078	< 0.001
	No	299 (100)	58 (52.70)		

MPP: Mycoplasma pneumoniae pneumonia.

conducted in Luzhou, China, which reported an MP positivity rate of 75% in children between the ages of 5 and 1 year[32]. However, some studies also report a higher risk of MP infection in children above > 5 years of age compared to those < 5 years of age[31]. Severe Mycoplasma infections are prevalent not only in children older than five years but also in those aged 2 to 4 years, and 10% of MP-infected patients admitted to the ICU were less than two years old. In addition, prior research identified MP as a significant cause of CAP in babies younger than one year[33]. Our findings are not easily compared to those of other studies because of the wide range of epidemiological conditions, varying populations, and different diagnostic modalities.

We also compared mild and severe MPP and found that the duration of fever and cough was longer in the severe MPP group than in the mild MPP group. Similarly, the high-sensitivity C-reactive protein, alanine transaminase, aspartate aminotransferase, and lactate dehydrogenase levels were significantly higher in the severe MPP cohort than in the mild MPP group. Paradoxically, the neutrophil count was significantly higher in the mild MPP group than in the severe MPP group, and we found that the neutrophil-to-lymphocyte ratio (NLR) did not significantly between mild MPP and severe MPP cases in children ($P > 0.05$). In another study of adults, the NLR was shown to have good prognostic value for short- and long-term mortality, ICU admission, and rehospitalization. This ratio is distinguished by

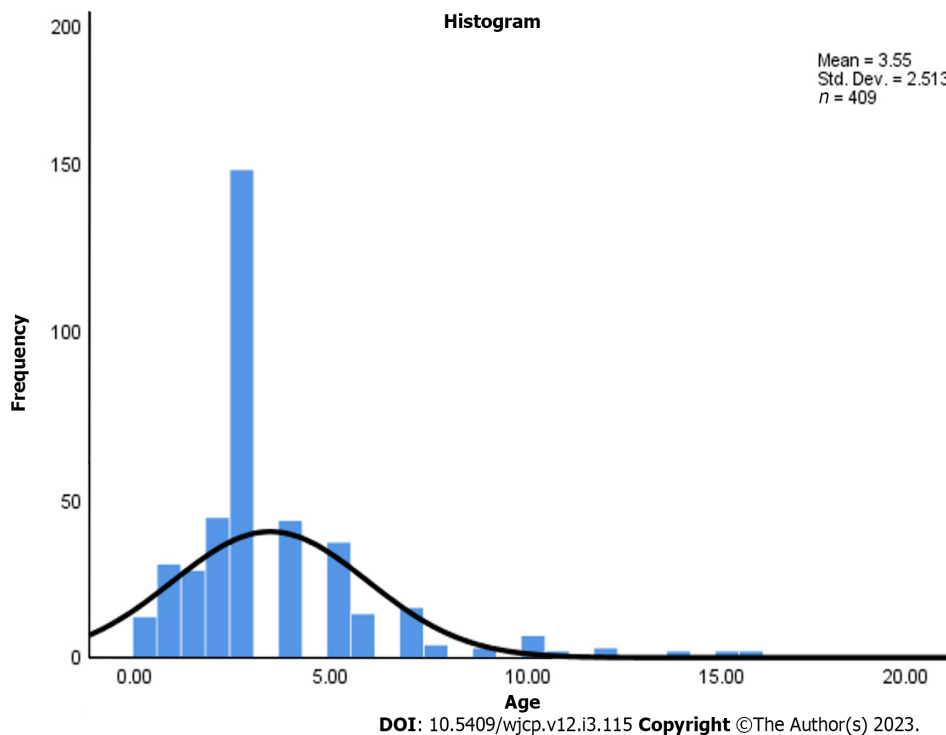


Figure 1 Age distribution of 409 children with *Mycoplasma Pneumoniae*-associated community-acquired pneumonia.

high death and morbidity rates, particularly among older individuals. As a result, the NLR was linked with post-CAP mortality better than standard pneumonia ratings (Patient-specific instrumentation; and Confusion, Urea, Respiratory rate, and Blood pressure, aged 65 and older, CURB-65)[34].

As a result, novel, simple, specific, and low-cost biomarkers to diagnose and monitor CAP are still needed. Neutrophilia and lymphocytopenia are innate immune system physiological responses to systemic inflammation. Lymphocytopenia is characterized by rapid apoptosis and the margination of lymphocytes in the reticuloendothelial system, liver, and splanchnic lymphatic system as well as lymphocyte redistribution throughout the lymphatic system. Neutrophilia is the opposite phenomenon and occurs during systemic inflammation due to neutrophil emargination and growth factor stimulation of stem cells (granulocyte-colony stimulating factor)[34]. In previously published research, WBC count and CRP were also demonstrated to be possible markers of pneumonia; however, they did not play a significant role in determining the causative pathogen of pneumonia, similar to our findings[35]. More importantly, the incidence of myocardial damage was significantly higher in the severe MPP group than in the mild MPP group. The remaining parameters, did not significantly differ between the two cohorts ($P > 0.05$).

Cardiac complications caused by MP are infrequent, with a prevalence rate of 1.0-8.5% and a slightly higher prevalence rate in adults than in children. Almost half of MP patients showed symptoms or evidence of cardiac abnormalities at a mean of 16 mo following infection. Constrictive pericarditis caused by MP infection has also been documented[20].

In some instances, MP-related extrapulmonary illnesses may be this infection's most obvious clinical issue, particularly in young people and children. MP infection has also been connected to several extrarespiratory symptoms. Numerous disorders affecting the skin, musculoskeletal, neurological, hematological, digestive, and renal systems have been described in pediatric populations[36]. CD4- T cells, B cells, and plasma cells invade the lungs, causing additional immunological amplification, including lymphocyte proliferation, immunoglobulin synthesis, and the release of proinflammatory cytokines. Total immunoglobulin, immunoglobulin A (IgA), IgM, and IgG levels in serum have previously been shown to rise throughout the convalescent phase of the illness; furthermore, IgE specific to MP is produced during infection[37]. The concentrations of serum cytokines, such as Interleukins (IL) IL-1, IL-4, and IL-6, also increase. The intensity of inflammation is determined by its degree. The production of acute-phase proteins, such as C-reactive protein, the amount of leukocytosis, the level of fibrinogen, and the rate of erythrocyte sedimentation are all pathogenetically relevant in pneumonia, determining the severity of the illness and increased mortality[38].

Our study highlighted the clinical parameters that should be focused on to differentiate mild and severe MPP cases. These parameters are crucial for pediatricians because they allow for rapid diagnosis and prompt treatment in cases of severe MPP.

This study's limitations include its retrospective nature and small sample size. Some data were omitted because they were missing and could not be extrapolated to represent hospitalized children with CAP throughout the year. Moreover, only cases were analyzed and this study lacked a control group.

CONCLUSION

Mycoplasma pneumoniae is the leading cause of community-acquired pneumonia. We found a significantly higher incidence of myocardial damage in children with severe MPP than in those with mild MPP. However, a causal link between severe MPP and myocardial damage has not yet been identified; therefore, future research is recommended to confirm this hypothesis.

ARTICLE HIGHLIGHTS

Research background

Community-acquired pneumonia (CAP) is a significant cause of inpatient hospitalization and mortality in children.

Research motivation

This is crucial for pediatricians as it would enable us to make a quick diagnosis and consequently prompt treatment in case of severe *Mycoplasma pneumoniae* pneumonia (MPP).

Research objectives

Our study highlighted which clinical parameters should be focused on to differentiate between mild and severe MPP.

Research methods

We identified children between 2 mo and 16 years of age with clinical and radiological findings consistent with CAP.

Research results

We found that the duration of fever and cough was longer in the severe MPP group than in the mild MPP group. Similarly, the high sensitivity C-reactive protein levels, procalcitonin, alanine transaminase, aspartate aminotransferase, and lactate dehydrogenase were significantly higher in the severe MPP cohort than in the mild MPP group. Paradoxically, the neutrophil count was significantly higher in the mild MPP group than in the severe MPP group.

Research conclusions

The incidence of myocardial damage was significantly higher in the severe MPP group than in mild MPP cases.

Research perspectives

It is unknown whether there is a causal link between severe MPP and myocardial damage; therefore, to ascertain this hypothesis, future research is recommended.

FOOTNOTES

Author contributions: Yusuf SO conducted data collection, analysis, and manuscript drafting; Chen P conceived the study and supervised the entire study process; All authors read and approved the final manuscript.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of The Second Hospital of Jilin University (In 2022, research review No. 073). Parents of all eligible children gave their informed consent for inclusion before they were admitted to the hospital. The confidentiality of the patients was ensured throughout the study.

Informed consent statement: This study consists of two parts: (1) We collected children's medical history, diagnosis and supplementary examination in the inpatients department through the hospital computer; and (2) the results of this study may provide information for future clinical activities. At the same time, we will keep the children's information and privacy strictly confidential. We promise to use it only for this study. Without permission, we will

not disclose this information to third parties. We make every effort to protect the privacy of the personal medical data. We will not use any patients name or patients ID.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: No additional data is available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Shukri Omar Yusuf 0000-0002-9111-1501; Peng Chen 0000-0001-8243-191X.

S-Editor: Liu JH

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- 1 **Leung AKC**, Wong AHC, Hon KL. Community-Acquired Pneumonia in Children. *Recent Pat Inflamm Allergy Drug Discov* 2018; **12**: 136-144 [PMID: 29932038 DOI: 10.2174/1872213X12666180621163821]
- 2 **Otheo E**, Rodríguez M, Moraleda C, Domínguez-Rodríguez S, Martín MD, Herreros ML, Vázquez C, Folgueira MD, Pérez-Rivilla A, Jensen J, López A, Berzosa A, Sanz de Santaefemia FJ, Jiménez AB, Sainz T, Llorente M, Santos M, Garrote E, Muñoz C, Sánchez P, Illán M, Coca A, Barrios A, Pacheco M, Arquero C, Gutiérrez L, Epalza C, Rojo P, Serna-Pascual M, Mota I, Moreno S, Galán JC, Tagarro A; VALS-DANCE and PCAPE Working Groups. Viruses and Mycoplasma pneumoniae are the main etiological agents of community-acquired pneumonia in hospitalized pediatric patients in Spain. *Pediatr Pulmonol* 2022; **57**: 253-263 [PMID: 34633153 DOI: 10.1002/ppul.25721]
- 3 **Chi H**, Huang YC, Liu CC, Chang KY, Lin HC, Chang LY, Ho YH, Tsao KC, Mu JJ, Huang LM, Hsieh YC; Taiwan Pediatric Infectious Disease Alliance. Characteristics and etiology of hospitalized pediatric community-acquired pneumonia in Taiwan. *J Formos Med Assoc* 2020; **119**: 1490-1499 [PMID: 32682702 DOI: 10.1016/j.jfma.2020.07.014]
- 4 **Rejas J**, Sicras-Mainar A, Sicras-Navarro A, Lwoff N, Méndez C. All-cause community acquired pneumonia cost by age and risk in real-world conditions of care in Spain. *Expert Rev Pharmacoecon Outcomes Res* 2022; **22**: 853-867 [PMID: 34949148 DOI: 10.1080/14737167.2022.2020649]
- 5 **Ning G**, Wang X, Wu D, Yin Z, Li Y, Wang H, Yang W. The etiology of community-acquired pneumonia among children under 5 years of age in mainland China, 2001-2015: A systematic review. *Hum Vaccin Immunother* 2017; **13**: 2742-2750 [PMID: 28922613 DOI: 10.1080/21645515.2017.1371381]
- 6 **Liu L**, Maharjan S, Sun JL, Li YC, Cheng HJ. Prevalence and clinical characteristics of septicemia in children with Mycoplasma pneumoniae pneumonia. *J Int Med Res* 2021; **49**: 3000605211021733 [PMID: 34167353 DOI: 10.1177/03000605211021733]
- 7 **Zhang Y**, Huang Y, Ai T, Luo J, Liu H. Effect of COVID-19 on childhood Mycoplasma pneumoniae infection in Chengdu, China. *BMC Pediatr* 2021; **21**: 202 [PMID: 33910509 DOI: 10.1186/s12887-021-02679-z]
- 8 **Naghib M**, Hatam-Jahromi M, Niktab M, Ahmadi R, Kariminik A. Mycoplasma pneumoniae and toll-like receptors: A mutual avenue. *Allergol Immunopathol (Madr)* 2018; **46**: 508-513 [PMID: 29331619 DOI: 10.1016/j.aller.2017.09.021]
- 9 **Gong H**, Sun B, Chen Y, Chen H. The risk factors of children acquiring refractory mycoplasma pneumoniae pneumonia: A meta-analysis. *Medicine (Baltimore)* 2021; **100**: e24894 [PMID: 33725960 DOI: 10.1097/MD.00000000000024894]
- 10 **Yan C**, Xue G, Zhao H, Feng Y, Li S, Cui J, Ni S, Sun H. Molecular and clinical characteristics of severe Mycoplasma pneumoniae pneumonia in children. *Pediatr Pulmonol* 2019; **54**: 1012-1021 [PMID: 31119869 DOI: 10.1002/ppul.24327]
- 11 **Fan L**, Li D, Zhang L, Hao C, Sun H, Shao X, Xu J, Chen Z. Pediatric clinical features of Mycoplasma pneumoniae infection are associated with bacterial P1 genotype. *Exp Ther Med* 2017; **14**: 1892-1898 [PMID: 28962100 DOI: 10.3892/etm.2017.4721]
- 12 **Zhou H**, Chen X, Li J. Effect of Methylprednisolone Plus Azithromycin on Fractional Exhaled Nitric Oxide and Peripheral Blood Eosinophils in Children with Refractory Mycoplasma Pneumoniae Pneumonia. *J Coll Physicians Surg Pak* 2022; **32**: 33-36 [PMID: 34983144 DOI: 10.29271/jcsp.2022.01.33]
- 13 **Waites KB**, Xiao L, Liu Y, Balish MF, Atkinson TP. Mycoplasma pneumoniae from the Respiratory Tract and Beyond. *Clin Microbiol Rev* 2017; **30**: 747-809 [PMID: 28539503 DOI: 10.1128/CMR.00114-16]
- 14 **Channappanavar R**, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017; **39**: 529-539 [PMID: 28466096 DOI: 10.1007/s00281-017-0629-x]
- 15 **Jiang Z**, Zhou R, Leung PHM, Deng Z, Li S. An attenuated multiple genetic mutant of Mycoplasma pneumoniae imparts good immuno-protection against M. pneumoniae pneumonia in BALB/c mice. *Microb Pathog* 2022; **165**: 105463 [PMID: 35240287 DOI: 10.1016/j.micpath.2022.105463]
- 16 **Shah SS**. Mycoplasma pneumoniae as a Cause of Community-Acquired Pneumonia in Children. *Clin Infect Dis* 2019; **68**:

- 13-14 [PMID: 29788200 DOI: 10.1093/cid/ciy421]
- 17 **Jiang Y**, Wang W, Zhang Z, Ma X, Sang Y, Wang J, Xu G, Feng Q, Zhao S. Serum amyloid a, C-reactive protein, and procalcitonin levels in children with Mycoplasma pneumoniae infection. *J Clin Lab Anal* 2022; **36**: e24265 [PMID: 35148010 DOI: 10.1002/jcla.24265]
- 18 **Khatib M**, Elbaz-Greener G, Nitzan O, Soboh S, Peretz A, Hazanov E, Kinany W, Halahla Y, Grosman-Rimon L, Houle H, Amir O, Carasso S. Unmasking Myocardial Dysfunction in Patients Hospitalized for Community-Acquired Pneumonia Using a 4-Chamber 3-Dimensional Volume/Strain Analysis. *J Digit Imaging* 2022; **35**: 1654-1661 [PMID: 35705794 DOI: 10.1007/s10278-022-00665-0]
- 19 **Nagashima M**, Higaki T, Satoh H, Nakano T. Cardiac thrombus associated with Mycoplasma pneumoniae infection. *Interact Cardiovasc Thorac Surg* 2010; **11**: 849-851 [PMID: 20847069 DOI: 10.1510/icvts.2010.242115]
- 20 **Li CM**, Gu L, Yin SJ, Yang R, Xie Y, Guo XZ, Fu YX, Cheng D. Age-specific Mycoplasma pneumoniae pneumonia-associated myocardial damage in children. *J Int Med Res* 2013; **41**: 1716-1723 [PMID: 24026772 DOI: 10.1177/0300060513497559]
- 21 **Paz A**, Potasman I. Mycoplasma-associated carditis. Case reports and review. *Cardiology* 2002; **97**: 83-88 [PMID: 11978954 DOI: 10.1159/000057677]
- 22 **Metlay JP**, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; **200**: e45-e67 [PMID: 31573350 DOI: 10.1164/rccm.201908-1581ST]
- 23 **Yang M**, Meng F, Gao M, Cheng G, Wang X. Cytokine signatures associate with disease severity in children with Mycoplasma pneumoniae pneumonia. *Sci Rep* 2019; **9**: 17853 [PMID: 31780733 DOI: 10.1038/s41598-019-54313-9]
- 24 **Liu J**, Zhao F, Lu J, Xu H, Liu H, Tang X, Yang H, Zhang J, Zhao S. High Mycoplasma pneumoniae loads and persistent long-term Mycoplasma pneumoniae DNA in lower airway associated with severity of pediatric Mycoplasma pneumoniae pneumonia. *BMC Infect Dis* 2019; **19**: 1045 [PMID: 31823740 DOI: 10.1186/s12879-019-4667-y]
- 25 **Kim CH**, Lee J. Mycoplasma pneumoniae Pleural Effusion in Adults. *J Clin Med* 2022; **11** [PMID: 35268372 DOI: 10.3390/jcm11051281]
- 26 **Zhou Y**, Wang J, Chen W, Shen N, Tao Y, Zhao R, Luo L, Li B, Cao Q. Impact of viral coinfection and macrolide-resistant mycoplasma infection in children with refractory Mycoplasma pneumoniae pneumonia. *BMC Infect Dis* 2020; **20**: 633 [PMID: 32847534 DOI: 10.1186/s12879-020-05356-1]
- 27 **Rothstein TE**, Cunningham SA, Rieke RA, Mainella JM, Mutchler MM, Patel R. Macrolide Resistance in Mycoplasma pneumoniae, Midwestern United States, 2014 to 2021. *Antimicrob Agents Chemother* 2022; **66**: e0243221 [PMID: 35311520 DOI: 10.1128/aac.02432-21]
- 28 **Li ZJ**, Zhang HY, Ren LL, Lu QB, Ren X, Zhang CH, Wang YF, Lin SH, Zhang XA, Li J, Zhao SW, Yi ZG, Chen X, Yang ZS, Meng L, Wang XH, Liu YL, Wang X, Cui AL, Lai SJ, Jiang T, Yuan Y, Shi LS, Liu MY, Zhu YL, Zhang AR, Zhang ZJ, Yang Y, Ward MP, Feng LZ, Jing HQ, Huang LY, Xu WB, Chen Y, Wu JG, Yuan ZH, Li MF, Wang Y, Wang LP, Fang LQ, Liu W, Hay SI, Gao GF, Yang WZ; Chinese Centers for Disease Control and Prevention (CDC) Etiology of Respiratory Infection Surveillance Study Team. Etiological and epidemiological features of acute respiratory infections in China. *Nat Commun* 2021; **12**: 5026 [PMID: 34408158 DOI: 10.1038/s41467-021-25120-6]
- 29 **Chen J**, Zhang J, Lu Z, Chen Y, Huang S, Li H, Lin S, Yu J, Zeng X, Ji C, Zheng Y, Dai F, Dong W, Xu H, Chen W, Jin X, Cui Z, Qiao J, Qin W, Chen H, Jiang W, Zhang X, Song J, Shao J, Su W, Wang C, Liu F, Zhao Y, Zou Y, Guo R, Zhang L, Wu J, Yuan S, Tang M, Wu Y, Lin J, Chen X, Sun X, Yin Y. Mycoplasma pneumoniae among Chinese Outpatient Children with Mild Respiratory Tract Infections during the Coronavirus Disease 2019 Pandemic. *Microbiol Spectr* 2022; **10**: e0155021 [PMID: 35138173 DOI: 10.1128/spectrum.01550-21]
- 30 **Su M**, Wang Q, Li D, Wang LL, Wang CY, Wang JL, Zhang Q, Du LY, Liu JY, Xie GC. Prevalence and clinical characteristics of hospitalized children with community-acquired Mycoplasma pneumoniae pneumonia during 2017/2018, Chengde, China. *Medicine (Baltimore)* 2021; **100**: e23786 [PMID: 33592835 DOI: 10.1097/MD.00000000000023786]
- 31 **Medjo B**, Atanaskovic-Markovic M, Radic S, Nikolic D, Lukac M, Djukic S. Mycoplasma pneumoniae as a causative agent of community-acquired pneumonia in children: clinical features and laboratory diagnosis. *Ital J Pediatr* 2014; **40**: 104 [PMID: 25518734 DOI: 10.1186/s13052-014-0104-4]
- 32 **Chen A**, Song L, Chen Z, Luo X, Jiang Q, Yang Z, Hu L, He J, Zhou L, Yu H. Immunoglobulin M profile of viral and atypical pathogens among children with community acquired lower respiratory tract infections in Luzhou, China. *BMC Pediatr* 2019; **19**: 280 [PMID: 31409320 DOI: 10.1186/s12887-019-1649-6]
- 33 **Lee KL**, Lee CM, Yang TL, Yen TY, Chang LY, Chen JM, Lee PI, Huang LM, Lu CY. Severe Mycoplasma pneumoniae pneumonia requiring intensive care in children, 2010-2019. *J Formos Med Assoc* 2021; **120**: 281-291 [PMID: 32948415 DOI: 10.1016/j.jfma.2020.08.018]
- 34 **Cataudella E**, Giraffa CM, Di Marca S, Pulvirenti A, Alaimo S, Pisano M, Terranova V, Corriere T, Ronsisvalle ML, Di Quattro R, Stancanelli B, Giordano M, Vancheri C, Malatino L. Neutrophil-To-Lymphocyte Ratio: An Emerging Marker Predicting Prognosis in Elderly Adults with Community-Acquired Pneumonia. *J Am Geriatr Soc* 2017; **65**: 1796-1801 [PMID: 28407209 DOI: 10.1111/jgs.14894]
- 35 **Hu S**, Zhu Y, Dong D, Wang B, Zhou Z, Wang C, Tian J, Peng Y. Chest Radiographs Using a Context-Fusion Convolution Neural Network (CNN): Can It Distinguish the Etiology of Community-Acquired Pneumonia (CAP) in Children? *J Digit Imaging* 2022; **35**: 1079-1090 [PMID: 35585465 DOI: 10.1007/s10278-021-00543-1]
- 36 **Poddighe D**. Extra-pulmonary diseases related to Mycoplasma pneumoniae in children: recent insights into the pathogenesis. *Curr Opin Rheumatol* 2018; **30**: 380-387 [PMID: 29432224 DOI: 10.1097/BOR.0000000000000494]
- 37 **Stelmach I**, Podsiadłowicz-Borzecka M, Grzelewski T, Majak P, Stelmach W, Jerzyńska J, Popławska M, Dziadek J. Humoral and cellular immunity in children with Mycoplasma pneumoniae infection: a 1-year prospective study. *Clin Diagn Lab Immunol* 2005; **12**: 1246-1250 [PMID: 16210492 DOI: 10.1128/CDLI.12.10.1246-1250.2005]
- 38 **Aminjonovich AA**. Treatment and diagnostic methods of pneumonia in children. *J Adv Res Stab* 2022; **16**: 560-566

Observational Study

Psychiatric disorders and caregiver burden in children with transfusion dependent β -thalassaemia and their caregivers

Samiksha Sahu, Amit Agrawal, Jyotsna Shrivastava, Sudhir Tonk

Specialty type: Pediatrics**Provenance and peer review:**

Invited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Liao JX, China; Shahriari M, Iran**Received:** January 28, 2023**Peer-review started:** January 28, 2023**First decision:** February 20, 2023**Revised:** January 31, 2023**Accepted:** March 31, 2023**Article in press:** March 31, 2023**Published online:** June 9, 2023**Samiksha Sahu**, Department of Psychiatry, Gandhi Medical College, Bhopal 462030, Madhya Pradesh, India**Amit Agrawal, Jyotsna Shrivastava, Sudhir Tonk**, Department of Pediatrics, Gandhi Medical College, Bhopal 462030, Madhya Pradesh, India**Corresponding author:** Amit Agrawal, MD, Associate Professor, Department of Pediatrics, Gandhi Medical College, Hamidia Hospital Campus, Bhopal 462030, Madhya Pradesh, India. agrawaldramit@yahoo.co.in

Abstract

BACKGROUND

Children with thalassemia need care from the first years of life owing to the physical and psychological effects of their disorder. Thalassemia is a concern not only for the children's physical health but also the mental health of themselves and their caregivers.

AIM

To screen the psychosocial problems and assessment of psychiatric morbidities among thalassaemic children and their caretakers, along with an assessment of caregiver burden in them.

METHODS

In this observational cross-sectional study, children with transfusion-dependent thalassemia, were included and were assessed for psychiatric morbidity and global functioning. Their parents were assessed for psychiatric morbidity and the caregiver burden they faced. All the parents completed two different questionnaires to assess their knowledge about the psycho-social functioning [using Pediatric Symptom Checklist-35 (PSC-35)] of their children and the level of the burden faced by them by Caregiver Burden Scale (CBS).

RESULTS

A total of 46 children (28 boys and 18 girls) with transfusion-dependent thalassemia with a mean age of 8.83 ± 2.70 years and 46 parents (12 fathers and 34 mothers) were included in this study. More than 32 children had some psychosocial problems on screening by PSC-35. On assessment by CBS moderate caregiver burden was perceived in domains of general strain, isolation, disappointment, emotional involvement, and environment. A total of 65.3% of

children and 62.7% of parents were diagnosed with psychiatric problems.

CONCLUSION

Thalassemia affects not only the persons with the disorder but also their caregivers in several aspects, including their psychosocial well-being. This study emphasizes the role of a supportive group in the psychological well-being of caregivers, which could be used to prevent the pathological effects of caregiver burden and enhance their psychological well-being through counselling.

Key Words: Thalassemia; Children; Caregiver burden scale; Psychiatric morbidity

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Thalassemia is a major public health problem because of its high prevalence ranging from 2%-5%. Like other chronic illnesses, patients with thalassemia are vulnerable to emotional and behavioral problems making them susceptible to a myriad of psychiatric disorders. The emotional and psychological problems faced by thalassaemic children and their caregivers are often overlooked resulting in increased suffering and poor outcome. In this observational, cross-sectional study we analyze 46 children with transfusion-dependent Thalassemia for the presence of psychiatric disorders along with the caregiver burden experienced by the caregivers of these children.

Citation: Sahu S, Agrawal A, Shrivastava J, Tonk S. Psychiatric disorders and caregiver burden in children with transfusion dependent β -thalassaemia and their caregivers. *World J Clin Pediatr* 2023; 12(3): 125-132

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/125.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.125>

INTRODUCTION

Thalassemia is a major public health problem because of its high prevalence ranging from 2%-5%, it extends from parts of Africa, the Mediterranean throughout the Middle East, Southeast Asia, and the Indian subcontinent[1-3]. Each year 50000-100000 children die of Thalassemia major in low- and middle-income countries[4]. The carrier rate for the beta thalassaemia gene varies from 1%-2% in Southern India to 3%-15% in Northern India. Children with thalassemia major present with pallor, failure to thrive, intercurrent infections, and hepatosplenomegaly, and they are generally diagnosed between 6 mo and 2 years of life. If undiagnosed and untreated, more than 90% do not survive beyond 3 to 4 years of age[5]. Similar to other chronic illnesses, patients with thalassemia are vulnerable to emotional and behavioral problems[6]. These children are susceptible to anxiety and depression due to fear of separation from family, restricted social activity, physical and facial deformities, fear of death, and limitations in school and outdoor activities. It has been observed that up to 80% of children with thalassaemia are likely to have psychological problems like anxiety disorder, depression, and oppositional defiant disorder[2]. Psychosocial burden is perceived even more in adolescents when they are confronted with various difficulties like identity formation and developing intimate relationships dealing with work. Their physical appearance and absence of sexual development is the major obstacle to social and personal life. Thalassemia also affects the caregivers' mental health, and family life as it causes lots of financial strain leads to ignorance of other children, and hampers occupational duties due to its long-term complications, and burdensome medical protocols[7-9]. There are many studies about psychiatric problems and the quality of life of patients with thalassemia[10]. Understanding of the psychiatric aspect of this disease is still in its infancy. Therefore, we planned this study to assess the occurrence of psychiatric disorders amongst children and their caregivers as well as to assess the caregiver burden in children of transfusion-dependent β thalassaemia major.

MATERIALS AND METHODS

This observational, cross-sectional study was conducted in the department of Pediatrics of a tertiary care teaching institution in central India over a period of one year. Prior approval from the institutional ethics and research committee was obtained. Children with an established diagnosis of transfusion-dependant β thalassemia major in the age range of 5 to 16 years and their caregivers regularly attending the department for blood transfusion were chosen for the study. A sample size of 46 patients was

calculated to complete the objective of the study using the formula ($n = 4pq/L^2$) where prevalence (p) was 3%, $q = (100-p)$, and allowable error (L) was 5%. Written consent was taken from the parents/caregiver and assent was taken from children above seven years of age. Children, with other chronic disorders like epilepsy and comorbid neurological conditions like pre-existing mental retardation, developmental delay, and cerebral palsy and thalassaemic children less than five years and more than 16 years of age, were excluded. Relevant information including socio-demographic profile, age at diagnosis, details of chelation therapy, and blood transfusion was collected in a predesigned proforma. Socio-economic status was assessed using Modified Prasad's classification[11].

After recruitment, the complete physical and systemic examination was done by the paediatrician. The parents of the recruited children were given two questionnaires: Pediatric Symptom Checklist-35 (PSC-35) and Caregiver Burden Scale (CBS)[12]. PSC-35 is a parent-reported questionnaire designed to assess the psychosocial functioning of children in the domains of attention, externalizing, and internalizing symptoms. It has a sensitivity of 80% to 95% and specificity of 68% to 100%. The PSC consists of 35 items that are rated as "never", "sometimes", or "often present" (scored 0, 1, and 2, respectively). The scores for all 35 items are summed up to calculate the total score. For children aged 6 through 16 years, the cut-off score is 28 or higher while the cut-off is 24 or higher for 4- and 5-year-old children. Children who scored above the cut-off were referred for Psychiatric assessment.

CBS had 22 questions about different aspects of caregivers' burden and it has factor analysis to yield results about 5 indices - general strain (8 questions), disappointment (5 questions), emotional involvement (3 questions), isolation (3 questions), and environment (3 questions)[13]. Scoring was done on a scale of 1-4 (not at all, seldom, sometimes, and often). The total burden index was the mean of all 22 items and the higher scores indicated a greater burden. The total burden of each domain was divided into three groups: Low burden (1.00-1.99), moderate burden (2.00-2.99), and high burden (3.00-4.00)[14]. All the children who met the cut-off score on PSC-35 were clinically interviewed by the Professor in psychiatry and were diagnosed using DSM-IV TR. All the parents, who perceived a higher burden of illness, were also interviewed by a psychiatrist and were diagnosed and managed accordingly. Quantitative variables were analyzed in terms of mean and SD. Qualitative data was depicted in numbers and percentages.

RESULTS

A total of 46 children and their parents were included in this study, out of which 28 were males and 18 were females. Among parents 12 were fathers and 34 were mothers. The mean age of children was 8.83 ± 2.70 years. Most of them were staying in Urban settings (63%). 58.69% of the population were belonging to nuclear families. Patients came from all the socio-economic strata of society but the lower class was dominant. Demographic details of the study population have been given in Table 1. The mean medical expense per month was $11.89\% \pm 6.27\%$ of the total family income. In terms of caregiver burden, the caregivers have faced a moderate amount of burden in terms of general strain, isolation, disappointment, emotional involvement, and environment (Table 2). A total of 35 out of the 46 children scored above the cut-off score in assessment on PSC-35 and out of them, 30 children were diagnosed with various psychiatric disorders like major depressive disorder (15.2%), anxiety disorder (19.6%), attention deficit hyperactivity disorder (ADHD) (8.7%), elimination disorder (19.6%), panic disorder (2.2%) as shown in Table 3. Whereas in caregivers, 28.2% of caregivers suffer from depression, 4.3% from bipolar disorder, substance use disorder (10.9%), somatisation disorder (13.04 %), and 6.6% suffered from anxiety disorder (Table 3).

DISCUSSION

Thalassemia is among the most common hemoglobinopathy in India. It has become a major health problem for patients and their families in many countries due to the cost of treatment which involves regular transfusions, iron chelation, medical follow-ups, and hospitalisations[15,16]. In recent years, attention is drawn to the evaluation of psychiatric disorders, and caregiver burden among patients and their caregivers[17,18]. Our study highlights the sociodemographic variables, caregiver burden, and psychiatric morbidities in children suffering from transfusion-dependent Thalassemia Major and their parents. In our study, the mean age of the children was 8.83 ± 2.70 years with a male preponderance which is commonly seen in Indian settings[19]. However, studies done in the Middle East, Mediterranean, and west have shown the equal incidence of diseases in both sexes[20,21-24]. This male preponderance has been attributed to a gender bias, rather than an actual dominance of disease in the boys. Various studies across India have seen that a boy child is taken to a health facility more often than a girl child[25]. We further found that the majority of the caregiver (73.91 %) were females, this finding may be attributed to the Asian culture of parenting where mothers tend to stay at home and take care of their children. We have found, similarly, a significant impairment in the mental health of the caregivers of β -thalassaemic children, while their children undergo years of treatment, they often face isolation, strain,

Table 1 Demographic details of the study population

Variable	Male (28)	Female (18)	Total, n (%)
Age (children)			
4-8 years	10	9	19 (41.30)
9-12 years	12	5	17 (36.95)
13-16 years	6	4	10 (21.73)
Age (parents)			
< 20 years	2	5	7 (15.2)
21-30	6	18	24 (52.17)
31-40	3	9	12 (26)
> 40	1	2	3 (6.5)
Residence			
Rural	15	2	17 (37)
Urban	13	16	29 (63)
Family type			
Nuclear	17	10	27 (58.69)
Joint	11	8	19 (41.30)
Socioeconomic status (prasad's scale)			
Upper middle class	3	4	7 (15.21)
Middle class	7	3	10 (21.7)
Lower middle class	6	5	11 (23.91)
Lower class	12	6	18 (39.13)

Table 2 Caregiver burden in the parents of thalassaemic children

Items	Mean
General strain	2.77
Isolation	2.93
Disappointment	2.77
Emotional involvement	2.78
Environment	2.75

and disappointment. Most of them suffer from moderate caregiver burden. As mothers are emotionally more vulnerable and they undertake the caregiver role in our society we found a higher ratio of burden in females caregiver, our finding is by a study done by Sinno *et al*[26] and a study done in Iranian mothers of thalassaemic children where they also observed high caregiver burden and strain[27].

Children and families suffering from any chronic illness have a significant impact on their mental health. Parents' anxiety about their child's illness may lead to restrictions on many normal activities of childhood and can prevent the overall development of the child. These things in the long run can make a child prone to many psychiatric disorders. Along with children even parents of these children faces isolation, and emotional and financial burden in their life, over time the parents' attitude may result in over-protective behaviour or open rejection. The child's feelings and reaction to his illness may affect his relationships with his siblings, peers, and his parents[28]. Studies done in the past 25 years have shown that the prevalence of Psychiatric disorders in thalassaemic children ranged from 23 to 80%, and these problems affect treatment compliance[29]. In the present study, 65.3% of the thalassaemic children had a psychiatric problem and Among caregivers, 62.67% had psychiatric problems which is in accordance with the results of the previous studies[4,5,13]. Depression which is associated with medical illness is one of the important subgroups of mood disorders. The increased prevalence of depression has been associated with chronic medical diseases, and the prevalence of depression increases with co-occurring medical conditions[13]. We found that 15.2% of children suffered from Major Depressive disorder

Table 3 Psychiatric diagnosis among thalassaemic children and caregiver, n (%)

Psychiatric Disorder	Children	Caregiver
Major depressive disorder	7 (15.2)	13 (28.2)
Bipolar I disorder	0 (0.0)	2 (4.3)
Generalized anxiety disorder	9 (19.6)	2 (4.3)
ADHD	4 (8.7)	0 (0.0)
Elimination disorder	9 (19.6)	0 (0.0)
Panic attack	1 (2.2)	1 (2.2)
Substance use disorder	0 (0.0)	5 (10.9)
Somatization disorder	0 (0.0)	6 (13.04)
Total	30 (65.3)	29 (62.67)

ADHD: Attention deficit hyperactivity disorder.

earlier studies have noted a similar trend. In our study, we found that 28.2% of parents of children with Beta Thalassemia Major suffered from a major depressive disorder. In a previous study, UL Haq *et al*[30] found that most of the caregivers suffered from mild depression which is similar to our finding. In a study done for the evaluation of depression in mothers of patients with thalassemia or hematological malignancies, Shargi *et al*[31] reported the frequency of depression as 51%.

In the present study, 19% of patients were found to have nocturnal enuresis. In an earlier study, Beratis found that 12 % of their sample of pre-adolescent children with Thalassemia had nocturnal enuresis. Aydin *et al*[7] reported the prevalence of nocturnal enuresis to be 8% of children with TM. As we have not investigated the renal function in our study, it will not be possible to comment on the etiological factor of nephropathy. The impact of nocturnal enuresis extends to the caregiver as well adding up their miseries, as they have to wake up every night or change and wash their beddings. Generalized anxiety disorder, was seen in more than 19% of children followed by ADHD and panic attacks. Not many studies have assessed the long-term effect of chronic anaemia on the attention and hyperactivity of children, but some studies should be encouraged to study these aspects of long-term illness[31]. A significant number of parents suffered from somatization disorder (13.04%), generalized anxiety disorder, and bipolar disorder. This high percentage of somatisation disorder indicates the caregivers' fragile mental state as they are using neurotic defenses to deal with the struggle of life. We found that substance use disorder was seen in 10.9% of parents, it can be assumed that keeping aside the genetic susceptibility we may attribute substance use to cope with problems and hardships which accompany the lives of these parents. Studies done in Bangalore reported a high prevalence of psychiatric problems in caregivers of thalassaemic children which includes substance use disorder and depression[29]. Our study was limited by the small sample size. Also, it was a hospital-based study so the results cannot be generalized.

CONCLUSION

Our study showed that the parents of children with transfusion-dependent thalassemia major suffer from high caregiver burden and many of them also suffered from dysthymic disorder, somatoform disorder, and substance addictions. These children also suffered from various psychiatric problems like generalized anxiety disorder, elimination disorder, dysthymic disorder, and other psychiatric ailments. Due to their chronic condition and associated psychiatric morbidity, they have slight impairment in global functioning. Our study highlights the importance of comprehensive care and appropriate psychiatric intervention for thalassaemic children and their caregivers.

ARTICLE HIGHLIGHTS

Research background

Thalassemia is highly prevalent in Indian Subcontinent with prevalence rates varying from 2%–5%. These children and their caregivers experience multiple emotional and psychological problems stemming from the poor physical health of the child and resultant recurrent hospitalisations.

Research motivation

Psychiatric co-morbidities in these children and their caregivers have remained unexplored resulting in high emotional and psychological suffering. Assessing the same would result in the recognition of high psychiatric co-morbidities faced by this subset leading to the holistic care of these patients.

Research objectives

Current study aimed to screen the psychosocial problems and assessment of psychiatric morbidities among thalassaemic children and their caretakers, along with an assessment of caregiver burden in them. The objectives of the study were all met implicating the high prevalence of psychiatric co-morbidities faced by these patients.

Research methods

In this observational cross-sectional study, children with transfusion-dependent thalassemia were included and were assessed for psychiatric morbidity and global functioning. Their parents were assessed for the psychiatric morbidity and caregiver burden faced by them. All the parents completed two different questionnaires to assess their knowledge about the psycho-social functioning [using Pediatric Symptom Checklist-35 (PSC-35)] of their children and the level of the burden faced by them by Caregiver Burden Scale (CBS).

Research results

A total of 46 children (28 boys and 18 girls) with transfusion-dependent thalassemia with a mean age of 8.83 ± 2.70 years and 46 parents (12 fathers and 34 mothers) were included in this study. More than 32 children had some psychosocial problems on screening by PSC-35. On assessment by CBS moderate caregiver burden was perceived in domains of general strain, isolation, disappointment, emotional involvement, and environment. A total of 65.3% of children and 62.7% of parents were diagnosed with psychiatric problems.

Research conclusions

The study implicated a high burden of psychiatric disorders like generalized anxiety disorder, elimination disorder, and dysthymic disorder among children. The caregivers were also revealed to be suffering from an entire spectrum of psychiatric disorders ranging from dysthymic disorders to substance addictions.

Research perspectives

More such research should be conducted with a larger sample size to better gauge the extent of psychiatric co-morbidities among these patients. There is a need to bring about a paradigm shift in the healthcare protocols to ensure holistic care of these patients and their caregivers.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Priyash Jain, Senior Resident, Department of Psychiatry for his valuable technical support in editing the final manuscript.

FOOTNOTES

Author contributions: Sahu S participated in the data collection, and interpretation of data and executed the study; Tonk S participated in the data collection, and interpretation of data; Agrawal A participated in the data analysis and manuscript writing; Srivastava J participated in drafting and editing the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics committee of Gandhi Medical College.

Informed consent statement: All study participants, or their legal guardians, provided informed written consent before study enrolment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement – a checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – a checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: India

ORCID number: Amit Agrawal 0000-0001-6316-6700; Jyotsna Shrivastava 0000-0002-5322-4791.

S-Editor: Xing YX

L-Editor: A

P-Editor: Xing YX

REFERENCES

- 1 **Cappellini MD**, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. Guidelines for the Clinical Management of Thalassaemia [Internet]. 2nd Revised edition. Nicosia (CY): Thalassaemia International Federation; 2008 [PMID: 24308075]
- 2 **Weatherall DJ**, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. *Bull World Health Organ* 2001; **79**: 704-712 [PMID: 11545326]
- 3 **Roy T**, Chatterjee SC. The experiences of adolescents with thalassemia in West Bengal, India. *Qual Health Res* 2007; **17**: 85-93 [PMID: 17170246 DOI: 10.1177/1049732306296400]
- 4 **Alzahrani RA**, Almutairi OM, Alghoraibi MS, Alabdulwahed MS, Abaalkhail MK, Alhawish MK, Alosaimy MT. Quality of life in transfusion-dependent thalassemia patients. *J Taibah Univ Med Sci* 2017; **12**: 465-470 [PMID: 31435280 DOI: 10.1016/j.jtumed.2017.05.006]
- 5 **Verma IC**, Choudhry VP, Jain PK. Prevention of thalassemia: a necessity in India. *Indian J Pediatr* 1992; **59**: 649-654 [PMID: 1340849 DOI: 10.1007/BF02859390]
- 6 **Keşkek SO**, Kirim S, Turhan A, Turhan FG. Depression in subjects with beta-thalassemia minor. *Ann Hematol* 2013; **92**: 1611-1615 [PMID: 23892926 DOI: 10.1007/s00277-013-1851-9]
- 7 **Aydin B**, Yaprak I, Akarsu D, Okten N, Ulgen M. Psychosocial aspects and psychiatric disorders in children with thalassemia major. *Acta Paediatr Jpn* 1997; **39**: 354-357 [PMID: 9241900 DOI: 10.1111/j.1442-200x.1997.tb03752.x]
- 8 **Saini A**, Chandra J, Goswami U, Singh V, Dutta AK. Case-control study of psychosocial morbidity in β Thalassemia Major. *J Pediatr* 2007; **516**-20 [DOI: 10.1016/j.jpeds.2007.01.025]
- 9 **Johnson MK**, Mollborn S. Growing up Faster, Feeling Older: Hardship in Childhood and Adolescence. *Soc Psychol Q* 2009; **72**: 39-60 [PMID: 21921972 DOI: 10.1177/019027250907200105]
- 10 **Yengil E**, Acipayam C, Kokacya MH, Kurhan F, Oktay G, Ozer C. Anxiety, depression and quality of life in patients with beta-thalassemia major and their caregivers. *Int J Clin Exp Med* 2017; **2165**-2172 [PMID: 25232402]
- 11 **Pandey VK**, Aggarwal P, Kakkar R. Modified BG Prasad Socio-economic Classification, Update-2019. *Indian J Community Health* 2019; **31**: 150-152 [DOI: 10.47203/ijch.2019.v31i01.025]
- 12 **Y-PSC PS**. Pediatric Symptom Checklist. *J Dev Behav Pediatr* 1994; **15**: 191-197
- 13 **Elmståhl S**, Malmberg B, Annerstedt L. Caregiver's burden of patients 3 years after stroke assessed by a novel caregiver burden scale. *Arch Phys Med Rehabil* 1996; **77**: 177-182 [PMID: 8607743 DOI: 10.1016/s0003-9993(96)90164-1]
- 14 **Al-Rawashdeh SY**, Lennie TA, Chung ML. Psychometrics of the Zarit Burden Interview in caregivers of patients with heart failure. *J Cardiovasc Nurs* 2011; **31**: E21-E28 [PMID: 27617563 DOI: 10.1097/JCN.0b0000000000000348]
- 15 **Wong LP**, George E, Tan JA. Public perceptions and attitudes toward thalassaemia: Influencing factors in a multi-racial population. *BMC Public Health* 2011; **11**: 193 [PMID: 21447191 DOI: 10.1186/1471-2458-11-193]
- 16 **Loukopoulos D**. Haemoglobinopathies in Greece: prevention programme over the past 35 years. *Indian J Med Res* 2011; **134**: 572-576 [PMID: 22089622]
- 17 **Hajibeigi B**, Azarkeyvan A, Alavian SM, Lankarani MM, Assari S. Anxiety and depression affects life and sleep quality in adults with beta-thalassemia. *Indian J Hematol Blood Transfus* 2009; **25**: 59-65 [PMID: 23100977 DOI: 10.1007/s12288-009-0015-5]
- 18 **Maughan B**, Collishaw S, Stringaris A. Depression in childhood and adolescence. *J Can Acad Child Adolesc Psychiatry* 2013; **22**: 35-40 [PMID: 23390431]
- 19 **Bandyopadhyay B**, Nandi S, Mitra K, Mandal PK, Mukhopadhyay S, Biswas AB. A comparative study on perceptions and practices among parents of thalassaemic children attending two different institutions. *Indian J Community Med* 2018; **28**: 1-5 [DOI: 10.4103/2395-2113.251436]
- 20 **Olivieri NF**. The beta-thalassemias. *N Engl J Med* 1999; **341**: 99-109 [PMID: 10395635 DOI: 10.1056/NEJM199907083410207]
- 21 **Wang K**, Yi T, Wu WT, Lu J, He LN, Zhou HP, Ke JW, Liu FD. Investigation of the Distribution of Thalassemia in Children in Jiangxi Province, the People's Republic of China. *Hemoglobin* 2022; **46**: 272-276 [PMID: 36317662 DOI: 10.1080/03630269.2022.2138429]
- 22 **Ren ZM**, Xiao WW, Liu SX, Liu YQ, Li B, Chen YS. [Genotypic and Phenotypic Analysis of $\alpha\beta$ -Thalassemia in Children]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2019; **27**: 1232-1235 [PMID: 31418385 DOI: 10.19746/j.cnki.issn.1009-2137.2019.04.039]

- 23 **Deyde VM**, Lo BB, Khalifa IO, Ly B, Ball A, Fattoum S. Epidemiological profile of hemoglobinopathies in the Mauritanian population. *Ann Hematol* 2002; **81**: 320-321 [PMID: [12107561](#) DOI: [10.1007/s00277-002-0471-6](#)]
- 24 **Hafeez M**, Aslam M, Ali A, Rashid Y, Jafri H. Regional and ethnic distribution of beta thalassemia mutations and effect of consanguinity in patients referred for prenatal diagnosis. *J Coll Physicians Surg Pak* 2007; **17**: 144-147 [PMID: [17374299](#)]
- 25 **Trehan A**, Sharma N, Das R, Bansal D, Marwaha RK. Clinicoinvestigational and demographic profile of children with thalassemia major. *Indian J Hematol Blood Transfus* 2015; **31**: 121-126 [PMID: [25548457](#) DOI: [10.1007/s12288-014-0388-y](#)]
- 26 **Sinno SM**, Killen M. Moms at work and dads at home: Children's evaluations of parental roles. *Applied Developmental Science* 2009; **13**: 16-29 [DOI: [10.1080/10888690802606735](#)]
- 27 **Shahraki-Vahed A**, Firouzkouhi M, Abdollahimohammad A, Ghalgaie J. Lived experiences of Iranian parents of beta-thalassemia children. *J Multidiscip Healthc* 2017; **10**: 243-251 [PMID: [28721064](#) DOI: [10.2147/JMDH.S132848](#)]
- 28 **Rifaya M**, Rajapaksa S, Prematilaka G, Hettiarachchi N. Socio-demographic and psychological aspects of children with thalassaemia. *Sri Lanka J Child Health* 2011; **40**: 16 [DOI: [10.4038/sljch.v40i1.2863](#)]
- 29 **Hongally C**, Benakappa AD, Reena S. Study of behavioral problems in multi-transfused thalassemic children. *Indian J Psychiatry* 2012; **54**: 333-336 [PMID: [23372235](#) DOI: [10.4103/0019-5545.104819](#)]
- 30 **UL Haq F**, Khan AM, Yaqoob U, Sheikh RJ, Salam O, Zubair U. Effect of Child Thalassemia on the Mental Health of their Caregivers. *Int J Ment Health Psychiatry* 2017; **3** [DOI: [10.4172/2471-4372.1000143](#)]
- 31 **Sharghi A**, Karbakhsh M, Nabaei B, Meysamie A, Farrokhi A. Depression in mothers of children with thalassemia or blood malignancies: a study from Iran. *Clin Pract Epidemiol Ment Health* 2006; **2**: 27 [PMID: [17020622](#) DOI: [10.1186/1745-0179-2-27](#)]

Observational Study

Evaluation of children and adults with post-COVID-19 persistent smell, taste and trigeminal chemosensory disorders: A hospital based study

Sherifa Ahmed Hamed, Eman Bahaa Kamal-Eldeen, Mohamed Azzam Abdel-Razek Ahmed

Specialty type: Pediatrics**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0**P-Reviewer:** Byeon H, South Korea;
Suvvari TK, India**Received:** February 27, 2023**Peer-review started:** February 27, 2023**First decision:** March 15, 2023**Revised:** March 16, 2023**Accepted:** April 20, 2023**Article in press:** April 20, 2023**Published online:** June 9, 2023**Sherifa Ahmed Hamed**, Department of Neurology and Psychiatry, Assiut University, Faculty of Medicine, Assiut 71516, Egypt**Eman Bahaa Kamal-Eldeen**, Department of Pediatrics, Assiut University, Faculty of Medicine, Assiut 71516, Egypt**Mohamed Azzam Abdel-Razek Ahmed**, Department of ENT, Assiut University, Faculty of Medicine, Assiut 71516, Egypt**Corresponding author:** Sherifa Ahmed Hamed, MD, Professor, Department of Neurology and Psychiatry, Assiut University, Faculty of Medicine, Assiut University Street, Assiut 71516, Egypt. hamedsherifa@aun.edu.eg

Abstract

BACKGROUND

Smell disorders are the most frequent persistent coronavirus disease 2019 (COVID-19) complications.

AIM

To describe the patterns and characteristics of persistent smell and taste disorders in Egyptian patients.

METHODS

Assessment was done to 185 patients (adults = 150, age: 31.41 ± 8.63 years; children = 35; age: 15.66 ± 1.63 years). Otolaryngology and neuropsychiatric evaluations were done. Measurements included: A clinical questionnaire (for smell and taste); sniffin' odor, taste and flavor identification tests and the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS).

RESULTS

Duration of disorders was 11.53 ± 3.97 ms (6-24 ms). Parosmia ($n = 119$; 64.32%) was developed months after anosmia (3.05 ± 1.87 ms). Objective testing showed anosmia in all, ageusia and flavor loss in 20% ($n = 37$) and loss of nasal and oral trigeminal sensations in 18% ($n = 33$) and 20% ($n = 37$), respectively. Patients had low scoring of sQOD-NS (11.41 ± 3.66). There were no specific differences in other demographics and clinical variables which could distinguish post-COVID-19

smell and taste disorders in children from adults.

CONCLUSION

The course of smell and taste disorders are supportive of the nasal and oral neuronal compromises. Post-COVID-19 taste and trigeminal disorders were less frequent compared to smell disorders. Post-COVID-19 flavor disorders were solely dependent on taste and not smell disorders. There were no demographics, clinical variables at onset or specific profile of these disorders in children compared to adults.

Key Words: Post-COVID-19 complications; Anosmia; Ageusia; Trigeminal sensory loss; Parosmia; Quality of life

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Smell loss is the most frequent acute manifestation of coronavirus disease 2019 (COVID-19) infection with an estimated prevalence of 40%-86% in adults and 16%-20% in children. Smell disorders (loss or distortion) are also the most frequent long-lasting complications of COVID-19 infection with an estimated prevalence of 20%-40% in adults. Compared to smell, taste disorders are less frequent acute manifestation of viral infection (occurring in 10%-42% of adults) and long-lasting complications of COVID-19 infection. Reports about the prevalence and prognosis of these disorders in children are few or even lacking compared to adults. Also the mechanisms and treatment of these persistent disorders are still challenges. Evidence from experimental studies suggested that injury and degeneration of the neuronal olfactory and gustatory sensory epithelia by severe peripheral viral infection and its immunopathology and the delay or lack of neuronal regeneration might contribute to these disorders. Here, we tried to determine the predictors for persistent disorders and distinguish their differences in children compared to adults.

Citation: Hamed SA, Kamal-Eldeen EB, Ahmed MAAR. Evaluation of children and adults with post-COVID-19 persistent smell, taste and trigeminal chemosensory disorders: A hospital based study. *World J Clin Pediatr* 2023; 12(3): 133-150

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/133.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.133>

INTRODUCTION

Several months after the initial description of the severe acute coronavirus disease 2019 (COVID-19) infection, many data emerged about the prevalence of its mild manifestations including smell and taste disorders. The majority of reports about post-COVID-19 smell and taste disorders were devoted for adult population. Meta-analyses studies reported an estimated prevalence of 40%-86% for smell loss and 10.2%-42% for taste loss in adults infected with COVID-19[1]. Smell loss has been found to be the hallmark or the isolated symptom of COVID-19 infection in 25%-44% of adults[2]. Reports about these disorders in children and adolescents as a manifestation of COVID-19 infection are few and their results are highly variable[3-5]. In the meta-analysis study done by Yan *et al*[4], the authors estimated that the pooled prevalence of post-COVID-19 anosmia, ageusia, anosmia or ageusia and both anosmia and ageusia in children were 16% (95%CI: 8.2-23.8), 9.2% (95%CI: 4.3-14.2), 15.5% (95%CI: 10.3-20.7) and 20.2% (95%CI: 14.1-26.3), respectively. Smell disorders were found to be the most frequent long-lasting or persistent (months to years) COVID-19 complications in approximately 20%-40% of adults[6-8], however, the systematic estimation of the prevalence of these disorder in children is lacking.

Studies reported two main patterns for smell loss (with or without taste loss) as acute manifestations of COVID-19 infection: (1) Sudden smell loss in association with general, systemic or other ear, nose and throat (ENT) viral manifestations. This was the most frequent pattern. It might occur either at the same time with other viral manifestations (22.8%-88.0%)[9,10], after the recovery of other viral manifestations (26.6%-65.4%)[11], or before the onset of other manifestations (11.8%)[9]; and (2) Isolated smell loss without any other viral manifestations (approximately 16%-19.4%)[10].

Studies also reported two prognoses for these disorders. They are: (1) Transient deficits which resolved within days to weeks after onset (mean: Approximately 20 d). This was the most frequent prognosis occurring in 60%-80% of patients[12-14]; and (2) Long-lasting/persistent disorders (deficits and distortions) lasting for months to years. The long-lasting/persistent disorders have been reported to occur in 20%-40% of patients[14].

Studied found that the nose and mouth are the main sites for entry of β -coronaviruses (CoVs) into the body including severe acute respiratory syndrome coronavirus 1 [15], Middle east respiratory syndrome coronavirus (MERS-CoV) [16] and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [17, 18]. The olfactory epithelial cells, the sustentacular, Bowman's gland, micovillar cells (but not neuronal cells or receptors) are overloaded by the angiotensin-converting enzyme type 2 (ACE2) receptors, which are the targets for viral entry into the body [19]. In golden Syrian hamsters, the researchers observed infection of large proportion of sustentacular cells by SARS-CoV-2 within few days after its instillation, followed by desquamation and infiltration of immune cells into the olfactory epithelium and lamina propria, disorganization of the epithelial structure and loss of cilia necessary for olfactory transduction. The authors also observed partial restoration of the epithelium within approximately 2 wk [17, 18]. Authors suggested that the relatively fast recovery (approximately 15 d) observed in the majority of patients (60%-80%) after COVID-19 infection is compatible with the rapid regeneration of the non-neuronal olfactory epithelial cells in hamsters and the partial recovery of the olfactory epithelium within 1-2 wk. However, the mechanisms that cause long-lasting/persistent smell loss and distortion are due to the dysfunction or destruction of the olfactory neurons due to viral infection and the disorganization of the olfactory receptors within the epithelium [20, 21].

Post-COVID-19 taste disorders are less frequent compared to smell disorders and their pathogenesis is understudied. In animal models, researchers found that ACE2 and sialic acid receptors are the tongue cells by which SARS-CoV-2 enters the body. Sialic acid is a salivary mucin component. Mucin conveys the molecules of tastants into taste pores to prevent their enzymatic degradation [22]. It has been suggested that SARS-CoV-2 infection could interfere with the transport of tastants and accelerate their degradation.

This work aimed to determine the patterns of post-COVID-19 smell and taste disorders at onset in a cohort of adults and children and quantify the extent of these disorders using validated objective measures. The intra- (within the same group) and inter- (adults *vs* children) individual variability in demographics, clinical characteristics and quality of life variables, were determined. The inter-individual variability of clinical characteristics within the same family members infected with COVID-19 was also explored. This is the first study in our country which systematically evaluated adults as well as children with post-COVID-19 persistent smell and taste disorders.

MATERIALS AND METHODS

Study design, period and region

This was a cross-sectional observational study carried throughout a period of a year (August 2020 to September 2021). The initial sample size was 320 patients with post-COVID-19 persistent smell and taste disorders. The diagnosis of COVID-19 infection was relied on the high clinical suspicion (*i.e.* having sudden onset of smell and taste deficits during the locally active COVID-19 pandemic in absence of obvious alternative explanation), and according to the World Health Organization (WHO) interim guidance [23]. Patients were recruited from the out-patient clinic (for care of post-COVID-19 ENT disorders in children and adults) of the Otolaryngology department of Assiut University Hospital (a tertiary referral hospital), Assiut, Egypt. Inclusion criteria: (1) Adults and children with sudden onset of smell loss during the active COVID-19 pandemic in absence of alternative causes; and (2) Persistence of smell disorders (with or without taste disorders) for ≥ 6 mo. Smell disorder was defined as subjective complete or partial smell loss or distortion. Taste disorder was defined as subjective loss or distortion of all (total) or any (partial) of the 5 basic tastes (sweet, salt, sour, bitter and umami). Flavor disorder was defined as subjective loss of aroma of foods and drinks. Exclusion Criteria: (1) Progressive smell and taste loss; (2) An existing cause which could explain the patient's disorders as otolaryngological conditions (*i.e.*, rhinitis, rhinosinusitis or any nasal disorders), head or nasal surgery or trauma, unusual exposure to toxins, chemicals or metals or regular intake of drugs; and (3) Medical, neurologic or psychiatric diseases which are known causes of smell or taste disorders, *e.g.* brain tumors (*e.g.* olfactory groove meningioma, pituitary adenoma with suprasellar extension, *etc.*), temporal lobe epilepsy, Parkinson's disease, Alzheimer's disease, *etc.*), or vitamin deficiencies (*e.g.* zinc or thiamine deficiencies).

After application of inclusion and exclusion criteria, 185 patients (adults = 150; Children = 35; males = 89, females = 96) were included for the final statistical analysis. Excluded were 135 adult patients due to presence of diabetes Mellitus ($n = 52$), rhinosinusitis ($n = 50$), psychosis ($n = 13$), allergic rhinitis ($n = 15$) and Parkinson's disease ($n = 5$). The statistical analyses were done to the included 185 patients.

Methods

Data collection: Detailed ENT evaluation was done by the consultant otolaryngologist (Ahmed MAA). Evaluation included routine clinical examination. It also included rhinoscopy and nasal endoscopy. Detailed medical and neuropsychiatric histories and examinations (Hamed SA and Kamal-Eldeen EB) were done. Clinical data were gathered during face to face interviewing. The data included: (1) Demographics: Age, gender, residence, smoking habit, and socioeconomic status. The socioeconomic status was classified according to the Socio-Economic Scale [24] into high, middle, low or very low; (2)

COVID-19 infection inquiries included: Manifestations and their severity, investigations, course, recurrence, comorbidities, consequences and previous treatments' for smell and taste disorders. The severity of viral infection manifestations at the onset were classified as: Mild: Slight symptoms, no viral pneumonia or hypoxia and normal chest imaging; moderate: Fever, dry cough, dyspnea and tachypnea and abnormal chest radiology (*i.e.* manifestation of pneumonia); severe: Either dyspnea, respiratory rate $> 30/\text{min}$, or a $\text{PaO}_2/\text{FiO}_2 < 300 \text{ mmHg}$ or $\text{SpO}_2 < 90\%$ on room air (*i.e.* manifestations of severe pneumonia and severe respiratory distress); and critical: Which included acute respiratory distress syndrome, respiratory failure, multiorgan failure or sepsis or septic shock [*i.e.* requirements for admission to the intensive care unit (ICU)] [23]; and (3) The patterns and prognoses of COVID-19 infection in contacts (*i.e.* incubation carriers) were also determined.

A clinically designed questionnaire

It was a questionnaire for clinical data collection and included the questionnaire component (for smell and taste) of the National Health and Nutrition Examination Survey [25]. The answers to questions characterized the individual differences' in perception and intensity of appetizing aroma and scents; sweetness, saltiness, sourness and bitterness of foods and drinks (which helps to differentiate taste as a gustatory, as opposed to flavor which is a function of retronasal olfaction) and pungent odorants and tastants (*i.e.* with strong trigeminal compounds; nippy, blazing, hot or irritant as black pepper, mustard, vinegar, ginger, cinnamon, chiles, mint gum and spices). Data were also gathered about the demographics and clinical characteristics of close contacts infected with COVID-19.

The occurrence of anosmia, hyposmia, dysosmia, parosmia, phantosmia, ageusia, dysgeusia or distortion of aroma, had been differentiated in the questionnaire. Anosmia is the term used to define the absence or loss of the sense of smell. Hyposmia is the decreased sense of smell. A distortion of the sense of smell is defined as dysosmia. Dysosmia has two types, parosmia and phantosmia. Parosmia refers to a perception of different odor of an odorant than it was in the past. Cacosmia is a type of parosmia in which the odor, which was previously enjoyable, is smelled as repulsive or offensive. Phantosmia is the perception of an odor in absence of actual stuff to be smelled. Ageusia refers to the loss of sense of taste. Hypogeusia is a diminished sense of taste. Dysgeusia refers to the distortion of the sense of taste. In this study, we used the term dysgeusia to refer to distortion of taste as well as flavor (or aroma).

Sniffin' odor identification test

Sniffin' odor identification test (SOIT) was used for quantitative assessment of smell (orthonasal olfaction) loss. We used 16 odorants familiar to Egyptians [26]. They were tea, vanilla, coconut, cacao, coriander, cardamom, thyme, fennel, clove, green cumin, garlic, mixed oregano, old Rumi cheese chips, cinnamon, black pepper and ginger. Odorants were kept in opaque containers and arranged in order so that cinnamon, black pepper and ginger were the last to be tested (*i.e.* three hot smells with strong nasal trigeminal sensory stimulation). The examiner covered the patient's eyes with a blindfold before exposure to the odorants; then asked the patient to smell each substance as often as liked or even to choose from four named odorants options. Each nostril was examined separately and the correct answer received one point. The total score of SOIT equals 16. Normosmia was considered if total SOIT's scoring ranged from 12 to 16, hyposmia if it ranged from 9 to 11, and anosmia if ≤ 8 .

Taste identification test

This test was used for quantitative assessment of taste loss. We used sugar (sweet), salt (salty), lemon (sour), old Rumi cheese chips (umami) and coffee (bitter), the five basic tastants. They were kept in opaque containers. Coffee was the last to be tasted as it may alter subsequent taste perceptions if tasted first. The patient's eyes were covered with a blindfold and nostrils were plugged with cotton to block concurrent smell. The examiner put half a teaspoon of a tastant on the patient's hand and allowed him/her to taste as often as liked, then rinsed the mouth with tap water after each tastant's exposure.

Flavor identification test

The same 16 substances of SOIT were used to test flavor (retronasal olfaction) which were tea, vanilla, coconut, cacao, coriander, cardamom, thyme, fennel, clove, green cumin, garlic, mixed oregano, old Rumi cheese chips, cinnamon, black pepper and ginger. Tastants were kept in opaque containers and arranged in order so that cinnamon, black pepper and ginger were the last to be tasted (*i.e.* tastants with strong oral trigeminal sensory stimulation). The patient's eyes were covered with a blindfold and nostrils were plugged with cotton to block concurrent smell (orthonasal olfaction). The examiner put half tea spoonful from each tastant on the patient's hand and asked the patient to taste as much substance as often as liked to recognize it. The total score of the test equals 16. Normal flavor was considered if total score ranged from 12 to 16, impaired (partial loss) if it ranged from 9 to 11, and complete loss if ≤ 8 .

Psychiatric interviewing

It was done for determination of comorbid psychiatric condition (s) in response to the presence of the

chemosensory disorders and for the differentiation between psychiatric symptoms and disorders. The impact of olfactory dysfunction on the quality of life (QoL) of patients has been evaluated by the Arabic translated and validated short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS). sQOD-NS is a seven-item questionnaire about the impact of smell disorder on social activities, eating behavior, annoyance and anxiety. The rating scale for each item is ranged from 0 to 3. A total score of 21 indicated no impact on QoL and zero scoring indicated severe impact[27].

Imaging studies

It included computed tomography (CT) on nasal cavities, anterior cranial fossa and sinuses as a part of ENT evaluation and CT of the brain as a part of neurologic evaluation.

Statistical analyses

Data were analyzed with SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Descriptive statistics were reported as numbers (%) and mean (SD). Comparative statistics (intra- and inter- individuals) between variables for adults and children were performed using independent sample *t*-test, Chi square test and Mann-Whitney U test. Correlation analyses was done between total scores of sQOD-NS and different demographic and clinical variables (age, gender, duration of disorders, presence or absence of parosmia, presence or absence of taste/flavor loss) using Spearman's correlation coefficient. The level of statistical significance was set at $P < 0.05$.

RESULTS

Demographics and patterns of viral infection at onset

This work included 185 patients. The majority were rural residents (64.86%) and of low socioeconomic status (51.9%) (Figure 1). The duration of persistent disorders at the period of the study ranged from 6 to 24 mo (mean = 11.53 ± 3.97 mo), among were 51.35% ($n = 95$) had duration of ≥ 12 mo. Patients had normal rhinoscopy, nasal endoscopy and CT on nasal cavities, anterior cranial fossa, and sinuses. None had previous hospital admission due to COVID-19 infection and none received vaccination by the time of the study. Patterns of viral infection at onset were isolated sudden smell (with or without taste loss) ($n = 63$, 34.5%) or sudden smell loss in concurrent association with systemic and/or ENT manifestations ($n = 122$, 65.95%). Systemic manifestations were reported in 54.05% ($n = 100$, or 100/185) and ENT (other than smell or taste disorders) manifestations were reported in 37.84% ($n = 70$ or 70/185). Fever ($> 38^\circ\text{C}$) was the most common systemic manifestation (100%). Sore throat was the most common ENT manifestation ($n = 36$, 51.34% or 36/70) (Figure 2). The duration of recovery of systemic and ENT manifestations varied from 3 to 21 d after onset (mean = 8.11 ± 3.69). The most frequently done investigations after onset for diagnosis of COVID-19 infection were complete blood count (CBC) ($n = 130$, 70.27%), serology ($n = 130$, 70.27%) and CT of the chest (particularly for patients with moderate manifestations of viral infection) ($n = 32$, 17.3%) (Figure 1). Only 43 (23.24%) did reverse transcription polymerase chain reaction (RT-PCR). The majority of patients (78.92%; $n = 146$) did frequent otolaryngology consultations (at onset and afterward) and received different treatment modalities for months, but none was effective (Figure 1). They included nasal irrigations, particularly patients with cacosmia, (duration: Range: 3–15 d, mean = 8.34 ± 3.86), local steroids (duration: Range: 6–60 d, mean = 18.28 ± 9.94), systemic steroids (duration: Range: 3–30 d, mean = 11.89 ± 6.41), and vitamins and supplements as omega-3 capsule, vitamin B complex (vitamins B1, B2, B6, B9, B12), vitamin C, vitamin E, zinc, selenium, L-carnitine and pentoxifylline tablets (duration: Range: 6–90 d, mean = 41.65 ± 24.04). The most frequently prescribed vitamins and supplements were zinc, omega 3 and vitamin B complex. Some patients (22.70%, $n = 42$) turned to facebook groups to share tips and vent to subjects with same symptoms. This group practiced sniffing strong odors (as essential oils or scents) or pungent herbs (duration: Range: 30–120 d, mean = 65.50 ± 32.84). However, none provided a beneficial effect. Few ($n = 39$, 21.08) neither did previous otolaryngology consultation nor received any treatment modalities (Figure 1).

Characteristics of contacts (incubation carriers)

The majority of patients ($n = 108$, 58.38%) were the only affected family member, the remaining ($n = 77$, 41.62%) had ≥ 1 household contact (range: 1–5) who developed systemic and/or ENT manifestations of COVID-19 infection at the same time as the patients or within the previous 2–4 wk before patients' onset. They developed complete recovery of systemic or ENT manifestations within 3 to 30 d (mean = 12.95 ± 5.97) and of smell and taste loss ($n = 40$, 21.62%) deficits within 2 to 30 d (mean = 5.03 ± 1.10) with the exception of 4 (2 mothers and 2 daughters, included in the study) who developed persistent smell and taste disorders. None of the completely recovered contacts developed distortion of chemosensations. Inter-individual manifestations were present in the same infected family members (mild, moderate or severe infection; systemic or ENT manifestations or both; fever, cough, diarrhea, fatigue, insomnia, uveitis, etc.). A prominent example was a family case cluster of 5 patients who demonstrated highly variable presentations, durations, severities, and progression of COVID-19 infection manifestations. The

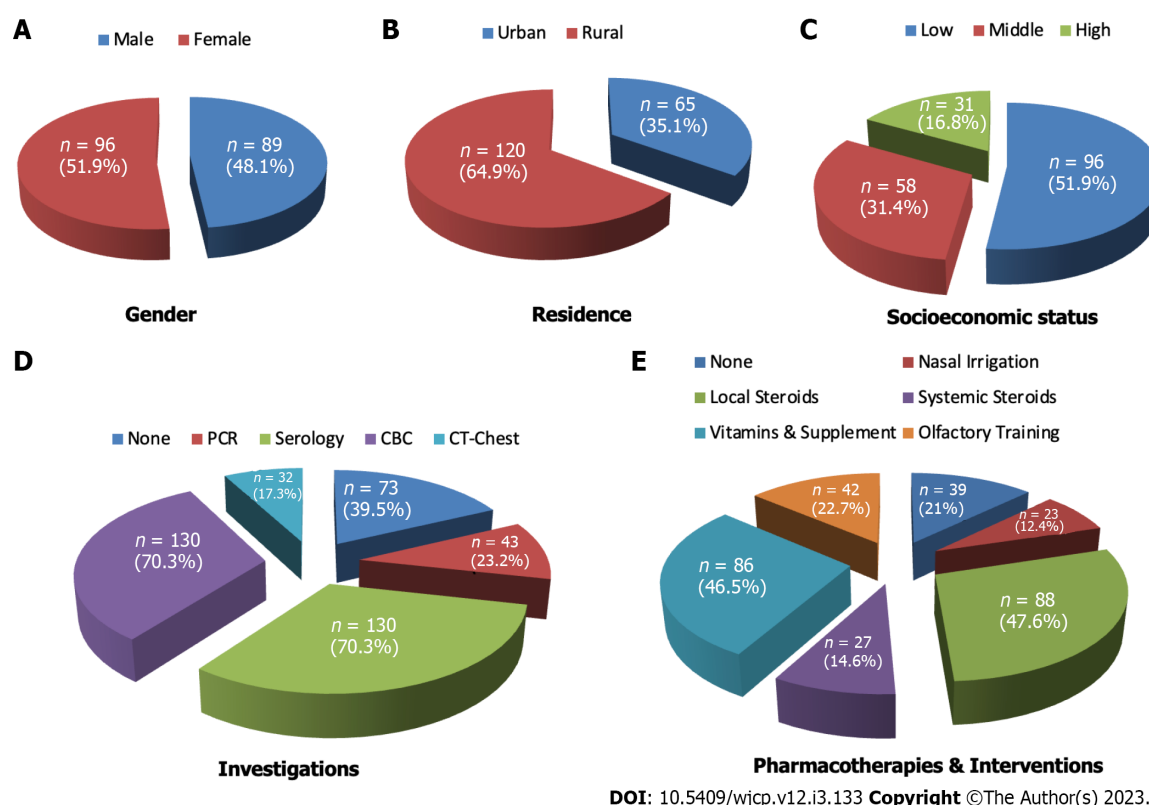


Figure 1 Demographics, laboratory and treatment characteristics of the studied patients. A: This study included 96 (51.9%) females and 89 (48.1%) males; B: The majority were rural residents (64.9%, $n = 120$), while 35.1% ($n = 65$) were urban residents; C: The majority were of low socioeconomic status (51.9%, $n = 96$), while 31.4% ($n = 58$) and 16.8% ($n = 31$) were of middle and high socioeconomic states, respectively; D: Investigations done by patients included serology and complete blood count (70.3%, $n = 130$), polymerase chain reaction (23.2%) and computed tomography-chest (17.3%, $n = 32$). While 39.5% ($n = 73$) did not do any investigations. E: The received pharmacotherapies and interventions to treat chemosensory disorders included local steroids (47.6%, $n = 88$), vitamins and supplements (46.5%, $n = 86$), olfactory training (22.7%, $n = 42$) and systemic steroids (12.4%, $n = 23$), while 22.7% of the patients ($n = 42$) did not receive any therapy. PCR: Polymerase chain reaction; CBC: Complete blood count; CT: Computed tomography.

presented patient (included in the study) was a 20-year old-female with persistent anosmia and ageusia for 14 mo duration and developed parosmia within approximately 3 mo after smell loss. She did not have other viral manifestations at onset. Her infected household contacts were: (1) A 58-year-old father with severe manifestations of viral infection (fever, cough, shortness of breath, myalgia and sore throat) and confirmed diagnosis of severe viral pneumonia due to COVID-19 infection. He was also admitted to ICU for weeks and markedly improved within approximately 30 d; (2) A 52-year old mother with fever, abdominal pain, severe diarrhea and myalgia for 15 d. She did home-isolation and recovered completely within approximately 21 d; (3) A 16-year old brother with moderate infection (fever, cough, sore throat and rhinorrhea or flu-like symptoms). He did self-isolation and completely recovered within about 7-14 d; and (4) A 23-year old brother with mild manifestations of low grade fever, minimal cough, sore throat and reversible smell and taste loss. He recovered completely within 7-10 d.

Manifestations of smell and taste disorders

Subjective manifestations: At presentation, all complained of severe smell loss. They firstly noticed the sudden inability to recognize cooking scents or odors. However, taste and flavor (aroma) losses and loss of nasal and mouth irritation by pungent odorants (odors with strong trigeminal stimulation) and tastants were the complaint of 79.46% ($n = 147$) (Figure 3). Examples of complaints: “I can no longer smell the familiar scent of my favorites from perfumes, food dishes, and drinks”; “I have forgotten what normal tastes and smells are like”, “I changed my eating habits by adding too much sugar or salt to food to try to make it taste better”; “the pungent tastes don't affect me”. One hundred and nineteen (64.32%) also complained of parosmia. The onset of development of parosmia was ≥ 2 mo after smell loss (range: 2–6 mo; mean = 3.05 ± 1.87 mo). Cacosmia was the complaint of 40.34% of patients with parosmia ($n = 48$ or 48/119). The smells experienced by patients with parosmia included burnt (like burnt hair or burnt leather), rotten (as spoiled or fermented food), gasoline, fecal, smoke or metallic (like copper), or chemical (like sulphur). However, the majority ($n = 65$, 54.62%) complained of unpleasant unknown odor which was difficult to describe (*i.e.* new). Examples of complaints: “I can't stand the scent of my own body sweat”; “smell of food was disgusting, repulsive and intolerable resulting in gastric upset”; “even tap water smells putrid”. None had phantosmia. Two experienced pleasant odors (1.68%) which

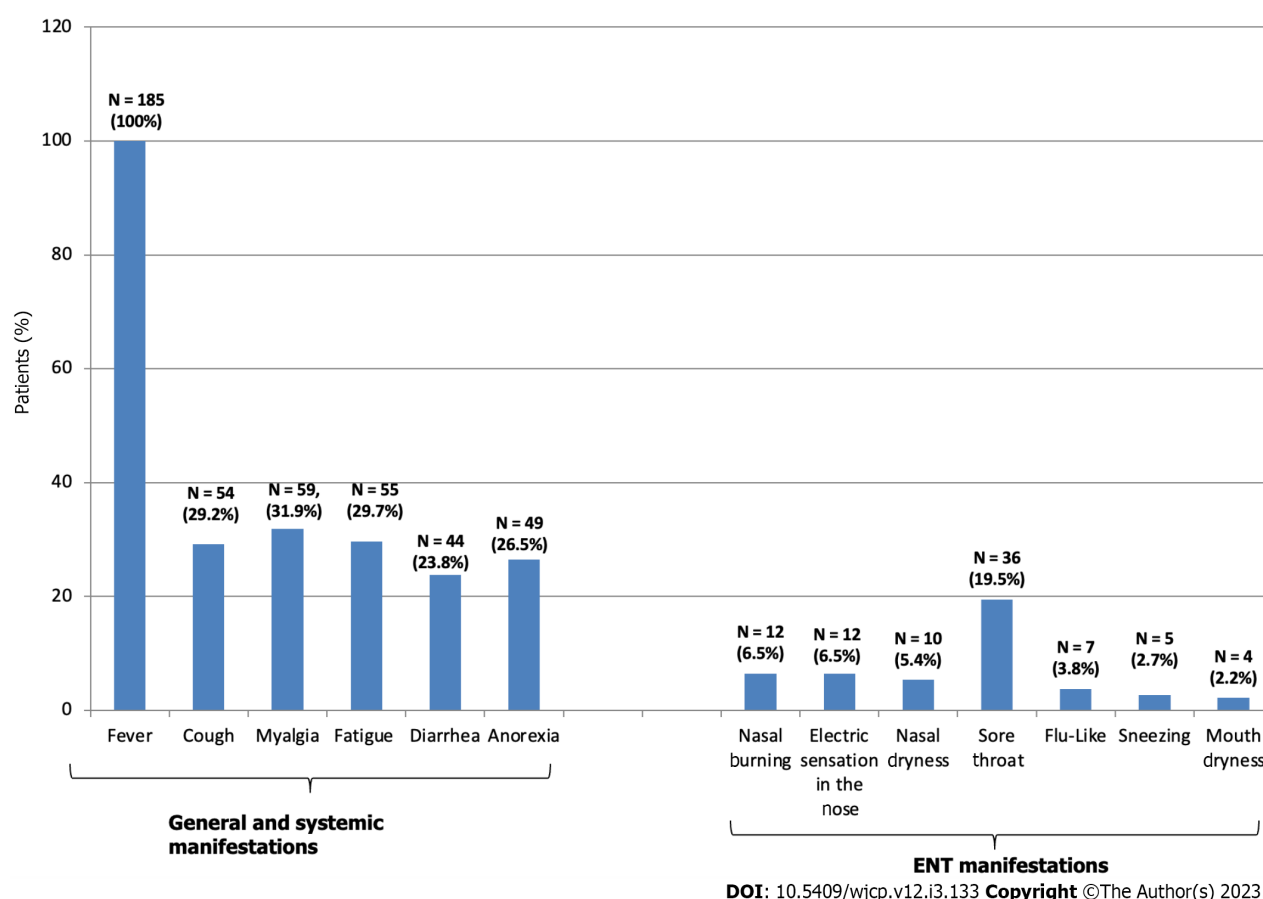


Figure 2 General, systemic and ear, nose and throat manifestations of viral infection of the studied patients. ENT: Ear, nose and throat.

were difficult to describe (*i.e.* unknown) (Figure 4). The majority of patients with parosmia complained of an aberrant taste with different foods and drinks similar to that being smelled. Few described aberrant tastes for only selective food types (*e.g.* proteins as meat, cheese, *etc.* or fruits as cucumber, Guava, *etc.*). But these distortions of taste/aroma were fluctuant in severity (*i.e.* not constant), however, five adults developed dysgeusia/distortion of flavor (approximately 1 mo) after improvement of parosmia, among were 3 described a taste/aroma of "metallic" and 2 had "soap" as dominant or the overriding sensation in the mouth for a whole range of foods and drinks including water.

Objective manifestations

Objective testing revealed that participants had anosmia (SOIT scoring ≤ 8). True ageusia was found in only 20% ($n = 37$) (Figure 4). Patients with ageusia also had flavor (retronasal olfaction) loss ($n = 37$, 20%). Loss of all type of taste sensation (*i.e.* complete or total ageusia) was the most frequent ($n = 21$, 56.76% or 21/37), however, few ($n = 16$, 43.24% or 16/37) had selective (or partial) ageusia (salt and sweet = 3, 18.75% or 3/16); bitter and sour = 6, 37.5% or 6/16; umami = 7, 43.75% or 7/16). Losses of nasal and oral trigeminal sensations were found in 18% ($n = 33$) and 20% ($n = 37$) of patients, respectively (Figure 4).

Consequences of smell and taste disorders

Consequences of smell and taste disorders on patients were anorexia ($n = 36$; 19.46%) (particularly with cacosmia), anxiety symptoms ($n = 21$; 11.35%), insomnia ($n = 12$; 6.49%) and headache ($n = 10$; 5.41%). None had psychiatric disorders. The results of sQOD-NS are shown in Table 1. Patients had low total score (11.41 ± 3.66) of quality of life due to these disorders. All were afraid of permanent loss of smell and taste. None did self-isolation after onset and the problems did not restrict the patient's social activities. Loss of appetite and even anorexia were reported by some patients particularly those with cacosmia but none developed significant weight loss.

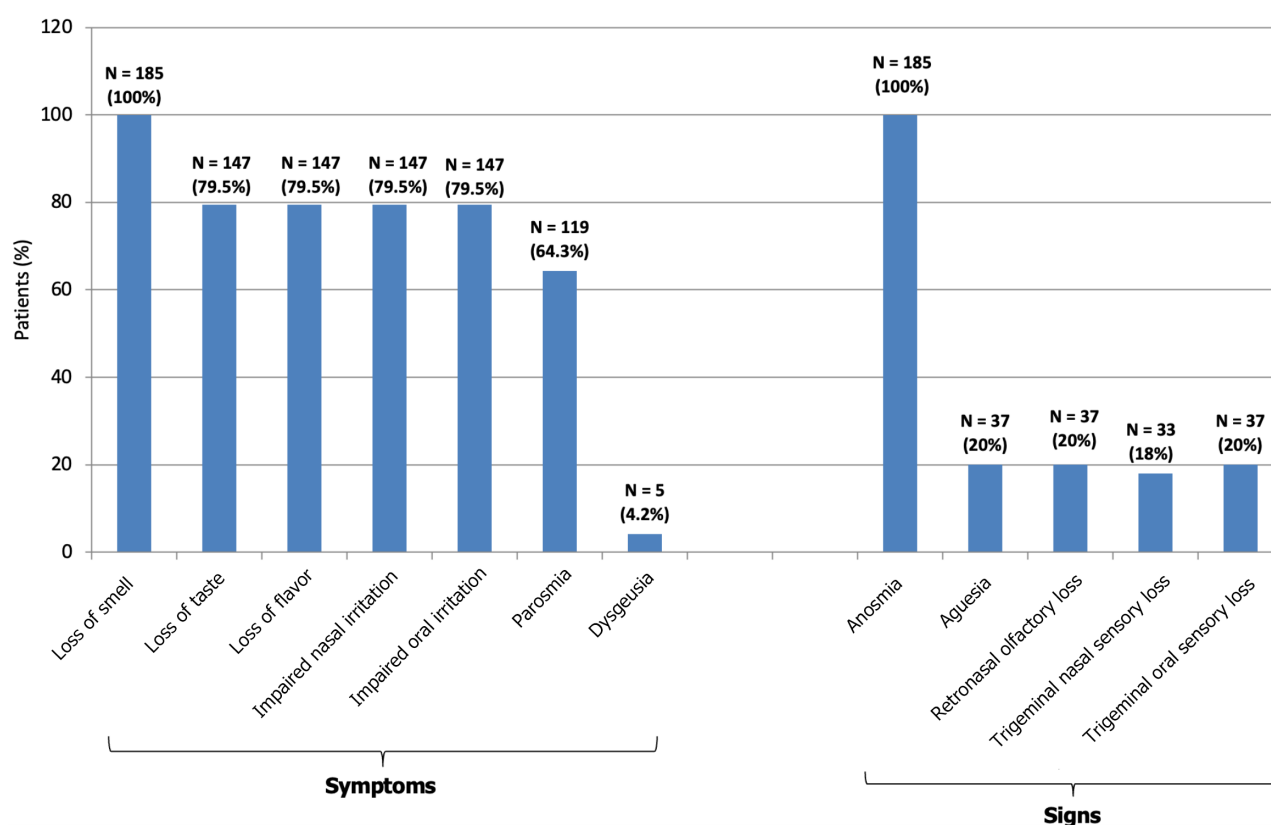
Comparative results between adults vs children

For each group (adults or children), no significant differences had been identified in relation to gender. No significant differences have been identified between adults and children in other demographics (with the exception that the majority of adults were rural residents), patterns of COVID-19 infection at onset and manifestations of disorders apart of the significantly lower frequency of children with loss of

Table 1 Results of the questionnaire of olfactory disorders-negative statements

sQOD-NS items	Patients	Adults	Children	P value
1 Changes in my sense of smell isolate me socially	0.0–3.0 (2.84 ± 0.57)	3	0.0–3.0 (2.17 ± 1.10)	0.0001
2 The problems with my sense of smell have a negative impact on my daily social activities	0.0–3.0 (2.84 ± 0.57)	3	0.0–3.0 (2.17 ± 1.10)	0.0001
3 The problems with my sense of smell make me more irritable	0.0–3.0 (1.19 ± 1.03)	0.0–3.0 (1.67 ± 0.99)	0.0–3.0 (1.31 ± 1.180)	0.497
4 Because of the problems with my sense of smell, I eat out less	0.0–3.0 (1.34 ± 1.06)	0.0–3.0 (1.18 ± 1.01)	1.0–3.0 (2.09 ± 0.85)	0.0001
5 Because of the problems with my sense of smell, I eat less than before (loss of appetite)	0.0–3.0 (1.66 ± 1.28)	0.0–3.0 (2.00 ± 1.03)	0.0–3.0 (2.00 ± 1.03)	0.0001
6 Because of the problems with my sense of smell, I have to make more effort to relax	0.0–3.0 (1.49 ± 1.11)	0.0–3.0 (1.35 ± 1.12)	0.0–3.0 (1.31 ± 1.180)	0.065
7 I'm afraid I'll never be able to get used to the problems with my sense of smell	0	0	0	-
Total score of sQOD-NS	2.0–18.0 (11.41 ± 3.66)	6.0–18.8 (11.49 ± 3.37)	2.0–18.0 (11.06 ± 4.74)	0.515

sQOD-NS: Questionnaire of olfactory disorders-negative statements.



DOI: 10.5409/wjcp.v12.i3.133 Copyright ©The Author(s) 2023.

Figure 3 Manifestations of smell, taste, flavor and trigeminal sensory disorders of the studied patients.

nasal trigeminal sensation compared to adults ($P = 0.025$) (Table 2). At presentation and compared to adults, the disorders had a moderate impact on many children daily routines and they caused restriction of food intake, lack of appetite or even anorexia, however, there was no significant difference in the total score of sQOD-NS for children compared to adults (Table 1).

Table 2 Comparative results of adults versus children with smell and taste disorders, *n* (%)

Characteristics	Adults (<i>n</i> = 150)	Child (<i>n</i> = 35)	<i>P</i> value
Age	20–50 (31.41 ± 8.63)	12–19 (15.66 ± 1.63)	-
Gender			0.952
Male	72 (48)	17 (48.6)	
Female	78 (52)	18 (51.4)	
Residence			0.009
Urban	46 (30.7)	19 (54.3)	
Rural	104 (69.3)	16 (45.7)	
Socio-economic status			0.589
Low	79 (52.7)	17 (48.6)	
Middle	47 (31.3)	11 (31.4)	
High	24 (16)	7 (20)	
Classification of patients			0.077
Mild COVID-19 infection	123 (82)	30 (85.7)	
- Minimal systemic manifestations	72 (58.54)	18 (51.43)	
- Isolated smell and taste loss	51 (41.46)	12 (34.29)	
Moderate COVID-19 infection	27 (18)	5 (14.3)	
Patterns of smell loss at onset (with or without taste loss)			0.593
Concurrent association with systemic and/or ENT viral manifestations at onset	99 (66)	23 (65.7)	
Isolated loss	51 (34)	12 (34.3)	
Systemic manifestations	82 (54.67)	18 (51.43)	0.897
Fever	82 (100)	18 (100)	
Cough	42 (51.22)	12 (66.67)	
Myalgia	49 (59.76)	10 (55.56)	
Fatigue	45 (54.88)	10 (55.56)	
Diarrhea	34 (41.46)	10 (55.56)	
Anorexia	31 (37.80)	18 (100)	
ENT manifestations	56 (53.33)	14 (40)	0.989
Nasal burning	9 (16.07)	3 (21.43)	
Electric like sensation in the nose	9 (16.07)	3 (21.43)	
Nasal dryness	8 (14.29)	2 (14.29)	
Sore throat	29 (51.79)	7 (50)	
Flu-like	5 (8.93)	2 (14.29)	
Sneezing	5 (8.93)	0	
Mouth dryness	4 (7.14)	0	
Duration of recovery of general, respiratory, gastrointestinal and other ENT manifestations; days	4–30 (12.55 ± 6.04)	5–15 (7.13 ± 2.69)	0.082
Previous treatment trials for smell and taste disorders			0.335
None	29 (19.3)	10 (28.57)	
Nasal irrigation	19 (12.67)	4 (11.43)	
Local steroids	65 (43.33)	23 (65.71)	
Systemic steroids	14 (9.33)	13 (37.14)	

Vitamins and supplements	69 (43.33)	17 (48.57)	
Olfactory training	25 (16.67)	17 (48.57)	
Consequences of sensory disorders			0.516
Headache	6 (4)	4 (11.43)	
Insomnia	10 (6.67)	2 (5.71)	
Anxiety	16 (10.67)	5 (14.29)	
Anorexia	31 (20.67)	5 (14.29)	
Recurrence of COVID-19 infection with smell loss	3 (2)	-	
Duration of disorders at presentation	6–24 (11.43 ± 3.87)	6–24 (11.96 ± 4.41)	0.515
< 12 mo	77 (51.33)	13 (52.38)	0.131
≥ 12 mo	73 (48.67)	22 (62.86)	
Onset of parosmia after smell loss	2–6 (3.60 ± 1.52)	1–5 (2.81 ± 1.47)	0.442
Parosmia	98 (65.33)	21 (60)	0.284
Types of parosmia	42 (42.86)	6 (28.57)	0.709
Unknown (unpleasant)	52 (53.06)	13 (52.38)	
Rotten	17 (17.35)	4 (19.05)	
Burnt	15 (15.31)	3 (14.29)	
Smoke	3 (3.06)	1 (4.76)	
Fecal	5 (5.10)	-	
Gasoline	2 (2.04)	-	
Metallic	2 (2.04)	-	
Unknown (pleasant)	2 (2.04)	-	
Dysgeusia	5 (3.33)	-	
Types of dysgeusia			
Metallic	3 (60)	-	
Soap	2 (40)	-	
Objective manifestations			
Anosmia (orthonasal olfactory loss)	150 (100)	35 (100)	-
Ageusia	30 (20)	7 (20)	0.918
Flavor loss (retronasal olfactory loss)	30 (20)	7 (20)	0.596
Nasal trigeminal sensory loss	30 (20)	3 (8.57)	0.025
Oral trigeminal sensory loss	30 (20)	7 (20)	0.918

Data are presented as number (%) and range (mean ± SD).

Analysis (adults versus children) was done using nonparametric tests: Independent Samples Mann-Whitney U test. Criteria: Alpha = 0.05, CI level = 95. COVID-19: Coronavirus disease 2019; ENT: Ear, nose and throat.

DISCUSSION

Studies which provided information about the prevalence, patterns and prognoses of post-COVID-19 smell and taste disorders are mainly from Europe and Asia. The majority were based on subjective self-evaluation or questionnaire completion of adult patients. The majority evaluated patients after short periods of follow-ups. Also little is known about the prevalence of these disorders in children. There are few reports which estimated the true frequency of these disorders after direct medical examination and comprehensive objective testing of patients over long periods (≥ 1 year) of follow-ups[7,8,28,29]. We provided the first detailed characterization of a cohort of Egyptian adults and children who developed persistent smell, taste and aroma disorders after COVID-19 infection.

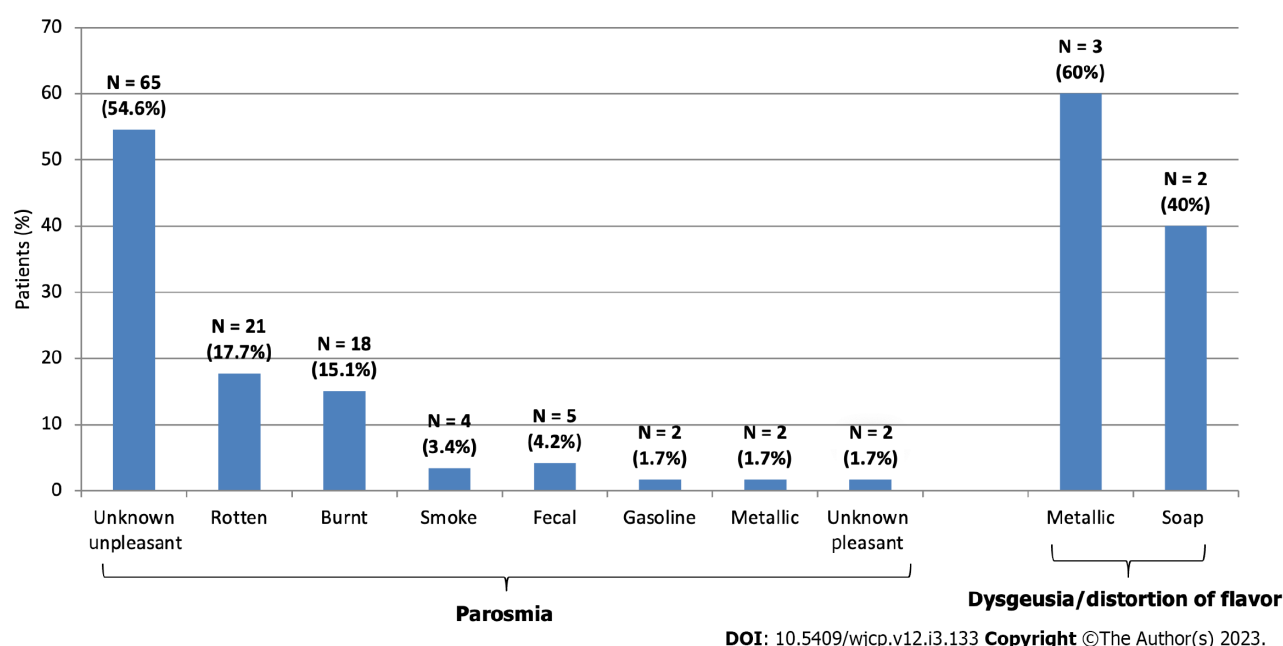


Figure 4 Types of parosmia and dysgeusia/distortion of flavor in the studied patients.

Despite the increasing number of publications of post-COVID-19 complications, there is no consensus definition for “persistent post-COVID-19 smell disorders”, because of the wide variability of the periods of follow-up of patients since the onset of acute viral manifestations. In adults, some used these terms if the duration of disorders exceeded a month while many suggested longer durations equal or more than 3 or 6 mo. They also suggested other terms for these complications as “Long-lasting COVID-19 disorders” and “Chronic COVID-19 disorders” [6,9,12,14]. In this study, we included participants with duration of disorders of at least 6 mo since onset of acute manifestations, among were 52.43% of the patients ($n = 97$) had duration of disorders for ≥ 12 mo and 6 patients had the disorders for 24 mo. Fortunato *et al* [28] reported persistent smell dysfunction in 70% of patients at one year after the onset of COVID-19 infection. Boscolo-Rizzo *et al* [7] reported persistent smell dysfunction in 46% of patients by objective testing after a median of 401 d after the onset of COVID-19 infection. Lechien *et al* [8] followed 171 patients with post-COVID-19 smell disorders for 24 mo and reported a prevalence of olfactory dysfunction to range from 2.9% to 29.8%. For children, the definition of persistent post-COVID-19 smell disorders has been suggested in March 2022 by the Delphi process (which involved both researchers and family advocates) as manifestations that are lasting in a child for ≥ 3 mo after the acute viral manifestations and cannot be explained by other known etiologies of smell disorders [29]. To our knowledge, there are only two reports for evaluation of smell and taste disorders in children [5,30]. In the study of Elvan-Tuz *et al* [30], the authors reported that in 8.4% of children, anosmia did not regress after a month since the onset of COVID-19 infection. In the study of Buonsenso *et al* [5], the authors found that 1.7% (13/784) of children had persistent smell disorders at a mean of 3 mo after the onset of COVID-19 infection.

In this study, it is obvious that the number of adults with persistent disorders was 2.9 higher than children. We could not provide a prevalence of the disorders in patients with previous COVID-19 infection in spite of the fact that the patients were recruited from the Otolaryngology out-patient clinic of the university hospital (a tertiary referral hospital). This is because the healthcare service in our country is patchy and distributed between private clinics and governmental and university hospitals’ clinics. Patients were mainly referred from specialist otolaryngologists to the university hospital for the purpose of comprehensive evaluation. We did not find gender difference in the development of smell disorders after COVID-19 infection which is consistent with most of the previous reports. Few found potential gender difference with higher susceptibility for females to develop smell and taste disorders compared to males [31].

The most frequently done investigations (in approximately 70%) by the patients at onset were CBC, quick serology testing (IgM/IgG), CT of the chest (17%) and RT-PCR, particularly in patients with moderate manifestations. However, 17.3% did not do any investigations particularly those with isolated disorders. It has been indicated that the sudden onset of chemosensory dysfunctions in absence of a cause to explain these conditions in the presence of active local pandemic are often the main warning manifestations and the strongest predictors of COVID-19 infection [10,11]. Studies reported that people with loss of smell and taste had six-fold higher odds of being infected with COVID-19 positive and loss of smell and taste were associated with 10-fold higher odds of COVID-19 diagnosis [31-33]. The followings are the possible reasons for paucity of investigations at onset: (1) The presence of household

members and intimately contacted friends at work places who experienced similar manifestations and diagnosed as having COVID-19 infection; (2) The information from the social media that smell and taste loss after COVID-19 infection are transient conditions in the majority of patients, *i.e.* disappear within weeks or few months (1-3 mo)[1,2,6,12]; (3) The reluctance to do investigations because of the minimal systemic manifestations or isolated disorders; (4) Polymerase chain reaction (PCR), serology and chest CT impose significant constraints on medical healthcare services in many parts of the world especially with limited infrastructure and resources and poor socioeconomic status of patients; and (5) Many healthcare providers are also reluctant to ask for investigations particularly if there was a delay for several weeks or months between the onset of chemosensory manifestations and the patient's realization of the olfactory evaluations. It has been indicated that the viral load is significantly reduced after 14 d from onset and the estimated false-negative PCR rates for SARS-CoV-2 are high[33].

In this study, participants who had infected household family members distinguished the heterogeneity in phenotypes and prognoses of smell and taste losses encountered in their contacts[34]. It has also been previously reported that COVID-19 exhibits wide variation in duration, severity, and progression of symptoms, even within same family (*i.e.* a familial cluster of COVID-19 infection)[10,11]. It is interesting to mention that none of the participants, who were the only affected family members (~60%) did self-isolation or limited their social activities or transmitted the viral infection to other close contacts at the acute stage. Therefore, the questions are: Whether minimal/mild manifestations or isolated deficits at onset are highly contagious or not?, and, whether self-quarantine is a requirement as previously announced by the WHO and the ENT UK or not? More data are required to prove these issues. The announced recommendations by the WHO and the ENT UK for self-isolation for those with *de novo* loss or smell or taste during the active pandemic of COVID-19 was not clear compared to the recommendation for persons in intimate contact with patients having active COVID-19 infection (which is self-isolation for ≥ 2 wk). Some suggested self-isolation for ≥ 7 d for those with *de novo* loss or smell or taste[10,11].

In this study, most of the participants (82%) had mild systemic or ENT manifestations at onset, among were 41.5% had isolated deficits in absence of any other viral manifestations. Many studies indicated that mild viral manifestations at onset could predict the prognosis of persistent smell disorders[9]. It has been suggested that the site and dosage of the initial viral burden, along with the effectiveness of the host's innate immune response to SARS-CoV-2 infection are important variables which potentially determine the spread of the virus within an individual and therefore the clinical course of infection, *i.e.* the high viral load in the upper airway could be correlated with reduction of the overwhelming host's immune response resulting in a less severe general and systemic viral infection [35]. However, persistent smell disorders have also been reported in patients with severe viral infection diagnosis at onset[1,2,6,12].

At presentation, all patients complained of severe deficits in smell and the majority (approximately 80%) complained of associated taste loss, loss of aroma perception when eating foods and drinking beverages and loss of smell and taste of pungent substances. While objective testing showed that all had anosmia (orthonasal olfactory loss), 20% had true ageusia, flavor loss (retronasal olfactory loss) and oral trigeminal chemosensory loss and 18% had nasal trigeminal chemosensory loss. This mismatch between subjective and objective findings is not surprising. This also can explain the wide variability in the estimated prevalence of these disorders (*i.e.* over estimation bias) as the majority of reports relied on subjective or self-reported manifestations. In general, it is often difficult to distinguish between taste and smell and the belief that taste loss is a secondary result of smell loss is true to a great extent. This usually reflects loss of flavor perception as a function of smell and not true loss of taste. Also there is an intimate functional correlation between the flavor and taste systems and the intimate central connections between the olfactory and trigeminal systems and the overlapping activations in the piriform cortex, the ventral insula, and the frontal cortex[36]. The majority of patients with ageusia (56.8%) had total loss of sensation for the 5 basic types (salt, sweet, bitter, sour and umami) (*i.e.* complete ageusia), while, 43.24% had specific losses (or partial ageusia) particularly for umami[6]. Previous studies reported true complete or partial ageusia due to COVID-19 infection in 10.2%-42%. Some authors also found selective loss for sweet and bitter tastes[1,9,37]. Schwab *et al*[37] followed more than 400 patients infected with COVID-19 for 4 mo and reported little or no recovery from ageusia in patients who did not regained normal taste after approximately 2 mo. The prevalence of true nasal sensory (trigeminal) loss has been estimated to be 18%-20% with COVID-19 infection and the true oral trigeminal sensory loss was reported in 20%-33%[38].

We observed that none of the patients reported ageusia or flavor loss or trigeminal sensory loss in absence of anosmia. Flavor and loss of oral trigeminal sensation were dependent on ageusia and not anosmia. Discoveries found that orally sourced odors share processing circuitry with taste internal odors to produce flavor preferences[39,40]. Furthermore, the oral trigeminal sensation is considered a part of flavor perception[41]. The occurrence of taste, flavor and trigeminal sensory losses at lower frequencies and the differential taste loss in some patients, support that viral infection could involve taste and trigeminal tissues independent to smell[40,42].

In this study, rhinorrhea was a less frequent nasal (15% or 7/46) and ENT manifestation (10% or 7/70) at onset of viral infection. This is consistent with previous reports which found that the prevalence of rhinorrhea and nasal congestion was 4%-25% in patients infected with COVID-19 prior to experiencing

anosmia[9,43]. We also observed that patients clearly distinguished their current conditions from the previously encountered fluctuation in the severity of smell and taste losses associated with runny nose, post-nasal discharge and congested and blocked nose associated with heavy cold or influenza. They mentioned that "previous nasal manifestations due to flu or influenza always resolve within days, and never affected taste of non-odorant tastants as sugar and salt".

In this study, parosmia was also the complaint of 64.3% ($n = 119$) of patients. They developed parosmia after anosmia by several months[9,44]. Recently, Ferreli *et al*[43] reported that reported persistent smell dysfunction in 15.1% and 13.1% at 12 and 18 mo after the onset of COVID-19 infection based on a self-reported smell score. They also observed that 23.1% of patients developed parosmia at 18 mo after the onset of COVID-19 infection. We observed that many patients believed that parosmia was a manifestation of smell recovery. Parosmia and particularly cacosmia were also the dominant cause for repeated otolaryngology consultations and the use of nasal douches as a trial to reduce the intensity of the repulsive odors. In this study, the majority of patients with parosmia reported fluctuation in the experience of the same aberrant odor in the oral cavity with different foods and drinks (dysgeusia/distortion of aroma). However, five patients reported dominance of metallic ($n = 3$) or soap ($n = 2$) perception as baseline for every food or drink including tap water. They also mentioned that the abnormal sensation in the oral cavity became more apparent, intense and repulsive after reduction of the intensity of parosmia. Dysgeusia, the distortion of taste after COVID-19 infection, has been reported previously[45]. Vaira *et al*[44] reported anosmia and aguesia in 77% (67/87), anosmia only in 2.3% (2/87) and dysgeusia in 20% (18/87) of patients after COVID-19 infection. Distortion of aroma was reported in approximately 12% of patients after COVID-19 infection[41].

In this study, we did not identified apparent difference in other different demographic and clinical variables between adults and children with persistent disorders. In the literature, studies which addressed persistent smell and taste disorders in children are scarce or poorly addressed[3-5]. This might be due to difficulty to apply objective testing or lack of standardized objective testing for smell and taste for children. In this study, symptoms of anxiety, insomnia, anorexia and headache were prominent among children compared to adults. They were often distressed by the impairments which hinder the enjoyment of food and hygiene problems related to body odor. It has been reported that the loss of the feeling of the depth and complexity of foods may result in anorexia, depression and anxiety. Deficits of olfaction disrupt the joy of eating and drinking and associated with the dangers of inability to know about the surrounding (*e.g.* environmental toxins as leaking gas or spoiled food). Parosmia as the constant repulsive odor is more distressing than loss of smell in many patients.

In this study, psychiatric evaluation at presentation and determination of quality of life in relation to smell disorders using sQOD-NS revealed lower performances and poor enjoyment of life particularly being afraid of development of permanent disorders. Smell and taste are essential for everyday life and psychological wellbeing. Many studies from Europe and Asia reported the adverse impact of long-lasting smell disorders on quality of life, personal-social functioning and mental health[45,46]. In a cross-sectional study by Bagheri *et al*[46] on 10069 participants responded to an online checklist which evaluated the sense of smell and taste. The results indicated a significant correlation between anosmia and SARSCoV2 infection, decreased taste sensation, and decreased quality of life. In the cross-sectional survey of Abdelhafiz *et al*[47], the researchers enrolled 502 participants from Egyptians infected with COVID-19; the authors reported high prevalence of mental health symptoms among healthcare workers. Overall, 77.3%, 69.5%, 79.3%, and 83.1% of all participants reported symptoms of, anxiety, insomnia, depression, and stress, respectively. There was no particular assessment of quality of life due to chemosensory disorders in the same patients.

The detailed mechanisms for the persistent smell and taste disorders after COVID-19 infection are still understudied. There are evidences which support that injury of the neuroepithelium is the cause of persistent olfactory disorders after COVID-19 infection[48-50], they include: (1) Previous studies found that the olfactory neuronal epithelium requires 1-3 mo or longer to regenerate, restore the odorant receptor mapping, restore the olfactory receptor connections and rewire the axons within the olfactory system after injury compared to non-neuronal olfactory epithelium (which have sustentacular, Bowman's and microvillar cells) which requires 1-3 wk for recovery after degeneration[21]. Zazhytska *et al*[50] found that in infected golden hamsters, SARS-CoV-2 caused severe, persistent and widespread disruption of mature olfactory receptors' nuclear genomic architecture. It also caused down regulation of olfactory receptors and olfactory sensory neuronal signaling genes for odor perception. The authors observed delayed olfactory neuronal transcription than sustentacular cells and persistent disruption of olfactory receptor's layer even after their restoration; (2) Studies indicated that parosmia is a step towards regeneration after olfactory receptors' or neuronal degeneration (*i.e.* step toward recovery) and the unpleasant smell will disappear with full recovery[20,21]; and (3) Studies suggested that the disturbance of the spatially organized pattern of the olfactory receptors within the epithelium following viral infection, scars and gliosis are the causes of lost odor (*i.e.* anosmia) and distortion of smell sensation (*i.e.* parosmia)[20,21,51]. Earlier in pandemic, some authors suggested that nasal dryness which is attributed to the injury of the mucin producing cells (*i.e.* Bowman's gland) by viral pathology, is the cause of aberrant nasal smell (or parosmia) because they reported high frequency of nasal dryness among their patients. Lechien *et al*[52] reported nasal dryness in $\geq 60\%$ of patients. They suggested that, this could be attributed to the damage of the mucous secreting olfactory cells (Bowman's glands) which

provide constant flow of mucous to the surface of the nasal epithelium to trap and dissolve odorous substances for the neurons. The findings of this and other studies do not support this suggestion because: Firstly, nasal dryness is an acute manifestation in some patients which recovered shortly within days to weeks like other ENT or systemic manifestations. In this study, only 5.4% ($n = 10$) had nasal dryness. Secondly, parosmia developed after recovery of acute manifestations by months. Thirdly, none of the contacts with transient smell loss developed parosmia.

The cause of nasal trigeminal sensory loss could be due to viral infection and damage to brush cells (or their feeding blood vessels). Brush cells are the microvilli columnar cells in the basal surface and in contact with afferent nerve endings of the trigeminal nerve responsible for transduction of nasal general sensation[53].

The mechanisms of taste disorders after COVID-19 infection are less studied compared to smell disorders. In animal models, researchers found that the family of CoVs, including MERS-CoV and SARS-CoV-2, potentially use multiple entry oral receptors, making taste bud cells being highly susceptible for SARS-CoV-2 infections. These sites include ACE2, sialic acid and toll like receptors (TLRs)[54,55]. The tongue taste buds express ACE2 and sialic acid[55,56]. Sialic acid is a salivary mucin component. Mucin conveys the molecules of tastants into taste pores to prevent their premature enzymatic degradation[22]. Therefore, infection with SARS-CoV-2 could interfere with glycoproteins mediated transport of tastants and accelerated the degradation of the gustatory particles which contribute to loss of taste. The main function of the TLRs is to recognize the common structural components of microorganisms and activate the endogenous inflammatory immune system. In-situ models of direct binding of coronavirus spike protein of SARS-CoV-2 with TLR 1, 4 and 6, have support the specific roles of these TLRs in severe inflammation of the tongue tissue[57].

We believe that this study have strengths: (1) Up to our knowledge, this is the first study done in Egypt to explore the patterns at onset and characteristics of children as well as adults with post-COVID-19 persistent smell and taste disorders. In general, the evaluations of these disorders in children are limited or even lacking; and (2) The measures used for objective evaluation of smell, taste and flavor sensations are validated and reliable and can be generalized for evaluation of functional recovery overtime of smell and taste disorders in Egyptians. However, this study has limitations: (1) It may appear that patients with persistent disorders have severe deficits (*i.e.* anosmia or ageusia). This might be due to the recruitment of patients from a tertiary referral hospital (a University Hospital). It is possible that patients with persistent less severe disorders (*i.e.* hyposmia or hypogeusia) were reluctant to seek medical advice or might visited other available healthcare services (*e.g.* private clinics); and (2) The number of included children is lower than adults. This could be due to lower frequency of these disorders in children compared to adults. Future studies are required to determine the prevalence of these disorders in pediatric population.

CONCLUSION

This study indicates that children can develop persistent smell and taste disorders due to COVID-19 infection similar to adults. The reported course of small and taste disorders are supportive of the peripheral neuronal compromise. True taste and trigeminal chemosensory disorders could be a complication of COVID-19 infection but with lower frequency compared to smell disorders and also might occur independent to smell disorders. Post-COVID-19 retronasal olfactory (flavor) disorders were solely dependent on taste and not on smell disorders. Smell and taste disorders significantly impair quality of life of patients particularly being afraid of permanent disorders. There were no clinical variables which characterize smell and taste disorders in children from adult patients.

ARTICLE HIGHLIGHTS

Research background

Smell loss with or without taste loss is the most frequent acute manifestation of coronavirus disease 2019 (COVID-19) infection with an estimated prevalence of 16%-20% in children and 40%-86% in adults. Smell disorders are also the most frequent complications of COVID-19 infection with an estimated prevalence of approximately 20%-40% of adults. This indicates that COVID-19 has high affinity to olfactory sensory epithelium (and to less extent gustatory sensory epithelium) compared to other parts of the body. Data from patients and their contacts showed that it is impossible to predict the prognosis of smell loss (*i.e.* none of the demographics, acute manifestations and severity at onset were predictors for the development of persistent disorders). It has been indicated that the mechanisms of transient smell and taste deficits due to COVID-19 infection are different from that of long-lasting/persistent disorders. It has been suggested that injury of the non-neuronal olfactory epithelial cells by viral infection and their rapid regeneration (within days to weeks) are the causes of transient smell deficits because these cells are important for the health of the neuronal cells. However, lasting smell disorders

are due to injury of the neuronal olfactory epithelial cells and disorganization of the receptors within the epithelium, because these cells require months to regenerate after injury and restore olfactory epithelium function. The mechanisms of taste disorders after COVID-19 infection are less understood compared to smell disorders but suggested to be due to injury of the gustatory sensory epithelium by viral infection and disturbed salivary milieu which is necessary for the function of the gustatory neurons.

Research motivation

The research hotspots include determination of (1) The patterns of smell and taste disorders at onset; (2) The course of these disorders till presentation; and (3) Whether or not there is/are distinguished features for children with these disorders which differentiate them from adult patients with the same disorders.

Research objectives

This study aimed to systematically evaluate patients with post-COVID-19 infection persistent smell and taste disorders because related studies from many areas of the world including our country are lacking. The descriptive characteristics of patients at onset and presentation and predictors for the development of these disorders were determined in children and adult populations.

Research methods

Data collection which included a clinical questionnaire (for smell and taste); objective testing which included the sniffin' odor, taste and flavor identification tests and the Questionnaire of Olfactory Disorders-Negative Statements for determination of quality of life in response to these disorders.

Research results

This study included 185 patients (adults = 150, age: 31.41 ± 8.63 years; children = 35; age: 15.66 ± 1.63 years) from both gender and had post-COVID-19 infection smell and taste disorders. The duration of the disorders till the time of presentation ranged from 6 to 24 mo (mean: 11.53 ± 3.97 mo) with nearly half of the patients had duration of at least a year. Parosmia was a frequent manifestation (64.32%) in patients with persistent anosmia and was developed after months from onset (3.05 ± 1.87 ms). Total or partial true ageusia, retronasal olfactory loss (or flavor) and trigeminal chemosensory loss were present in 18%-20% of patients. There were no significant differences in patterns at onset and clinical variables at onset and at presentation between children and adults with persistent disorders. These disorders significantly lower quality of life of patients.

Research conclusions

Persistent smell, taste and trigeminal chemosensory disorders are frequent post-COVID-19 complications in children similar to adults. There were no demographics, clinical variables at onset or specific profile of these disorders which distinguish children from adults' patients.

Research perspectives

Future studies are needed to: (1) Determine the prevalence of these disorders in children and in adults from understudied populations (*e.g.* Africans); (2) Determine the relationship between smell and taste disorders due to different COVID-19 variants (alpha, delta or omicron). In the literature, there were no relevant studies which stratified recovery according to COVID-19 variants. Here, the period of patients' recruitment in this study indicated a high possibility of being infected with the wild types of the virus; and (3) Understand the detailed cellular and molecular pathogenic aspects underlying long-lasting/persistent chemosensory disorders after COVID-19 infection.

FOOTNOTES

Author contributions: Hamed SA, Kamal-Eldeen EB and Ahmed MAA designed the conception, did data collection and physical examinations. Ahmed MAA did ear, nose and throat evaluation; Kamal-Eldeen EB and Ahmed MAA referred the patients to the neurologist (Hamed SA) and critically reviewed the manuscript; Hamed SA applied the objective measurements for smell and taste and the final statistical analyses, wrote the manuscript and had the final responsibility to submit the manuscript for publication; All authors had full access to raw data and verified the underlying data and interpretation of the results and final approval of the manuscript.

Institutional review board statement: The protocol of the study was in accordance to the revised Helsinki Declaration (2013) and approved by the medical research ethics committees of the Faculty of Medicine, Assiut University, Assiut, Egypt, No. AUH_SARS-CoV2_SAH/2019.

Informed consent statement: All study participants, or their guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Egypt

ORCID number: Sherifa Ahmed Hamed 0000-0002-1441-3530.

S-Editor: Li L

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- Koyama S**, Ueha R, Kondo K. Loss of Smell and Taste in Patients With Suspected COVID-19: Analyses of Patients' Reports on Social Media. *J Med Internet Res* 2021; **23**: e26459 [PMID: 33788699 DOI: 10.2196/26459]
- Blomberg B**, Mohn KG, Brokstad KA, Zhou F, Linchausen DW, Hansen BA, Lartey S, Onyango TB, Kuwelker K, Sævik M, Bartsch H, Tøndel C, Kittang BR; Bergen COVID-19 Research Group, Cox RJ, Langeland N. Long COVID in a prospective cohort of home-isolated patients. *Nat Med* 2021; **27**: 1607-1613 [PMID: 34163090 DOI: 10.1038/s41591-021-01433-3]
- Roge I**, Smane L, Kivite-Urtane A, Pucuka Z, Racko I, Klavina L, Pavare J. Comparison of Persistent Symptoms After COVID-19 and Other Non-SARS-CoV-2 Infections in Children. *Front Pediatr* 2021; **9**: 752385 [PMID: 34778143 DOI: 10.3389/fped.2021.752385]
- Yan Q**, Qiu D, Liu X, Guo X, Hu Y. Prevalence of Smell or Taste Dysfunction Among Children With COVID-19 Infection: A Systematic Review and Meta-Analysis. *Front Pediatr* 2021; **9**: 686600 [PMID: 34414141 DOI: 10.3389/fped.2021.686600]
- Buonsenso D**, Martino L, Morello R, De Rose C, Valentini P. Chronic Olfactory Dysfunction in Children with Long COVID: A Retrospective Study. *Children (Basel)* 2022; **9** [PMID: 36010141 DOI: 10.3390/children9081251]
- Niklassen AS**, Draef J, Huart C, Hintschich C, Bocksberger S, Trecca EMC, Klimek L, Le Bon SD, Altundag A, Hummel T. COVID-19: Recovery from Chemosensory Dysfunction. A Multicentre study on Smell and Taste. *Laryngoscope* 2021; **131**: 1095-1100 [PMID: 33404079 DOI: 10.1002/lary.29383]
- Boscolo-Rizzo P**, Hummel T, Hopkins C, Dibattista M, Menini A, Spinato G, Fabbris C, Emanuelli E, D'Alessandro A, Marzolino R, Zanelli E, Cancellieri E, Cargnelutti K, Fadda S, Borsetto D, Vaira LA, Gardenal N, Polesel J, Tirelli G. High prevalence of long-term olfactory, gustatory, and chemesthesis dysfunction in post-COVID-19 patients: a matched case-control study with one-year follow-up using a comprehensive psychophysical evaluation. *Rhinology* 2021; **59**: 517-527 [PMID: 34553706 DOI: 10.4193/Rhin21.249]
- Lechien JR**, Vaira LA, Saussez S. Prevalence and 24-month recovery of olfactory dysfunction in COVID-19 patients: A multicentre prospective study. *J Intern Med* 2023; **293**: 82-90 [PMID: 36000469 DOI: 10.1111/joim.13564]
- Lechien JR**, Chiesa-Estomba CM, Beckers E, Mustin V, Ducarme M, Journe F, Marchant A, Jouffé L, Barillari MR, Cammaroto G, Ciciu MP, Hans S, Saussez S. Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. *J Intern Med* 2021; **290**: 451-461 [PMID: 33403772 DOI: 10.1111/joim.13209]
- American Academy of Otolaryngology–Head and Neck Surgery**. Anosmia as a potential marker of COVID-19 infection - an update. Apr 1, 2020 [cited 6 June 2020]. Available from: <https://www.entnet.org/COVID-19/anosmia/>
- American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)**. Anosmia Reporting tool. 2020. [cited 28 September 2021]. Available from: <https://www.entnet.org/content/reporting-tool-patients-anosmia-related-COVID-19>
- Chapurin N**, Totten DJ, Chaballout B, Brennan J, Dennis S, Lubner R, Chowdhury NI, Turner JH, Trone T, Chandra RK. Differential olfactory outcomes in COVID-19: A large healthcare system population study. *Int Forum Allergy Rhinol* 2022; **12**: 108-111 [PMID: 34289262 DOI: 10.1002/alr.22870]
- Biadsee A**, Dagan O, Ormianer Z, Kassem F, Masarwa S, Biadsee A. Eight-month follow-up of olfactory and gustatory dysfunctions in recovered COVID-19 patients. *Am J Otolaryngol* 2021; **42**: 103065 [PMID: 33894627 DOI: 10.1016/j.amjoto.2021.103065]
- Estiri H**, Strasser ZH, Brat GA, Semenov YR; Consortium for Characterization of COVID-19 by EHR (4CE), Patel CJ, Murphy SN. Evolving phenotypes of non-hospitalized patients that indicate long COVID. *BMC Med* 2021; **19**: 249 [PMID: 34565368 DOI: 10.1186/s12916-021-02115-0]
- Sasinka M**, Plenta I, Pavlovic M, Izakovic V, Kaiserová E, Páleníková O, Stubna J. [Complications of immunosuppressive therapy in chronic nephropathies in children]. *Cesk Pediatr* 1976; **31**: 122-126 [PMID: 1269009]
- Zaki AM**, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man

- with pneumonia in Saudi Arabia. *N Engl J Med* 2012; **367**: 1814-1820 [PMID: 23075143 DOI: 10.1056/NEJMoa1211721]
- 17 **Bryche B**, St Albin A, Murri S, Lacôte S, Pulido C, Ar Gouilh M, Lesellier S, Servat A, Wasniewski M, Picard-Meyer E, Monchatre-Leroy E, Volmer R, Rampin O, Le Goffic R, Marianneau P, Meunier N. Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. *Brain Behav Immun* 2020; **89**: 579-586 [PMID: 32629042 DOI: 10.1016/j.bbi.2020.06.032]
 - 18 **Sia SF**, Yan LM, Chin AWH, Fung K, Choy KT, Wong AYL, Kaewpreedee P, Perera RAPM, Poon LLM, Nicholls JM, Peiris M, Yen HL. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. *Nature* 2020; **583**: 834-838 [PMID: 32408338 DOI: 10.1038/s41586-020-2342-5]
 - 19 **Letko M**, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020; **5**: 562-569 [PMID: 32094589 DOI: 10.1038/s41564-020-0688-y]
 - 20 **Yee KK**, Costanzo RM. Changes in odor quality discrimination following recovery from olfactory nerve transection. *Chem Senses* 1998; **23**: 513-519 [PMID: 9805635 DOI: 10.1093/chemse/23.5.513]
 - 21 **Iwema CL**, Fang H, Kurtz DB, Youngentob SL, Schwob JE. Odorant receptor expression patterns are restored in lesion-recovered rat olfactory epithelium. *J Neurosci* 2004; **24**: 356-369 [PMID: 14724234 DOI: 10.1523/JNEUROSCI.1219-03.2004]
 - 22 **Pushpass RG**, Pellicciotta N, Kelly C, Proctor G, Carpenter GH. Reduced Salivary Mucin Binding and Glycosylation in Older Adults Influences Taste in an In Vitro Cell Model. *Nutrients* 2019; **11** [PMID: 31554163 DOI: 10.3390/nu11102280]
 - 23 **World Health Organization**. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. Interim guidance. Jan 17, 2020. [cited 3 April 2023]. Available from: <https://www.who.int/publications-detail/Laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117>
 - 24 **El-Gilany A**, El-Wehady A, El-Wasify M. Updating and validation of the socioeconomic status scale for health research in Egypt. *East Mediterr Health J* 2012; **18**: 962-968 [PMID: 23057390 DOI: 10.26719/2012.18.9.962]
 - 25 **Rawal S**, Hoffman HJ, Honda M, Huedo-Medin TB, Duffy VB. The Taste and Smell Protocol in the 2011-2014 US National Health and Nutrition Examination Survey (NHANES): Test-Retest Reliability and Validity Testing. *Chemosens Percept* 2015; **8**: 138-148 [PMID: 27833669 DOI: 10.1007/s12078-015-9194-7]
 - 26 **Oleszkiewicz A**, Taut M, Sorokowska A, Radwan A, Kamel R, Hummel T. Development of the Arabic version of the "Sniffin' Sticks" odor identification test. *Eur Arch Otorhinolaryngol* 2016; **273**: 1179-1184 [PMID: 26173896 DOI: 10.1007/s00405-015-3718-2]
 - 27 **Mattos JL**, Edwards C, Schlosser RJ, Hyer M, Mace JC, Smith TL, Soler ZM. A brief version of the questionnaire of olfactory disorders in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2019; **9**: 1144-1150 [PMID: 31430061 DOI: 10.1002/alr.22392]
 - 28 **Fortunato F**, Martinelli D, Iannelli G, Milazzo M, Farina U, Di Matteo G, De Nittis R, Ascatisno L, Cassano M, Lopalco PL, Prato R. Self-reported olfactory and gustatory dysfunctions in COVID-19 patients: a 1-year follow-up study in Foggia district, Italy. *BMC Infect Dis* 2022; **22**: 77 [PMID: 35065619 DOI: 10.1186/s12879-022-07052-8]
 - 29 **Stephenson T**, Allin B, Nugawela MD, Rojas N, Dalrymple E, Pinto Pereira S, Soni M, Knight M, Cheung EY, Heyman I, CLoCk Consortium, Shafran R. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. *Arch Dis Child* 2022; **107**: 674-680 [PMID: 35365499 DOI: 10.1136/archdischild-2021-323624]
 - 30 **Elvan-Tuz A**, Karadag-Oncel E, Kiran S, Kanik-Yukse S, Gulhan B, Hacimustafaoglu M, Ozdem-Alatas S, Kuyucu N, Ozdemir H, Egil O, Elmas-Bozdemir S, Polat M, Bursal-Duramaz B, Cem E, Apaydin G, Teksam O; TURK-COVID-19-Anosmia Study Group; LAS VEGAS study investigators, PROVE Network and the Clinical Trial Network of the European Society of Anaesthesiology. Prevalence of Anosmia in 10.157 Pediatric COVID-19 Cases: Multicenter Study from Turkey. *Pediatr Infect Dis J* 2022; **41**: 473-477 [PMID: 35349499 DOI: 10.1097/INF.0000000000003526]
 - 31 **Sorokowski P**, Karwowski M, Misiak M, Marczak MK, Dziekan M, Hummel T, Sorokowska A. Sex Differences in Human Olfaction: A Meta-Analysis. *Front Psychol* 2019; **10**: 242 [PMID: 30814965 DOI: 10.3389/fpsyg.2019.00242]
 - 32 **Moein ST**, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol* 2020; **10**: 944-950 [PMID: 32301284 DOI: 10.1002/alr.22587]
 - 33 **Pecoraro V**, Negro A, Pirotti T, Trenti T. Estimate false-negative RT-PCR rates for SARS-CoV-2. A systematic review and meta-analysis. *Eur J Clin Invest* 2022; **52**: e13706 [PMID: 34741305 DOI: 10.1111/eci.13706]
 - 34 **Song WL**, Zou N, Guan WH, Pan JL, Xu W. Clinical characteristics of COVID-19 in family clusters: a systematic review. *World J Pediatr* 2021; **17**: 355-363 [PMID: 34170503 DOI: 10.1007/s12519-021-00434-z]
 - 35 **Ilyicheva TN**, Netesov SV, Gureyev VN. COVID-19, Influenza, and Other Acute Respiratory Viral Infections: Etiology, Immunopathogenesis, Diagnosis, and Treatment. Part I. COVID-19 and Influenza. *Mol Gen Microbiol Virol* 2022; **37**: 1-9 [PMID: 35936505 DOI: 10.3103/S0891416822010025]
 - 36 **Cain WS**, Murphy CL. Interaction between chemoreceptive modalities of odour and irritation. *Nature* 1980; **284**: 255-257 [PMID: 7360255 DOI: 10.1038/284255a0]
 - 37 **Schwab J**, Jensen CD, Fjaeldstad AW. Sustained Chemosensory Dysfunction during the COVID-19 Pandemic. *ORL J Otorhinolaryngol Relat Spec* 2021; **83**: 209-218 [PMID: 33789309 DOI: 10.1159/000515132]
 - 38 **Parma V**, Ohla K, Veldhuizen MG, Niv MY, Kelly CE, Bakke AJ, Cooper KW, Bouysset C, Pirastu N, Dibattista M, Kaur R, Liuzza MT, Pepino MY, Schöpf V, Pereda-Loth V, Olsson SB, Gerkin RC, Rohlf's Domínguez P, Albayay J, Farruggia MC, Bhutani S, Fjaeldstad AW, Kumar R, Menini A, Bensafi M, Sandell M, Konstantinidis I, Di Pizio A, Genovese F, Öztürk L, Thomas-Danguin T, Frasnelli J, Boesveldt S, Saatci Ö, Saraiva LR, Lin C, Golebiowski J, Hwang LD, Ozdener MH, Guàrdia MD, Laudamiel C, Ritchie M, Havlíček J, Pierron D, Roura E, Navarro M, Nolden AA, Lim J, Whitcroft KL, Colquitt LR, Ferdenzi C, Brindha EV, Altundag A, Macchi A, Nunez-Parra A, Patel ZM, Fiorucci S, Philpott CM, Smith BC, Lundström JN, Mucignat C, Parker JK, van den Brink M, Schmuker M, Fischmeister FPS, Heinbockel T, Shields VDC, Faraji F, Santamaría E, Fredborg WEA, Morini G, Olofsson JK, Jalessi M, Karni N, D'Errico A, Alizadeh R, Pellegrino R, Meyer P, Huat C, Chen B, Soler GM, Alwashahi MK, Welge-Lüssen A, Freiherr J, de Groot JHB, Klein H, Okamoto M, Singh PB, Hsieh JW; GCCR Group Author, Reed DR, Hummel T, Munger SD, Hayes JE. More Than Smell-COVID-19 Is Associated With Severe Impairment of Smell, Taste, and Chemesthesis. *Chem Senses*

- 2020; **45**: 609-622 [PMID: [32564071](#) DOI: [10.1093/chemse/bjaa041](#)]
- 39 **Blankenship ML**, Grigorova M, Katz DB, Maier JX. Retronasal Odor Perception Requires Taste Cortex, but Orthonasal Does Not. *Curr Biol* 2019; **29**: 62-69.e3 [PMID: [30581018](#) DOI: [10.1016/j.cub.2018.11.011](#)]
- 40 **Chaudhari N**, Roper SD. The cell biology of taste. *J Cell Biol* 2010; **190**: 285-296 [PMID: [20696704](#) DOI: [10.1083/jcb.201003144](#)]
- 41 **Hannum ME**, Koch RJ, Ramirez VA, Marks SS, Toskala AK, Herriman RD, Lin C, Joseph PV, Reed DR. Taste loss as a distinct symptom of COVID-19: a systematic review and meta-analysis. *Chem Senses* 2022; **47** [PMID: [35171979](#) DOI: [10.1093/chemse/bjac001](#)]
- 42 **Chen B**, Akshita J, Han P, Thaploo D, Kitzler HH, Hummel T. Aberrancies of Brain Network Structures in Patients with Anosmia. *Brain Topogr* 2020; **33**: 403-411 [PMID: [32297077](#) DOI: [10.1007/s10548-020-00769-2](#)]
- 43 **Ferrelli F**, Gaino F, Russo E, Di Bari M, Rossi V, De Virgilio A, Di Stadio A, Spriano G, Mercante G. Long-term olfactory dysfunction in COVID-19 patients: 18-month follow-up study. *Int Forum Allergy Rhinol* 2022; **12**: 1078-1080 [PMID: [35199476](#) DOI: [10.1002/alr.22990](#)]
- 44 **Vaira LA**, Hopkins C, Petrocelli M, Lechien JR, Chiesa-Estomba CM, Salzano G, Cucurullo M, Salzano FA, Saussez S, Boscolo-Rizzo P, Biglioli F, De Riu G. Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and prospective study. *J Laryngol Otol* 2020; **134**: 703-709 [PMID: [32782030](#) DOI: [10.1017/S0022215120001826](#)]
- 45 **Deng J**, Zhou F, Hou W, Silver Z, Wong CY, Chang O, Huang E, Zuo QK. The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis. *Ann N Y Acad Sci* 2021; **1486**: 90-111 [PMID: [33009668](#) DOI: [10.1111/nyas.14506](#)]
- 46 **Bagheri S**, Ghobadimoghadam S. Safety and Health Protection of Health Care Workers during the COVID-19 Pandemic. *Int J Community Based Nurs Midwifery* 2020; **8**: 362-363 [PMID: [33178860](#) DOI: [10.30476/IJCBNM.2020.86066.1319](#)]
- 47 **Abdelhafiz AS**, Ali A, Maaly AM, Mahgoub MA, Ziady HH, Sultan EA. Predictors of post-COVID symptoms in Egyptian patients: Drugs used in COVID-19 treatment are incriminated. *PLoS One* 2022; **17**: e0266175 [PMID: [35358268](#) DOI: [10.1371/journal.pone.0266175](#)]
- 48 **Maier EC**, Saxena A, Alsina B, Bronner ME, Whitfield TT. Sensational placodes: neurogenesis in the otic and olfactory systems. *Dev Biol* 2014; **389**: 50-67 [PMID: [24508480](#) DOI: [10.1016/j.ydbio.2014.01.023](#)]
- 49 **de Melo GD**, Lazarini F, Levallois S, Hautefort C, Michel V, Larrous F, Verillaud B, Aparicio C, Wagner S, Gheusi G, Kergoat L, Kornobis E, Donati F, Cokelaer T, Hervochon R, Madec Y, Roze E, Salmon D, Bourhy H, Lecuit M, Lledo PM. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. *Sci Transl Med* 2021; **13** [PMID: [33941622](#) DOI: [10.1126/scitranslmed.abf8396](#)]
- 50 **Zazhytska M**, Kodra A, Hoagland DA, Frere J, Fullard JF, Shayya H, McArthur NG, Moeller R, Uhl S, Omer AD, Gottesman ME, Firestein S, Gong Q, Canoll PD, Goldman JE, Roussos P, tenOever BR, Jonathan B Overdevest, Lomvardas S. Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. *Cell* 2022; **185**: 1052-1064.e12 [PMID: [35180380](#) DOI: [10.1016/j.cell.2022.01.024](#)]
- 51 **Murai A**, Iwata R, Fujimoto S, Aihara S, Tsuboi A, Muroyama Y, Saito T, Nishizaki K, Imai T. Distorted Coarse Axon Targeting and Reduced Dendrite Connectivity Underlie Dysosmia after Olfactory Axon Injury. *eNeuro* 2016; **3** [PMID: [27785463](#) DOI: [10.1523/ENEURO.0242-16.2016](#)]
- 52 **Lechien JR**, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, Chekkoury-Idrissi Y, Hans S, Delgado IL, Calvo-Henriquez C, Lavigne P, Falanga C, Barillari MR, Cammaroto G, Khalife M, Leich P, Souhay C, Rossi C, Journe F, Hsieh J, Edjlali M, Carlier R, Ris L, Lovato A, De Filippis C, Coppee F, Fakhry N, Ayad T, Saussez S. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020; **277**: 2251-2261 [PMID: [32253535](#) DOI: [10.1007/s00405-020-05965-1](#)]
- 53 **Genovese F**, Tizzano M. Microvillous cells in the olfactory epithelium express elements of the solitary chemosensory cell transduction signaling cascade. *PLoS One* 2018; **13**: e0202754 [PMID: [30212469](#) DOI: [10.1371/journal.pone.0202754](#)]
- 54 **Xu H**, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci* 2020; **12**: 8 [PMID: [32094336](#) DOI: [10.1038/s41368-020-0074-x](#)]
- 55 **Gadanec LK**, McSweeney KR, Qaradakh T, Ali B, Zulli A, Apostolopoulos V. Can SARS-CoV-2 Virus Use Multiple Receptors to Enter Host Cells? *Int J Mol Sci* 2021; **22** [PMID: [33498183](#) DOI: [10.3390/ijms22030992](#)]
- 56 **Sun XL**. The role of cell surface sialic acids for SARS-CoV-2 infection. *Glycobiology* 2021; **31**: 1245-1253 [PMID: [33909065](#) DOI: [10.1093/glycob/cwab032](#)]
- 57 **Choudhury A**, Mukherjee S. In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. *J Med Virol* 2020; **92**: 2105-2113 [PMID: [32383269](#) DOI: [10.1002/jmv.25987](#)]

Prospective Study

Prevalence of gastroesophageal reflux disease in children with extraesophageal manifestations using combined-video, multichannel intraluminal impedance-pH study

Sutha Eiamkulbutr, Termpong Dumrisilp, Anapat Sanpavat, Palittiya Sintusek

Specialty type: Gastroenterology and hepatology**Provenance and peer review:** Invited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0**P-Reviewer:** Lv L, China; Xiao Y, China**Received:** February 20, 2023**Peer-review started:** February 20, 2023**First decision:** April 8, 2023**Revised:** April 13, 2023**Accepted:** May 6, 2023**Article in press:** May 6, 2023**Published online:** June 9, 2023**Sutha Eiamkulbutr**, Department of Pediatrics, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand**Termpong Dumrisilp**, Department of Pediatrics, Bhumibol Adulyadej Hospital, Bangkok 10220, Thailand**Anapat Sanpavat**, Department of Pathology, Chulalongkorn University, Bangkok 10330, Thailand**Palittiya Sintusek**, Thai Pediatric Gastroenterology, Hepatology and Immunology Research Unit, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand**Corresponding author:** Palittiya Sintusek, MD, PhD, Associate Professor, Thai Pediatric Gastroenterology, Hepatology and Immunology Research Unit, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok 10330, Thailand. palittiya.s@chula.ac.th

Abstract

BACKGROUND

Gastroesophageal reflux disease (GERD) might be either a cause or comorbidity in children with extraesophageal problems especially as refractory respiratory symptoms, without any best methods or criterion for diagnosing it in children.

AIM

To evaluate the prevalence of extraesophageal GERD using conventional and combined-video, multichannel intraluminal impedance-pH (MII-pH), and to propose novel diagnostic parameters.

METHODS

The study was conducted among children suspected of extraesophageal GERD at King Chulalongkorn Memorial Hospital between 2019 and 2022. The children underwent conventional and/or combined-video MII-pH. The potential parameters were assessed and receiver operating characteristic was used for the significant parameters.

RESULTS

Of 51 patients (52.9% males), aged 2.24 years were recruited. The common problems were cough, recurrent pneumonia, and hypersecretion. Using MII-pH, 35.3% of the children were diagnosed with GERD by reflux index (31.4%), total reflux events (3.9%), and symptom indices (9.8%) with higher symptom recorded in the GERD group (94 *vs* 171, $P = 0.033$). In the video monitoring group ($n = 17$), there were more symptoms recorded (120 *vs* 220, $P = 0.062$) and more GERD (11.8% *vs* 29.4%, $P = 0.398$) by symptom indices. Longest reflux time and mean nocturnal baseline impedance were significant parameters for diagnosis with receiver operating characteristic areas of 0.907 ($P = 0.001$) and 0.726 ($P = 0.014$).

CONCLUSION

The prevalence of extraesophageal GERD in children was not high as expected. The diagnostic yield of symptom indices increased using video monitoring. Long reflux time and mean nocturnal baseline impedance are novel parameters that should be integrated into the GERD diagnostic criteria in children.

Key Words: Extraesophageal reflux; pH-impedance; Children; Gastroesophageal reflux; Mean nocturnal baseline impedance

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This was a retrospective and cross-sectional study with 51 children suspected extraesophageal gastrointestinal esophageal reflux disease (GERD). This study found the prevalence of GERD in these pediatric patients was 35.3% by using combined-video, multichannel intraluminal impedance-pH study. Moreover, longest reflux time and mean nocturnal baseline impedance were depicted as the significant parameters for GERD diagnosis with satisfied diagnostic value in children.

Citation: Eiamkulbutr S, Dumrisilp T, Sanpavat A, Sintusek P. Prevalence of gastroesophageal reflux disease in children with extraesophageal manifestations using combined-video, multichannel intraluminal impedance-pH study. *World J Clin Pediatr* 2023; 12(3): 151-161

URL: <https://www.wjgnet.com/2219-2808/full/v12/i3/151.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i3.151>

INTRODUCTION

Gastroesophageal reflux (GER) is a physiologic process that commonly occurs in infants. Gastroesophageal reflux disease (GERD) occurs when the refluxates cause troublesome symptoms. The incidence of GERD has increased in children (0.84 per 1000 persons-year)[1]. Its manifestation varies. Hence, a high index of suspicion is necessary, especially for extraesophageal manifestations[2]. In clinical practice, respiratory problems that are refractory to the standard treatment might be from the disease itself or are extraesophageal manifestations of GERD. Moreover, GERD can be a serious comorbidity that worsens those respiratory conditions. Consequently, the development of a standard tool to diagnose extraesophageal GERD and its prompt management are crucial.

There are many diagnostic tools for extraesophageal GERD, including pH monitoring, combined multichannel intraluminal impedance and pH (MII-pH) study, esophagogastroduodenoscopy (EGD) with biopsies, and laryngoscopy[3]. According to clinical practice guidelines for GERD diagnosis and management in children (North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition), the MII-pH study is the best diagnostic method for esophageal manifestations of GERD[4]. Recent studies in adults also propose that additional parameters from the MII-pH study, mean nocturnal baseline impedance (MNBI), and post-reflux swallow-induced peristaltic wave (PSPW), increase the diagnostic value of this tool[5]. However, there is scarce evidence to support the best method for diagnosing extraesophageal GERD in children. Further evaluation is necessary. The main purpose of this study is to determine the prevalence of GERD in children with extraesophageal symptoms using conventional and combined-video MII-pH studies. The secondary aim is to assess the diagnostic usefulness of combined-video MII-pH studies for GERD and other diagnostic parameters.

MATERIALS AND METHODS

Patient selection

The present study is a retrospective and cross-sectional study in children and adolescents with respiratory symptoms and other extraesophageal manifestations suggestive of GERD. Participants were treated at King Chulalongkorn Memorial Hospital (KCMH) from February 2019 to December 2021. Patients who had extraesophageal symptoms (cough, apnea or brief resolved unexplained event, uncontrolled asthma, recurrent pneumonia, stridor, hoarseness, chronic sinusitis with unknown causes, allergic rhinitis with difficulty to treatment), and who were between 1 mo and 18 years old were included in the study. The exclusion criteria were patients who were on proton pump inhibitors or prokinetics during MII-pH monitoring, unwillingness to participate in the study, and patients who were already known the other causes that could explain those extraesophageal symptoms.

The Chulalongkorn University Institutional Review Board approved this study (IRB 029/64). Informed consents and assents were obtained from the patient's guardians and patients, respectively, before recruitment to the study.

MI-pH study and/or video monitoring

According to the protocol, patients had to fast for one to two hours before a nasal impedance catheter with a pH probe (Pediatric ZandorpH catheter with one antimony and six impedance sensors with 1.5 cm interval, Laborie, The Netherlands) was distributed throughout the esophagus. The Strobel formula [6] was used to calculate the proper position of the catheter. Chest X-ray was then used to confirm that the pH probe was located at 2–3 vertebral distance from the diaphragm. During the MII-pH monitoring, all patients had their regular meals. Video monitoring was conducted simultaneously with MII-pH monitoring in 17 patients. The total time of monitoring after excluding meal periods was at least 18 h. The number of reflux events, the reflux index (RI), the symptom index (SI)/symptom sensitivity index (SSI)/symptom association probability (SAP), longest reflux time (LRT), the MNBI, and PSPW were recorded.

Pathological reflux is defined according to the position statement by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) Motility Working Group [6] as RI > 7% in children aged ≥ 1 year, and > 10% in children aged < 1 year, or if reflux episodes occur ≥ 70 times in children aged ≥ 1 year, and ≥ 100 times in children aged < 1 year or positive SI/SSI/SAP. Regarding symptom recoding, SI is calculated as (reflux-related symptom occurrences/total symptom events) × 100. SI is considered positive if the value is ≥ 50%. SSI is calculated as (number of symptom-associated reflux/total number of reflux episodes) × 100. If the percentage of SSI is ≥ 10%, it is considered positive. SAP is calculated by dividing the total measuring time into 2-min intervals, and creating a four-field contingency table: The number of intervals with and without GER symptoms, number of intervals with and without GER symptoms, number of intervals without GER and with the symptoms, and number of intervals without GER and symptoms. Fisher's exact test was performed for statistical examination of correlation. A percentage greater than 95% was considered positive.

Regarding the new parameters, MNBI was measured from the most distal impedance channel during sleep, with three 10-min time intervals that did not interfere with swallowing. The mean of these three values was then calculated. PSPW was defined as an antegrade 50% drop in impedance originating in the proximal esophagus within 30 s after the end of a reflux event and reaching the distal lumen. The PSPW index was calculated by the number of PSPW divided by the total number of refluxes [5,7].

Esophageal gross and histopathology finding

Within three months of the MII-pH study esophagogastroduodenoscopy with biopsy was performed on selected patients from recruitment according to decisions by the doctors in charge. The Los Angeles (LA) Classification [8] was routinely used to record endoscopic findings. The esophageal histopathology finding was reported by a pathologist using the modified Esohisto criteria as described in our previous study [8]. In short, a calculated severity score of 0–0.25 was considered normal and a score of ≥ 0.5 was regarded as esophagitis.

Statistical analysis

Data of categorical variables were expressed as percentages or proportions, and continuous variables as median [interquartile range (IQR)]. These variables were compared using Fisher's exact test and Wilcoxon signed ranks test as appropriate. Univariable and multivariable analyses were used to assess the independent factors of extraesophageal GERD from demographic variables and parameters from MII-pH analysis. Statistical significance was defined as *P* value < 0.05. Receiver operating characteristic analysis with calculation of the area under the curve was used to assess the diagnostic yield of the potential parameters of extraesophageal GERD. Statistical analysis was performed using SPSS software version 24.0.0 (SPSS Inc., Chicago, IL, United States) and Stata version 15.1 (Stata Corp, LLC, College Station, TX, United States).

RESULTS

Baseline characteristics of children with suspected extraesophageal GERD

There were 83 children with suspected extraesophageal GERD at KCMH from February 2019 to July 2022. Thirty-two participants were excluded from the present study because they received proton pump inhibitors/prokinetics during the MII-pH study ($n = 21$), had unwilling guardians ($n = 3$), and because they had known causes of respiratory symptoms ($n = 8$). Consequently, a total of 51 children were recruited and 17 of them underwent both the MII-pH study and video monitoring. Twenty-five children underwent upper endoscopy, while 22 underwent esophageal biopsy for histopathology. The median age of these 51 participants was 2.24 (1.11, 7.67) years and 27 (52.9%) participants were males. Their underlying diseases were multiple anomalies (47%), respiratory disorders (35.3%), and neurological disorders (17.7%). The most common extraesophageal symptoms indicated in the MII-pH study were cough (41.2%), recurrent pneumonia (25.5%), and hypersecretion (11.8%). However, 16 (31.4%) participants also had concurrent gastrointestinal symptoms. The median duration of MII-pH recording was 22.09 (20.20, 23.41) h. Only 265 symptoms were recorded by guardians, including cough ($n = 109$, 41.1%), irritability ($n = 54$, 20.4%), apparent secretion ($n = 24$, 9.1%), vomiting ($n = 34$, 12.8%), and heartburn ($n = 44$, 16.6%). In total, 18 (35.3%) participants were diagnosed with GERD using the MII-pH study. In the subgroup of children who underwent upper endoscopy ($n = 25$) and 22 of them had received esophageal tissue biopsy, 18 (72%) and 16 (72.7%), respectively, were diagnosed with GERD using the LA classification and modified Esophisto, respectively (Figure 1).

II-pH study

According to the diagnostic criteria by the BSPGHAN Motility Working Group[6], 18 participants had parameters that were compatible with GERD. A comparison between the GERD and non-GERD groups did not reveal any statistical difference in the baseline characteristics. Besides the parameters from the MII-pH study that were used for diagnosing GERD (total reflux event, reflux index, and symptom index), total symptom record (94 vs 171 times, $P = 0.033$), LRT (1.3 (0, 4.3) vs 17.2 (9.43, 38.55), $P < 0.001$), and MNBI (1897.69 (806.89) vs 1300.48 (600.31) ohms, $P = 0.008$), were significantly different between the non-GERD and GERD groups, respectively. Meanwhile, PSPW, another novel metric, did not show a significant difference between the groups [53.57 (27.59) vs 56.11 (15.7), $P = 0.721$]. In the multivariable analysis, LRT and MNBI were the independent parameters that were significantly differences in participants diagnosed with GERD ($P < 0.05$) (Table 1).

Combined MII-pH study with video monitoring

The MII-pH study with video monitoring was performed in 17 participants. By the novel combined video-MII-pH study is different from the conventional MII-pH study. The video-MII-pH study had conducted simultaneously with MII-pH monitoring and given the clinical symptoms recorded by the investigator that can make more accurate of symptoms in children who cannot even report their symptoms. Then we compared the symptoms that were recorded by the participants' guardians (conventional study) to the symptoms that were recorded by the video monitoring which is the same participants.

The total number of symptoms recorded from video by an investigator who simultaneously viewed throughout the recording, was detected higher than from participants' guardians even though there's no statistical significance (220 vs 120, $P = 0.062$. This led to an increase in the number of participants who were diagnosed with GERD by using symptom association indices (SI/SSI/SAP) ($n = 2$, 11.8% vs $n = 5$, 29.4%, $P = 0.398$) (Table 2).

Diagnostic value of the novel parameters from MII-pH study

When using the significant parameters from multivariable analysis to identify GERD, longest reflux duration and MNBI yielded an area under the curve (AUC) of 0.907 (95%CI: 0.802–1) and 0.726 (95%CI: 0.581–0.870), correspondingly. Combining these two parameters yielded an AUC of 0.914 (95%CI: 0.819–1) (Figure 2). A cutoff value of eight minutes for longest reflux duration had a sensitivity of 83.33% and a specificity of 90.91%. A cutoff value of 1466 ohm for MNBI had a sensitivity of 50.0% and a specificity of 33.33%.

DISCUSSION

The prevalence of extraesophageal GERD was 35.3% by using the MII-pH study in this study. Interestingly, 31.4% of children who had extraesophageal manifestations of GERD also had gastrointestinal symptoms. Total symptom record, LRT, and MNBI were the parameters that were significantly different between the GERD and non-GERD groups. LRT and MNBI were the independent parameters from multivariable analysis. Using video monitoring during MII-pH study to depict more symptom record increases the diagnostic yield of extraesophageal GERD.

Table 1 Demographic characteristics and parameters from Multichannel intraluminal impedance-pH study in children diagnosed with extraesophageal gastroesophageal reflux disease and no extraesophageal gastroesophageal reflux disease, *n*, (%)

Characteristics	No extraesophageal GERD (<i>n</i> = 33)	Diagnosed extraesophageal GERD by MII-pH study (<i>n</i> = 18)	P value	
			Univariable analysis	Multivariable analysis
Age (yr) (median, IQR)	1.67 (0.91, 3.38)	4.58 (1.70, 13.15)	0.174	
Age < 1 yr	10 (30.3)	2 (11.1)		
Age ≥ 1 yr	23 (69.7)	16 (88.9)		
Sex, male	17 (51.5)	10 (55.6)	1	
Underlying diseases			0.441	
Respiratory disorder				
Bronchiectasis	1 (3.03)	0		
Chronic lung disease	7 (21.21)	2 (11.11)		
Congenital hypoventilation syndrome	0	2 (11.11)		
Subglottic stenosis	0	1 (5.56)		
Tracheobronchomalacia	1 (3.03)	0		
Laryngomalacia	1 (3.03)	0		
BRUE	1 (3.03)	0		
Chronic cough	1 (3.03)	0		
Neurological disorder				
Swallowing dysfunction	2 (6.06)	1 (5.56)		
Spastic cerebral palsy	2 (6.06)	3 (16.67)		
Infantile spasm	1 (3.03)	0		
Multiple anomalies				
Syndromic disorder	6 (18.18)	2 (11.11)		
Non-syndromic disorder	9 (27.27)	7 (38.89)		
Indication for evaluation				
Extraesophageal symptoms			0.679	
Recurrent pneumonia	9 (27.3)	4 (22.2)		
Hypersecretion	4 (12.1)	2 (11.1)		
Cough	11 (33.3)	10 (55.6)		
Glossoptosis	1 (3.0)	0		
Tracheobronchomalacia	1 (3.0)	0		
Stridor	1 (3.0)	0		
Choking	4 (12.1)	1 (5.6)		
Chronic rhinosinusitis	0	1 (5.6)		
BRUEs	1 (3.0)	0		
Apnea	1 (3.0)	0		
Esophageal symptoms			0.293	
Vomiting	8 (24.2)	6 (38.9)		
Heartburn	1 (3.0)	1 (5.6)		
None	24 (72.7)	11 (61.1)		
Total recorded symptoms	94	171	0.033	0.064

(times, %)				
Cough	43 (45.75)	66 (38.60)	0.404	
Irritability	32 (34.04)	22 (12.86)	0.754	
Apparent secretion	7 (7.44)	17 (9.94)	0.346	
GI symptoms (vomiting or heartburn)	12 (12.77)	66 (38.60)	0.081	
Impedance parameters (median, IQR)				
Total time (hours)	22.12 (20.34, 24.04)	21.34 (19.97, 22.62)	0.391	
Reflux index ¹	0.40 (0, 1.45)	8.4 (4.43, 14.20)	0.001	
Longest reflux time (min)	1.3 (0, 4.30)	17.2 (9.43, 38.55)	0.001	
Total reflux events¹	12 (5.00, 37.50)	28 (18.50, 45.50)	0.032	0.012
Weakly acid reflux events				
Acid reflux events	9 (2.50, 27.00)	10 (3.75, 21.75)	0.79	
Nonacid reflux events	1 (0, 4.50)	15.5 (8.75, 25.25)	0.001	
Symptom indices	0 (0, 4.00)	0 (0, 1.00)	0.381	0.212
Symptom index ¹	0 (0, 0.00)	0 (0, 12.73)	0.208	
Symptom sensitivity index ¹	0 (0, 0.00)	0 (0, 1.40)	0.32	
Symptom associated index ¹	0 (0, 0.00)	0 (0, 85.63)	0.168	
MNBI (ohms) (mean, SD)	1897.69 (806.89)	1300.48 (600.31)	0.008	
PSPW (%) (mean, SD)	53.57 (27.59)	56.11 (15.70)	0.721	
Diagnosis GERD				
Gross finding (<i>n</i> = 25)	8/12 (66.7)	10/13 (76.9)	0.673	
Histopathology (<i>n</i> = 22)	6/11 (54.5)	10/11 (90.9)	0.149	

¹Significant factors in univariable analysis were not included in the multivariable analysis because of collinearity with criteria diagnosis gastroesophageal reflux disease using the MII-pH study.

BRUE: Brief resolved unexplained event; MNBI: Mean nocturnal baseline impedance; PSPW: Post-reflux swallow-induced peristaltic wave index; GERD: Gastroesophageal reflux disease; MII-pH: Multichannel intraluminal impedance-pH; IQR: Interquartile range.

Table 2 Comparing symptoms recorded by conventional and combined visual data object -monitoring in children who underwent multichannel intraluminal impedance-pH study (*n* = 17), *n*, (%)

Characteristics	Conventional MII-pH study	Combined video-MII-pH study	<i>P</i> value
Total recorded symptoms	120	220	0.062
Cough	31 (25.83)	46 (20.90)	0.259
Irritability	38 (31.67)	101 (45.90)	0.114
Apparent secretion	3 (2.50)	43 (19.55)	0.02
GI symptoms (vomiting or heartburn)	48 (40.00)	33 (15.00)	0.339
Symptom indices (median, IQR)			
Symptom index	0 (0–5.00)	0 (0–11.65)	0.306
Symptom sensitivity index	0 (0–2.65)	0 (0–5.80)	0.306
Symptom associated index	0 (0–37.60)	0 (0–93.15)	0.306
Diagnosis GERD using symptom indices	2 (11.76)	5 (29.41)	0.398

GI: Gastrointestinal; GERD: Gastroesophageal reflux disease; MII-pH: Multichannel intraluminal impedance-pH; IQR Interquartile range.

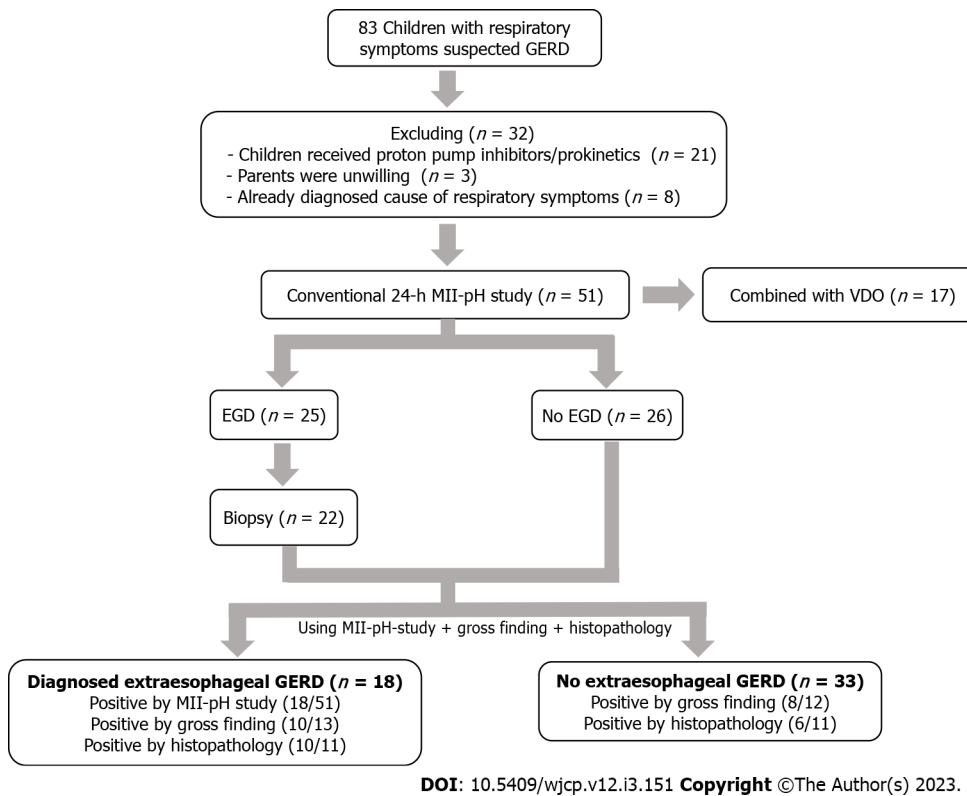


Figure 1 Recruitment of children with respiratory symptoms suggestive of gastroesophageal reflux disease. EGD: Esophagogastroduodenoscopy; GERD: Gastroesophageal reflux disease; MII-Ph: multichannel intraluminal impedance and pH.

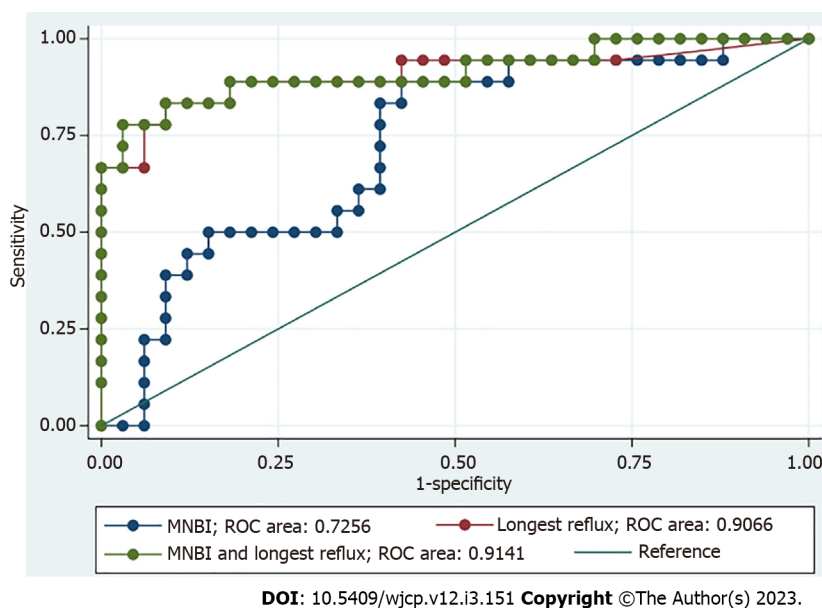


Figure 2 Area under the receiver operating characteristic curve of the novel parameters to diagnose extraesophageal gastroesophageal reflux disease. MNBI: Mean nocturnal baseline impedance; ROC: Receiver operating characteristic curve; GERD: Gastroesophageal reflux disease.

There are several debates over clinical symptoms of extraesophageal reflux disease in children because of heterogeneity, non-specificity, and unreliability. Moreover, the prevalence of extraesophageal GERD reflects the real burden and depends on the modalities for diagnosis. Hence, finding the best diagnostic tool for extraesophageal GERD is crucial. Many proposed diagnostic tools, such as oropharyngeal pH monitoring/salivary pepsin, have been studied with unsatisfactory results[9-11]. As a result, the present study was designed using MII-pH study and histopathology – which are the gold standard for diagnosing esophageal GERD – to be the gold standard diagnosis for extraesophageal GERD. Moreover, combined-video monitoring was performed in 17 participants. The present study

found that video monitoring increased the value of symptom-reflux association in extraesophageal GERD. This is congruent with our previous study which depicted a trend of symptom-reflux association with particular symptoms of GERD in children diagnosed with esophageal atresia[12]. The real-time video captured in MII-pH monitoring with physician symptom recordings had higher symptom indices. There were more symptoms recorded including cough, hypersecretion, irritability, and vomiting. There were also more GERD diagnoses secondary to the symptoms that were more trustworthy than conventional methods. These studies highlight that symptom recording by video monitoring in children increases the value of symptom association for GERD diagnosis.

Although identifying extraesophageal manifestation of GERD is challenging and needs evaluation regarding whether it represents true GERD or a mimicker, the present study found concomitant gastrointestinal symptoms or signs in a majority of these children. Moreover, esophagitis was also detected in a majority of children with extraesophageal symptoms in the present study. This might explain the gastrointestinal symptoms they experienced. The reflex theory is a possible explanation regarding why children with extraesophageal GERD also had gastrointestinal involvement. The theory suggests that reflux stimulates the vagus nerve in the esophagus leading to cough, bronchoconstriction, or other extraesophageal symptoms *via* vagally mediated reflexes[13,14]. However, previous studies demonstrated a lower prevalence of esophagitis in patients with extraesophageal GERD. A positive reflux-laryngitis varies from 5% up to 31% [15-18]. Routine upper endoscopy in all children with solely extraesophageal symptoms might be avoided. This invasive procedure should be preserved for patients who have both extraesophageal and esophageal manifestations of GERD. To increase the reliability of symptom assessment, we encourage the physician to have the dedicated history taking or possible video recording of symptoms during MII-pH study simultaneously with the routine symptom recorded by patients or their guardians. Upper endoscopy with biopsy is necessary and could increase the yield of GERD diagnosis in these selected children.

Besides using symptom association to diagnose extraesophageal GERD, we found that acid reflux was mainly present in the present study in accordance with Borrelli *et al*'s work. Borrelli *et al*[19] found that 66% of cough bursts were related to acid reflux episodes. However, different results were demonstrated by Zenzeri *et al*[20] who found predominantly weak acid and nonacid reflux in children with respiratory problems. Because of the lack of standardized protocol and children's conditions in previous studies, a large multicenter study regarding children with different manifestations is necessary to extend the knowledge and narrow the specific treatment for them. In the present study, a majority of children had complicated underlying diseases (multiple anomalies, respiratory disease, or neurological deficit) that increased the risk of esophageal motility disorder and reflux. This could explain the high predominance of acid reflux.

The pathogenesis of GERD is complex and multifactorial. Though abnormal transient esophageal relaxation is the main pathogenesis, other factors such as esophageal mucosal disease, esophageal dysmotility, gastroparesis, and anatomical defect (hiatal hernia, short segment of abdominal esophagus)-must be considered as aggravated risk factors of GERD[21]. Children with multiple comorbidities, especially neurological deficit, usually have sedentary lifestyles or are bedridden, and this affects gastrointestinal motility. We found that the LRT had statistically significant discriminate GERD and non-GERD children, reflexes the impairment of esophageal volume clearance as one of the pathogenesis of GERD[22,23]. However, there was no impairment of chemical clearance as shown by the insignificant difference in PSPW in both groups. MNBI is another parameter that can discriminate GERD from non-GERD children. MNBI represents esophageal integrity[5] and has a reasonably low value in GERD. To the best of our knowledge, PSPW and MNBI are the new impedance-pH parameters which are integral in the Lyon Consensus criteria for diagnosing GERD in adults[24]. The impact of PSPW and MNBI on increasing the yield of GERD diagnosis in children is rare. There is only one study concerning the impact of MNBI in children with GERD by Rosado-Arias *et al*[25]. That study found that a low MNBI is associated with a pathological AET. Our study is compatible with the study by Rosado-Arias *et al*[25] and confirmed the role of a low MNBI in helping the diagnostic yield of GERD. To the best of our knowledge, the present study is the first study to evaluate the PSPW parameter between GERD and non-GERD children. A previous study by Park *et al*[26] showed impairment of PSPW in adults with laryngopharyngeal reflux and esophageal GERD, but our study is incongruent with same. It is possible that the chemical clearance is important for the pathogenesis of extraesophageal GERD in adults *vs* in children. Further studies from multicenter or with the higher number of participants about PSPW and MNBI parameters, are crucial in aiding the diagnosis of GERD in children.

The certain strength of our study is that we integrated video monitoring into MII-pH study for diagnosing extraesophageal GERD in children. Moreover, the novel parameters (PSPW and MNBI) were evaluated to increase the yield of GERD diagnosis. However, there are some limitations. Firstly, it was a small number of children in a single center study. Therefore, the results are specific to the particular comorbidities that were present and cannot be extrapolated to children with previously healthy or less comorbidities. Secondly, because of the coronavirus disease 2019 pandemic, upper endoscopy was not performed in all children. Given this, there is the potential for selective bias and a high prevalence of children with extraesophageal GERD having esophagitis.

CONCLUSION

In conclusion, the prevalence of GERD was not as high as expected. Employing video monitoring into conventional MII-pH study increases the diagnostic yield of symptom indices. LRT and MNBI are novel parameters that should be integrated into the diagnostic criteria for GERD.

ARTICLE HIGHLIGHTS

Research background

Gastroesophageal reflux disease (GERD) might be either a cause or comorbidity in children with extraesophageal problems especially as refractory respiratory symptoms, without any best methods or criterion for diagnosing it in children.

Research motivation

Recent studies in adults also propose that additional parameters from the multichannel intraluminal impedance (MII)-pH study, mean nocturnal baseline impedance (MNBI), and post-reflux swallow-induced peristaltic wave, increase the diagnostic value of this tool. However, there has been scarce evidence to support the best method for diagnosing extraesophageal GERD in children.

Research objectives

To study the prevalence of extraesophageal GERD, especially in children who presented with refractory respiratory problems by using combined video-MII-pH study. Furthermore, to identify other parameters from MII-pH study that can help the diagnosis of extraesophageal GERD.

Research methods

Children with respiratory symptoms and other extraesophageal manifestations suggestive of GERD were enrolled to participate in the present study. MII-pH study and/or video monitoring and/or upper endoscopy with esophageal histopathology were performed. The prevalence of extraesophageal GERD and the novel diagnostic parameters to diagnose extraesophageal GERD were analyzed.

Research results

The prevalence of extraesophageal GERD was 35.3% by using the MII-pH study and 31.4% of children who had extraesophageal manifestations of GERD also had gastrointestinal symptoms. Total symptom record, longest reflux time (LRT), and MNBI were the parameters that were significantly different between the GERD and non-GERD groups. LRT and MNBI were the independent parameters from multivariable analysis. Using video monitoring during MII-pH study to depict more symptom record increases the diagnostic yield of extraesophageal GERD.

Research conclusions

In conclusion, the prevalence of GERD was not as high as expected. Employing video monitoring into conventional MII-pH study increases the diagnostic yield of symptom indices. LRT and MNBI are novel parameters that should be integrated into the diagnostic criteria for GERD.

Research perspectives

The diagnostic test for extraesophageal GERD in children is limited and there have been a few data support the favorable treatment outcome in these children. Hence, the extensive investigations in these difficult cases are needed and other mimic causes should be ruled out. Further study in aspect of esophageal manometry combined with video-MII-pH study and histopathology in various presentations of GERD should be initiated to extend the knowledge about the pathogenesis of GERD and hopefully, could tailor therapy for these patients.

ACKNOWLEDGEMENTS

We are grateful to all participants and their guardians in the present study; Voranush Chongsrisawat, Chomchanat Tubjareon, Sittichoke Prachuaphunychart, Atikan Sirichoompun, Nattakoon Potjalongsin, all physician and nurses for the great care to our patients.

FOOTNOTES

Author contributions: Eiamkulbutr S, Dumrisilp T and Sintusek P performed the upper endoscopy and MII-pH study; Eiamkulbutr S, Dumrisilp T collected all the data; Sanpavat A analyzed and interpreted the histopathological data; Eiamkulbutr S recorded all symptoms from video recording; Eiamkulbutr S and Sintusek P analyzed and interpreted the MII-pH study and wrote the manuscript; Sintusek P was responsible for designing, editing, and revising the manuscript; Sintusek P edited the intellectual content in the manuscript; all approved for the final version of the manuscript.

Supported by The Ratchadapiseksompotch Fund, Chulalongkorn University's Faculty of Medicine, King Chulalongkorn Memorial Hospital's Department of Pediatrics, and Chulalongkorn University's Faculty of Medicine (GA64/48).

Institutional review board statement: The study was reviewed and approved by the Chulalongkorn University Institutional Review Board approved this study (IRB 029/64).

Clinical trial registration statement: This study is registered at <https://www.thaiclinicaltrials.org/show/TCTR20210829001>. The registration identification number is TCTR20210829001.

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

Conflict-of-interest statement: The authors of this manuscript having no conflict of interest to disclose.

Data sharing statement: Data will be shared when investigators contact the corresponding author.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution-NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Thailand

ORCID number: Termpong Dumrisilp 0000-0001-7110-0664; Anapat Sanpavat 0000-0002-6425-3379; Palittiya Sintusek 0000-0003-4441-0151.

Corresponding Author's Membership in Professional Societies: American Association for the Study of Liver Diseases, 174508; European Society of Pediatric Gastroenterology, Hepatology and Nutrition, 1135.

S-Editor: Ma YJ

L-Editor: A

P-Editor: Ma YJ

REFERENCES

- Ruigómez A**, Wallander MA, Lundborg P, Johansson S, Rodriguez LA. Gastroesophageal reflux disease in children and adolescents in primary care. *Scand J Gastroenterol* 2010; **45**: 139-146 [PMID: 19961345 DOI: 10.3109/00365520903428606]
- Kleinman RE**. Walker's pediatric gastrointestinal disease. Sixth ed. Olivier-Jean Goulet GM-V IRS, Philip M, Sherman BLS, editor: House-USA; 2018
- Tolia V**, Vandenplas Y. Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children. *Aliment Pharmacol Ther* 2009; **29**: 258-272 [PMID: 19143046 DOI: 10.1111/j.1365-2036.2008.03879.x]
- Rosen R**, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **66**: 516-554 [PMID: 29470322 DOI: 10.1097/MPG.0000000000001889]
- Frazzoni L**, Frazzoni M, De Bortoli N, Ribolsi M, Tolone S, Russo S, Conigliaro RL, Penagini R, Fuccio L, Zagari RM, Savarino E. Application of Lyon Consensus criteria for GORD diagnosis: evaluation of conventional and new impedance-pH parameters. *Gut* 2022; **71**: 1062-1067 [PMID: 34376517 DOI: 10.1136/gutjnl-2021-325531]
- Mutalib M**, Rawat D, Lindley K, Borrelli O, Perring S, Auth MKH, Thapar N. BSPGHAN Motility Working Group position statement: paediatric multichannel intraluminal pH impedance monitoring-indications, methods and interpretation.

- Frontline Gastroenterol* 2017; **8**: 156-162 [PMID: 28839903 DOI: 10.1136/flgastro-2016-100796]
- 7 **Lundell LR**, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172-180 [PMID: 10403727 DOI: 10.1136/gut.45.2.172]
 - 8 **Schneider NI**, Plieschnegger W, Geppert M, Wigglinghaus B, Hoess GM, Eherer A, Wolf EM, Rehak P, Vieth M, Langner C. Validation study of the Esohisto consensus guidelines for the recognition of microscopic esophagitis (histoGERD Trial). *Hum Pathol* 2014; **45**: 994-1002 [PMID: 24746203 DOI: 10.1016/j.humpath.2013.12.013]
 - 9 **Mazzoleni G**, Vailati C, Lisma DG, Testoni PA, Passaretti S. Correlation between oropharyngeal pH-monitoring and esophageal pH-impedance monitoring in patients with suspected GERD-related extra-esophageal symptoms. *Neurogastroenterol Motil* 2014; **26**: 1557-1564 [PMID: 25208949 DOI: 10.1111/nmo.12422]
 - 10 **Dy F**, Amirault J, Mitchell PD, Rosen R. Salivary Pepsin Lacks Sensitivity as a Diagnostic Tool to Evaluate Extraesophageal Reflux Disease. *J Pediatr* 2016; **177**: 53-58 [PMID: 27453366 DOI: 10.1016/j.jpeds.2016.06.033]
 - 11 **Ploczek A**, Gębora-Kowalska B, Bialek J, Fendler W, Toporowska-Kowalska E. Esophageal Impedance-pH Monitoring and Pharyngeal pH Monitoring in the Diagnosis of Extraesophageal Reflux in Children. *Gastroenterol Res Pract* 2019; **2019**: 6271910 [PMID: 30944563 DOI: 10.1155/2019/6271910]
 - 12 **Maholarnkij S**, Sanpavat A, Decharun K, Dumrisilp T, Tubjareon C, Kanghom B, Patcharatrakul T, Chaijitraruch N, Chongsrisawat V, Sintusek P. Detection of reflux-symptom association in children with esophageal atresia by video-pH-impedance study. *World J Gastroenterol* 2020; **26**: 4159-4169 [PMID: 32821077 DOI: 10.3748/wjg.v26.i28.4159]
 - 13 **Blondeau K**, Sifrim D, Dupont L, Tack J. Reflux cough. *Curr Gastroenterol Rep* 2008; **10**: 235-239 [PMID: 18625132 DOI: 10.1007/s11894-008-0049-0]
 - 14 **Pauwels A**, Blondeau K, Dupont L, Sifrim D. Cough and gastroesophageal reflux: from the gastroenterologist end. *Pulm Pharmacol Ther* 2009; **22**: 135-138 [PMID: 19063984 DOI: 10.1016/j.pupt.2008.11.007]
 - 15 **de Bortoli N**, Nacci A, Savarino E, Martinucci I, Bellini M, Fattori B, Ceccarelli L, Costa F, Mumolo MG, Ricchiuti A, Savarino V, Berrettini S, Marchi S. How many cases of laryngopharyngeal reflux suspected by laryngoscopy are gastroesophageal reflux disease-related? *World J Gastroenterol* 2012; **18**: 4363-4370 [PMID: 22969200 DOI: 10.3748/wjg.v18.i32.4363]
 - 16 **Qua CS**, Wong CH, Gopala K, Goh KL. Gastro-oesophageal reflux disease in chronic laryngitis: prevalence and response to acid-suppressive therapy. *Aliment Pharmacol Ther* 2007; **25**: 287-295 [PMID: 17269990 DOI: 10.1111/j.1365-2036.2006.03185.x]
 - 17 **Reichel O**, Issing WJ. Should patients with pH-documented laryngopharyngeal reflux routinely undergo oesophagogastroduodenoscopy? *J Laryngol Otol* 2007; **121**: 1165-1169 [PMID: 17931449 DOI: 10.1017/S0022215107000680]
 - 18 **Suzuki T**, Seki Y, Okamoto Y, Hoppo T. Hypopharyngeal multichannel intraluminal impedance leads to the promising outcome of antireflux surgery in Japanese population with laryngopharyngeal reflux symptoms. *Surg Endosc* 2018; **32**: 2409-2419 [PMID: 29218658 DOI: 10.1007/s00464-017-5940-z]
 - 19 **Borrelli O**, Marabotto C, Mancini V, Aloï M, Macri F, Falconieri P, Lindley KJ, Cucchiara S. Role of gastroesophageal reflux in children with unexplained chronic cough. *J Pediatr Gastroenterol Nutr* 2011; **53**: 287-292 [PMID: 21865976 DOI: 10.1097/MPG.0b013e318216e1ad]
 - 20 **Zenzeri L**, Quitadamo P, Tambucci R, Ummarino D, Poziello A, Miele E, Staiano A. Role of non-acid gastro-esophageal reflux in children with respiratory symptoms. *Pediatr Pulmonol* 2017; **52**: 669-674 [PMID: 27736035 DOI: 10.1002/ppul.23619]
 - 21 **Rybak A**, Pesce M, Thapar N, Borrelli O. Gastro-Esophageal Reflux in Children. *Int J Mol Sci* 2017; **18** [PMID: 28763023 DOI: 10.3390/ijms18081671]
 - 22 **Sintusek P**, Mutalib M, Thapar N. Gastroesophageal reflux disease in children: What's new right now? *World J Gastrointest Endosc* 2023; **15**: 84-102 [PMID: 37034973 DOI: 10.4253/wjge.v15.i3.84]
 - 23 **Tack J**, Pandolfino JE. Pathophysiology of Gastroesophageal Reflux Disease. *Gastroenterology* 2018; **154**: 277-288 [PMID: 29037470 DOI: 10.1053/j.gastro.2017.09.047]
 - 24 **Gyawali CP**, Kahrlas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, Vaezi M, Sifrim D, Fox MR, Vela MF, Tutuian R, Tack J, Bredenoord AJ, Pandolfino J, Roman S. Modern diagnosis of GERD: the Lyon Consensus. *Gut* 2018; **67**: 1351-1362 [PMID: 29437910 DOI: 10.1136/gutjnl-2017-314722]
 - 25 **Rosado-Arias Y**, Toro-Monjaraz EM, Cervantes-Bustamante R, Zarate-Mondragon F, Cadena-Leon J, Ignorosa-Arellano K, Loredó-Mayer A, Ramírez-Mayans J. Low Mean Nocturnal Baseline Impedance is Associated With a Pathological Acid Exposure Time in Children. *J Pediatr Gastroenterol Nutr* 2022; **74**: 215-220 [PMID: 34694265 DOI: 10.1097/MPG.0000000000003331]
 - 26 **Park JS**, Van der Wall H, Falk GL. Post-reflux swallow-induced peristaltic wave is impaired in laryngopharyngeal and gastro-oesophageal reflux disease. *Clin Physiol Funct Imaging* 2022; **42**: 8-14 [PMID: 34605162 DOI: 10.1111/cpf.12729]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2023 September 9; 12(4): 162-243



Contents

Quarterly Volume 12 Number 4 September 9, 2023

EVIDENCE REVIEW

- 162 Use of endolumenal functional lumen imaging probe in investigating paediatric gastrointestinal motility disorders
White E, Mutalib M

REVIEW

- 171 Role of gastrointestinal health in managing children with autism spectrum disorder
Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R, Alhawamdeh R

MINIREVIEWS

- 197 Gastrointestinal and nutritional care in pediatric neuromuscular disorders
Dipasquale V, Morello R, Romano C

ORIGINAL ARTICLE

Retrospective Cohort Study

- 205 Accidental ingestion of foreign bodies/harmful materials in children from Bahrain: A retrospective cohort study
Isa HM, Aldoseri SA, Abduljabbar AS, Alsulaiti KA

Retrospective Study

- 220 Safety and efficacy of intravitreal anti vascular endothelial growth factor for severe posterior retinopathy of prematurity with flat fibrovascular proliferation
Maitra P, Prema S, Narendran V, Shah PK
- 230 Radiation dose analysis of computed tomography coronary angiography in Children with Kawasaki disease
Bhatt MC, Singhal M, Pilania RK, Bansal SC, Khandelwal N, Gupta P, Singh S

CASE REPORT

- 237 Transient hyperphosphatasemia in a toddler with COVID-19 infection: A case report and literature review
Sukhupanyarak P, Phatarakijrurund V

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Pediatrics*, Sonay Aydin, MD, PhD, Associate Professor, Chief, Department of Radiology, Erzincan Binali Yildirim University, Başbaglar Mahalles, Haci Ali Akin Caddesi No:32, Erzincan, 24100, Turkey. sonay.aydin@erzincan.edu.tr

AIMS AND SCOPE

The primary aim of the *World Journal of Clinical Pediatrics* (WJCP, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCP mainly publishes articles reporting research results and findings obtained in the field of pediatrics and covering a wide range of topics including anesthesiology, cardiology, endocrinology, gastroenterology, hematology, immunology, infections and infectious diseases, medical imaging, neonatology, nephrology, neurosurgery, nursing medicine, perinatology, pharmacology, respiratory medicine, and urology.

INDEXING/ABSTRACTING

The WJCP is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The WJCP's CiteScore for 2022 is 1.7 and Scopus CiteScore rank 2022: Pediatrics, perinatology and child health is 176/306.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; Production Department Director: Xiang Li; Editorial Office Director: Xu Guo.

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2219-2808/editorialboard.htm>

PUBLICATION DATE

September 9, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Use of endolumenal functional lumen imaging probe in investigating paediatric gastrointestinal motility disorders

Emily White, Mohamed Mutalib

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D, D

Grade E (Poor): E

P-Reviewer: Batta A, India; Lee ACW, Singapore

Received: July 9, 2023

Peer-review started: July 9, 2023

First decision: July 19, 2023

Revised: August 9, 2023

Accepted: August 23, 2023

Article in press: August 23, 2023

Published online: September 9, 2023



Emily White, Mohamed Mutalib, Department of Paediatric Gastroenterology, Evelina London Children's Hospital, London SE1 7EH, United Kingdom

Mohamed Mutalib, Faculty of Life Sciences and Medicine, King's College London, London SE1 7EH, United Kingdom

Corresponding author: Mohamed Mutalib, MD, Doctor, Lecturer, Department of Paediatric Gastroenterology, Evelina London Children's Hospital, Westminster Bridge Road, London SE1 7EH, United Kingdom. mohamed.mutalib@gstt.nhs.uk

Abstract

Investigating gastrointestinal (GI) motility disorders relies on diagnostic tools to assess muscular contractions, peristalsis propagation and the integrity and coordination of various sphincters. Manometries are the gold standard to study the GI motor function but it is increasingly acknowledged that manometries do not provide a complete picture in relation to sphincters competencies and muscle fibrosis. Endolumenal functional lumen imaging probe (EndoFLIP) an emerging technology, uses impedance planimetry to measure hollow organs cross sectional area, distensibility and compliance. It has been successfully used as a complementary tool in the assessment of the upper and lower oesophageal sphincters, oesophageal body, the pylorus and the anal canal. In this article, we aim to review the uses of EndoFLIP as a tool to investigate GI motility disorders with a special focus on paediatric practice. The majority of EndoFLIP studies were conducted in adult patients but the uptake of the technology in paediatrics is increasing. EndoFLIP can provide a useful complementary data to the existing GI motility investigation in both children and adults.

Key Words: Endolumenal functional lumen imaging probe; Paediatric; Gastrointestinal motility

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Manometries are commonly used to investigate gastrointestinal (GI) motility disorders albeit with acknowledged limitation to their diagnostic yield. Endolumenal functional lumen imaging probe (EndoFLIP), an emerging technology uses impedance planimetry to provide cross sectional area, distensibility and diameter of a hollow organ. EndoFLIP is increasingly used as an adjunct diagnostic tool to provide diagnostic information and to guide therapy for many GI motility disorders.

Citation: White E, Motalib M. Use of endolumenal functional lumen imaging probe in investigating paediatric gastrointestinal motility disorders. *World J Clin Pediatr* 2023; 12(4): 162-170

URL: <https://www.wjgnet.com/2219-2808/full/v12/i4/162.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i4.162>

INTRODUCTION

Investigating gastrointestinal (GI) motor function requires a careful assessment of muscle contractions and sphincters function[1]. Manometries can directly measure the lumen-generated pressure and are considered the gold standard to evaluate the strength and propagation of muscle contractions, peristalsis velocity and the integrity and coordination of different types of GI sphincters[2]. Sequential multi-channel impedances, in isolation or combined with manometry, will evaluate the directional flow and the bolus transit[3]. However, it has long been recognised that the competency of GI sphincters does not always relate to the tightness of their contractions[4-6]. Measuring the resistance to distension, also known as distensibility assessment, can provide an accurate geometric measurement of the sphincters and a plethora of diagnostic information[7].

Endolumenal functional lumen imaging probe (EndoFLIP) uses the principles of impedance planimetry, a technical term that describes the measuring of the cross-sectional area (CSA) of a distending bag by using an internal electrical impedance measurement[8,9]. EndoFLIP consists of 16 sensors and a solid state pressure transducer placed inside a distensible and compliant balloon to provide a measurement length of 8 or 16 cm[10]. EndoFLIP is used during endoscopy under the same anaesthesia. To obtain the desired data, the balloon is filled with a conducting fluid (in a predetermined volume) (Figure 1), then the system will run a constant alternating current and the voltage difference between the excitation and the detection electrodes is measured[11]. The voltage is mathematically proportioned to the CSA of the balloon, from which, the balloon diameter can easily be calculated[12]. The EndoFLIP data will be presented as geometric plots and will provide the following values: Distensibility is the resistance of the luminal wall to a distending force, compliance is the change in volume in response to a change in pressure, the CSA, the internal diameter of the balloon and the intra balloon pressure[13,14] (Figure 2A).

EndoFLIP has been increasingly used in clinical practice to study the lower oesophageal sphincter (LOS), the pylorus and the anal sphincters[11]. It has also been used to assess distensibility of the oesophageal body in conditions such as eosinophilic oesophagitis (EoE)[15] and to guide surgical interventions (*e.g.*, during and post fundoplication)[16]. Recently, EndoFLIP topography was developed allowing real life display of the balloon diameter continuum during volumetric distension. Oesophageal body contraction can then be visualised and analysed[17,18] (Figure 3).

In this article, we aim to review the use of EndoFLIP as a tool to investigate GI motility disorders with a special focus on paediatric practice. We searched PubMed database for English Language literature on the following keywords: EndoFLIP; Gastrointestinal Disorders; GI disorders; oesophagus; pylorus; rectum; anorectum; paediatric; children using AND/OR combination as appropriate. The extracted articles were reviewed and their salient findings were summarised and presented in the headings below.

Uses of EndoFLIP in the oesophagus

The oesophageal body, the LOS and the upper oesophageal sphincter were the most commonly studied part of the GI tract in regards to EndoFLIP measurement[19]. Normative values from healthy adults have been recently published in a meta-analysis[20].

Achalasia

Achalasia is an uncommon oesophageal motility disorder, characterised by impaired relaxation of the LOS and absent or spastic oesophageal body contractions[21]. It has three distinct types based on peristalsis patterns: Absent peristalsis in type I, pan-oesophageal body pressurisation in type II and an abnormal peristalsis with premature contractions in type III [22]. Impaired LOS relaxation is the hallmark of all three types. High resolution oesophageal manometry (HROM) is universally agreed on as the gold standard tool to diagnose and characterise achalasia[23].

In adults, EndoFLIP assessment of LOS can appropriately identify patients with achalasia who may have a normal integrated relaxation pressure but other features of achalasia[4,6]. EndoFLIP was able to bridge a gap in the understanding of the physiological behaviour of the LOS and the limitation of HROM as a sole diagnostic tool for major oesophageal motor disorders[24,25]. LOS distensibility index (DI) of < 2 mm²/mmHg is strongly suggestive of an obstructive process and is significantly lower in patients with achalasia compared to healthy volunteers[21,26,27]. LOS DI also appears to correlate well with achalasia symptoms prior to and after therapeutic interventions; achieving a definitive increase in DI after pneumatic dilatation was reported to be associated with improved clinical response[26,28]. Using DI,

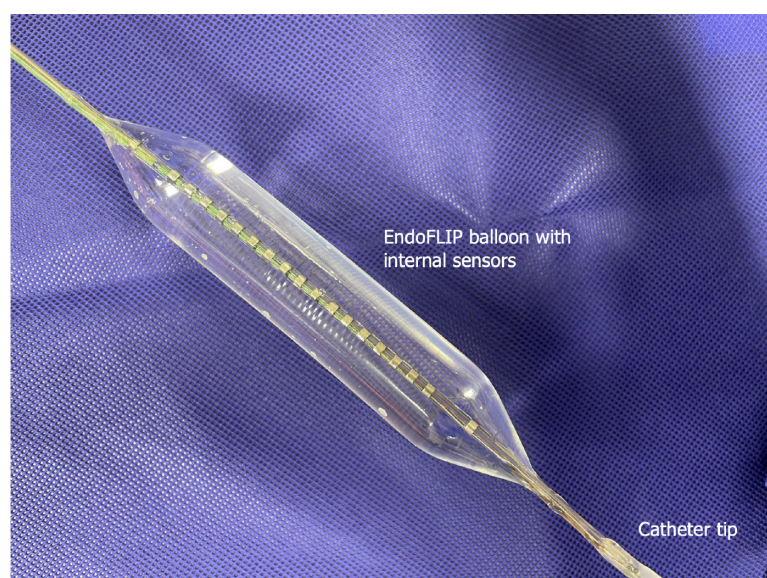


Figure 1 Endolumenal functional lumen imaging probe catheter (filled). EndoFLIP: Endolumenal functional lumen imaging probe.

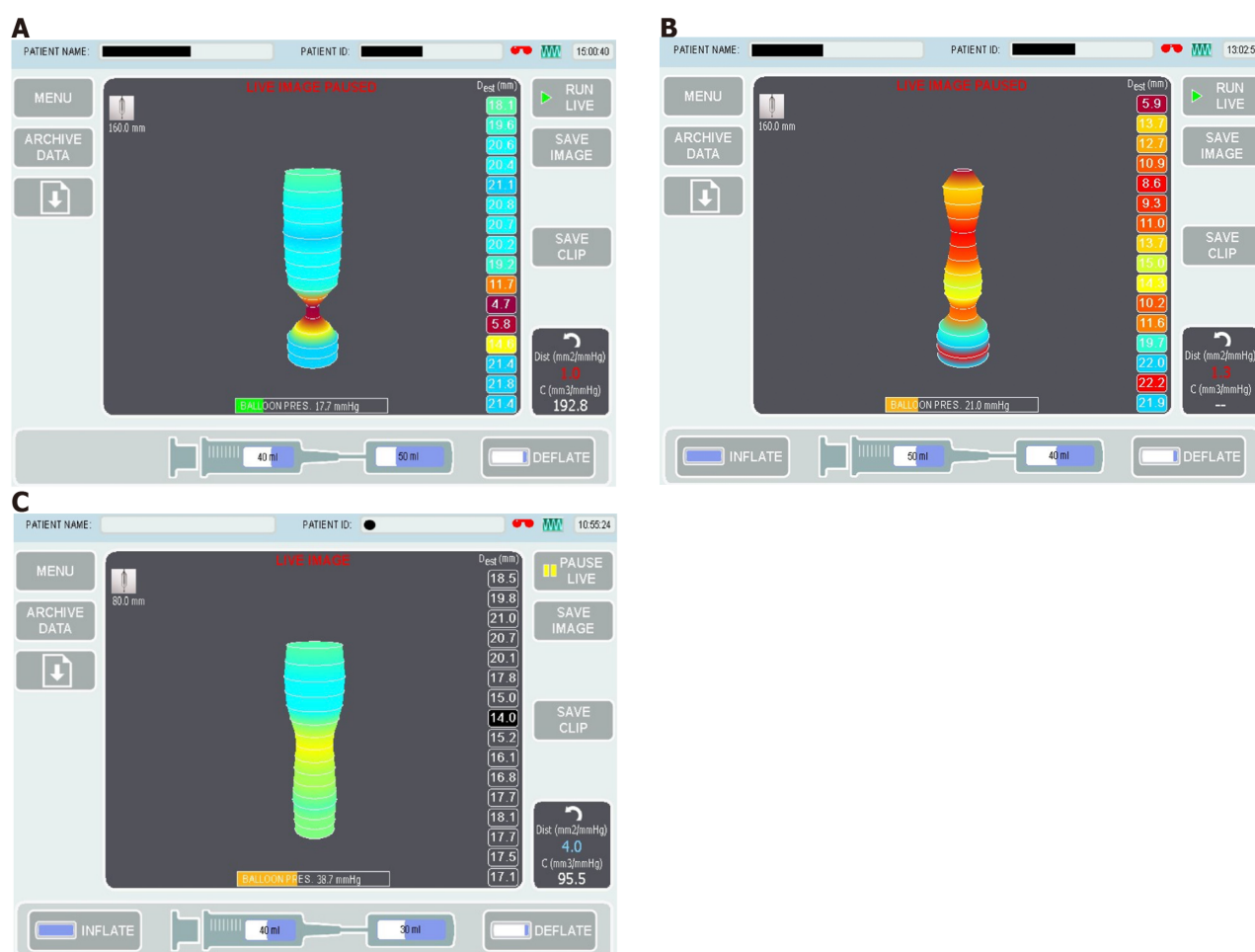


Figure 2 Endolumenal functional lumen imaging probe measurement. A: Endolumenal functional lumen imaging probe (EndoFLIP) measurement for a child with achalasia; B: EndoFLIP measurement from a child with eosinophilic oesophagitis; C: EndoFLIP measurement from a child with repaired oesophageal atresia.

CSA and balloon pressure as complementary data can help predict response to therapeutic interventions [Heller's myotomy and peroral endoscopic myotomy (POEM)] in patients with achalasia[29-31], however, the data on the use of EndoFLIP parameters as a predictor of pneumatic dilatation response is conflicting, Rohof *et al*[26] experience showed a

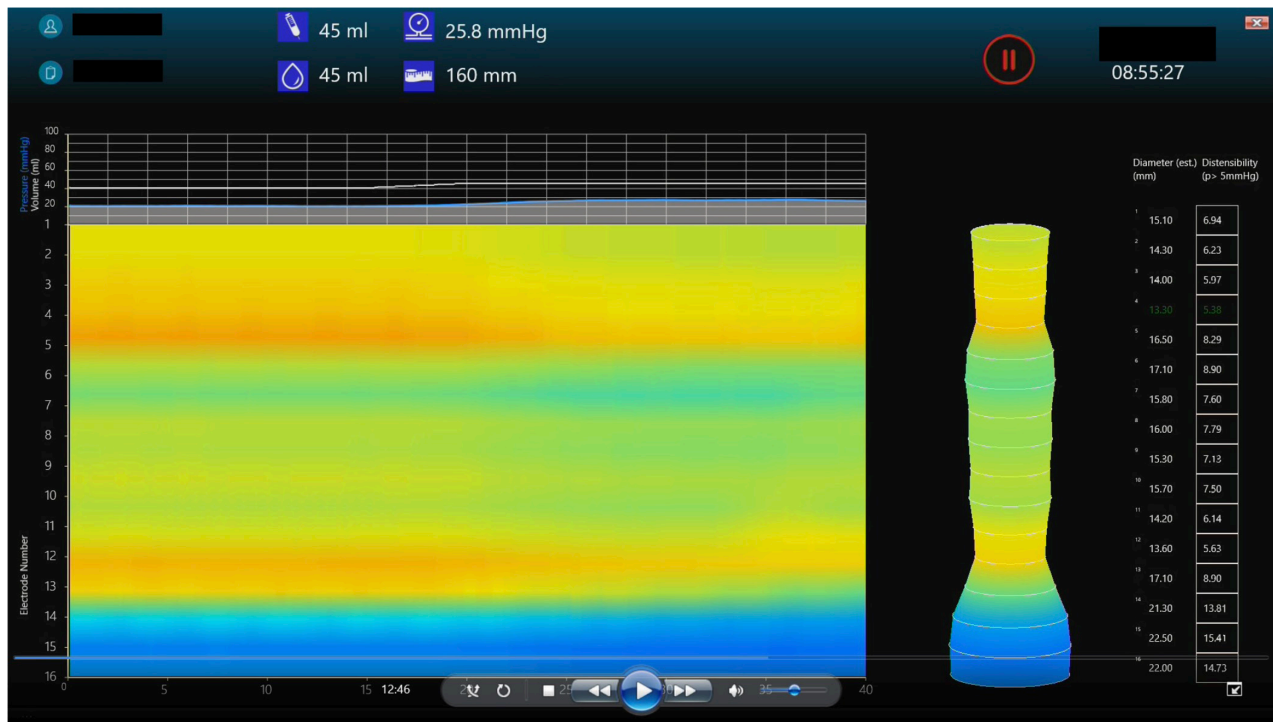


Figure 3 Endolumenal functional lumen imaging probe topography from a child with eosinophilic oesophagitis.

positive outcome while Smeets *et al*[32] reports no added therapeutic benefits.

In paediatrics, EndoFLIP has been used intra-operatively during POEM and laparoscopic myotomy to guide and assess the immediate post-procedural DI[33,34]. The authors have reported a significant improvement in DI from baseline and a successful clinical outcome. Howk *et al*[33] have reported on the use of intra-operative EndoFLIP with the balloon inflated throughout the procedure to guide the myotomy length and provide a real time feedback on DI and CSA. Their use of EndoFLIP resulted in a shorter operative time. Figure 2A is showing EndoFLIP data from a child with type 1 achalasia showing reduced LOS DI and diameter.

EoE

EoE is a chronic immune mediated and eosinophil predominant inflammation characterised by symptoms related to oesophageal dysfunction[35]. EoE is associated with many types of oesophageal motility disorders and often thought to be secondary to oesophageal remodelling and fibrosis[36,37]. Oesophageal strictures and luminal narrowing are also common in patients with EoE[38,39]. Early identification of lamina propria fibrosis is crucial in guiding therapeutic strategies and endoscopic assessment but mucosal biopsies have a poor correlation with the degree of oesophageal fibrosis[40,41]. HROM findings are not specific or sensitive to EoE motility disorders and they do not describe a characteristic pattern for EoE symptoms[42,43].

In adults, EndoFLIP can provide an accurate information in relation to oesophageal distensibility and compliance. Reduced oesophageal distensibility is reported in both children and adults with EoE and is associated with increased risk of food bolus impaction and the need for oesophageal dilatation[40,44]. Distensibility is also significantly reduced in children with active EoE compared to an age matched control and the natural increase in oesophageal distensibility normally observed with age, appeared to plateau in children with EoE[44,45]. This may represent a fibrotic remodelling or a separate EoE phenotype[44]. Figure 2B is a child with EoE and reduced diameter/distensibility.

In paediatrics, a reduced oesophageal distensibility was reported in children with EoE and high endoscopic reference score part of (EREF)[44]. In EREF, rings and strictures are considered as features of fibrosis and remodelling changes, while oedema, furrows and exudates are considered as features of inflammatory changes[46]. It is increasingly recognised that inflammatory features can progress to fibrosis and remodelling in the context of EoE and although children can predominantly present with inflammatory EoE phenotype, early fibrosis in paediatric patients is commonly described[44, 45]. Oesophageal DI, but not CSA or diameter, has a strong correlation with endoscopic fibrostenotic severity and history of food bolus impaction in paediatrics independent of age, height or oesophageal inflammation[44]. Oesophageal DI < 4.5 mm²/mmHg has been suggested as a predictor of the presence of grade II rings in children[44]. The association between EndoFLIP findings, particularly DI, and the degree of EoE inflammation in paediatric is conflicting and is in contrast to adult studies which showed no correlation between reduced DI and the degree of oesophageal inflammation[40]. This is likely to represent the small scales of paediatric studies and the difference in selection criteria.

Gastrooesophageal reflux disease

Limited data is available on the use of EndoFLIP for the assessment of patient with gastrooesophageal reflux disease (GORD) and is mostly from adult studies. In adults, there were contradicting results regarding DI of the gastroeso-

phageal junction (GOJ) in the context of GORD[47,48]. In one study, GOJ DI was reported to be higher in patients with GORD compared to controls irrespective of the presence of distal oesophagitis, but the authors did not look for the presence of hiatal hernia[47]. Hiatal hernia is an important factor that may independently affect GOJ morphological studies, although in a separate study, Lottrup *et al*[49] have reported on the usefulness of EndoFLIP in identification and assessment of hiatal hernia. In another study, the authors did not find a statistically significant difference in the measurements of GOJ DI between patients with GORD and healthy volunteers but they did acknowledge the presence of many independent confounding factors (*e.g.*, obesity)[48].

EndoFLIP can provide a useful tool in the assessment of fundoplication and can be used intraoperatively during anti-reflux surgery. Using FLIP intraoperatively can provide a real time measurement of GOJ DI and diameter, although direct clinical outcome data is lacking, proxy data appeared to support the clinical outcome associated with certain EndoFLIP values[16,50,51].

Oesophageal atresia and oesophageal strictures

EndoFLIP offers a promising tool to study the oesophageal morphology post oesophageal atresia repair. One small paediatric study has reported on the use of EndoFLIP to assess the geometry of OGJ, oesophageal body distensibility and anastomotic strictures. They have reported a DI within published normal values for the oesophageal body and the OGJ, while their data on FLIP measurements of the anastomosis site were combined with other diagnostic modalities to help guide therapeutic and prognostic directions[52]. Figure 2C is a child with repaired oesophageal atresia showed a reduced diameter at the site of anastomotic scare and a dilated oesophageal segment above.

Another retrospective paediatric study has reported on the use of EndoFLIP and the FLIP dilatation catheter EsoFLIP in assessment and management of different types of oesophageal strictures in children. They reported a potential clinical benefit of reduction in procedural time and achieving a larger diameter changes post dilatation[53]. Both studies recruited a small number of children in a retrospective manner affecting their wider applicability. With such limited data, the use of EndoFLIP in the assessment of children with repaired oesophageal atresia and/or oesophageal strictures is to be explored.

Uses of EndoFLIP in the pylorus

In contrast to LOS, the pyloric sphincter did not receive the same level of diagnostic scrutiny. Although the pylorus plays a vital role in regulating gastric emptying (GE), the association between symptom severity and measured GE remains poor[54]. In part, this can be explained by the complex role of the pylorus sphincter compared to other GI sphincters. Detailed assessment of post prandial period reported that GE occurred during the relaxation of the pylorus and was driven primarily by the pressure generated by gastric tone and content (pressure pump) rather than the effect of antral contraction wave (peristalsis pump)[55]. On the other hand, contraction of the pylorus in the face of gastric peristalsis wave will lead to bolus retention and gastric content mixing. However, the pylorus pressure measurements did not differ in patients with normal or delayed GE[54,56].

In adults, geometric assessment of the pylorus by EndoFLIP has been widely studied in patients with gastroparesis or with symptoms suggestive of gastroparesis (such as nausea and vomiting)[57-59]. Pylorus DI has been found to correlate with GE and gastroparesis symptoms, a promising finding to identify a group of patients who may respond to targeted pylorus therapy[58,59].

EndoFLIP catheter is usually inserted *per os* under direct endoscopic vision and prior to endoscopic intubation of the pylorus. The effect of anaesthesia and sedation on the EndoFLIP findings are yet to be studied. Pylorus geometric measurements are often taken after the EndoFLIP balloon is filled with a predetermined volume of 20, 30, 40 and 50 mL. Pylorus DI was significantly lower in patients with gastroparesis compared to healthy volunteers, but there was no difference in DI between diabetic gastroparesis and other forms of the disorder[19]. Early satiety and postprandial fullness were inversely correlated to pylorus CSA and diameter, this has been the only clear association between a diagnostic investigation and symptoms of gastroparesis, in contrast to other investigative modalities such as GE scintigraphy and manometry[58]. Although the authors were unable to offer a concrete explanation of this association, and the absence of correlation with any EndoFLIP parameters and other gastroparesis symptoms, it is possible that the pylorus opening diameter rather than distensibility or compliance is the driving force behind these two symptoms but further research is needed to study this hypothesis.

EndoFLIP has also been used to predict clinical response to intra pylorus Botulinum Toxin injection[60]. Patients with gastroparesis and an abnormal pylorus EndoFLIP measurements appear to show sustained symptom improvement at 3 mo compared to gastroparesis patients with normal FLIP parameters[60]. A similar clinical response was also observed post pylorus dilatation and gastric POEM guided by EndoFLIP findings in patients with therapy refractory gastroparesis[59,61].

In paediatrics, Hirsch *et al*[62] have reported in a retrospective observational study in children with nausea and vomiting that the pylorus distensibility were lower in children with delayed GE compared to the normal GE group but the differences were not statistically significant. This is likely to be secondary to small sample size and patient selection. In the same study, EndoFLIP did not predict the symptomatic response to intra pylorus Botulinum Toxin injection[62]. A likely explanation is the selection criteria for included children as 44% had normal GE and previous adult studies did not show correlation between EndoFLIP and the reported symptoms of nausea and vomiting.

We have recently published our experience in using pylorus EndoFLIP in children with neuromuscular disorders and the response to Botulinum Toxin injection[63]. In our cohort, children with symptoms suggestive of gastroparesis had abnormal EndoFLIP measurements according to both adults and previous paediatric studies. We reported good symptoms improvement, weight gain and feed tolerance after Botulinum Toxin injections, a response that had been replicated after repeat injections 6-9 mo later. We did observe a trend of improvement in EndoFLIP measurements even

though the FLIP remeasurements were obtained due to symptoms recurrence. Our sample size was small and we did not measure GE due to the comorbidities present in our studied group[63]. Figure 4 is from a child with gastroparesis showed reduced pylorus distensibility. EndoFLIP usage in the assessment of pylorus sphincter is increasing and appear to show promising diagnostic data, symptom correlation with GE and most importantly, it can identify a subset of patients who can response to targeted pylorus therapy.

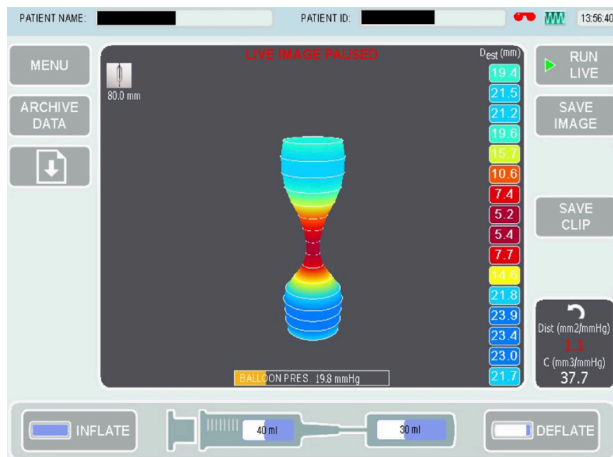


Figure 4 Endolumenal functional lumen imaging probe of the pylorus sphincter from a child with gastroparesis showing reduced pylorus distensibility.

Uses of EndoFLIP in the anal sphincter

There are very few studies reporting on the use of EndoFLIP in assessment of the geometry of the anal canal, all were from adult patient and healthy volunteers[64-66]. To date, there is no published paediatric study. Although there was a general harmony on the methods used in all published studies, there were no agreement on the relevant FLIP measurements or their applicability to clinical practice. All published studies have reported a higher anal distensibility in patients with faecal incontinence compared to healthy volunteers, however, the clinical utility of such a finding is yet to be explored.

CONCLUSION

EndoFLIP is a promising tool to further improve our ability to understand the motility function of the GI tract. By providing a detailed geometric assessment to the oesophageal lumen and various sphincters in the GI tract, EndoFLIP findings are complementary to the existing GI motility investigations, but the data does not support the use of EndoFLIP to replace standard GI motility investigations. EndoFLIP has been successfully used to aid diagnosis and to guide therapeutic interventions. EndoFLIP studies in paediatrics are lagging behind adult studies but they have replicated some of adult results. The absence of normative values for children may limit the wider uptake within paediatrics but with the increase in complexity and prevalence of paediatric GI motility disorders, EndoFLIP can provide a valuable diagnostic and prognostic data.

FOOTNOTES

Author contributions: White E wrote the draft; Mutalib M wrote and edited the manuscript; and all authors approved the final version of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United Kingdom

ORCID number: Mohamed Mutalib 0000-0001-8869-9466.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- Keller J, Bassotti G, Clarke J, Dinning P, Fox M, Grover M, Hellström PM, Ke M, Layer P, Malagelada C, Parkman HP, Scott SM, Tack J, Simren M, Törnblom H, Camilleri M; International Working Group for Disorders of Gastrointestinal Motility and Function. Expert consensus document: Advances in the diagnosis and classification of gastric and intestinal motility disorders. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 291-308 [PMID: 29622808 DOI: 10.1038/nrgastro.2018.7]
- Rao SS, Camilleri M, Hasler WL, Maurer AH, Parkman HP, Saad R, Scott MS, Simren M, Soffer E, Szarka L. Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies. *Neurogastroenterol Motil* 2011; **23**: 8-23 [PMID: 21138500 DOI: 10.1111/j.1365-2982.2010.01612.x]
- Bogte A, Bredenoord AJ, Oors J, Siersema PD, Smout AJ. Assessment of bolus transit with intraluminal impedance measurement in patients with esophageal motility disorders. *Neurogastroenterol Motil* 2015; **27**: 1446-1452 [PMID: 26284688 DOI: 10.1111/nmo.12642]
- Ponds FA, Bredenoord AJ, Kessing BF, Smout AJ. Esophagogastric junction distensibility identifies achalasia subgroup with manometrically normal esophagogastric junction relaxation. *Neurogastroenterol Motil* 2017; **29** [PMID: 27458129 DOI: 10.1111/nmo.12908]
- Carlson DA, Lin Z, Kahrilas PJ, Sternbach J, Hungness ES, Soper NJ, Balla M, Listernick Z, Tye M, Ritter K, Craft J, Ciolino JD, Pandolfino JE. High-Resolution Impedance Manometry Metrics of the Esophagogastric Junction for the Assessment of Treatment Response in Achalasia. *Am J Gastroenterol* 2016; **111**: 1702-1710 [PMID: 27698386 DOI: 10.1038/ajg.2016.442]
- Triggs JR, Carlson DA, Beveridge C, Kou W, Kahrilas PJ, Pandolfino JE. Functional Luminal Imaging Probe Panometry Identifies Achalasia-Type Esophagogastric Junction Outflow Obstruction. *Clin Gastroenterol Hepatol* 2020; **18**: 2209-2217 [PMID: 31778806 DOI: 10.1016/j.cgh.2019.11.037]
- Pandolfino JE, Shi G, Curry J, Joehl RJ, Brasseur JG, Kahrilas PJ. Esophagogastric junction distensibility: a factor contributing to sphincter incompetence. *Am J Physiol Gastrointest Liver Physiol* 2002; **282**: G1052-G1058 [PMID: 12016131 DOI: 10.1152/ajpgi.00279.2001]
- Gyawali CP, Bredenoord AJ, Conklin JL, Fox M, Pandolfino JE, Peters JH, Roman S, Staiano A, Vaezi MF. Evaluation of esophageal motor function in clinical practice. *Neurogastroenterol Motil* 2013; **25**: 99-133 [PMID: 23336590 DOI: 10.1111/nmo.12071]
- McMahon BP, Rao SS, Gregersen H, Kwiatek MA, Pandolfino JE, Drewes AM, Krarup AL, Lottrup C, Frøkjær JB. Distensibility testing of the esophagus. *Ann N Y Acad Sci* 2011; **1232**: 331-340 [PMID: 21950823 DOI: 10.1111/j.1749-6632.2011.06069.x]
- Savarino E, di Pietro M, Bredenoord AJ, Carlson DA, Clarke JO, Khan A, Vela MF, Yadlapati R, Pohl D, Pandolfino JE, Roman S, Gyawali CP. Use of the Functional Lumen Imaging Probe in Clinical Esophagology. *Am J Gastroenterol* 2020; **115**: 1786-1796 [PMID: 33156096 DOI: 10.14309/ajg.0000000000000773]
- Hirano I, Pandolfino JE, Boeckxstaens GE. Functional Lumen Imaging Probe for the Management of Esophageal Disorders: Expert Review From the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol* 2017; **15**: 325-334 [PMID: 28212976 DOI: 10.1016/j.cgh.2016.10.022]
- McMahon BP, Frøkjær JB, Liao D, Kunwald P, Drewes AM, Gregersen H. A new technique for evaluating sphincter function in visceral organs: application of the functional lumen imaging probe (FLIP) for the evaluation of the oesophago-gastric junction. *Physiol Meas* 2005; **26**: 823-836 [PMID: 16088071 DOI: 10.1088/0967-3334/26/5/019]
- Donnan EN, Pandolfino JE. EndoFLIP in the Esophagus: Assessing Sphincter Function, Wall Stiffness, and Motility to Guide Treatment. *Gastroenterol Clin North Am* 2020; **49**: 427-435 [PMID: 32718562 DOI: 10.1016/j.gtc.2020.04.002]
- Carlson DA, Gyawali CP, Khan A, Yadlapati R, Chen J, Chokshi RV, Clarke JO, Garza JM, Jain AS, Katz P, Konda V, Lynch K, Schnoll-Sussman FH, Spechler SJ, Vela MF, Prescott JE, Baumann AJ, Donnan EN, Kou W, Kahrilas PJ, Pandolfino JE. Classifying Esophageal Motility by FLIP Panometry: A Study of 722 Subjects With Manometry. *Am J Gastroenterol* 2021; **116**: 2357-2366 [PMID: 34668487 DOI: 10.14309/ajg.0000000000001532]
- Nicodème F, Hirano I, Chen J, Robinson K, Lin Z, Xiao Y, Gonsalves N, Kwasny MJ, Kahrilas PJ, Pandolfino JE. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2013; **11**: 1101-1107.e1 [PMID: 23591279 DOI: 10.1016/j.cgh.2013.03.020]
- Su B, Attar M, Wong H, Callahan ZM, Kuchta K, Stearns S, Linn JG, Denham W, Haggerty SP, Ujiki MB. Using a standardized intra-operative endoflip protocol during fundoplication to identify factors that affect distensibility. *Surg Endosc* 2021; **35**: 5717-5723 [PMID: 32970210 DOI: 10.1007/s00464-020-08034-0]
- Carlson DA, Lin Z, Kahrilas PJ, Sternbach J, Donnan EN, Friesen L, Listernick Z, Moggi B, Pandolfino JE. The Functional Lumen Imaging Probe Detects Esophageal Contractility Not Observed With Manometry in Patients With Achalasia. *Gastroenterology* 2015; **149**: 1742-1751 [PMID: 26278501 DOI: 10.1053/j.gastro.2015.08.005]
- Carlson DA, Kahrilas PJ, Ritter K, Lin Z, Pandolfino JE. Mechanisms of repetitive retrograde contractions in response to sustained esophageal distension: a study evaluating patients with postfundoplication dysphagia. *Am J Physiol Gastrointest Liver Physiol* 2018; **314**: G334-G340 [PMID: 29351396 DOI: 10.1152/ajpgi.00368.2017]
- Desprez C, Roman S, Leroi AM, Gourcerol G. The use of impedance planimetry (Endoscopic Functional Lumen Imaging Probe, EndoFLIP®) in the gastrointestinal tract: A systematic review. *Neurogastroenterol Motil* 2020; **32**: e13980 [PMID: 32856765 DOI: 10.1111/nmo.13980]
- Bredenoord AJ, Rancati F, Lin H, Schwartz N, Argov M. Normative values for esophageal functional lumen imaging probe measurements: A meta-analysis. *Neurogastroenterol Motil* 2022; **34**: e14419 [PMID: 35665566 DOI: 10.1111/nmo.14419]
- Savarino E, Bhatia S, Roman S, Sifrim D, Tack J, Thompson SK, Gyawali CP. Achalasia. *Nat Rev Dis Primers* 2022; **8**: 28 [PMID: 35513420 DOI: 10.1038/s41572-022-00356-8]
- Yadlapati R, Kahrilas PJ, Fox MR, Bredenoord AJ, Prakash Gyawali C, Roman S, Babaei A, Mittal RK, Rommel N, Savarino E, Sifrim D, Smout A, Vaezi MF, Zerbib F, Akiyama J, Bhatia S, Bor S, Carlson DA, Chen JW, Cisternas D, Cock C, Coss-Adame E, de Bortoli N, Defilippi C, Fass R, Ghoshal UC, Gonlachanvit S, Hani A, Hebbard GS, Wook Jung K, Katz P, Katzka DA, Khan A, Kohn GP, Lazarescu A,

- Lenglinier J, Mittal SK, Omari T, Park MI, Penagini R, Pohl D, Richter JE, Serra J, Sweis R, Tack J, Tatum RP, Tutuian R, Vela MF, Wong RK, Wu JC, Xiao Y, Pandolfino JE. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0(©). *Neurogastroenterol Motil* 2021; **33**: e14058 [PMID: 33373111 DOI: 10.1111/nmo.14058]
- 23 **Vaezi MF**, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. *Am J Gastroenterol* 2020; **115**: 1393-1411 [PMID: 32773454 DOI: 10.14309/ajg.0000000000000731]
- 24 **Mearin F**, Malagelada JR. Complete lower esophageal sphincter relaxation observed in some achalasia patients is functionally inadequate. *Am J Physiol Gastrointest Liver Physiol* 2000; **278**: G376-G383 [PMID: 10712256 DOI: 10.1152/ajpgi.2000.278.3.G376]
- 25 **Ghosh SK**, Kahrilas PJ, Lodhia N, Pandolfino JE. Utilizing intraluminal pressure differences to predict esophageal bolus flow dynamics. *Am J Physiol Gastrointest Liver Physiol* 2007; **293**: G1023-G1028 [PMID: 17855763 DOI: 10.1152/ajpgi.00384.2007]
- 26 **Rohof WO**, Hirsch DP, Kessing BF, Boeckxstaens GE. Efficacy of treatment for patients with achalasia depends on the distensibility of the esophagogastric junction. *Gastroenterology* 2012; **143**: 328-335 [PMID: 22562023 DOI: 10.1053/j.gastro.2012.04.048]
- 27 **Pandolfino JE**, de Ruigh A, Nicodème F, Xiao Y, Boris L, Kahrilas PJ. Distensibility of the esophagogastric junction assessed with the functional lumen imaging probe (FLIP™) in achalasia patients. *Neurogastroenterol Motil* 2013; **25**: 496-501 [PMID: 23413801 DOI: 10.1111/nmo.12097]
- 28 **Jain AS**, Carlson DA, Triggs J, Tye M, Kou W, Campagna R, Hungness E, Kim D, Kahrilas PJ, Pandolfino JE. Esophagogastric Junction Distensibility on Functional Lumen Imaging Probe Topography Predicts Treatment Response in Achalasia-Anatomy Matters! *Am J Gastroenterol* 2019; **114**: 1455-1463 [PMID: 30741739 DOI: 10.14309/ajg.0000000000000137]
- 29 **Teitelbaum EN**, Soper NJ, Pandolfino JE, Kahrilas PJ, Hirano I, Boris L, Nicodème F, Lin Z, Hungness ES. Esophagogastric junction distensibility measurements during Heller myotomy and POEM for achalasia predict postoperative symptomatic outcomes. *Surg Endosc* 2015; **29**: 522-528 [PMID: 25055891 DOI: 10.1007/s00464-014-3733-1]
- 30 **Holmstrom AL**, Campagna RJ, Carlson DA, Pandolfino JE, Soper NJ, Hungness ES, Teitelbaum EN. Comparison of preoperative, intraoperative, and follow-up functional lumen imaging probe measurements in patients undergoing myotomy for achalasia. *Gastrointest Endosc* 2021; **94**: 509-514 [PMID: 33662363 DOI: 10.1016/j.gie.2021.02.031]
- 31 **Hsing LC**, Choi K, Jung KW, Joo S, Kim N, Kim GH, Na HK, Ahn JY, Lee J, Kim DH, Choi KD, Song HJ, Lee GH, Jung HY. The Predictive Value of Intraoperative Esophageal Functional Luminal Imaging Probe Panometry in Patients With Achalasia Undergoing Peroral Endoscopic Myotomy: A Single-center Experience. *J Neurogastroenterol Motil* 2022; **28**: 474-482 [PMID: 35799241 DOI: 10.5056/jnm21186]
- 32 **Smeets FG**, Masclee AA, Keszthelyi D, Tjwa ET, Conchillo JM. Esophagogastric junction distensibility in the management of achalasia patients: relation to treatment outcome. *Neurogastroenterol Motil* 2015; **27**: 1495-1503 [PMID: 26264119 DOI: 10.1111/nmo.12651]
- 33 **Hawk AA**, Clifton MS, Garza JM, Durham MM. Impedance planimetry (EndoFLIP) assisted laparoscopic esophagomyotomy in pediatric population. *J Pediatr Surg* 2022; **57**: 1000-1004 [PMID: 35659759 DOI: 10.1016/j.jpedsurg.2022.05.004]
- 34 **Yeung F**, Wong IYH, Chung PHY, Wong KKY, Law SYK, Tam PKH. Peroral Endoscopic Myotomy with EndoFLIP and Double-Endoscope: Novel Techniques for Achalasia in Pediatric Population. *J Laparoendosc Adv Surg Tech A* 2018; **28**: 343-347 [PMID: 29215957 DOI: 10.1089/lap.2017.0268]
- 35 **Dhar A**, Haboubi HN, Attwood SE, Auth MKH, Dunn JM, Sweis R, Morris D, Epstein J, Novelli MR, Hunter H, Cordell A, Hall S, Hayat JO, Kapur K, Moore AR, Read C, Sami SS, Turner PJ, Trudgill NJ. British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. *Gut* 2022; **71**: 1459-1487 [PMID: 35606089 DOI: 10.1136/gutjnl-2022-327326]
- 36 **Chai C**, Krishnan U. Dysmotility in Eosinophilic Esophagitis. *Front Pediatr* 2022; **10**: 853754 [PMID: 35295702 DOI: 10.3389/fped.2022.853754]
- 37 **Carlson DA**, Shehata C, Gonsalves N, Hirano I, Peterson S, Prescott J, Farina DA, Schauer JM, Kou W, Kahrilas PJ, Pandolfino JE. Esophageal Dysmotility Is Associated With Disease Severity in Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol* 2022; **20**: 1719-1728.e3 [PMID: 34768010 DOI: 10.1016/j.cgh.2021.11.002]
- 38 **Hoofien A**, Dias JA, Malamisura M, Rea F, Chong S, Oudshoorn J, Nijenhuis-Hendriks D, Otte S, Papadopolou A, Romano C, Gottrand F, Miravet VV, Orel R, Oliva S, Junquera CG, Zaleski A, Urbonas V, Garcia-Puig R, Gomez MJM, Dominguez-Ortega G, Auth MK, Kori M, Ben Tov A, Kalach N, Velde SV, Furman M, Miele E, Marderfeld L, Roma E, Zevit N. Pediatric Eosinophilic Esophagitis: Results of the European Retrospective Pediatric Eosinophilic Esophagitis Registry (RetroPEER). *J Pediatr Gastroenterol Nutr* 2019; **68**: 552-558 [PMID: 30540712 DOI: 10.1097/MPG.0000000000002215]
- 39 **Cheng E**, Souza RF, Spechler SJ. Tissue remodeling in eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1175-G1187 [PMID: 23019192 DOI: 10.1152/ajpgi.00313.2012]
- 40 **Kwiatk MA**, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* 2011; **140**: 82-90 [PMID: 20858491 DOI: 10.1053/j.gastro.2010.09.037]
- 41 **Lin Z**, Kahrilas PJ, Xiao Y, Nicodème F, Gonsalves N, Hirano I, Pandolfino JE. Functional luminal imaging probe topography: an improved method for characterizing esophageal distensibility in eosinophilic esophagitis. *Therap Adv Gastroenterol* 2013; **6**: 97-107 [PMID: 23503784 DOI: 10.1177/1756283X12470017]
- 42 **Nennstiel S**, Bajbouj M, Becker V, Slotta-Huspenina J, Wagenpfeil S, Schmid RM, Schlag C. High-resolution manometry in patients with eosinophilic esophagitis under topical steroid therapy-a prospective observational study (HIMEOS-study). *Neurogastroenterol Motil* 2016; **28**: 599-607 [PMID: 26891170 DOI: 10.1111/nmo.12753]
- 43 **Visaggi P**, Ghisa M, Barberio B, Marabotto E, de Bortoli N, Savarino E. Systematic Review: esophageal motility patterns in patients with eosinophilic esophagitis. *Dig Liver Dis* 2022; **54**: 1143-1152 [PMID: 35090825 DOI: 10.1016/j.dld.2022.01.003]
- 44 **Hoffmann NV**, Keeley K, Wechsler JB. Esophageal Distensibility Defines Fibrostenotic Severity in Pediatric Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol* 2023; **21**: 1188-1197.e4 [PMID: 36122653 DOI: 10.1016/j.cgh.2022.08.044]
- 45 **Menard-Katcher C**, Benitez AJ, Pan Z, Ahmed FN, Wilkins BJ, Capocelli KE, Liacouras CA, Verma R, Spergel JM, Furuta GT, Muir AB. Influence of Age and Eosinophilic Esophagitis on Esophageal Distensibility in a Pediatric Cohort. *Am J Gastroenterol* 2017; **112**: 1466-1473 [PMID: 28508868 DOI: 10.1038/ajg.2017.131]
- 46 **Hirano I**, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut* 2013; **62**: 489-495 [PMID: 22619364 DOI: 10.1136/gutjnl-2011-301817]
- 47 **Lee JM**, Yoo IK, Kim E, Hong SP, Cho JY. The Usefulness of the Measurement of Esophagogastric Junction Distensibility by EndoFLIP in the Diagnosis of Gastroesophageal Reflux Disease. *Gut Liver* 2021; **15**: 546-552 [PMID: 33115968 DOI: 10.5009/gnl20117]

- 48 **Tucker E**, Sweis R, Anggiansah A, Wong T, Telakis E, Knowles K, Wright J, Fox M. Measurement of esophago-gastric junction cross-sectional area and distensibility by an endoluminal functional lumen imaging probe for the diagnosis of gastro-esophageal reflux disease. *Neurogastroenterol Motil* 2013; **25**: 904-910 [PMID: [23981175](#) DOI: [10.1111/nmo.12218](#)]
- 49 **Lottrup C**, McMahon BP, Ejstrup P, Ostapiuk MA, Funch-Jensen P, Drewes AM. Esophagogastric junction distensibility in hiatus hernia. *Dis Esophagus* 2016; **29**: 463-471 [PMID: [25789842](#) DOI: [10.1111/dote.12344](#)]
- 50 **Wu H**, Attaar M, Wong HJ, Campbell M, Kuchta K, Denham EW 3rd, Linn J, Ujiki MB. Impedance Planimetry (Endoflip) and Ideal Distensibility Ranges for Optimal Outcomes after Nissen and Toupet Fundoplication. *J Am Coll Surg* 2022; **235**: 420-429 [PMID: [35972160](#) DOI: [10.1097/XCS.0000000000000273](#)]
- 51 **Fanous M**, Wei W. The Outcomes of Performing Partial Fundoplication Based on Endoflip Versus Manometric Findings. *Am Surg* 2022; **88**: 908-914 [PMID: [34794325](#) DOI: [10.1177/00031348211054565](#)]
- 52 **Destro F**, Costanzo S, Durante E, Carcassola MS, Meroni M, Brunero M, Riccio A, Calcaterra V, Pelizzo G. Utility of Functional Lumen Imaging Probe in Long-Term Follow-Up of Children with Esophageal Atresia: A Single-Center Retrospective Study. *Children (Basel)* 2022; **9** [PMID: [36291362](#) DOI: [10.3390/children9101426](#)]
- 53 **Ng K**, Mogul D, Hollier J, Khashab MA. Utility of functional lumen imaging probe in esophageal measurements and dilations: a single pediatric center experience. *Surg Endosc* 2020; **34**: 1294-1299 [PMID: [31187234](#) DOI: [10.1007/s00464-019-06898-5](#)]
- 54 **Soliman H**, Gourcerol G. Targeting the pylorus in gastroparesis: From physiology to endoscopic pyloromyotomy. *Neurogastroenterol Motil* 2023; **35**: e14529 [PMID: [36594414](#) DOI: [10.1111/nmo.14529](#)]
- 55 **Wuestenberghs F**, Gourcerol G. Pyloric distensibility in health and disease. *Am J Physiol Gastrointest Liver Physiol* 2021; **321**: G133-G138 [PMID: [34160292](#) DOI: [10.1152/ajpgi.00460.2020](#)]
- 56 **Sullivan A**, Temperley L, Ruban A. Pathophysiology, Aetiology and Treatment of Gastroparesis. *Dig Dis Sci* 2020; **65**: 1615-1631 [PMID: [32350720](#) DOI: [10.1007/s10620-020-06287-2](#)]
- 57 **Snape WJ**, Lin MS, Agarwal N, Shaw RE. Evaluation of the pylorus with concurrent intraluminal pressure and EndoFLIP in patients with nausea and vomiting. *Neurogastroenterol Motil* 2016; **28**: 758-764 [PMID: [26813266](#) DOI: [10.1111/nmo.12772](#)]
- 58 **Malik Z**, Sankineni A, Parkman HP. Assessing pyloric sphincter pathophysiology using EndoFLIP in patients with gastroparesis. *Neurogastroenterol Motil* 2015; **27**: 524-531 [PMID: [25712043](#) DOI: [10.1111/nmo.12522](#)]
- 59 **Jehangir A**, Malik Z, Petrov RV, Parkman HP. EndoFLIP and Pyloric Dilation for Gastroparesis Symptoms Refractory to Pyloromyotomy/Pyloroplasty. *Dig Dis Sci* 2021; **66**: 2682-2690 [PMID: [32749636](#) DOI: [10.1007/s10620-020-06510-0](#)]
- 60 **Desprez C**, Melchior C, Wuestenberghs F, Zalar A, Jacques J, Leroi AM, Gourcerol G. Pyloric distensibility measurement predicts symptomatic response to intrapyloric botulinum toxin injection. *Gastrointest Endosc* 2019; **90**: 754-760.e1 [PMID: [31028783](#) DOI: [10.1016/j.gie.2019.04.228](#)]
- 61 **Attaar M**, Su B, Wong HJ, Kuchta K, Denham W, Haggerty S, Linn J, Ujiki MB. Significant changes in impedance planimetry (EndoFLIP™) measurements after peroral pyloromyotomy for delayed gastric emptying. *Surg Endosc* 2022; **36**: 1536-1543 [PMID: [33742274](#) DOI: [10.1007/s00464-021-08441-x](#)]
- 62 **Hirsch S**, Nurko S, Liu E, Rosen R. A prospective study of intrapyloric botulinum toxin and EndoFLIP in children with nausea and vomiting. *Neurogastroenterol Motil* 2022; **34**: e14428 [PMID: [35811408](#) DOI: [10.1111/nmo.14428](#)]
- 63 **Popescu M**, White E, Mutalib M. EndoFLIP assessment of pyloric sphincter in children: a single-center experience. *Transl Gastroenterol Hepatol* 2023; **8**: 17 [PMID: [37197257](#) DOI: [10.21037/tgh-22-58](#)]
- 64 **Desprez C**, Gourcerol G, Savoye-Collet C, Bridoux V, Duflot T, Leroi AM. Relationship between anal functional lumen imaging probe (EndoFLIP®) results and the clinical presentation of faecal incontinence. *Colorectal Dis* 2022; **24**: 1379-1389 [PMID: [35717676](#) DOI: [10.1111/codi.16225](#)]
- 65 **Alqudah MM**, Gregersen H, Drewes AM, McMahon BP. Evaluation of anal sphincter resistance and distensibility in healthy controls using EndoFLIP ©. *Neurogastroenterol Motil* 2012; **24**: e591-e599 [PMID: [23072480](#) DOI: [10.1111/nmo.12028](#)]
- 66 **Zifan A**, Sun C, Gourcerol G, Leroi AM, Mittal RK. Endoflip vs high-definition manometry in the assessment of fecal incontinence: A data-driven unsupervised comparison. *Neurogastroenterol Motil* 2018; **30**: e13462 [PMID: [30216661](#) DOI: [10.1111/nmo.13462](#)]



Role of gastrointestinal health in managing children with autism spectrum disorder

Mohammed Al-Beltagi, Nermin Kamal Saeed, Adel Salah Bediwy, Reem Elbeltagi, Rawan Alhawamdeh

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Chew KS, Malaysia;
Morais MB, Brazil

Received: July 10, 2023

Peer-review started: July 10, 2023

First decision: August 8, 2023

Revised: August 8, 2023

Accepted: August 17, 2023

Article in press: August 17, 2023

Published online: September 9, 2023



Mohammed Al-Beltagi, Pediatric Department, Faculty of Medicine, Tanta University, Algharbia, Tanta 31511, Egypt

Mohammed Al-Beltagi, Pediatrics, Univeristy Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al Habib Medical Group, Manama, Manama 26671, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Pathology Department, Salmaniya Medical Complex, Ministry of Health, Manama, Manama 12, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Pathology Department, Irish Royal College of Surgeon, Bahrain, Muharraq, Busaiteen 15503, Bahrain

Adel Salah Bediwy, Pulmonology Department, Faculty of Medicine, Tanta University, Algharbia, Tanta 31527, Egypt

Adel Salah Bediwy, Pulmonology Department, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al Habib Medical Group, Manama, Manama 26671, Bahrain

Reem Elbeltagi, Medicine, The Royal College of Surgeons in Ireland-Bahrain, Muharraq, Busiateen 15503, Bahrain

Rawan Alhawamdeh, Pediatrics Research, and Development Department, Genomics Creativity and Play Center, Manama, Manama 0000, Bahrain

Rawan Alhawamdeh, Pediatrics Research, and Development Department, SENSORYME Dubai 999041, United Arab Emirates

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Academic Editor, Chairman, Consultant Physician-Scientist, Professor, Researcher, Pediatric Department, Faculty of Medicine, Tanta University, Al Bahr Street, Algharbia, Tanta 31511, Egypt.
mbelrem@hotmail.com

Abstract

Children with autism spectrum disorders (ASD) or autism are more prone to gastrointestinal (GI) disorders than the general population. These disorders can significantly affect their health, learning, and development due to various factors such as genetics, environment, and behavior. The causes of GI disorders in children with ASD can include gut dysbiosis, immune dysfunction, food sensit-

ivities, digestive enzyme deficiencies, and sensory processing differences. Many studies suggest that numerous children with ASD experience GI problems, and effective management is crucial. Diagnosing autism is typically done through genetic, neurological, functional, and behavioral assessments and observations, while GI tests are not consistently reliable. Some GI tests may increase the risk of developing ASD or exacerbating symptoms. Addressing GI issues in individuals with ASD can improve their overall well-being, leading to better behavior, cognitive function, and educational abilities. Proper management can improve digestion, nutrient absorption, and appetite by relieving physical discomfort and pain. Alleviating GI symptoms can improve sleep patterns, increase energy levels, and contribute to a general sense of well-being, ultimately leading to a better quality of life for the individual and improved family dynamics. The primary goal of GI interventions is to improve nutritional status, reduce symptom severity, promote a balanced mood, and increase patient independence.

Key Words: Gastrointestinal disorders; Autism spectrum disorders, Children; Gut microbiota; Ketogenic diet; Gluten-free casein-free diet, Dietary management

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Children with autism spectrum disorder often experience gastrointestinal (GI) disorders that can significantly impact their health, learning, and development. Various factors, including genetics, environment, and behavior, can cause these disorders. Common causes include gut dysbiosis, immune dysfunction, food sensitivity, digestive enzyme deficiencies, and sensory processing differences. Proper management can improve well-being, cognitive function, behavior, and educational abilities. GI interventions enhance nutrition, reduce symptoms, promote balanced moods, and increase independence.

Citation: Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R, Alhawamdeh R. Role of gastrointestinal health in managing children with autism spectrum disorder. *World J Clin Pediatr* 2023; 12(4): 171-196

URL: <https://www.wjgnet.com/2219-2808/full/v12/i4/171.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i4.171>

INTRODUCTION

The prevalence of autism spectrum disorders (ASD) has increased since Leo Kanner was first illustrated in 1943 and continues to rise[1]. ASD is a neurodevelopmental disorder, which includes, in addition to autism, Asperger's disorder, and pervasive developmental disorder-not otherwise specified. Pervasive developmental disorders, which include Rett's disorder, childhood disintegrative disorder, and overactive disorder, are also related. It may overlap with attention deficit hyperactivity disorder[2]. The prevalence of ASD varies from country to country, with an average of 1% worldwide. In the United States, the incidence of ASD can be as high as 1/59 in 2014, according to the centres for disease control and prevention[3], while it can reach 1/64 in the United Kingdom[4]. The prevalence of ASD may be underestimated in some parts of the world, such as Bahrain, where it is estimated to be 1/1000, due to missed diagnoses and lack of official recordings[1]. ASD is more common in boys than girls, with a higher prevalence in non-Hispanic white children and a lower prevalence in Hispanic and African American/black children, with variability in Asian/Pacific residents[5]. Although the exact cause of ASD remains unclear, it is widely accepted that the development of this condition is influenced by a complex interplay of various factors, including genetic predisposition, biological determinants such as advanced parental age, and environmental, immunological, and psychosocial factors[6].

ASD presents in various ways and is characterized by a combination of social, cognitive, sensory, motor, and perceptual symptoms that typically emerge before age three. Children with ASD exhibit behaviors, communication patterns, social interactions, and learning styles that differ from typically developing children. They may struggle with social communication and interaction, including difficulty giving eye contact, displaying limited expressions of emotion, and showing little interest in others or playing with them. They may also have restricted interests, such as playing with the same toys in the same way repeatedly, becoming agitated over minor changes in routine, and developing an obsessive interest in specific parts of objects, the environment, or the body. Additionally, they may engage in repetitive or stereotyped behaviors, such as repeating words, phrases, or sections of videos, flapping their hands, rocking their body, or spinning in circles. Children with ASD may also experience delays in language development, movement, sensory, and cognitive or learning skills[7,8].

It has been observed that children with ASD are at a higher risk of developing medical comorbidities than the general population. These medical conditions can adversely affect their overall health, hinder their learning abilities, and worsen their autistic symptoms. Among the common medical conditions observed in patients with ASD, gastrointestinal (GI) disorders are particularly prevalent[9]. In this review, we highlight the connection between GI issues and ASD, emphasizing the importance of understanding the role of GI health in managing ASD.

Prevalence of GI disorders in children with ASD

It has been observed that patients with ASD commonly experience GI problems, with a prevalence rate between 46% and 84% in children with ASD. These problems manifest in numerous ways, including food intolerance and/or sensitivities, nausea and/or vomiting, chronic constipation, chronic diarrhea, gastroesophageal reflux and/or disease, chronic flatulence, abdominal discomfort, ulcers, inflammatory bowel disease, colitis, and/or failure to thrive. Additionally, food allergies are more prevalent in children with ASD, with a rate of 20%-25% compared to only 5%-8% in children without ASD[10]. Several factors contribute to this higher prevalence (Figure 1). It is established that genetic factors participate in both ASD and GI disorders. Specific genetic mutations and variations are detected in individuals with ASD, which may impact the development and operation of the GI system[11]. One of the primary reasons is an imbalance and microbiota and dysregulation in the gut microbiota. Children with ASD often exhibit dysbiosis, resulting in GI issues[12]. Another factor is immune system dysfunction, which some children with ASD experience. This can lead to gut inflammation and further contribute to GI problems. Food sensitivities and allergies, particularly to gluten and casein, are also more common in children with ASD. These sensitivities can trigger symptoms like abdominal pain, diarrhea, and constipation. In addition, some children with ASD may have deficiencies in digestive enzymes, which can impact the breakdown of food components. This inadequate enzyme activity can lead to malabsorption and GI disturbances[13]. It's not uncommon for children with ASD to experience GI motility issues, which can lead to problems like constipation or diarrhea. These issues can arise from various factors, including abnormal serotonin levels linked to ASD and GI dysfunction[14]. Children with ASD frequently display selective and limited eating habits, leading to unbalanced diets that lack essential nutrients. These dietary restrictions may contribute to GI issues like constipation or diarrhea[15]. Additionally, individuals with ASD often exhibit sensory processing differences, making them hypersensitive or hyposensitive to sensory stimuli. These differences may affect their perception of GI sensations, resulting in discomfort or altered responses to normal digestive processes[16]. Unfortunately, the general public, some parents, and professionals may misinterpret sudden improper behaviors due to GI discomfort from children with ASD as lousy behavior that came up from nowhere or just to avoid activity. For instance, during an activity, the child might have severe abdominal or GI pain that forces him/her to scream and move from the place. Meanwhile, the adults may interpret the child's behavior as improper and escape trial. Children with ASD are more liable to have dysautonomia and abnormal dietary metabolites. Furthermore, gut and brain communications are bidirectional through the gut-brain axis. Children with ASD often have altered gut-brain communication, leading to an impaired gut-brain axis. This can contribute to digestive issues and affect GI function[17]. Children with ASD frequently display selective and limited eating habits, leading to unbalanced diets that lack essential nutrients. Their insistence on sticking to stereotypical diets can result in inadequate fiber and fluid intake, causing GI symptoms. These dietary restrictions may also contribute to GI issues like constipation or diarrhea[15]. Certain medications can also affect bowel function, such as stimulants causing abdominal pain and beta-blockers causing constipation, diarrhea, and stomach irritation[18].

Children with ASD may experience pain and discomfort due to GI disorders, which can interfere with their learning. Children with ASD who are nonverbal may exhibit behavioral problems like posturing, self-injury, or outbursts without apparent causes due to unrecognized GI disorders, specifically reflux esophagitis and disaccharide malabsorption. However, these manifestations may be mistakenly overlooked as a behavioral problem instead of a medical condition since many children with ASD have difficulty expressing their symptoms or discomfort to their parents or physicians. Lactase deficiency, common in children with ASD and not associated with intestinal inflammation or injury, may also contribute to abdominal discomfort, pain, and obvious behavioral problems[19]. It can be challenging to diagnose GI symptoms in children with ASD due to the lack of established clinical guidelines that prioritize routine assessment of potential medical conditions or GI issues in this population. This is particularly challenging because many children with ASD are nonverbal and cannot convey pain or discomfort through language. Even those who can communicate verbally may have trouble describing subjective experiences or symptoms compared to their typically developing children. As a result, guidelines that specifically address this issue are crucial[20]. Healthcare professionals should know that children with ASD may experience GI dysfunction, mainly if they exhibit unusual postures or movements, have trouble sleeping, are intolerant to certain foods, or display aggressive or self-harming behaviors. To properly assess these issues, clinicians should gather a comprehensive GI and nutritional history covering the patient's eating habits, allergies or food sensitivities, and bowel movements in children with ASD[21].

It's essential to consider a child's sleep history when diagnosing underlying GI disorders, as they may manifest as disturbed sleeping patterns[22]. Healthcare providers should thoroughly review the child's medication, growth history, and sleep habits. Additionally, they should be able to identify vocal, sensory, or motor behaviors that may indicate the presence of pain related to GI disorders. Vocal behaviors associated with GI disorders may include throat clearing, guttural sounds, spitting up in infants, ear rubbing, habitual coughing, or difficulty swallowing. Motor behaviors related to GI disorders include seeking belly pressure, pointing behaviors, certain repetitive behaviors, abnormal neck or body posture, and aggressive or self-injurious behaviors. Studies have shown a strong correlation between aggressive behavior and underlying GI disorders[23], and more severe autistic features tend to be linked to severe GI symptoms. GI disorder symptoms are more likely associated with sleep disruptions and food intolerances. Therefore, clinicians should consider these associations when assessing and treating comorbidities and screening for constipation, diarrhea, or soiling of underwear in children with ASD with prominent rigid-compulsive symptoms[24].

If a child with ASD experiences eczema, vocal, sensory, or motor signs, aggressive or self-injurious behaviors, chronic constipation or diarrhea, or chronic spitting or vomiting, pediatricians should consider referring them for GI evaluation. It is common for children with ASD who exhibit GI symptoms to have increased intestinal permeability. One way to evaluate this is by measuring plasma zonulin level, a valuable blood marker[25]. Endoscopy can also reveal signs of allergic esophagitis, acid reflux damage, allergic changes, or evidence of inflammatory bowel disease in patients with ASD and abdominal manifestations[26]. Effective medical treatment of GI disorders may lead to improvements in

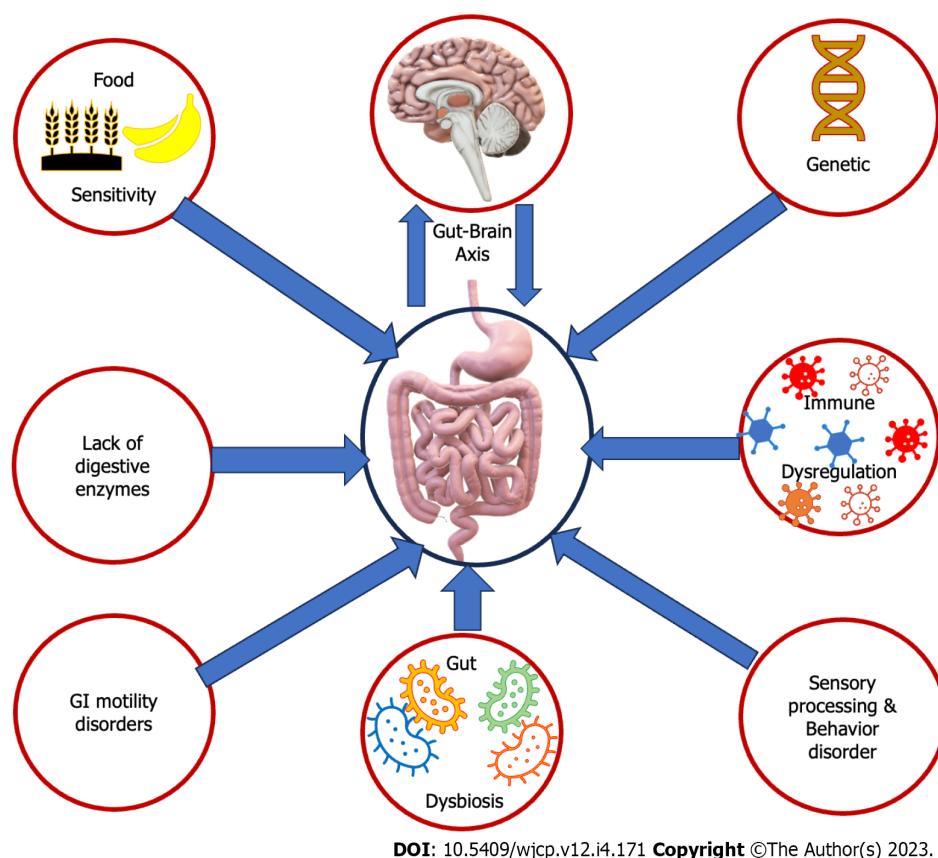


Figure 1 Increase the prevalence of gastrointestinal disorders in children with autism spectrum disorders. These factors may include genetic variations, abnormal gut-brain axis, dysbiosis, immune dysfunction, food sensitivities, digestive enzyme deficiencies, sensory processing and integration differences, dysautonomia, and abnormal behaviors. GI: Gastrointestinal.

behavioral problems. If abdominal pain or discomfort is present, psychotropic medications may not be effective and may even worsen the problem due to GI adverse effects. The microbiota-gut-brain axis is an emerging concept that suggests modulation of the gut microbiota could lead to new therapeutic modalities for different complex central nervous system disorders[27].

While studies have not found a higher prevalence of celiac disease in ASD, it's important to note that one child out of 68 with celiac disease may develop ASD, and one child out of 130 with ASD may develop celiac disease. Even without GI symptoms, those with celiac disease have been found to have a strong association with epilepsy, cerebral calcifications, and positive responses to dietary changes. Investigating and treating celiac disease, non-celiac gluten sensitivity, and epilepsy could potentially lead to positive outcomes for those with ASD, even without typical GI symptoms or overt seizures[28]. It's crucial to consider non-celiac gluten or wheat sensitivity in children with ASD, especially if they have irritable bowel symptoms and a history of atopy and allergies[29]. Medical professionals should also be aware of the possibility of non-celiac gluten sensitivity in patients with ASD who present with atopic disease, migraine, mood, and anxiety disorders. While many children with ASD have experienced positive results from a gluten-free, soy-free, and dairy-free diet, it's crucial to have a celiac test performed before attempting any dietary changes. The gluten-free diet remains the only effective treatment for those with gluten sensitivity, regardless of the manifestations. It's essential to prioritize the overall health and well-being of patients with ASD, and understanding the potential impact of diet and gluten sensitivity can lead to better outcomes[30].

Understanding the gut-brain connection in children with ASD

The idea of the “second brain” pertains to the enteric nervous system, an intricate network of neurons in the GI tract's walls. The enteric nervous system is also known as the “gut brain” or “second brain” because it can function autonomously from the central nervous system. It has its own reflexes and sensory abilities[31]. The enteric nervous system consists of millions of neurons communicating with each other and the central nervous system *via* the vagus nerve and other nerve pathways. It plays a crucial role in regulating different digestion aspects, such as food movement through the digestive tract, secretion of digestive enzymes, and absorption of nutrients[32]. The connection between the brain and gut is a complex interconnection known as the gut-brain axis. This pathway allows for two-way communication between the central nervous and GI systems. It comprises various components, including the enteric nervous system, gut microbiota, immune system, and autonomic nervous system[33]. The gut-brain axis regulates physiological processes like digestion and metabolism, influencing cognitive function, behavior, and other brain functions. Communication between the gut and brain is facilitated through various mechanisms, such as neurocrine and endocrine

pathways[34]. Within the digestive system are trillions of microorganisms collectively known as the gut microbiota. These microorganisms are vital in maintaining gut health, digestion, nutrient absorption, and immune function and significantly impact human health, including their influence on brain development and function[35]. The gut microbiota is a crucial part of the gut-brain axis and is involved in signaling from the gut microbiota to the brain. The brain, in turn, can influence the composition of gut microbiota and control it through neurotransmitters such as serotonin and dopamine, neuromuscular control of peristalsis, stress-induced cortisol, and stimulation of mucus secretion. On the other hand, the gut affects the brain through vagus nerve activation, neuropeptides, and neurotransmitters like leptin and serotonin, immune signaling through secretory immunoglobulin A, and mucous membrane barrier integrity signaling through zonulin protein and short chain fatty acids (SCFAs) like butyrate[36,37]. Additionally, the microbiota can impact the brain through various mechanisms, like the production of neurotransmitters such as gamma-aminobutyric acid, serotonin, and dopamine, the production of SCFAs like butyric acid, propionic acid, and acetic acid, stimulation of the sympathetic nervous system, and induction of mucosal serotonin release, subsequently affecting memory and learning processes in the brain[38].

Children with ASD experience numerous changes that disrupt their gut-brain axis. One significant change is an imbalance in their gut microbiota composition, known as dysbiosis. This imbalance can disrupt the gut's normal functioning, potentially contributing to the development of ASD symptoms[39]. Research has shown that children with ASD have reduced microbial diversity, overgrowth of certain harmful bacteria, and imbalances in the beneficial to pathogenic bacteria ratio compared to neurotypical individuals. These changes can impact the production of essential metabolites, neurotransmitters, neuronal sensory processing and integration, and immune signaling molecules, affecting brain development and behavior. The gut microbiota also can produce and modulate neurotransmitters, including serotonin, dopamine, and gamma-aminobutyric acid[12]. These neurotransmitters are critical in regulating mood, sensory processing and integration, behavior, and cognition. Disruptions in the gut microbiota can lead to imbalances in neurotransmitter production, potentially impacting the neurodevelopmental processes associated with ASD. Serotonin, a hormone linked to social behavior and communication, has been found to have altered levels in individuals with ASD. In addition, imbalances in gamma-aminobutyric acid levels have been linked to anxiety and behavioral issues commonly seen in children with ASD[40]. Gut dysbiosis may contribute to GI symptoms commonly observed in children with ASD, such as abdominal pain, constipation, and diarrhea[41].

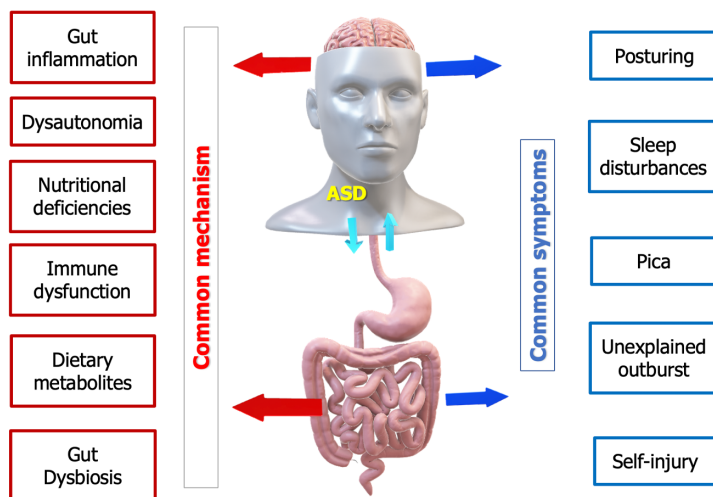
There is a link between the gut and brain in individuals with ASD that goes beyond microbial composition and neuroactive compounds. Children with ASD have been observed to experience GI inflammation and immune dysregulation, and chronic inflammation. When the immune system in the gut is activated, it can release pro-inflammatory cytokines that can communicate with the brain, causing changes in neural function[42]. Furthermore, immune dysregulation may lead to a compromised blood-brain barrier, which can allow immune cells and inflammatory molecules to enter the brain, resulting in additional effects on neurological processes[43]. Chronic inflammation in the gut can lead to a "leaky gut", which is an increased intestinal permeability. Increased gut permeability allows bacteria and their byproducts, such as lipopolysaccharides, to pass into the bloodstream, causing systemic inflammation and immune activation[44]. Such inflammation can affect the blood-brain barrier and contribute to neuroinflammation, impacting brain function and behavior and potentially contributing to the cognitive and behavioral symptoms observed in children with ASD[45]. The gut-brain connection is also influenced by metabolic and nutritional factors, which are critical components. Children with ASD often have altered metabolic profiles and frequent nutrient deficiencies. Deficiencies in vitamins, minerals, and essential fatty acids affect brain development and function. Additionally, the composition and diversity of the gut microbiota can be influenced by dietary factors, which can impact the gut-brain axis[46].

Research on the gut-brain connection in children with ASD presents new opportunities for diagnosis and treatment. By studying the composition and function of gut microbiota and examining gut permeability and immune markers, potential biomarkers for ASD diagnosis may be uncovered. Furthermore, interventions that target the gut microbiota, such as probiotics, prebiotics, and dietary adjustments, have shown promise in mitigating ASD-related symptoms and improving overall well-being[47]. To further understand the gut-brain connection in children with ASD, more comprehensive research is necessary. Longitudinal studies are required to determine whether gut dysbiosis precedes the onset of ASD symptoms or is a consequence of the disorder. Additionally, investigating the impact of early-life interventions, like breastfeeding and antibiotic exposure, on the gut microbiota and subsequent ASD risk is crucial. Technological advancements, such as metagenomics and metabolomics, will provide more comprehensive insights into the mechanisms underlying the gut-brain connection in ASD[48].

Common symptoms and common mechanisms for GI and ASD spectrum disorders

While GI disorders and ASD are distinct conditions, some overlapping symptoms and potential shared mechanisms exist (Figure 2). It's important to note that researchers are still studying these associations, and the exact nature of the relationship between GI disorders and ASD is not fully understood[20]. Some common GI symptoms include abdominal pain, diarrhea, constipation, bloating, and gastroesophageal reflux, observed in individuals with ASD and may contribute to their behavioral and sensory issues. Both GI disorders and ASD also involve sensory sensitivities, such as heightened responses to certain textures, physical pressure, movement, sounds, tastes, and smells. Additionally, many individuals with both conditions exhibit food selectivity, preferring specific foods while avoiding others, and may limit their diet due to food intolerances and/or sensitivities[49].

Common mechanisms between the two conditions include gut-brain axis disruptions, gut and systemic inflammation, altered serotonin levels, and genetic factors. For example, alterations in gut microbiota composition, intestinal permeability, and abnormal immune responses have been implicated in GI disorders and ASD[44]. Chronic low-grade inflammation in the gut may lead to systemic inflammation, which can affect brain function and contribute to cognitive, sensory processing and integration, and behavioral symptoms seen in ASD. Additionally, altered serotonin levels have



DOI: 10.5409/wjcp.v12.i4.171 Copyright ©The Author(s) 2023.

Figure 2 The mutual interaction between autism spectrum disorders and gastrointestinal disorders. ASD: Autism spectrum disorders.

been found in both conditions, suggesting a potential link between them[50]. Furthermore, GI disorders and ASD have a genetic component, and certain genetic variations may make individuals more susceptible to developing one condition when the other is present[51].

Gastroesophageal reflux

Gastroesophageal reflux is a common GI issue where stomach acid and contents flow back into the esophagus. It can affect individuals with or without ASD, but studies suggest that those with ASD may have a higher prevalence of gastroesophageal reflux[52]. The exact reasons for this are not fully understood, but possible factors include delayed gastric emptying, abnormal esophageal motility, and differences in sensory processing[20].

Individuals with ASD who suffer from gastroesophageal reflux may exhibit abnormal behaviors due to various factors. Although the link between gastroesophageal reflux and abnormal behaviors in ASD is not entirely understood, sensory sensitivities are believed to play a significant role[53]. This is because discomfort related to gastroesophageal reflux can trigger physical discomfort and pain, leading to irritability, restlessness, or agitation, which may manifest as abnormal behaviors[54]. Communication challenges may also contribute to the problem, as patients with ASD may have difficulty expressing their discomfort or pain verbally. Instead, they may use unconventional ways of communicating their distress, such as self-stimulating or challenging behaviors[55]. Individuals with ASD thrive on routines and predictability, making gastroesophageal reflux significantly disrupt their daily routines. For instance, mealtimes or feeding schedules may be affected, leading to frustration or anxiety, which can trigger changes in behavior or increased rigidity in following established patterns. Heightened anxiety and stress levels can trigger or exacerbate abnormal behaviors to cope with physical and emotional discomfort[21].

Diagnosing gastroesophageal reflux in individuals with ASD can be difficult as they may exhibit atypical or subtle symptoms. These could include irritability, behavioral changes, eating refusal, gagging, choking, or discomfort during feeding. Communication difficulties may further hinder their ability to accurately express or describe their symptoms [52]. As such, it is crucial to identify the signs of gastroesophageal reflux and seek appropriate medical attention. A healthcare professional specializing in ASD can determine the underlying cause of gastroesophageal reflux and suggest treatments like dietary adjustments, medications to reduce acid reflux, or other interventions as required[56]. Managing gastroesophageal reflux in individuals with ASD involves following standard guidelines for gastroesophageal reflux treatment. These may include making lifestyle changes such as adjusting their diet, elevating their head during sleep, managing their weight, and refraining from lying down right after eating. Depending on the severity of the condition, medications like antacids, proton pump inhibitors, or histamine-2 receptor blockers may be prescribed to reduce acid production or neutralize stomach acid[57].

Helping individuals with ASD communicate their discomfort and pain can be achieved through various methods, such as alternative communication, visual aids, or assistive technology[58]. Additionally, sensory therapy plans and integration strategies can be implemented at home to manage discomfort related to gastroesophageal reflux. This can involve activities that provide sensory input, offering comfort items like weighted blankets or fidget toys, or creating a sensory-friendly eating environment[59]. Consulting certified occupational therapists with a sensory integration specialty can be beneficial in creating specific plans to address abnormal sensory processes that contribute to behaviors associated with gastroesophageal reflux. These plans may include using sensory tools, training alternative coping skills, providing visual schedules, or employing positive reinforcement techniques[60]. Establishing routines and maintaining predictability can also help individuals with ASD manage disruptions caused by gastroesophageal reflux. Precise visual schedules and social stories can assist them in understanding and preparing for changes in their daily routine[61]. Consistent monitoring, follow-up, and open communication between caregivers, healthcare professionals, and educators are essential for effectively managing gastroesophageal reflux in individuals with ASD[62].

Abdominal pain

Individuals with ASD commonly report experiencing abdominal pain, which can have varying severities and causes, including GI and non-GI factors. To determine the underlying cause, conducting a comprehensive differential diagnosis is significantly essential. Several GI causes may affect individuals with ASD. These include gastroesophageal reflux disease, constipation, irritable bowel syndrome, food intolerances or sensitivities, and inflammatory bowel disease[5]. Gastroesophageal reflux disease is caused by stomach acid flowing back into the esophagus and can cause discomfort and irritation. Constipation can be more prevalent in individuals with ASD and may lead to abdominal pain. Irritable bowel syndrome is a functional GI disorder characterized by changes in bowel habits, bloating, and abdominal pain. Some individuals with ASD may have specific intolerances or sensitivities to certain foods, such as gluten or lactose. Inflammatory bowel disease, including crohn's disease and ulcerative colitis, involves chronic digestive tract inflammation and can cause abdominal pain[63].

Aside from GI causes, other factors can lead to abdominal pain, such as sensory sensitivities, urinary tract infections, musculoskeletal issues, anxiety and stress, and medication side effects. Individuals with ASD may experience heightened sensory responses, leading to discomfort from certain sensations like pressure on the abdomen, clothing textures, or internal sensations. Urinary tract infections, including bladder infections, can also cause abdominal pain, especially for those with difficulty expressing or communicating their symptoms[64]. Muscle strain, spasms, or other musculoskeletal problems can result in abdominal pain. Emotional factors like anxiety and stress can also have physical manifestations like abdominal pain. Furthermore, some medications used to treat ASD symptoms or other co-occurring conditions may list abdominal pain as a potential side effect[65].

Diagnosing abdominal pain in children with ASD can be challenging due to various factors. Communication and behavioral differences associated with ASD can make it difficult to assess the severity and identify the potential underlying causes of the pain. Children with ASD may have difficulty expressing their symptoms verbally or have limited communication skills[66]. Describing the location, intensity, or nature of their abdominal pain can be challenging, making it difficult for healthcare providers to assess the severity of the pain and identify potential underlying causes. They may also have heightened sensory sensitivities that can affect their perception and response to pain[67]. They may exhibit atypical reactions or engage in self-injury as a response to pain, which can complicate diagnosis. In addition, abdominal pain can present with various underlying causes, some of which may overlap with common behavioral or GI symptoms seen in ASD. Differentiating between primary GI issues and pain-related behaviors associated with ASD can be complex[68].

Diagnostic overshadowing is another problem involving correctly identifying abdominal pain in children with ASD. Healthcare providers may attribute symptoms solely to a child's ASD rather than considering other potential underlying medical conditions[69]. Abdominal pain may be overlooked or dismissed as a behavioral issue related to ASD, leading to delayed diagnosis and appropriate treatment. Furthermore, children with ASD often experience high anxiety levels and have difficulty coping with medical procedures or assessments, making it harder to conduct thorough physical examinations, laboratory tests, or imaging studies to identify the cause of abdominal pain[70]. It can be challenging for some patients with ASD to access appropriate healthcare, as they may encounter various barriers. These barriers can range from difficulties in healthcare settings to sensory overload or difficulty adapting to new environments. Unfortunately, limited access to healthcare can lead to delays in diagnosis and appropriate treatment, especially when addressing abdominal pain[71].

When children with ASD experience abdominal pain, they may express their discomfort differently. They may resort to aggression or self-injurious behaviors if they cannot effectively communicate their pain or frustration. Additionally, they may become more agitated or irritable, exhibit social withdrawal or isolation, and display changes in eating habits or disruptive behaviors during mealtimes. Chronic abdominal pain can also increase anxiety and emotional dysregulation, leading to outbursts, meltdowns, or heightened anxiety levels. Furthermore, sleep disturbances can occur, which can further exacerbate behavioral challenges and affect overall well-being and functioning[66,72].

To address these challenges, healthcare professionals may employ various strategies. One method uses visual aids, such as visual pain scales or communication boards, to help children express their pain levels and location[73]. Another approach is closely observing behavioral changes or non-verbal cues that may indicate discomfort or pain. Involving parents, caregivers, or teachers familiar with the child's behavior patterns can also provide valuable insights into changes in behavior or routines. A multidisciplinary team of pediatricians, gastroenterologists, psychologists, and occupational therapists can provide a comprehensive assessment and accurate diagnosis in complex cases[56]. It is crucial to acknowledge that every person with ASD is unique, and their medical background, sensory processing profiles, and behavioral patterns differ. Individual situations must be considered when assessing and addressing abdominal discomfort[74].

Diarrhea

Diarrhea can occur in individuals with ASD, just as it can affect anyone else. While diarrhea is not directly related to ASD, individuals with ASD may be more prone to specific GI issues, including diarrhea. Diarrhea can affect individuals with ASD for various reasons, and certain factors may increase these patients' diarrhea risk. These factors include sensory sensitivities and dietary preferences, dietary changes and restrictions, food intolerances and sensitivities, GI disorders, medications and supplements, and anxiety and stress. Pica is also a significant risk factor for diarrhea in children with ASD[49]. Pica, which is eating non-food items, is a behavior sometimes exhibited by individuals with ASD. While pica itself may not directly cause diarrhea, there are several ways by which ingesting non-food substances can increase the risk of developing GI issues, including diarrhea. These include irritation of the digestive system, blockages in the digestive tract, bacterial or parasitic infections, and nutritional imbalances. It's important to understand that pica is a complex

behavior with various underlying causes and can occur in individuals with or without ASD[75]. Chronic diarrhea could result from immune dysfunction, irritable bowel syndrome, inflammatory bowel disease, intestinal infection, food allergies, celiac disease, lactose intolerance, or excessive intake of sugary liquids such as fruit juices. In some cases, fecal encopresis due to severe chronic constipation can be misdiagnosed as chronic diarrhea[76]. However, it is essential to remember that not all individuals with ASD will experience diarrhea or have an increased risk compared to the general population. Each person is unique, and other co-occurring conditions or individual factors may also play a role[8].

Sometimes, children with ASD may display behaviors that resemble or are mistaken for diarrhea. These behaviors can be categorized into four groups: Sensory-seeking behaviors, repetitive or ritualistic behaviors, communication difficulties, and sensory sensitivities[77]. Sensory-seeking behaviors involve playing with materials that may resemble the appearance or consistency of diarrhea, such as enjoying squishing or smearing substances like playdough, mud, or other malleable materials, which may appear similar to diarrhea but are not actual fecal matter[78]. Repetitive behaviors may involve movements or actions around the diaper area that can be mistaken for diarrhea. Still, it is crucial to differentiate between purposeful behaviors and physical neuro-sensory symptoms. Children with ASD may have difficulties expressing themselves verbally, leading to unconventional means of communication that may be misinterpreted as indicating diarrhea. Lastly, sensory sensitivities can cause discomfort or aversion to certain physical sensations around the diaper area, which may be misinterpreted as diarrhea[79].

Managing diarrhea in patients with ASD requires a personalized approach that considers both general strategies for diarrhea management and specific considerations for the individual's unique needs and challenges associated with ASD. Hydration is crucial to keep the individual hydrated, and a balanced diet that includes easy-to-digest and gentle foods is key. Probiotics can help restore the natural balance of gut flora and aid digestion; medications or supplements may be necessary in some cases. Visual and social support, sensory accommodation, communication support, and personalized strategies are crucial for managing diarrhea effectively. It's essential to collaborate with healthcare professionals, clinical occupational therapists specialized and certified in sensory integration, and caregivers familiar with the individual's abilities to provide tailored strategies for managing diarrhea[80,81].

Constipation

Constipation is a common GI problem that individuals with ASD may be more susceptible to. While there is no direct link between ASD and constipation, some studies suggest that individuals with ASD are prone to experiencing constipation 3.5 times more than the general population[82]. The reasons for this are unclear, but several factors could contribute. Many individuals with ASD have sensory sensitivities, including sensitivities to certain textures or tastes of food. This may result in a limited diet lacking fiber-rich foods, leading to constipation. Some individuals with ASD may have limited food preferences or engage in selective eating patterns that exclude fruits, vegetables, and other high-fiber foods necessary for regular bowel movements[83]. Individuals with ASD may have difficulty recognizing and responding to bodily cues, such as the urge to have a bowel movement. This can lead to a delay in seeking a restroom or actively avoiding using the bathroom due to sensory sensitivities or rigid routines[84]. Some medications commonly prescribed for individuals with ASD, such as antipsychotics or certain antiepileptic drugs, can have constipation as a side effect, which can exacerbate the problem. Differences in the gut microbiome of individuals with ASD have been found in some studies, and changes in gut microbiota can influence bowel function and potentially contribute to constipation[85].

For individuals with ASD, constipation can sometimes lead to or be interpreted as abnormal behaviors. Although the precise connection between constipation and such behaviors is not yet fully understood, several factors could contribute to this association. One factor is sensory sensitivities, as many individuals with ASD are sensitive to certain sensations, and this discomfort can extend to constipation[86]. The physical discomfort and pain caused by constipation may lead to increased irritability, restlessness, or agitation, which could manifest as abnormal behaviors[87]. Communication challenges can also be a factor, as some individuals with ASD may have difficulty verbally expressing their discomfort or pain. They may instead resort to unconventional methods of communicating their distress[66]. Furthermore, individuals with ASD rely heavily on routines and predictability, and constipation can interfere with their daily routines, causing frustration or anxiety, leading to changes in behavior or increased rigidity in following established patterns[88]. Finally, constipation can cause discomfort and pain, leading to increased anxiety and stress levels in individuals with ASD, which can trigger or worsen abnormal behaviors to cope with physical and emotional distress[89].

When evaluating constipation in children with ASD, a comprehensive investigation is necessary to identify root causes and appropriate interventions. It's crucial to obtain a detailed medical history to understand the child's bowel habits, diet, fluid intake, and any previous diagnoses or treatments related to constipation. A physical examination is necessary to identify signs of constipation and any physical abnormalities that could contribute to it. A bowel movement diary can provide valuable information about bowel patterns, triggers, and dietary habits[90]. A dietary assessment is also essential to identify potential dietary factors contributing to constipation and assess the intake of fiber-rich foods, fruits, vegetables, and fluids[91]. Toileting skills should be evaluated to determine any challenges or difficulties related to recognizing the need to use the bathroom or any routines that may interfere with regular bowel movements[92]. Additional medical tests may be necessary to determine the severity of constipation or rule out underlying conditions. Collaboration with specialists may be beneficial in complex cases or if there are concerns about underlying medical conditions. An individualized management plan can be developed to address sensory sensitivities, communication challenges, or behavioral factors that may impact the child's ability to manage constipation effectively[93].

When dealing with constipation-related behaviors in individuals with ASD, it's essential to consider several approaches. Firstly, recognizing the signs of constipation and seeking medical intervention is vital. It's advisable to consult a healthcare professional experienced in ASD, as they can help identify the underlying cause of constipation and recommend appropriate treatments such as dietary modifications, fiber supplements, stool softeners, or laxatives[88]. Secondly, encouraging and facilitating effective communication can help individuals with ASD express their discomfort

and pain. Alternative communication methods, such as visual aids or assistive technology, can enhance communication and reduce frustration[58]. Thirdly, sensory strategies can help manage discomfort related to constipation. This may include providing sensory input through appropriate sensory activities, offering comfort items like weighted blankets or fidget toys, or creating a sensory-friendly bathroom environment to make bowel movements more comfortable[94]. Fourthly, collaborating with behavioral therapists or professionals experienced in working with individuals with ASD can be helpful. They can develop behavior support plans that address the specific abnormal behaviors associated with constipation. Strategies may include teaching alternative coping skills, providing visual schedules, or implementing positive reinforcement techniques[95]. Lastly, maintaining established routines and predictability as much as possible can help individuals with ASD manage the disruptions caused by constipation. Clear visual schedules and social stories can help them understand and prepare for changes in their daily routine[96].

All the previous strategies should work hand in hand with strategies aimed at relieving constipation. One effective strategy is adjusting one's diet to include fiber, fruits, vegetables, and whole grains. Individuals with sensory sensitivities may need gradual food diversification and the introduction of new textures and tastes[97]. Staying hydrated by drinking plenty of fluids, especially water, can help soften the stool and ease bowel movements[98]. Establishing a regular bathroom routine, preferably after meals, can also help develop a consistent routine for bowel movements. Regular exercise and physical activity can stimulate bowel movements and promote healthy digestion. If constipation persists and is associated with medication side effects, consulting with a healthcare professional is essential to explore potential adjustments in medication or additional treatments[99]. Regular follow-up and monitoring are crucial to assess the effectiveness of interventions and make necessary adjustments.

Coeliac disease

Coeliac disease and ASD are two distinct medical conditions that can sometimes exist simultaneously in an individual. Coeliac disease is an autoimmune condition that is triggered by consuming foods that contain gluten. It affects the small intestine, leading to inflammation and damage to the lining, which may cause various GI symptoms and nutritional deficiencies[100]. Although some studies and case reports suggest a possible link between coeliac disease and ASD, the exact nature of this connection remains unclear. Some scientists suggest that shared genetic or immune system abnormalities might contribute to some individuals' co-occurrence of these conditions[101]. However, further research is necessary to understand this association's underlying mechanisms and prevalence. Despite studies finding no higher prevalence of coeliac disease in patients with ASD, one child per 68 children with coeliac disease will develop ASD, and one child per 130 children with ASD will develop coeliac disease[9]. There is a strong association between coeliac disease, even in the absence of GI symptoms, epilepsy, and cerebral calcifications, and positive responses to dietary changes in these patients. Investigation and treatment of coeliac disease, non-coeliac gluten sensitivity (NCGS), and epilepsy, even without typical GI symptoms or overt seizures, could yield positive outcomes for patients with ASD[28].

It is essential to consider the possibility of non-coeliac gluten or wheat sensitivity in children with ASD, who are more likely to have atopy and allergies, especially if they show symptoms of irritable bowel[29]. When neurological manifestations with probable autoimmune etiology are unclear, it is recommended to determine the transglutaminase-2 autoantibody titer to consider the possibility of gluten sensitivity[102]. The relationship between coeliac disease and abnormal behavior in children with ASD is complex and not yet fully understood. Both coeliac disease and ASD share some symptoms, such as GI issues, irritability, anxiety, and sleep disturbances[103]. Consuming gluten can lead to inflammation and other immune responses that may affect behavior and cognition. Coeliac disease can also cause nutrient deficiencies, such as deficiencies in vitamins and minerals, which might contribute to abnormal behavior or exacerbate existing behavioral challenges in children with ASD[104]. While implementing a gluten-free diet in children with ASD who have coeliac disease or gluten sensitivity may improve behavior, communication, and social interaction, the evidence in this area is limited. Not all studies have shown consistent results. It's important to note that the impact of coeliac disease on behavior can vary among individuals[102].

It's worth noting that having coeliac disease doesn't necessarily mean an individual has ASD, and vice versa. These conditions can occur separately. However, if a child with ASD experiences GI symptoms or other signs that suggest coeliac disease, it's crucial to seek advice from a healthcare professional. Diagnosing coeliac disease in children with ASD follows a similar process to diagnosing coeliac disease in the general population, such as measuring tissue transglutaminase antibody test, determining HLA typing, and performing intestinal biopsies[105]. The gluten-free diet is currently the only effective treatment available and should be recommended for all patients with gluten sensitivity, regardless of the type of manifestations. Medical professionals should be aware of the possibility of NCGS in some patients with ASD, particularly those with atopic disease, migraine, mood, and anxiety disorders. Although many children with ASD improve on a gluten-free, soy-free, and dairy-free diet, it is essential to perform a celiac test before attempting this diet[106].

Impact of GI disorders on children with ASD

GI disorders can significantly impact children with ASD. GI disorders can affect all the child's life aspects; behavior, quality of life and well-being, social interaction: Communication abilities, education capabilities, and sleep patterns, and increase the risk of epilepsy. There is a strong correlation between GI symptoms and the severity of ASD, indicating that children more severely affected by ASD are likely to have severe GI symptoms. Health professionals should consider the possibility of GI dysfunction in patients with ASD, especially those presenting with strange posturing or movements, sleep disorders, food intolerances, and aggressive or self-injurious behaviors[80]. [Table 1](#) summarizes the impact of GI disorders on the various life aspects of patients with ASD.

Table 1 Impact of gastrointestinal disorders on children with autism spectrum disorders

Domain	The impact
Patient's behavior	Abnormal posturing, self-injury, sudden outbursts, social withdrawal or isolation, and changes in eating habits Self-stimulatory behaviors Toe walking, increased irritability, restlessness, and agitation Poor attention, reduced food intake, or avoidance of certain foods Poor response to psychotropic medications
Patient's social interaction	Difficult engagement in social interactions Anxiety, irritability, and withdrawal from social situations with social avoidance Decrease the ability to engage in social play, follow social cues, or maintain relationships with peers and family members Poor development of social skills
Patient's sleep	Disrupted sleep patterns Disruption of sleep-wake cycles regulation
Patient's epilepsy	Altered brain electrical activity Increased risk of epileptic tendencies Decrease epilepsy thresholds Interactions with anti-epileptic medications
Patient's education	Increase absenteeism and poor attendance Poor academic performance Poor participation Decreased ability to concentrate Poor engagement in learning activities Reduced motivation and participation in classroom activities Poor participation in group activities Poor participation in food-related activities Poor cognitive functioning
Patient's quality of life	Poor eating, sleeping, and social interactions Reduced appetite, causing poor nutrition and weight loss

Impact on the patient's behavior

GI disorders can cause pain-induced agitation and irritability in children, leading to abnormal behaviors in individuals with ASD. For instance, GI pain may be mistaken for behavioral issues like abnormal posturing, self-injury, sudden outbursts, social withdrawal or isolation, and changes in eating habits. Individuals with ASD and oesophageal ulcerations may exhibit self-stimulatory behaviors in response to the pain or discomfort they experience[79]. Additionally, gastroesophageal reflux can lead to frequent nighttime awakenings. If the patient is experiencing constipation, it can lead to a range of behavioral changes such as toe walking, increased irritability, restlessness, and agitation. The patient may also experience abnormal sleep patterns, such as difficulties falling asleep, frequent awakenings, or restless sleep, resulting in daytime irritability, fatigue, and behavioral challenges[107]. Constipation can cause poor attention, reduced food intake, or avoidance of certain foods. Additionally, toilet training problems could be caused by chronic diarrhea or constipation. If the patient with ASD frequently digs into the rectal area, it could indicate anal itching, which parasitic infestations like enterobiasis may cause. However, if the GI disorder is identified and treated with medical intervention, the behavioral problem may decrease. It's important to note that psychotropic medications may not be effective and could worsen the issue if they have adverse GI effects, especially when abdominal pain or discomfort is present[108]. Table 2 summarizes the different behavior changes associated with GI disorders in individuals with ASD.

Impact on the patient's social interaction

For individuals with ASD, GI disorders can significantly affect their social interactions. The GI disorders-related discomfort can make it difficult for individuals with ASD to engage in social interactions, leading to anxiety, irritability, or a desire to withdraw from social situations[109]. The sensory discomfort associated with GI issues, like nausea or GI

Table 2 The different behavior changes that result from various gastrointestinal disorders

GI disorder	Behavior changes
Gastroesophageal reflux with/without ulcerations	Self-stimulatory behaviors (commonly called stimming) Constant eating/drinking/swallowing (grazing behavior) Frequent nighttime awakenings, abnormal posturing, pushing out the jaw, straining the neck, and tapping the throat, increased self-injury, and other challenging behaviors
Abdominal pain	Increased anxiety levels and emotional dysregulation, leading to outbursts and meltdowns Repetitive rocking and other repetitive behaviors. Blinking, sudden screaming, spinning, and fixed look Agitation: Pacing, jumping up and down Sleep disturbances, exacerbating the behavioral challenges and affecting overall well-being and functioning
Constipation	Tip-toe walking Increased irritability, restlessness, and agitation Abnormal sleep patterns, such as difficulties falling asleep, frequent awakenings, or restless sleep Daytime irritability, poor attention, fatigue, and behavioral challenges Reduced food intake, or avoidance of certain foods Toilet training problems
Diarrhea	Social withdrawal if the child is experiencing discomfort or embarrassment due to diarrhea Increased self-stimulatory behaviors like engagement in repetitive or self-stimulatory behaviors to self-soothe, especially during the time of discomfort Toilet training problems Change appetite with changing eating patterns or food preferences

distress, can be overwhelming and make it challenging for individuals to focus on social interactions or be present in social environments. The discomfort or pain caused by GI disorders may also interfere with verbal communication or affect the individual's ability to engage in reciprocal conversation, leading to limited social interactions and potential misunderstandings[67]. In addition, GI disorders-related behavioral changes can impact social interactions by affecting their ability to engage in social play, follow social cues, or maintain relationships with peers and family members. Meanwhile, GI disorders can increase anxiety in individuals with ASD, leading to social avoidance. They may develop fear or anxiety related to social situations due to concerns about experiencing GI symptoms or being unable to manage them in public. This social avoidance can limit opportunities for social interaction and hinder the development of social skills[110].

Impact on the patient's sleep

Individuals with ASD spectrum disorder often experience disrupted sleep patterns due to GI disorders. Studies have found a higher prevalence of GI issues among those with ASD, although the exact relationship between the two is still being researched. Symptoms such as constipation, diarrhea, abdominal pain, and acid reflux can cause significant discomfort and pain, making it challenging for people with ASD to fall asleep and stay asleep[111]. Moreover, sensory sensitivities among people with ASD can exacerbate the discomfort caused by such symptoms, making relaxation and sleep difficult. As individuals with ASD rely on routines and predictability to feel secure, any disruptions caused by GI disorders can lead to increased anxiety and difficulty in transitioning to sleep[112]. Changes in diet, medication, or medical procedures can also contribute to sleep disturbances. Additionally, GI disorders can disrupt the regulation of sleep-wake cycles, affecting the production and regulation of hormones and neurotransmitters essential for sleep regulation[113]. Therefore, it is crucial to address GI issues in people with ASD to manage physical symptoms and improve overall well-being. Effective management strategies may involve dietary modifications, medication, behavioral interventions, and addressing sensory sensitivities. Pediatric gastroenterologists and ASD-specializing dietitians can collaborate to develop these strategies[114].

Impact on the patient's brain activities and epileptic tendencies

Individuals with ASD who experience GI disorders may be at risk of epileptic tendencies due to the potential influence on brain electrical activities. The gut-brain axis facilitates bidirectional communication between the gut and brain, meaning disruptions in the gut, such as inflammation, altered gut microbiota, or intestinal permeability, can impact brain function and neural electrical activities[115]. Therefore, GI disorders in individuals with ASD may contribute to dysregulation in brain electrical activities through this gut-brain connection[116].

GI disorders have the potential to cause inflammation in the gut, which in turn releases pro-inflammatory molecules that can affect the brain and lead to neuroinflammation. This neuroinflammation has been linked to various neurological conditions, including epilepsy, and can result in altered brain electrical activity and an increased likelihood of seizures [40]. Chronic inflammation in the gut may also contribute to developing or worsening epileptic tendencies. Interestingly, some individuals with ASD, epilepsy, and GI disorders may share genetic factors contributing to these conditions. Specifically, genetic variations and mutations related to GI function and neuronal excitability can increase the risk of epilepsy [117]. These shared genetic factors may influence brain electrical activities and contribute to the co-occurrence of GI disorders and epileptic tendencies in individuals with ASD [118].

Individuals with ASD who are prone to epilepsy may experience seizures triggered by GI disorders, especially when combined with sensory sensitivities. Specific triggers, including certain foods, GI pain, or changes in gut microbiota, can increase the likelihood of seizures in susceptible individuals [119]. GI discomfort or inflammation can lower the seizure threshold and cause abnormal brain electrical activities. It is crucial to consider potential interactions between medications used to treat GI disorders and those prescribed for epilepsy [120]. Some medications, such as antacids, proton pump inhibitors, or antibiotics, may affect the efficacy of antiepileptic drugs or increase the risk of adverse effects. Careful management and medication monitoring are essential to minimize potential interactions and ensure optimal treatment for both conditions [121].

It is crucial to understand how GI disorders affect brain electrical activities and epileptic tendencies in individuals with ASD to provide comprehensive care [44]. A multidisciplinary approach involving gastroenterologists, neurologists, and other healthcare professionals must address GI and neurological aspects. Treatment strategies may include dietary modifications, targeted therapies for GI disorders, antiepileptic medications, and lifestyle adjustments to manage both conditions effectively. It is important to note that while there is an association between ASD, GI disorders, and epilepsy, the exact mechanisms underlying these relationships are still being investigated [122]. The impact of GI disorders on brain electrical activities and epileptic tendencies can vary among individuals with ASD, making personalized care plans tailored to each person's unique needs and challenges essential for optimal outcomes [123].

Impact on the child's learning

For individuals with ASD, GI disorders can significantly impact their learning and education. These disorders can affect various aspects of a student's educational experience, including academic performance, attendance, participation, and overall well-being [124]. GI disorders can impact education for individuals with ASD in different ways. GI disorders often cause physical discomfort and pain, making it challenging for students to concentrate and engage in learning activities. Persistent abdominal pain, bloating, or other symptoms can distract and affect students' ability to focus on their studies [125]. GI disorders can cause fatigue and a lack of energy in individuals with ASD, reducing motivation and participation in classroom activities. This makes it difficult for students to actively engage in lessons, complete assignments, or participate in group activities. Many individuals with ASD have sensitivities/over-responsivity that extend to food textures, pressure, tastes, smells, and GI movement [126]. In the case of GI disorders, certain foods or dietary restrictions may be necessary, which can further limit food choices and cause additional stress or anxiety for the student. This can make it difficult for them to navigate school environments where food-related activities are common [127]. Severe GI symptoms may lead to increased absenteeism from school. Students with ASD who experience frequent GI distress may need to miss school days or leave early due to discomfort or medical appointments. This can result in missed instruction, reduced participation in classroom activities, and disruptions in educational progress [128]. GI disorders can contribute to behavioral changes and emotional distress in individuals with ASD. The discomfort and pain associated with GI issues can lead to increased irritability, anxiety, or even meltdowns. These behavioral and emotional challenges can disrupt the learning environment and entirely hinder the student's ability to engage in educational activities [129]. Research suggests that there may be a bidirectional relationship between GI health and cognitive functioning. GI inflammation and imbalances in gut bacteria may affect mental processes, including attention, concentration, memory, and executive functioning. Consequently, students with ASD and GI disorders may experience difficulties in sensory and information processing and integration, problem-solving, and academic achievement [130]. Some individuals with autism and GI disorders may require specific dietary modifications to manage their symptoms. These dietary restrictions may limit their food choices and require accommodations in school settings. Collaborating with school staff may be necessary to ensure meeting the student's nutritional needs while maintaining a safe and inclusive environment [131].

Collaboration is key in addressing the educational impact of GI disorders on individuals with ASD. Educators, school staff, and parents can work together to support these students by implementing various strategies. This includes maintaining open communication between all parties to comprehensively understand the student's needs and challenges [132]. It also involves creating a supportive and understanding school environment that considers the unique needs and challenges of students with ASD and GI disorders. Sensory-friendly strategies, like providing quiet spaces for breaks and accommodating sensory sensitivities related to food, can also be implemented. Developing individualized learning plans or 504 plans in collaboration with healthcare professionals and families is crucial to address the student's specific needs [133]. Providing access to appropriate healthcare interventions, such as medication management, dietary adjustments, or therapies to manage GI symptoms, is also essential. Communication and collaboration between healthcare providers and school personnel help ensure consistency in managing the student's GI issues [134].

Academic accommodations should be offered. These accommodations may include flexible schedules, extra time for assignments or tests, and access to support services like occupational therapy and clinical psychology counseling. Creating a supportive and inclusive classroom environment that promotes understanding, empathy, and tolerance for individual differences is also crucial [135]. Sensory needs can be addressed through sensory environments, breaks, or by utilizing personalized/customized sensory tools by occupational therapists-sensory integration specialists to alleviate discomfort or anxiety related to GI issues. By addressing the impact of GI disorders on education and providing

appropriate support, individuals with ASD can have a better chance of achieving their learning goals and maximizing their potential[67].

Impact on the patient's quality of life

Individuals with ASD may experience a significant decline in their quality of life due to GI disorders. These disorders, including constipation, diarrhea, acid reflux, and abdominal pain, can cause persistent physical discomfort and pain. The discomfort can be distressing and affect daily activities, such as eating, sleeping, and social interactions[136]. It can also reduce appetite, cause poor nutrition, and lead to weight loss, further affecting overall health and well-being. Many individuals with ASD have sensory sensitivities, and GI symptoms can exacerbate these sensitivities[137]. The discomfort caused by GI issues, such as bloating or stomach pain, can be overwhelming for individuals with heightened sensory sensitivity, leading to increased anxiety and challenges in daily activities. Individuals with ASD often rely on routines and predictability to feel secure and comfortable. GI disorders can disrupt daily routines, increasing stress and anxiety [67]. Changes in diet, medication regimens, or medical procedures related to managing GI issues may require adjustments to established routines, which can be challenging for individuals with ASD and impact their overall quality of life. GI symptoms can affect social interactions and participation in activities[138]. Individuals with ASD may experience embarrassment, anxiety, or discomfort due to GI issues, leading to social withdrawal or avoidance of certain situations. This can impact their ability to form and maintain relationships, participate in social events, and engage in educational or vocational settings. Living with GI disorders can affect the emotional well-being of individuals with ASD [139]. Chronic pain, discomfort, and the challenges of managing GI symptoms can increase stress, anxiety, and depression. These emotional factors can further impact the overall quality of life and make engaging in activities and enjoying daily life difficult[140].

Improving the quality of life for individuals with ASD requires addressing their GI disorders. Seeking medical evaluation and management from healthcare professionals, such as pediatric gastroenterologists, occupational therapists specializing in sensory integration, and dietitians specializing in ASD, can effectively treat GI symptoms. Treatment options may include dietary modifications, medications, behavioral interventions, and occupational therapy based on sensory integration[56]. Equally important is providing support and understanding within the individual's social environment, including family, friends, and educators. Creating a supportive and inclusive environment that accommodates the individual's needs and ensures access to appropriate healthcare and educational resources can significantly enhance their overall quality of life[141]. It is essential to recognize that each person with ASD and GI disorders is unique, and the impact on their quality of life may vary. Therefore, a personalized approach that considers the individual's specific needs, challenges, and strengths is essential for promoting their well-being and enhancing their overall quality of life[142].

GI tract as a key for the diagnosis and evaluation of ASD

There is no definitive way to diagnose ASD based on examining the GI tract. Healthcare professionals, like psychiatrists, psychologists, and developmental pediatricians, primarily rely on behavioral assessments and observations to diagnose ASD. These assessments evaluate a person's social interactions, communication skills, and repetitive or restricted behaviors[143]. Although some have claimed that specific tests, such as stool analysis or measurements of specific gut bacteria, could help diagnose ASD, no consistent scientific evidence supports these claims[144]. Therefore, these tests are not regarded as reliable diagnostic tools for ASD. However, specific GI tests may lead to a higher likelihood of developing ASD or experiencing more severe symptoms of ASD.

Gut microbiota print

Research suggests that changes to a child's intestinal microbiota during their early years can impact their emotional and cognitive development later on. Specifically, certain species of bacteria found in the gut microbiota (or the absence of others) may play a significant role in the development of ASD[145,146]. Jendraszak *et al*[147] showed that children with ASD have a distinct fecal microbiota pattern different from the neurotypically developed children with lower *Bifidobacterium* spp. Kang *et al*[148] conducted a study comparing the bacterial composition in fecal samples from 19 children with ASD who had varying GI symptoms and 20 neurotypical controls with minimal GI symptoms. They used high-throughput sequencing of the 16S rDNA gene. The study found that the presence of autistic symptoms, rather than the severity of GI symptoms, was associated with lower levels of the bacterial genera *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae*. Furthermore, in their research, Adam *et al*[149] discovered a significant correlation between the severity of ASD and GI symptoms. This suggests that children with more severe ASD are more prone to experiencing intense GI symptoms and vice versa. It is also possible that underlying GI issues could contribute to the severity of ASD symptoms. However, it is regrettable that two recent meta-analyses have revealed inconsistent outcomes in investigating the intestinal microbiota of children with ASD through cohort studies[150,151].

A study by Wu *et al*[152] aimed to confirm previous research on the gut microbiome's association with ASD. They utilized machine learning techniques to identify potential biomarkers for ASD through feature selection and classification evaluation in training, validation, and independent diagnosis cohorts. The results revealed that *Prevotella*, *Roseburia*, *Ruminococcus*, *Megasphaera*, and *Streptococcus* could be potential biomarkers for ASD. *Prevotella* showed significant differences between patients with ASD and typical neuro-developers. Qureshi *et al*[153] investigated the differences in gut microbial metabolites between children with ASD and GI disorders and typically developing children without GI disorders. They also examined the effects of gut microbiota transfer therapy (MTT) on the fecal metabolites of the group with ASD. Using machine learning, they created 5-metabolite fecal models for classification, which showed significant changes before and after gut MTT. The developed multivariate metabolite models can potentially categorize children

with ASD from typically developed children effectively. These machine-learning models can also diagnose children with ASD by comparing their gut microbiome data with subjects with and without ASD. However, these findings did not align with the prediction model established by Zhai *et al*[154]. Various factors, such as environmental conditions and calculation methods, may influence intestinal microbiota composition. Additionally, the quality control of sequencing data may also affect the prediction model's accuracy[155]. Further studies are necessary to explore the gut microbiome's characteristics in ASD, particularly regarding interventions.

Alterations in gut permeability

Research has found that patients with ASD often experience changes in the integrity of their intestinal barrier. In one study, 75% of patients with ASD showed a reduction in the expression of "tight junction" components that form the barrier in the intestine[156]. Zonulin is a protein that regulates the tight junctions between enterocytes and controls how permeable the intestines are. In patients with ASD, the zonulin levels were higher than in healthy controls, which was associated with the severity of ASD symptoms[157]. This suggests that zonulin could be a valuable biomarker for a subgroup of children with ASD who have GI issues related to changes in intestinal integrity. Still, not all studies have confirmed this[158].

GI Tract as a key component in the management of ASD

Effectively managing GI disorders in patients with ASD can significantly benefit their overall well-being, improving their quality of life, better behavior, cognitive function, and educational abilities[159]. Addressing underlying GI issues such as chronic constipation, diarrhea, or gastroesophageal reflux can help alleviate physical discomfort and pain experienced by individuals with ASD. This can, in turn, lead to better digestion, enhanced nutrient absorption, and improved appetite. Properly addressing GI problems can also positively impact mood, attention, irritability, and hyperactivity, potentially reducing challenging behaviors[20]. As individuals with ASD often face communication and social interaction challenges, relieving GI symptoms can improve comfort, reduce distress, and better regulate their sensory systems, creating a more favorable environment for communication and social engagement[21]. Promoting a balanced gut microbiota may also positively affect brain function and cognition in individuals with ASD[160]. Relief from GI symptoms can improve sleep patterns, increase energy levels, and contribute to a general sense of well-being, ultimately leading to a better quality of life for the individual and improved family dynamics[161]. Therefore, the main aim of GI interventions is not to treat ASD but to improve nutritional status, reduce concomitant symptoms, ensure a balanced mood with decreasing anxiety, impulse control, aggression, and stereotypy, and increase the patient's independence.

Dietary intervention: Treating ASD through dietary interventions has garnered attention and research, although there is limited and contentious scientific evidence to support their effectiveness. It is crucial to recognize that ASD is a multifaceted neurological condition with diverse symptoms and underlying causes, and there is no universally applicable treatment. Nonetheless, specific dietary interventions have been studied in the context of ASD. Many individuals with ASD turn to nutritional interventions, with or without clinical supervision, to help alleviate GI and behavioral symptoms [162]. Different types of dietary interventions can be used for ASD, grouped into four main categories: elimination dietary therapy [e.g., gluten-/casein-free diet, oligoantigenic diet, and specific carbohydrate diet (SCD)], modification dietary therapy (e.g., modified ketogenic diet), supplementation dietary therapy (e.g., minerals, vitamins like Vitamin B6, high dose Vitamin B12, and Vitamin D, antioxidants/polyphenolic compounds, omega 3, omega 6, and camel milk), and exclusion dietary therapy (e.g., excluding food additives)[163]. Although there is significant interest in nutritional interventions for individuals with ASD, there is currently no consensus on the optimal dietary approach to pursue[164]. A meta-analysis conducted by Yu *et al*[165] has revealed that implementing specific dietary therapies can effectively improve the core symptoms associated with ASD. Adopting a gluten-free diet has been shown to impact social behaviors positively. Despite the promising outcomes, it is essential to note that the small sample size of randomized controlled trials currently limits the effectiveness of dietary therapy for ASD. Therefore, further well-designed and high-quality clinical trials are required to validate these conclusions.

Gluten-free casein-free (GFCF) diet

Eliminating gluten and casein from the diet is a commonly discussed approach for managing ASD. These proteins are found in wheat, other grains, and dairy products. The belief is that they may exacerbate ASD symptoms in certain individuals. It has been observed that children with ASD may have a sensitivity or intolerance to gluten and casein and may exhibit elevated levels of antibodies against certain substances, namely anti-gliadin, anti-casein, and dipeptidyl peptidase 4-a digestive enzyme that plays a crucial role in the breakdown of gliadin into various peptides including gliadinomorphin-7 which has "opioid activity", able to increase gut membrane permeability, stimulate opioid receptors, and decrease social interaction observed in children with ASD. Gluten also induces a state of systemic inflammation, including neuroinflammation[166,167]. It should be noted that among individuals with ASD, some may also have celiac disease or non-celiac gluten sensitivity. A double-blind, randomized controlled study by Hyman *et al*[168] involved 14 children between the ages of 3 and 5 with ASD. These children were put on a GFCF diet, and after 6 wk, they were given "dietary challenges" in the form of weekly snacks containing either gluten, casein, gluten plus casein, or neither. The children were monitored for an additional three months after three months of challenges. The study's findings indicate that the dietary challenges did not significantly affect the children's sleep quality, hyperactivity, or ASD behaviors. According to a systematic review conducted by Piwowarczyk *et al*[169], there is little evidence to support the effectiveness of a GFCF diet in alleviating symptoms of ASD in children. A recent meta-analysis by Quan *et al*[170] suggests that a GFCF diet may effectively reduce stereotypical behaviors and improve cognition in children with ASD. Despite most studies being single-blind, the potential benefits of a GFCF diet are encouraging. There is a need for further studies

on a larger scale to confirm these findings.

SCD

A SCD is a dietary approach that limits the intake of complex carbohydrates and specific sugars such as grains, starchy vegetables, lactose, and most processed sugars that are difficult to digest and may negatively affect gut health. On the other side, it allows the intake of specific types of carbohydrates that are believed to be easier to digest, such as monosaccharides and certain disaccharides. It is commonly used to manage conditions such as inflammatory bowel disease and celiac disease. This diet is believed to improve gut health, reduce inflammation, and potentially alleviate some ASD symptoms associated with gut-related issues[171,172]. Although some anecdotes exist on individuals with ASD experiencing better behavior, digestion, and overall well-being through the SCD, scientific research on its effectiveness for ASD is limited. Most studies have been hindered by limitations such as small sample sizes, absence of control groups, and variations in study design, making it difficult to arrive at definite conclusions regarding its efficacy. Therefore, it is crucial to approach SCD for ASD with caution and under the guidance of healthcare professionals[173,174].

Ketogenic diet

The ketogenic diet is a high-fat, low-carbohydrate, and adequate-protein diet that has gained attention for its potential therapeutic effects in various neurological conditions, including epilepsy. The ketogenic diet aims to shift the body's metabolism into ketosis, which primarily relies on fat for energy instead of carbohydrates. This metabolic state is likely to affect brain function and neurotransmitter activity, which may have implications for individuals with neurological conditions[175]. There are some physicians and families who have looked into using the ketogenic diet as a way to improve symptoms of ASD. Research suggests that the ketogenic diet can positively affect children with ASD by improving energy metabolism, reducing oxidative stress, controlling neurotransmitters, inhibiting the mammalian target of the rapamycin signaling pathway, and modulating the gut microbiota. These neuroprotective benefits demonstrate the ketogenic diet's potential as a helpful intervention for children with ASD[176]. The effectiveness of the ketogenic diet in addressing ASD symptoms is highly individualized and varies greatly depending on the child and their family's unique situation[177].

Although there have been some reports of anecdotal evidence showing improvement in behavior, communication, and social interaction, there has not been much research done on the effects of this diet on ASD. It's worth mentioning that while the ketogenic diet has shown some promise as a treatment for ASD, the scientific evidence is limited and inconclusive due to small sample sizes and a lack of control groups in most studies[178]. This makes it difficult to draw definitive conclusions about its effectiveness. Additionally, the ketogenic diet is highly specialized and restrictive, requiring close monitoring and supervision from healthcare professionals such as registered dietitians or physicians specializing in ketogenic diets. It can be challenging to implement and maintain, and there are potential risks and nutritional concerns, particularly for growing children[179]. When considering using the ketogenic diet for managing ASD, monitoring and providing proper guidance is essential. This includes assessing the need for dietary modifications, monitoring nutritional adequacy, and ensuring overall health and well-being[180].

Camel milk therapy

Camel milk is a nutritious and healthy alternative to cow's milk. It contains essential vitamins, minerals, and immunoglobulins, providing hypoallergenic, antioxidant, antibacterial, and antiviral properties. Moreover, it is easier to digest than milk from other ruminants making it more appealing to a broader range of consumers[181]. Recently, there has been growing interest in using camel milk as a possible aid for ASD. Camel milk advocates believe that it possesses distinct properties that could benefit individuals with ASD. Both research and personal accounts have suggested that camel milk may contain certain properties that could benefit those with ASD. These include lower lactose levels, unique protein structures, higher levels of vitamins and minerals, possible immune-regulating effects, and the ability to reduce oxidant stress[182,183]. Many people with ASD and their families have reported experiencing better behavior, digestion, and overall health after incorporating camel milk into their diet. According to the research conducted by Al-Ayadhi *et al*[184], the consumption of camel milk for a period of two weeks has been found to enhance the Childhood Autism Rating Scale (CARS), Social Responsiveness Scale (SRS), and ASD treatment evaluation checklist in children with ASD, as compared to those who consumed a placebo. According to a meta-analysis conducted by Kandeel and El-Deeb[185], the use of raw and boiled camel milk in treating ASD led to significantly lower CARS scores compared to the use of a placebo. The use of camel milk may be limited due to its comparatively high cost and short shelf-life. When it comes to discussing the potential benefits of camel milk for ASD symptoms, it's crucial to be cautious. The current research in this field is insufficient and frequently relies on small-scale studies with methodological constraints[186]. To ascertain the actual impact of camel milk on ASD symptoms, we require more rigorous and controlled studies.

High-dose Methylcobalamin (Vitamin B12) therapy

Methylcobalamin, or Vitamin B12, is a crucial nutrient that occurs naturally in the body. It is vital in various biochemical processes, including DNA synthesis and maintaining the nervous system[187,188]. Recent studies have examined the potential use of high-dose Methylcobalamin therapy to help individuals with ASD. Supporters of this therapy claim that it can enhance language and communication skills, behavior, attention, and overall well-being. They suggest it may have neuroprotective and neurotrophic effects, influencing brain function and behavior in people with ASD[189-191]. Research has shown that methylcobalamin may affect the redox status and potentially improve the clinical symptoms associated with ASD[192]. Some individuals with ASD may also have metabolic or genetic issues that could impact their vitamin B12 levels or metabolism[193]. Therefore, they can get benefit from methylcobalamin therapy.

A study by Čorejová *et al*[194] found that a 200-d treatment with 500 µg methylcobalamin orally daily gradually improved the clinical and psychological condition of children and adults with ASD. The social domain showed the most significant improvement, followed by cognitive, behavioral, and communication characteristics. The study also established a strong correlation between the changes in the clinical and psychological status and the level of reduced glutathione and reduced/oxidized glutathione ratio. According to a meta-analysis conducted by Rossignol and Frye [195], administering subcutaneous injections of methylcobalamin Vitamin B12 (64.5-75 µg/kg/dose two-to-three times weekly) can effectively improve metabolic abnormalities and clinical symptoms of ASD. These symptoms include expressive communication, personal and domestic daily living skills, interpersonal, play-leisure, and coping social skills, as well as sleep disorders, GI symptoms, hyperactivity, tantrums, nonverbal intellectual quotient, vision, eye contact, echolalia, stereotypy, anemia, and nocturnal enuresis. However, it should be noted that some patients may experience mild non-serious side effects such as hyperactivity, irritability, trouble sleeping, aggression, and worsening behaviors [195]. However, there are limitations to these studies, such as small sample sizes, lack of control groups, and variations in study design, making it difficult to determine the effectiveness of Methylcobalamin therapy for ASD.

Omega-3 supplement

Omega-3 fatty acids are vital polyunsaturated fats crucial to brain function and development. They are commonly found in fatty fish like salmon, mackerel, and sardines, as well as in some plant-based sources such as flaxseeds and walnuts [196]. Studies suggest that omega-3 fatty acids have anti-inflammatory and neuroprotective properties, which may support cognitive and behavioral processes, brain health, and development[197]. Although researchers have shown interest in exploring the potential benefits of omega-3 fatty acids, specifically eicosapentaenoic acid and docosahexaenoic acid, as a dietary intervention for ASD, the scientific evidence in this area is still limited and inconclusive[198]. Some studies indicate that omega-3 fatty acid supplementation may help address deficiencies associated with certain omega-3 fatty acids in the blood of some individuals with ASD, potentially improving ASD symptoms[199]. According to a meta-analysis conducted by Cheng *et al*[200], it has been found that omega-3 fatty acid supplementation may have positive effects on hyperactivity, lethargy, and stereotypy in individuals with ASD. However, the results of studies investigating the effects of omega-3 fatty acid supplementation in individuals with ASD have been mixed, and more extensive, well-controlled studies are needed to establish the efficacy and optimal dosing of omega-3 fatty acids for ASD[201]. Although omega-3 fatty acids may have potential benefits, they should be considered as part of a comprehensive treatment plan for ASD that includes a range of evidence-based interventions, therapies, educational strategies, and support services tailored to the specific needs of each person with ASD[199].

Other nutritional supplements

Studies have been conducted to investigate the effects of dietary supplements like vitamin B6, selenium, and magnesium on patients with ASD. Vitamin B6, a water-soluble vitamin, is crucial in various physiological processes, such as synthesizing brain function compounds and metabolizing neurotransmitters and amino acids[202]. Vitamin B6 supplementation has been explored as a potential treatment for ASD, but the scientific evidence supporting its effectiveness is limited and inconclusive. The interest in vitamin B6 for ASD stems from its involvement in the metabolism of neurotransmitters like dopamine and serotonin, which play a crucial role in brain function and behavior[203,204]. Some studies have examined the effects of vitamin B6 and magnesium supplementation, known as the “B6-Mg protocol”, on individuals with ASD. While some studies have reported improvements in certain behaviors like social interaction, communication, and sensory issues, others have shown no significant effects. Study results may be due to differences in study design, participant characteristics, and outcome measures[205]. When discussing dietary interventions for ASD, it is crucial to exercise prudence and consider the unique needs, preferences, and circumstances of each individual with ASD. A holistic treatment approach for ASD typically comprises a blend of therapies, educational interventions, support services, and customized strategies tailored to the specific requirements of the individual[206].

Oral antifungal gut decontamination: There has been research into the possibility of fungi overgrowth in the GI tract contributing to ASD. Some scientists and medical professionals believe that excessive growth of fungi in the gut (gut dysfungemia hypothesis) may affect the behaviors and symptoms associated with ASD. The toxins released by an overgrowth of *Candida* species, a type of fungi, can enter the bloodstream and impact the brain, potentially leading to ASD symptoms. However, it is essential to remember that there is currently limited and inconclusive scientific evidence to support this theory[207]. Baker and Shaw[208] tested this theory by treating a child with symptomatic ASD. They found heavy GI fungal colonization with *Aspergillus*. They used the antifungal probiotic *Saccharomyces boulardii*, followed by increasing doses of itraconazole for strong antifungal therapy. The child experienced complete recovery from all ASD symptoms and even developed excellent academic, athletic, and musical skills. The recovery was accompanied by a significant reduction in urine markers of *Aspergillus* colonization, supporting the theory[208]. In a systematic review conducted by Herman and Herman[209], it was found that there were no significant differences between patients with and without antifungal medication. Therefore, it cannot be confirmed that *Candida* overgrowth is linked to ASD in children or causes ASD. Additionally, their findings do not entirely support the theory that *Candida* overgrowth is associated with GI issues and impacts ASD-related behavioral symptoms. Although there have been reports of changes in gut fungal composition among individuals with ASD, such as higher levels of *Candida* species, the link between increased gut candidiasis and ASD has not been definitively established. Small sample sizes, methodological issues, and inconsistent results often limit these studies.

Modification of gut microbiota: Researchers interested in managing ASD have given a growing interest in microbiota-based interventions, which involve modifying the gut microbiota. The gut microbiota is a diverse community of microor-

ganisms that reside in the GI tract and play a crucial role in various aspects of health, including immune function, metabolism, and brain development[210]. Research studies have revealed that people with ASD may have different gut microbiota compared to those without the condition. This has prompted researchers to explore whether gut microbiota plays a role in developing and expressing ASD symptoms. The goal is to improve ASD-related symptoms by adjusting the gut microbiota to a healthier composition[47]. There are different approaches to modifying the gut microbiota, including: Antibiotics and dietary interventions, probiotic and prebiotic interventions, and fecal microbiota transplant (FMT) therapy.

Antibiotics and dietary interventions

There is a conflicting opinion regarding the beneficial use of antibiotics in restoring gut dysbiosis and reducing GI and behavioral symptoms in children with ASD. However, there are still ongoing debates surrounding the use of antibiotics. Antibiotics eliminate harmful and beneficial bacteria in patients with ASD, which may increase the likelihood of GI illnesses in affected children. As a result, antibiotic therapy may not be the most effective approach for restoring gut microbiota balance[211]. Studies have demonstrated that a Mediterranean diet can improve GI health, cardiovascular diseases, and neurobehavioral health outcomes[212]. The effectiveness of a ketogenic diet has also been explored, with positive results in mitigating neurobehavioral symptoms[213]. The gluten-free and GFCF diet is another popular approach, with some studies showing favorable results in improving symptoms such as communication, social interaction, and GI issues[214]. However, recent studies have shown that restrictive diets can potentially have harmful effects, resulting in nutrient deficiencies and high costs for families. The standard of dietary intervention is also strict and may not apply to all ASD patients[215].

Probiotic and prebiotic interventions

Probiotics are microorganisms that can provide health benefits when taken in sufficient quantities. There have been studies on using specific probiotic strains to balance gut bacteria and potentially improve symptoms in people with ASD [216]. However, the evidence for the effectiveness of probiotics in treating ASD is limited and inconsistent[217]. Prebiotics are non-digestible fibers that can promote the growth of healthy gut bacteria. By consuming prebiotics, the gut microbiota can become more balanced[218]. Some studies have looked into the effects of prebiotic supplements on individuals with ASD, but further research is required to determine the impact on ASD symptoms[219]. As the gut-brain axis has two-way communication, probiotic intervention may decrease the prevalence of ASD by affecting related gene expression in infants. However, the specificity of the gut microbiota in different patients suggests the need for precision medicine tailored to specific subpopulations of patients[220].

According to Sanctuary *et al*[221] pilot study, the intake of *Bifidobacterium infantis* probiotic and a bovine colostrum product for five weeks was well-tolerated and effectively lowered the occurrence of specific GI symptoms. Additionally, it reduced the occurrence of certain abnormal behaviors. Furthermore, a study by Kong *et al*[222] found that using a combination of *Lactobacillus plantarum* PS128 probiotic for 28 wk and oxytocin for 12 wk resulted in significant improvement in the SRS, aberrant behavior checklist, and clinical global impression scale. The combination also led to the growth of favorable gut microbiome network hubs. The study also revealed that the effectiveness of the combination treatment in enhancing social cognition is highly linked to the abundance of the *Eubacterium hallii* group.

FMT therapy

A potential solution for gut dysbiosis in children with ASD is a FMT. This procedure transfers fecal microbiota from healthy donors into an individual's GI tract to balance their gut microbiota. FMT has shown promising results in treating certain GI conditions and can improve GI and neurobehavioral symptoms in younger children with ASD[223]. However, it may only work for some older patients. Despite its benefits, FMT can cause adverse reactions in some patients, so a modified protocol called MTT was developed. MTT involves oral vancomycin treatment, bowel cleansing, and oral or rectal administration of standardized human gut microbiota[224]. Studies have shown that MTT can improve behavioral symptoms and increase the diversity of gut bacteria in children with ASD. The effects of MTT can last for at least two years after treatment. These results suggest that overall gut microbe rebalancing may be a promising approach to treating gut microbiota dysbiosis in ASD[47]. However, FMT use in ASD is still in its early stages and requires further research to establish its safety and efficacy.

When seeking interventions for individuals with ASD, it is essential to remember that while microbiota-based treatments show promise, they are still a developing field. Further research is necessary to determine their effectiveness, optimal protocols, and long-term effects on those with ASD[225]. Healthcare professionals with expertise in this field are recommended to oversee these interventions. Additionally, a comprehensive approach that includes evidence-based therapies, educational interventions, support services, and individualized strategies tailored to the specific needs of each person with ASD should be considered. Modifying the gut microbiota should be viewed as a component of a more extensive treatment plan, and healthcare professionals should be consulted when deciding on specific interventions[226].

Limitations of the study

It's important to remember that there are some limitations to the article's findings regarding the association between GI health and ASD symptoms. While the article suggests a potential link, it cannot definitively establish a causal relationship. It's worth noting that many of the studies included in the review relied on observational data or retrospective analysis, which may introduce biases and confounding factors that can impact the results. Additionally, some of the studies were limited by small sample sizes or specific populations, making it difficult to generalize the

findings. To better understand the relationship between these factors, we need more large-scale studies with strong controls to minimize potential biases and confounding factors.

CONCLUSION

This review article delves into the extensive research on the connection between GI health and ASD. We have summarized the key findings from the literature, highlighted areas of agreement and disagreement, and examined the implications of these outcomes for future research. Children with ASD are more susceptible to GI disorders than the general population, which can significantly impact their health, learning, and development due to genetic, environmental, and behavioral factors. GI disorders can arise from gut dysbiosis, immune dysfunction, food sensitivities, digestive enzyme deficiencies, and sensory processing and integration differences. Current research suggests that numerous children with ASD experience GI disorders, and effective management is critical. Behavioral assessments and observations are the preferred methods for diagnosing ASD, and GI tests are not consistently supported by scientific evidence for reliable diagnostic tools. However, certain GI tests may increase the risk of developing ASD or experiencing more severe symptoms. Addressing GI problems in individuals with ASD can improve their overall well-being, leading to better behavior, cognitive function, and learning abilities. Properly addressing GI issues can relieve physical discomfort and pain, promoting better digestion, enhanced nutrient absorption, and improved appetite. Alleviating GI symptoms can improve sleep patterns, increase energy levels, and contribute to a general sense of well-being, ultimately leading to a better quality of life for the individual and improved family dynamics. The primary objective of GI interventions is to improve nutritional status, reduce symptom severity, promote a balanced mood, and increase patient independence.

Recommendation

It is essential to support research on GI disorders' causes, mechanisms, and treatments in children with ASD. Healthcare professionals should receive training on diagnosing and treating such conditions and implementing evidence-based interventions. Effective management of GI problems can be achieved through medical team intervention and management, occupational therapy based on sensory integration in all settings the child uses, communication, and behavior support plans. Early identification and treatment of these disorders can improve overall well-being and prevent long-term complications. A multi-transdisciplinary approach is often necessary to provide comprehensive care.

ACKNOWLEDGEMENTS

We thank the anonymous referees for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M developed the idea and wrote the manuscript; Saeed NK wrote the microbiological parts of the manuscript; Elbeltagi R wrote the dietary part of the manuscript; Bediwy AS collected the scientific articles; Alhawamdeh R revised the psychological aspects of the manuscript; All the authors revised the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Bahrain

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207; Adel Salah Bediwy 0000-0002-0281-0010; Reem Elbeltagi 0000-0001-9969-5970; Rawan Alhawamdeh 0000-0003-3501-6275.

Corresponding Author's Membership in Professional Societies: Faculty of Medicine, Tanta University, Egypt; University Medical Center, King Abdulla Medical City. Arabian Gulf University.

S-Editor: Qu XL

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- 1 **Ratajczak HV.** Theoretical aspects of autism: causes--a review. *J Immunotoxicol* 2011; **8**: 68-79 [PMID: [21299355](#) DOI: [10.3109/1547691X.2010.545086](#)]
- 2 **McBain RK,** Karedy V, Cantor JH, Stein BD, Yu H. Systematic Review: United States Workforce for Autism-Related Child Healthcare Services. *J Am Acad Child Adolesc Psychiatry* 2020; **59**: 113-139 [PMID: [31150751](#) DOI: [10.1016/j.jaac.2019.04.027](#)]
- 3 **McPartland J,** Volkmar FR. Autism and related disorders. *Handb Clin Neurol* 2012; **106**: 407-418 [PMID: [22608634](#) DOI: [10.1016/B978-0-444-52002-9.00023-1](#)]
- 4 **Baird G,** Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, Charman T. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet* 2006; **368**: 210-215 [PMID: [16844490](#) DOI: [10.1016/S0140-6736\(06\)69041-7](#)]
- 5 **Al-Biltagi M,** Saeed NK, Qaraghuli S. Gastrointestinal disorders in children with autism: Could artificial intelligence help? *Artif Intell Gastroenterol* 2022; **3**
- 6 **Becerra TA,** von Ehrenstein OS, Heck JE, Olsen J, Arah OA, Jeste SS, Rodriguez M, Ritz B. Autism spectrum disorders and race, ethnicity, and nativity: a population-based study. *Pediatrics* 2014; **134**: e63-e71 [PMID: [24958588](#) DOI: [10.1542/peds.2013-3928](#)]
- 7 **Bahmani M,** Sarrafchi A, Shirzad H, Rafieian-Kopaei M. Autism: Pathophysiology and Promising Herbal Remedies. *Curr Pharm Des* 2016; **22**: 277-285 [PMID: [26561063](#) DOI: [10.2174/1381612822666151112151529](#)]
- 8 **Hyman SL,** Levy SE, Myers SM; COUNCIL ON CHILDREN WITH DISABILITIES, SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics* 2020; **145** [PMID: [31843864](#) DOI: [10.1542/peds.2019-3447](#)]
- 9 **Al-Beltagi M.** Autism medical comorbidities. *World J Clin Pediatr* 2021; **10**: 15-28 [PMID: [33972922](#) DOI: [10.5409/wjcp.v10.i3.15](#)]
- 10 **Xu G,** Snetselaar LG, Jing J, Liu B, Strathearn L, Bao W. Association of Food Allergy and Other Allergic Conditions With Autism Spectrum Disorder in Children. *JAMA Netw Open* 2018; **1**: e180279 [PMID: [30646068](#) DOI: [10.1001/jamanetworkopen.2018.0279](#)]
- 11 **Rylaarsdam L,** Gumez-Gamboa A. Genetic Causes and Modifiers of Autism Spectrum Disorder. *Front Cell Neurosci* 2019; **13**: 385 [PMID: [31481879](#) DOI: [10.3389/fncel.2019.00385](#)]
- 12 **Fattorusso A,** Di Genova L, Dell'Isola GB, Mencaroni E, Esposito S. Autism Spectrum Disorders and the Gut Microbiota. *Nutrients* 2019; **11** [PMID: [30823414](#) DOI: [10.3390/nu11030521](#)]
- 13 **Bresnahan M,** Hornig M, Schultz AF, Gunnes N, Hirtz D, Lie KK, Magnus P, Reichborn-Kjennerud T, Roth C, Schjølberg S, Stoltenberg C, Surén P, Susser E, Lipkin WI. Association of maternal report of infant and toddler gastrointestinal symptoms with autism: evidence from a prospective birth cohort. *JAMA Psychiatry* 2015; **72**: 466-474 [PMID: [25806498](#) DOI: [10.1001/jamapsychiatry.2014.3034](#)]
- 14 **Gabriele S,** Sacco R, Altieri L, Neri C, Urbani A, Bravaccio C, Riccio MP, Iovene MR, Bombace F, De Magistris L, Persico AM. Slow intestinal transit contributes to elevate urinary p-cresol level in Italian autistic children. *Autism Res* 2016; **9**: 752-759 [PMID: [26437875](#) DOI: [10.1002/aur.1571](#)]
- 15 **Schröder SS,** Danner UN, Spek AA, van Elburg AA. Problematic eating behaviours of autistic women-A scoping review. *Eur Eat Disord Rev* 2022; **30**: 510-537 [PMID: [35701074](#) DOI: [10.1002/erv.2932](#)]
- 16 **Marco EJ,** Hinkley LB, Hill SS, Nagarajan SS. Sensory processing in autism: a review of neurophysiologic findings. *Pediatr Res* 2011; **69**: 48R-54R [PMID: [21289533](#) DOI: [10.1203/PDR.0b013e3182130c54](#)]
- 17 **Yu Y,** Zhao F. Microbiota-gut-brain axis in autism spectrum disorder. *J Genet Genomics* 2021; **48**: 755-762 [PMID: [34373221](#) DOI: [10.1016/j.jgg.2021.07.001](#)]
- 18 **Harris C,** Card B. A pilot study to evaluate nutritional influences on gastrointestinal symptoms and behavior patterns in children with Autism Spectrum Disorder. *Complement Ther Med* 2012; **20**: 437-440 [PMID: [23131376](#) DOI: [10.1016/j.ctim.2012.08.004](#)]
- 19 **Fulceri F,** Morelli M, Santocchi E, Cena H, Del Bianco T, Narzisi A, Calderoni S, Muratori F. Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. *Dig Liver Dis* 2016; **48**: 248-254 [PMID: [26748423](#) DOI: [10.1016/j.dld.2015.11.026](#)]
- 20 **Wasilewska J,** Klukowski M. Gastrointestinal symptoms and autism spectrum disorder: links and risks - a possible new overlap syndrome. *Pediatric Health Med Ther* 2015; **6**: 153-166 [PMID: [29388597](#) DOI: [10.2147/PHMT.S85717](#)]
- 21 **Madra M,** Ringel R, Margolis KG. Gastrointestinal Issues and Autism Spectrum Disorder. *Psychiatr Clin North Am* 2021; **44**: 69-81 [PMID: [33526238](#) DOI: [10.1016/j.psc.2020.11.006](#)]
- 22 **Yang XL,** Liang S, Zou MY, Sun CH, Han PP, Jiang XT, Xia W, Wu LJ. Are gastrointestinal and sleep problems associated with behavioral symptoms of autism spectrum disorder? *Psychiatry Res* 2018; **259**: 229-235 [PMID: [29091821](#) DOI: [10.1016/j.psychres.2017.10.040](#)]
- 23 **Prosperi M,** Santocchi E, Muratori F, Narducci C, Calderoni S, Tancredi R, Morales MA, Guiducci L. Vocal and motor behaviors as a possible expression of gastrointestinal problems in preschoolers with Autism Spectrum Disorder. *BMC Pediatr* 2019; **19**: 466 [PMID: [31779607](#) DOI: [10.1186/s12887-019-1841-8](#)]
- 24 **Holingue C,** Newill C, Lee LC, Pasricha PJ, Daniele Fallin M. Gastrointestinal symptoms in autism spectrum disorder: A review of the literature on ascertainment and prevalence. *Autism Res* 2018; **11**: 24-36 [PMID: [28856868](#) DOI: [10.1002/aur.1854](#)]
- 25 **Ajamian M,** Steer D, Rosella G, Gibson PR. Serum zonulin as a marker of intestinal mucosal barrier function: May not be what it seems. *PLoS One* 2019; **14**: e0210728 [PMID: [30640940](#) DOI: [10.1371/journal.pone.0210728](#)]
- 26 **Coury DL,** Ashwood P, Fasano A, Fuchs G, Geraghty M, Kaul A, Mawe G, Patterson P, Jones NE. Gastrointestinal conditions in children with autism spectrum disorder: developing a research agenda. *Pediatrics* 2012; **130** Suppl 2: S160-S168 [PMID: [23118247](#) DOI: [10.1542/peds.2012-0900N](#)]
- 27 **Mukhtar K,** Nawaz H, Abid S. Functional gastrointestinal disorders and gut-brain axis: What does the future hold? *World J Gastroenterol* 2019; **25**: 552-566 [PMID: [30774271](#) DOI: [10.3748/wjg.v25.i5.552](#)]
- 28 **Genuis SJ,** Bouchard TP. Celiac disease presenting as autism. *J Child Neurol* 2010; **25**: 114-119 [PMID: [19564647](#) DOI: [10.1177/0883073809336127](#)]
- 29 **Rubenstein E,** Schieve L, Bradley C, DiGuseppi C, Moody E, Thomas K, Daniels J. The prevalence of gluten free diet use among preschool children with autism spectrum disorder. *Autism Res* 2018; **11**: 185-193 [PMID: [29155492](#) DOI: [10.1002/aur.1896](#)]
- 30 **Niewinski MM.** Advances in celiac disease and gluten-free diet. *J Am Diet Assoc* 2008; **108**: 661-672 [PMID: [18375224](#) DOI: [10.1016/j.jada.2008.01.011](#)]

- 31 **Rao M**, Gershon MD. The bowel and beyond: the enteric nervous system in neurological disorders. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 517-528 [PMID: [27435372](#) DOI: [10.1038/nrgastro.2016.107](#)]
- 32 **Furness JB**, Callaghan BP, Rivera LR, Cho HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. *Adv Exp Med Biol* 2014; **817**: 39-71 [PMID: [24997029](#) DOI: [10.1007/978-1-4939-0897-4_3](#)]
- 33 **Carabotti M**, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol* 2015; **28**: 203-209 [PMID: [25830558](#)]
- 34 **Saeed NK**, Al-Beltagi M, Bediwy AS, El-Sawaf Y, Toema O. Gut microbiota in various childhood disorders: Implication and indications. *World J Gastroenterol* 2022; **28**: 1875-1901 [PMID: [35664966](#) DOI: [10.3748/wjg.v28.i18.1875](#)]
- 35 **Bull MJ**, Plummer NT. Part 1: The Human Gut Microbiome in Health and Disease. *Integr Med (Encinitas)* 2014; **13**: 17-22 [PMID: [26770121](#)]
- 36 **Strandwitz P**. Neurotransmitter modulation by the gut microbiota. *Brain Res* 2018; **1693**: 128-133 [PMID: [29903615](#) DOI: [10.1016/j.brainres.2018.03.015](#)]
- 37 **Osadchiy V**, Martin CR, Mayer EA. The Gut-Brain Axis and the Microbiome: Mechanisms and Clinical Implications. *Clin Gastroenterol Hepatol* 2019; **17**: 322-332 [PMID: [30292888](#) DOI: [10.1016/j.cgh.2018.10.002](#)]
- 38 **Mayer EA**, Tillisch K, Gupta A. Gut/brain axis and the microbiota. *J Clin Invest* 2015; **125**: 926-938 [PMID: [25689247](#) DOI: [10.1172/JCI76304](#)]
- 39 **Srikantha P**, Mohajeri MH. The Possible Role of the Microbiota-Gut-Brain-Axis in Autism Spectrum Disorder. *Int J Mol Sci* 2019; **20** [PMID: [31035684](#) DOI: [10.3390/ijms20092115](#)]
- 40 **Chen Y**, Xu J, Chen Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients* 2021; **13** [PMID: [34205336](#) DOI: [10.3390/nu13062099](#)]
- 41 **Martínez-González AE**, Andreo-Martínez P. The Role of Gut Microbiota in Gastrointestinal Symptoms of Children with ASD. *Medicina (Kaunas)* 2019; **55** [PMID: [31357482](#) DOI: [10.3390/medicina55080408](#)]
- 42 **Siniscalco D**, Schultz S, Brigida AL, Antonucci N. Inflammation and Neuro-Immune Dysregulations in Autism Spectrum Disorders. *Pharmaceuticals (Basel)* 2018; **11** [PMID: [29867038](#) DOI: [10.3390/ph11020056](#)]
- 43 **Robinson-Agramonte MLA**, Noris García E, Fraga Guerra J, Vega Hurtado Y, Antonucci N, Semprún-Hernández N, Schultz S, Siniscalco D. Immune Dysregulation in Autism Spectrum Disorder: What Do We Know about It? *Int J Mol Sci* 2022; **23** [PMID: [35328471](#) DOI: [10.3390/ijms23063033](#)]
- 44 **Dargenio VN**, Dargenio C, Castellana S, De Giacomo A, Laguardia M, Schettini F, Francavilla R, Cristofori F. Intestinal Barrier Dysfunction and Microbiota-Gut-Brain Axis: Possible Implications in the Pathogenesis and Treatment of Autism Spectrum Disorder. *Nutrients* 2023; **15** [PMID: [37049461](#) DOI: [10.3390/nu15071620](#)]
- 45 **Madore C**, Leyrolle Q, Lacabanne C, Benmamar-Badel A, Joffre C, Nadjar A, Layé S. Neuroinflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega 3, and Microbiota. *Neural Plast* 2016; **2016**: 3597209 [PMID: [27840741](#) DOI: [10.1155/2016/3597209](#)]
- 46 **van De Sande MM**, van Buul VJ, Brouns FJ. Autism and nutrition: the role of the gut-brain axis. *Nutr Res Rev* 2014; **27**: 199-214 [PMID: [25004237](#) DOI: [10.1017/S0954422414000110](#)]
- 47 **Taniya MA**, Chung HJ, Al Mamun A, Alam S, Aziz MA, Emon NU, Islam MM, Hong SS, Podder BR, Ara Mimi A, Aktar Suchi S, Xiao J. Role of Gut Microbiome in Autism Spectrum Disorder and Its Therapeutic Regulation. *Front Cell Infect Microbiol* 2022; **12**: 915701 [PMID: [35937689](#) DOI: [10.3389/fcimb.2022.915701](#)]
- 48 **Brett BE**, de Weerth C. The microbiota-gut-brain axis: A promising avenue to foster healthy developmental outcomes. *Dev Psychobiol* 2019; **61**: 772-782 [PMID: [30640409](#) DOI: [10.1002/dev.21824](#)]
- 49 **Leader G**, Abberton C, Cunningham S, Gilmartin K, Grudzien M, Higgins E, Joshi L, Whelan S, Mannion A. Gastrointestinal Symptoms in Autism Spectrum Disorder: A Systematic Review. *Nutrients* 2022; **14** [PMID: [35406084](#) DOI: [10.3390/nu14071471](#)]
- 50 **Israelyan N**, Margolis KG. Reprint of: Serotonin as a link between the gut-brain-microbiome axis in autism spectrum disorders. *Pharmacol Res* 2019; **140**: 115-120 [PMID: [30658882](#) DOI: [10.1016/j.phrs.2018.12.023](#)]
- 51 **Yoon SH**, Choi J, Lee WJ, Do JT. Genetic and Epigenetic Etiology Underlying Autism Spectrum Disorder. *J Clin Med* 2020; **9** [PMID: [32244359](#) DOI: [10.3390/jcm9040966](#)]
- 52 **Kamionkowski S**, Shibli F, Ganocy S, Fass R. The relationship between gastroesophageal reflux disease and autism spectrum disorder in adult patients in the United States. *Neurogastroenterol Motil* 2022; **34**: e14295 [PMID: [34859933](#) DOI: [10.1111/nmo.14295](#)]
- 53 **Dominick KC**, Davis NO, Lainhart J, Tager-Flusberg H, Folstein S. Atypical behaviors in children with autism and children with a history of language impairment. *Res Dev Disabil* 2007; **28**: 145-162 [PMID: [16581226](#) DOI: [10.1016/j.ridd.2006.02.003](#)]
- 54 **Yasuda Y**, Hashimoto R, Nakae A, Kang H, Ohi K, Yamamori H, Fujimoto M, Hagihira S, Takeda M. Sensory cognitive abnormalities of pain in autism spectrum disorder: a case-control study. *Ann Gen Psychiatry* 2016; **15**: 8 [PMID: [26949409](#) DOI: [10.1186/s12991-016-0095-1](#)]
- 55 **Edelson SM**. Understanding Challenging Behaviors in Autism Spectrum Disorder: A Multi-Component, Interdisciplinary Model. *J Pers Med* 2022; **12** [PMID: [35887624](#) DOI: [10.3390/jpm12071127](#)]
- 56 **Buie T**, Campbell DB, Fuchs GJ 3rd, Furuta GT, Levy J, Vandewater J, Whitaker AH, Atkins D, Bauman ML, Beaudet AL, Carr EG, Gershon MD, Hyman SL, Jirapinyo P, Jyonouchi H, Kooros K, Kushak R, Levitt P, Levy SE, Lewis JD, Murray KF, Natowicz MR, Sabra A, Wershil BK, Weston SC, Zeltzer L, Winter H. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics* 2010; **125** Suppl 1: S1-18 [PMID: [20048083](#) DOI: [10.1542/peds.2009-1878C](#)]
- 57 **Linday LA**, Tsiouris JA, Cohen IL, Shindeldecker R, DeCresce R. Famotidine treatment of children with autistic spectrum disorders: pilot research using single subject research design. *J Neural Transm (Vienna)* 2001; **108**: 593-611 [PMID: [11459079](#) DOI: [10.1007/s007020170059](#)]
- 58 **Brignell A**, Chenausky KV, Song H, Zhu J, Suo C, Morgan AT. Communication interventions for autism spectrum disorder in minimally verbal children. *Cochrane Database Syst Rev* 2018; **11**: CD012324 [PMID: [30395694](#) DOI: [10.1002/14651858.CD012324.pub2](#)]
- 59 **Addison LR**, Piazza CC, Patel MR, Bachmeyer MH, Rivas KM, Milnes SM, Oddo J. A comparison of sensory integrative and behavioral therapies as treatment for pediatric feeding disorders. *J Appl Behav Anal* 2012; **45**: 455-471 [PMID: [23060661](#) DOI: [10.1901/jaba.2012.45-455](#)]
- 60 **Cooper K**, Loades ME, Russell AJ. Adapting Psychological Therapies for Autism - Therapist Experience, Skills and Confidence. *Res Autism Spectr Disord* 2018; **45**: 43-50 [PMID: [30245739](#) DOI: [10.1016/j.rasd.2017.11.002](#)]
- 61 **Lima Antão JYF**, Oliveira ASB, Almeida Barbosa RT, Crocetta TB, Guarnieri R, Arab C, Massetti T, Antunes TPC, Silva APD, Bezerra LMP, Mello Monteiro CB, Abreu LC. Instruments for augmentative and alternative communication for children with autism spectrum disorder: a systematic review. *Clinics (Sao Paulo)* 2018; **73**: e497 [PMID: [30517284](#) DOI: [10.6061/clinics/2017/e497](#)]

- 62 **Rodriguez L**, Morley-Fletcher A, Winter H, Timothy B. Evaluation of Gastroesophageal Reflux Disease in Children on the Autism Spectrum: A Study Evaluating the Tolerance and Utility of the BRAVO Wireless pH Monitoring. *J Pediatr Gastroenterol Nutr* 2022; **75**: 450-454 [PMID: 35830732 DOI: 10.1097/MPG.0000000000003561]
- 63 **Lanyi J**, Flynn C, Mannion A, Maher L, Naughton K, Leade G. Abdominal Pain in Children and Adolescents with Autism Spectrum Disorder: a Systematic Review. *Rev J Autism Dev Disord* ; **9**: 280-289 [DOI: 10.1007/s40489-021-00257-8]
- 64 **Neuhaus E**, Bernier RA, Tham SW, Webb SJ. Gastrointestinal and Psychiatric Symptoms Among Children and Adolescents With Autism Spectrum Disorder. *Front Psychiatry* 2018; **9**: 515 [PMID: 30405456 DOI: 10.3389/fpsy.2018.00515]
- 65 **Cvejic RC**, Arnold SRC, Foley KR, Trollor JN. Neuropsychiatric profile and psychotropic medication use in adults with autism spectrum disorder: results from the Australian Longitudinal Study of Adults with Autism. *BJPsych Open* 2018; **4**: 461-466 [PMID: 30450225 DOI: 10.1192/bjo.2018.64]
- 66 **Fitzpatrick R**, McGuire BE, Lydon HK. Improving pain-related communication in children with autism spectrum disorder and intellectual disability. *Paediatr Neonatal Pain* 2022; **4**: 23-33 [PMID: 35546916 DOI: 10.1002/pne2.12076]
- 67 **Mazurek MO**, Vasa RA, Kalb LG, Kanne SM, Rosenberg D, Keefer A, Murray DS, Freedman B, Lowery LA. Anxiety, sensory over-responsivity, and gastrointestinal problems in children with autism spectrum disorders. *J Abnorm Child Psychol* 2013; **41**: 165-176 [PMID: 22850932 DOI: 10.1007/s10802-012-9668-x]
- 68 **Allely CS**. Pain sensitivity and observer perception of pain in individuals with autistic spectrum disorder. *ScientificWorldJournal* 2013; **2013**: 916178 [PMID: 23843740 DOI: 10.1155/2013/916178]
- 69 **Solomon O**, Heritage J, Yin L, Maynard DW, Bauman ML. 'What Brings Him Here Today?': Medical Problem Presentation Involving Children with Autism Spectrum Disorders and Typically Developing Children. *J Autism Dev Disord* 2016; **46**: 378-393 [PMID: 26463739 DOI: 10.1007/s10803-015-2550-2]
- 70 **Mingins JE**, Tarver J, Waite J, Jones C, Surtees AD. Anxiety and intellectual functioning in autistic children: A systematic review and meta-analysis. *Autism* 2021; **25**: 18-32 [PMID: 33198481 DOI: 10.1177/1362361320953253]
- 71 **Strömberg M**, Liman L, Bang P, Igelström K. Experiences of Sensory Overload and Communication Barriers by Autistic Adults in Health Care Settings. *Autism Adulthood* 2022; **4**: 66-75 [PMID: 36600905 DOI: 10.1089/aut.2020.0074]
- 72 **Minshawi NF**, Hurwitz S, Fodstad JC, Biebl S, Morriss DH, McDougale CJ. The association between self-injurious behaviors and autism spectrum disorders. *Psychol Res Behav Manag* 2014; **7**: 125-136 [PMID: 24748827 DOI: 10.2147/PRBM.S44635]
- 73 **McTee HM**, Mood D, Fredrickson T, Thrasher A, Bonino AY. Using Visual Supports to Facilitate Audiological Testing for Children With Autism Spectrum Disorder. *Am J Audiol* 2019; **28**: 823-833 [PMID: 31689370 DOI: 10.1044/2019_AJA-19-0047]
- 74 **Young S**, Hollingdale J, Absoud M, Bolton P, Branney P, Colley W, Craze E, Dave M, Deeley Q, Farrag E, Gudjonsson G, Hill P, Liang HL, Murphy C, Mackintosh P, Murin M, O'Regan F, Ougrin D, Rios P, Stover N, Taylor E, Woodhouse E. Guidance for identification and treatment of individuals with attention deficit/hyperactivity disorder and autism spectrum disorder based upon expert consensus. *BMC Med* 2020; **18**: 146 [PMID: 32448170 DOI: 10.1186/s12916-020-01585-y]
- 75 **Fields VL**, Soke GN, Reynolds A, Tian LH, Wiggins L, Maenner M, DiGiuseppi C, Kral TVE, Hightshoe K, Ladd-Acosta C, Schieve LA. Association between pica and gastrointestinal symptoms in preschoolers with and without autism spectrum disorder: Study to Explore Early Development. *Disabil Health J* 2021; **14**: 101052 [PMID: 33358227 DOI: 10.1016/j.dhjo.2020.101052]
- 76 **Shankar S**, Rosenbaum J. Chronic diarrhoea in children: A practical algorithm-based approach. *J Paediatr Child Health* 2020; **56**: 1029-1038 [PMID: 32725734 DOI: 10.1111/jpc.14986]
- 77 **Kirby AV**, Boyd BA, Williams KL, Faldowski RA, Baranek GT. Sensory and repetitive behaviors among children with autism spectrum disorder at home. *Autism* 2017; **21**: 142-154 [PMID: 27091950 DOI: 10.1177/1362361316632710]
- 78 **Call CR**, Williams ME, Lau D, Nyp SS. The Complexity of Making a Diagnosis. *J Dev Behav Pediatr* 2020; **41**: 242-244 [PMID: 32091456 DOI: 10.1097/DBP.0000000000000792]
- 79 **Chakraborty P**, Carpenter KHL, Major S, Deaver M, Vermeer S, Herold B, Franz L, Howard J, Dawson G. Gastrointestinal problems are associated with increased repetitive behaviors but not social communication difficulties in young children with autism spectrum disorders. *Autism* 2021; **25**: 405-415 [PMID: 32972215 DOI: 10.1177/1362361320959503]
- 80 **Holingue C**, Poku O, Pfeiffer D, Murray S, Fallin MD. Gastrointestinal concerns in children with autism spectrum disorder: A qualitative study of family experiences. *Autism* 2022; **26**: 1698-1711 [PMID: 34903078 DOI: 10.1177/13623613211062667]
- 81 **Holingue C**, Kalb LG, Musci R, Lukens C, Lee LC, Kaczaniuk J, Landrum M, Buie T, Fallin MD. Characteristics of the autism spectrum disorder gastrointestinal and related behaviors inventory in children. *Autism Res* 2022; **15**: 1142-1155 [PMID: 35302292 DOI: 10.1002/aur.2707]
- 82 **Ofei SY**, Fuchs GJ 3rd. Constipation Burden in Children with Autism Spectrum Disorder: Emergency Department and Healthcare Use. *J Pediatr* 2018; **202**: 12-13 [PMID: 30025674 DOI: 10.1016/j.jpeds.2018.06.057]
- 83 **Harris HA**, Micali N, Moll HA, van Berckelaer-Onnes I, Hillegers M, Jansen PW. The role of food selectivity in the association between child autistic traits and constipation. *Int J Eat Disord* 2021; **54**: 981-985 [PMID: 33594728 DOI: 10.1002/eat.23485]
- 84 **Wiggins LD**, Nadler C, Hepburn S, Rosenberg S, Reynolds A, Zubler J. Toileting Resistance Among Preschool-Age Children with and Without Autism Spectrum Disorder. *J Dev Behav Pediatr* 2022; **43**: 216-223 [PMID: 35170572 DOI: 10.1097/DBP.0000000000001036]
- 85 **Fu SC**, Lee CH, Wang H. Exploring the Association of Autism Spectrum Disorders and Constipation through Analysis of the Gut Microbiome. *Int J Environ Res Public Health* 2021; **18** [PMID: 33466802 DOI: 10.3390/ijerph18020667]
- 86 **Marler S**, Ferguson BJ, Lee EB, Peters B, Williams KC, McDonnell E, Macklin EA, Levitt P, Margolis KG, Beversdorf DQ, Veenstra-VanderWee J. Association of Rigid-Compulsive Behavior with Functional Constipation in Autism Spectrum Disorder. *J Autism Dev Disord* 2017; **47**: 1673-1681 [PMID: 28289979 DOI: 10.1007/s10803-017-3084-6]
- 87 **Sparks B**, Cooper J, Hayes C, Williams K. Constipation in Children with Autism Spectrum Disorder Associated with Increased Emergency Department Visits and Inpatient Admissions. *J Pediatr* 2018; **202**: 194-198 [PMID: 29866597 DOI: 10.1016/j.jpeds.2018.05.004]
- 88 **Maslen C**, Hodge R, Tie K, Laugharne R, Lamb K, Shankar R. Constipation in autistic people and people with learning disabilities. *Br J Gen Pract* 2022; **72**: 348-351 [PMID: 35772989 DOI: 10.3399/bjgp22X720077]
- 89 **Failla MD**, Gerdes MB, Williams ZJ, Moore DJ, Cascio CJ. Increased pain sensitivity and pain-related anxiety in individuals with autism. *Pain Rep* 2020; **5**: e861 [PMID: 33235944 DOI: 10.1097/PR9.0000000000000861]
- 90 **Coe A**, Ciricillo J, Mansi S, El-Chammas K, Santucci N, Bali N, Lu PL, Damrongmanee A, Fei L, Liu C, Kaul A, Williams KC. Evaluation of Chronic Constipation in Children With Autism Spectrum Disorder. *J Pediatr Gastroenterol Nutr* 2023; **76**: 154-159 [PMID: 36705696 DOI: 10.1097/MPG.0000000000003561]

- 10.1097/MPG.0000000000003662]
- 91 **Sanctuary MR**, Kain JN, Angkustsiri K, German JB. Dietary Considerations in Autism Spectrum Disorders: The Potential Role of Protein Digestion and Microbial Putrefaction in the Gut-Brain Axis. *Front Nutr* 2018; **5**: 40 [PMID: 29868601 DOI: 10.3389/fnut.2018.00040]
- 92 **Mannion K**, Leader A, Geraldine. The Assessment and Treatment of Toileting Difficulties in Individuals with Autism Spectrum Disorder and Other Developmental Disabilities. *Rev J Autism Dev Disord* 2017; **4**: 1-15 [DOI: 10.1007/s40489-017-0107-3]
- 93 **Peeters B**, Noens I, Philips EM, Kuppens S, Benninga MA. Autism spectrum disorders in children with functional defecation disorders. *J Pediatr* 2013; **163**: 873-878 [PMID: 23522863 DOI: 10.1016/j.jpeds.2013.02.028]
- 94 **Piccin S**, Crippa A, Nobile M, Hardan AY, Brambilla P. Video modeling for the development of personal hygiene skills in youth with autism spectrum disorder. *Epidemiol Psychiatr Sci* 2018; **27**: 127-132 [PMID: 29122040 DOI: 10.1017/S2045796017000610]
- 95 **Reche-Olmedo L**, Torres-Collado L, Compañ-Gabucio LM, Garcia-de-la-Hera M. The Role of Occupational Therapy in Managing Food Selectivity of Children with Autism Spectrum Disorder: A Scoping Review. *Children (Basel)* 2021; **8** [PMID: 34828737 DOI: 10.3390/children811024]
- 96 **Alhuzimi T**. Stress and emotional wellbeing of parents due to change in routine for children with Autism Spectrum Disorder (ASD) at home during COVID-19 pandemic in Saudi Arabia. *Res Dev Disabil* 2021; **108**: 103822 [PMID: 33271447 DOI: 10.1016/j.ridd.2020.103822]
- 97 **Inoue R**, Sakaue Y, Kawada Y, Tamaki R, Yasukawa Z, Ozeki M, Ueba S, Sawai C, Nonomura K, Tsukahara T, Naito Y. Dietary supplementation with partially hydrolyzed guar gum helps improve constipation and gut dysbiosis symptoms and behavioral irritability in children with autism spectrum disorder. *J Clin Biochem Nutr* 2019; **64**: 217-223 [PMID: 31138955 DOI: 10.3164/jcbs.18-105]
- 98 **Mulay KV**, Karthik SV. Managing constipation in children with ASD - A challenge worth tackling. *Pediatr Neonatol* 2022; **63**: 211-219 [PMID: 35190271 DOI: 10.1016/j.pedneo.2021.11.009]
- 99 **Furuta GT**, Williams K, Kooros K, Kaul A, Panzer R, Coury DL, Fuchs G. Management of constipation in children and adolescents with autism spectrum disorders. *Pediatrics* 2012; **130** Suppl 2: S98-105 [PMID: 23118260 DOI: 10.1542/peds.2012-0900H]
- 100 **Giuffrè M**, Gazzin S, Zoratti C, Llido JP, Lanza G, Tiribelli C, Moretti R. Celiac Disease and Neurological Manifestations: From Gluten to Neuroinflammation. *Int J Mol Sci* 2022; **23** [PMID: 36555205 DOI: 10.3390/ijms232415564]
- 101 **Croall ID**, Hoggard N, Hadjivassiliou M. Gluten and Autism Spectrum Disorder. *Nutrients* 2021; **13** [PMID: 33572226 DOI: 10.3390/nu13020572]
- 102 **Yu XB**, Uhde M, Green PH, Alaedini A. Autoantibodies in the Extraintestinal Manifestations of Celiac Disease. *Nutrients* 2018; **10** [PMID: 30127251 DOI: 10.3390/nu10081123]
- 103 **Ahmed E**, Mansour A, Amer A, Barakat T, Baz H. Screening of gastrointestinal symptoms and celiac disease in children with autism spectrum disorder. *The Egyptian Journal of Otolaryngology* 2022; **38** [DOI: 10.1186/s43163-022-00270-6]
- 104 **Aljada B**, Zohni A, El-Matary W. The Gluten-Free Diet for Celiac Disease and Beyond. *Nutrients* 2021; **13** [PMID: 34836247 DOI: 10.3390/nu13113993]
- 105 **Abdel-Maksoud M**, Aly El-Gabry D, Al Kayoumi T, Alketbi J, Mohamednour D, Elhassan Elamin M, Subhash Reddy M, Al Yafei ZA, Stip E, Abdel Aziz K, Arnane D. Measures of gluten-related reactivity in children with autism spectrum disorders in the absence of overt gastrointestinal symptoms: a pilot study from the United Arab Emirates. *J Int Med Res* 2020; **48**: 300060520952655 [PMID: 32959707 DOI: 10.1177/0300060520952655]
- 106 **Radzikowski A**, Wojnar M, Kulus M, Zalewski T. [Evaluation of the effect of gluten-free diet on nutritional status of children with florid celiac disease]. *Pediatr Pol* 1989; **64**: 150-154 [PMID: 2602046]
- 107 **Khanijow V**, Prakash P, Emsellem HA, Borum ML, Doman DB. Sleep Dysfunction and Gastrointestinal Diseases. *Gastroenterol Hepatol (N Y)* 2015; **11**: 817-825
- 108 **Koch E**, Demontis D. Drug repurposing candidates to treat core symptoms in autism spectrum disorder. *Front Pharmacol* 2022; **13**: 995439 [PMID: 36172193 DOI: 10.3389/fphar.2022.995439]
- 109 **Vellingiri B**, Aishwarya SY, Benita Jancy S, Sriram Abhishek G, Winster Suresh Babu H, Vijayakumar P, Narayanasamy A, Mariappan S, Sangeetha R, Valsala Gopalakrishnan A, Parthasarathi R, Iyer M. An anxious relationship between Autism Spectrum Disorder and Gut Microbiota: A tangled chemistry? *J Clin Neurosci* 2022; **99**: 169-189 [PMID: 35286970 DOI: 10.1016/j.jocn.2022.03.003]
- 110 **Mazefsky CA**, Schreiber DR, Olino TM, Minshew NJ. The association between emotional and behavioral problems and gastrointestinal symptoms among children with high-functioning autism. *Autism* 2014; **18**: 493-501 [PMID: 24104507 DOI: 10.1177/1362361313485164]
- 111 **Bresciani G**, Da Lozzo P, Lega S, Bramuzzo M, Di Leo G, Dissegna A, Colonna V, Barbi E, Carrozzi M, Devescovi R. Gastrointestinal Disorders and Food Selectivity: Relationship with Sleep and Challenging Behavior in Children with Autism Spectrum Disorder. *Children (Basel)* 2023; **10** [PMID: 36832380 DOI: 10.3390/children10020253]
- 112 **Parmar KR**, Porter CS, Dickinson CM, Pelham J, Baimbridge P, Gowen E. Visual Sensory Experiences From the Viewpoint of Autistic Adults. *Front Psychol* 2021; **12**: 633037 [PMID: 34168586 DOI: 10.3389/fpsyg.2021.633037]
- 113 **Zhao M**, Tuo H, Wang S, Zhao L. The Effects of Dietary Nutrition on Sleep and Sleep Disorders. *Mediators Inflamm* 2020; **2020**: 3142874 [PMID: 32684833 DOI: 10.1155/2020/3142874]
- 114 **Berry RC**, Novak P, Withrow N, Schmidt B, Rarback S, Feucht S, Criado KK, Sharp WG. Nutrition Management of Gastrointestinal Symptoms in Children with Autism Spectrum Disorder: Guideline from an Expert Panel. *J Acad Nutr Diet* 2015; **115**: 1919-1927 [PMID: 26164551 DOI: 10.1016/j.jand.2015.05.016]
- 115 **Ding M**, Lang Y, Shu H, Shao J, Cui L. Microbiota-Gut-Brain Axis and Epilepsy: A Review on Mechanisms and Potential Therapeutics. *Front Immunol* 2021; **12**: 742449 [PMID: 34707612 DOI: 10.3389/fimmu.2021.742449]
- 116 **Saurman V**, Margolis KG, Luna RA. Autism Spectrum Disorder as a Brain-Gut-Microbiome Axis Disorder. *Dig Dis Sci* 2020; **65**: 818-828 [PMID: 32056091 DOI: 10.1007/s10620-020-06133-5]
- 117 **Zahra A**, Wang Y, Wang Q, Wu J. Shared Etiology in Autism Spectrum Disorder and Epilepsy with Functional Disability. *Behav Neurol* 2022; **2022**: 5893519 [PMID: 35530166 DOI: 10.1155/2022/5893519]
- 118 **Pan PY**, Taylor MJ, Larsson H, Almqvist C, Lichtenstein P, Lundström S, Bölte S. Genetic and environmental contributions to co-occurring physical health conditions in autism spectrum condition and attention-deficit/hyperactivity disorder. *Mol Autism* 2023; **14**: 17 [PMID: 37085910 DOI: 10.1186/s13229-023-00548-3]
- 119 **Darch H**, McCafferty CP. Gut microbiome effects on neuronal excitability & activity: Implications for epilepsy. *Neurobiol Dis* 2022; **165**: 105629 [PMID: 35033659 DOI: 10.1016/j.nbd.2022.105629]
- 120 **Al-Beltagi M**, Saeed NK. Epilepsy and the gut: Perpetrator or victim? *World J Gastrointest Pathophysiol* 2022; **13**: 143-156 [PMID: 36187601]

DOI: [10.4291/wjgp.v13.i5.143](https://doi.org/10.4291/wjgp.v13.i5.143)]

- 121 **Yibirin M**, De Oliveira D, Valera R, Plitt AE, Lutgen S. Adverse Effects Associated with Proton Pump Inhibitor Use. *Cureus* 2021; **13**: e12759 [PMID: [33614352](https://pubmed.ncbi.nlm.nih.gov/33614352/) DOI: [10.7759/cureus.12759](https://doi.org/10.7759/cureus.12759)]
- 122 **Kerr M**; Guidelines Working Group, Scheepers M, Arvio M, Beavis J, Brandt C, Brown S, Huber B, Iivanainen M, Lousse AC, Martin P, Marson AG, Prasher V, Singh BK, Veendrick M, Wallace RA. Consensus guidelines into the management of epilepsy in adults with an intellectual disability. *J Intellect Disabil Res* 2009; **53**: 687-694 [PMID: [19527434](https://pubmed.ncbi.nlm.nih.gov/19527434/) DOI: [10.1111/j.1365-2788.2009.01182.x](https://doi.org/10.1111/j.1365-2788.2009.01182.x)]
- 123 **Jiang CC**, Lin LS, Long S, Ke XY, Fukunaga K, Lu YM, Han F. Signalling pathways in autism spectrum disorder: mechanisms and therapeutic implications. *Signal Transduct Target Ther* 2022; **7**: 229 [PMID: [35817793](https://pubmed.ncbi.nlm.nih.gov/35817793/) DOI: [10.1038/s41392-022-01081-0](https://doi.org/10.1038/s41392-022-01081-0)]
- 124 **Mallory C**, Keehn B. Implications of Sensory Processing and Attentional Differences Associated With Autism in Academic Settings: An Integrative Review. *Front Psychiatry* 2021; **12**: 695825 [PMID: [34512416](https://pubmed.ncbi.nlm.nih.gov/34512416/) DOI: [10.3389/fpsy.2021.695825](https://doi.org/10.3389/fpsy.2021.695825)]
- 125 **Nikolov RN**, Bearss KE, Lettinga J, Erickson C, Rodowski M, Aman MG, McCracken JT, McDougle CJ, Tierney E, Vitiello B, Arnold LE, Shah B, Posey DJ, Ritz L, Scahill L. Gastrointestinal symptoms in a sample of children with pervasive developmental disorders. *J Autism Dev Disord* 2009; **39**: 405-413 [PMID: [18791817](https://pubmed.ncbi.nlm.nih.gov/18791817/) DOI: [10.1007/s10803-008-0637-8](https://doi.org/10.1007/s10803-008-0637-8)]
- 126 **Santhanam SP**. An Interactive and Neurodiversity-Affirming Approach to Communication Supports for Autistic Students Through Videogaming. *Lang Speech Hear Serv Sch* 2023; **54**: 120-139 [PMID: [36626352](https://pubmed.ncbi.nlm.nih.gov/36626352/) DOI: [10.1044/2022_LSHSS-22-00027](https://doi.org/10.1044/2022_LSHSS-22-00027)]
- 127 **Doreswamy S**, Bashir A, Guarecuco JE, Lahori S, Baig A, Narra LR, Patel P, Heindl SE. Effects of Diet, Nutrition, and Exercise in Children With Autism and Autism Spectrum Disorder: A Literature Review. *Cureus* 2020; **12**: e12222 [PMID: [33489626](https://pubmed.ncbi.nlm.nih.gov/33489626/) DOI: [10.7759/cureus.12222](https://doi.org/10.7759/cureus.12222)]
- 128 **Hillier A**, Goldstein J, Murphy D, Trietsch R, Keeves J, Mendes E, Queenan A. Supporting university students with autism spectrum disorder. *Autism* 2018; **22**: 20-28 [PMID: [28683558](https://pubmed.ncbi.nlm.nih.gov/28683558/) DOI: [10.1177/1362361317699584](https://doi.org/10.1177/1362361317699584)]
- 129 **Ferguson BJ**, Dovgan K, Takahashi N, Beversdorf DQ. The Relationship Among Gastrointestinal Symptoms, Problem Behaviors, and Internalizing Symptoms in Children and Adolescents With Autism Spectrum Disorder. *Front Psychiatry* 2019; **10**: 194 [PMID: [31024357](https://pubmed.ncbi.nlm.nih.gov/31024357/) DOI: [10.3389/fpsy.2019.00194](https://doi.org/10.3389/fpsy.2019.00194)]
- 130 **Mitreä L**, Nemeş SA, Szabo K, Teleky BE, Vodnar DC. Guts Imbalance Imbalances the Brain: A Review of Gut Microbiota Association With Neurological and Psychiatric Disorders. *Front Med (Lausanne)* 2022; **9**: 813204 [PMID: [35433746](https://pubmed.ncbi.nlm.nih.gov/35433746/) DOI: [10.3389/fmed.2022.813204](https://doi.org/10.3389/fmed.2022.813204)]
- 131 **Cermak SA**, Curtin C, Bandini LG. Food selectivity and sensory sensitivity in children with autism spectrum disorders. *J Am Diet Assoc* 2010; **110**: 238-246 [PMID: [20102851](https://pubmed.ncbi.nlm.nih.gov/20102851/) DOI: [10.1016/j.jada.2009.10.032](https://doi.org/10.1016/j.jada.2009.10.032)]
- 132 **Bowman KS**, Suarez VD, Weiss MJ. Standards for Interprofessional Collaboration in the Treatment of Individuals With Autism. *Behav Anal Pract* 2021; **14**: 1191-1208 [PMID: [34868822](https://pubmed.ncbi.nlm.nih.gov/34868822/) DOI: [10.1007/s40617-021-00560-0](https://doi.org/10.1007/s40617-021-00560-0)]
- 133 **Carlier S**, Vorlet P, Sá Dos Reis C, Malamateniou C. Strategies, challenges and enabling factors when imaging autistic individuals in Swiss medical imaging departments. *J Med Imaging Radiat Sci* 2022 [PMID: [36504166](https://pubmed.ncbi.nlm.nih.gov/36504166/) DOI: [10.1016/j.jmir.2022.11.002](https://doi.org/10.1016/j.jmir.2022.11.002)]
- 134 **Dineen-Griffin S**, Garcia-Cardenas V, Williams K, Benrimoj SI. Helping patients help themselves: A systematic review of self-management support strategies in primary health care practice. *PLoS One* 2019; **14**: e0220116 [PMID: [31369582](https://pubmed.ncbi.nlm.nih.gov/31369582/) DOI: [10.1371/journal.pone.0220116](https://doi.org/10.1371/journal.pone.0220116)]
- 135 **Bailey AJ**. The neuroscience of autism education. *Autism Res* 2008; **1**: 207 [PMID: [19360670](https://pubmed.ncbi.nlm.nih.gov/19360670/) DOI: [10.1002/aur.36](https://doi.org/10.1002/aur.36)]
- 136 **Leader G**, O'Reilly M, Gilroy SP, Chen JL, Ferrari C, Mannion A. Comorbid Feeding and Gastrointestinal Symptoms, Challenging Behavior, Sensory Issues, Adaptive Functioning and Quality of Life in Children and Adolescents with Autism Spectrum Disorder. *Dev Neurorehabil* 2021; **24**: 35-44 [PMID: [32496834](https://pubmed.ncbi.nlm.nih.gov/32496834/) DOI: [10.1080/17518423.2020.1770354](https://doi.org/10.1080/17518423.2020.1770354)]
- 137 **Brede J**, Babb C, Jones C, Elliott M, Zanker C, Tchaturia K, Serpell L, Fox J, Mandy W. "For Me, the Anorexia is Just a Symptom, and the Cause is the Autism": Investigating Restrictive Eating Disorders in Autistic Women. *J Autism Dev Disord* 2020; **50**: 4280-4296 [PMID: [32274604](https://pubmed.ncbi.nlm.nih.gov/32274604/) DOI: [10.1007/s10803-020-04479-3](https://doi.org/10.1007/s10803-020-04479-3)]
- 138 **Babinska K**, Celusakova H, Belica I, Szapuova Z, Waczulikova I, Nemcsicsova D, Tomova A, Ostatnikova D. Gastrointestinal Symptoms and Feeding Problems and Their Associations with Dietary Interventions, Food Supplement Use, and Behavioral Characteristics in a Sample of Children and Adolescents with Autism Spectrum Disorders. *Int J Environ Res Public Health* 2020; **17** [PMID: [32882981](https://pubmed.ncbi.nlm.nih.gov/32882981/) DOI: [10.3390/ijerph17176372](https://doi.org/10.3390/ijerph17176372)]
- 139 **Dovgan K**, Gynegrowski K, Ferguson BJ. Bidirectional relationship between internalizing symptoms and gastrointestinal problems in youth with Autism Spectrum Disorder. *J Autism Dev Disord* 2022 [PMID: [35441914](https://pubmed.ncbi.nlm.nih.gov/35441914/) DOI: [10.1007/s10803-022-05539-6](https://doi.org/10.1007/s10803-022-05539-6)]
- 140 **Salleh MR**. Life event, stress and illness. *Malays J Med Sci* 2008; **15**: 9-18
- 141 **Andrulis DP**, Brach C. Integrating literacy, culture, and language to improve health care quality for diverse populations. *Am J Health Behav* 2007; **31** Suppl 1: S122-S133 [PMID: [17931131](https://pubmed.ncbi.nlm.nih.gov/17931131/) DOI: [10.5555/ajhb.2007.31.suppl.S122](https://doi.org/10.5555/ajhb.2007.31.suppl.S122)]
- 142 **Oakley BF**, Tillmann J, Ahmad J, Crawley D, San José Cáceres A, Holt R, Charman T, Banaschewski T, Buitelaar J, Simonoff E, Murphy D, Loth E. How do core autism traits and associated symptoms relate to quality of life? Findings from the Longitudinal European Autism Project. *Autism* 2021; **25**: 389-404 [PMID: [33023296](https://pubmed.ncbi.nlm.nih.gov/33023296/) DOI: [10.1177/1362361320959959](https://doi.org/10.1177/1362361320959959)]
- 143 **Hodges H**, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. *Transl Pediatr* 2020; **9**: S55-S65 [PMID: [32206584](https://pubmed.ncbi.nlm.nih.gov/32206584/) DOI: [10.21037/tp.2019.09.09](https://doi.org/10.21037/tp.2019.09.09)]
- 144 **Garcia-Gutierrez E**, Narbad A, Rodríguez JM. Autism Spectrum Disorder Associated With Gut Microbiota at Immune, Metabolomic, and Neuroactive Level. *Front Neurosci* 2020; **14**: 578666 [PMID: [33117122](https://pubmed.ncbi.nlm.nih.gov/33117122/) DOI: [10.3389/fnins.2020.578666](https://doi.org/10.3389/fnins.2020.578666)]
- 145 **Dinan TG**, Cryan JF. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. *J Physiol* 2017; **595**: 489-503 [PMID: [27641441](https://pubmed.ncbi.nlm.nih.gov/27641441/) DOI: [10.1113/JP273106](https://doi.org/10.1113/JP273106)]
- 146 **Hughes HK**, Rose D, Ashwood P. The Gut Microbiota and Dysbiosis in Autism Spectrum Disorders. *Curr Neurol Neurosci Rep* 2018; **18**: 81 [PMID: [30251184](https://pubmed.ncbi.nlm.nih.gov/30251184/) DOI: [10.1007/s11910-018-0887-6](https://doi.org/10.1007/s11910-018-0887-6)]
- 147 **Jendraszak M**, Gałęcka M, Kotwicka M, Regdos A, Pazgrat-Patan M, Andrusiewicz M. Commercial microbiota test revealed differences in the composition of intestinal microorganisms between children with autism spectrum disorders and neurotypical peers. *Sci Rep* 2021; **11**: 24274 [PMID: [34931007](https://pubmed.ncbi.nlm.nih.gov/34931007/) DOI: [10.1038/s41598-021-03794-8](https://doi.org/10.1038/s41598-021-03794-8)]
- 148 **Kang DW**, Park JG, Ilhan ZE, Wallstrom G, Lobaer J, Adams JB, Krajmalnik-Brown R. Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. *PLoS One* 2013; **8**: e68322 [PMID: [23844187](https://pubmed.ncbi.nlm.nih.gov/23844187/) DOI: [10.1371/journal.pone.0068322](https://doi.org/10.1371/journal.pone.0068322)]
- 149 **Adams JB**, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. *BMC Gastroenterol* 2011; **11**: 22 [PMID: [21410934](https://pubmed.ncbi.nlm.nih.gov/21410934/) DOI: [10.1186/1471-230X-11-22](https://doi.org/10.1186/1471-230X-11-22)]
- 150 **Xu M**, Xu X, Li J, Li F. Association Between Gut Microbiota and Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *Front Psychiatry* 2019; **10**: 473 [PMID: [31404299](https://pubmed.ncbi.nlm.nih.gov/31404299/) DOI: [10.3389/fpsy.2019.00473](https://doi.org/10.3389/fpsy.2019.00473)]

- 151 **Iglesias-Vázquez L**, Van Ginkel Riba G, Arijia V, Canals J. Composition of Gut Microbiota in Children with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *Nutrients* 2020; **12** [PMID: [32192218](#) DOI: [10.3390/nu12030792](#)]
- 152 **Wu T**, Wang H, Lu W, Zhai Q, Zhang Q, Yuan W, Gu Z, Zhao J, Zhang H, Chen W. Potential of gut microbiome for detection of autism spectrum disorder. *Microb Pathog* 2020; **149**: 104568 [PMID: [33096147](#) DOI: [10.1016/j.micpath.2020.104568](#)]
- 153 **Qureshi F**, Adams J, Hanagan K, Kang DW, Krajmalnik-Brown R, Hahn J. Multivariate Analysis of Fecal Metabolites from Children with Autism Spectrum Disorder and Gastrointestinal Symptoms before and after Microbiota Transfer Therapy. *J Pers Med* 2020; **10** [PMID: [33023268](#) DOI: [10.3390/jpm10040152](#)]
- 154 **Zhai Q**, Cen S, Jiang J, Zhao J, Zhang H, Chen W. Disturbance of trace element and gut microbiota profiles as indicators of autism spectrum disorder: A pilot study of Chinese children. *Environ Res* 2019; **171**: 501-509 [PMID: [30743242](#) DOI: [10.1016/j.envres.2019.01.060](#)]
- 155 **Galloway-Peña J**, Hanson B. Tools for Analysis of the Microbiome. *Dig Dis Sci* 2020; **65**: 674-685 [PMID: [32002757](#) DOI: [10.1007/s10620-020-06091-y](#)]
- 156 **Fiorentino M**, Sapone A, Senger S, Camhi SS, Kadziński SM, Buie TM, Kelly DL, Cascella N, Fasano A. Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Mol Autism* 2016; **7**: 49 [PMID: [27957319](#) DOI: [10.1186/s13229-016-0110-z](#)]
- 157 **Esnafoglu E**, Cırık S, Ayyıldız SN, Erdil A, Ertürk EY, Dağlı A, Noyan T. Increased Serum Zonulin Levels as an Intestinal Permeability Marker in Autistic Subjects. *J Pediatr* 2017; **188**: 240-244 [PMID: [28502607](#) DOI: [10.1016/j.jpeds.2017.04.004](#)]
- 158 **Dalton N**, Chandler S, Turner C, Charman T, Pickles A, Loucas T, Simonoff E, Sullivan P, Baird G. Gut permeability in autism spectrum disorders. *Autism Res* 2014; **7**: 305-313 [PMID: [24339339](#) DOI: [10.1002/aur.1350](#)]
- 159 **Patusco R**, Ziegler J. Role of Probiotics in Managing Gastrointestinal Dysfunction in Children with Autism Spectrum Disorder: An Update for Practitioners. *Adv Nutr* 2018; **9**: 637-650 [PMID: [30202938](#) DOI: [10.1093/advances/nmy031](#)]
- 160 **Mangiola F**, Ianiro G, Franceschi F, Fagioli S, Gasbarrini G, Gasbarrini A. Gut microbiota in autism and mood disorders. *World J Gastroenterol* 2016; **22**: 361-368 [PMID: [26755882](#) DOI: [10.3748/wjg.v22.i1.361](#)]
- 161 **Ali T**, Choe J, Awab A, Wagener TL, Orr WC. Sleep, immunity and inflammation in gastrointestinal disorders. *World J Gastroenterol* 2013; **19**: 9231-9239 [PMID: [24409051](#) DOI: [10.3748/wjg.v19.i48.9231](#)]
- 162 **Karhu E**, Zukerman R, Eshraghi RS, Mittal J, Deth RC, Castejon AM, Trivedi M, Mittal R, Eshraghi AA. Nutritional interventions for autism spectrum disorder. *Nutr Rev* 2020; **78**: 515-531 [PMID: [31876938](#) DOI: [10.1093/nutrit/nuz092](#)]
- 163 **Taha Z**, Abdalhai KA. A Review of the Efficacy of the Dietary Intervention in Autism Spectrum Disorder. *Open Access Maced J Med Sci* 2021; **18** [DOI: [10.3889/oamjms.2021.5743](#)]
- 164 **Amadi CN**, Orish CN, Frazzoli C, Orisakwe OE. Dietary interventions for autism spectrum disorder: An updated systematic review of human studies. *Psychiatriki* 2022; **33**: 228-242 [PMID: [35477082](#) DOI: [10.22365/jpsych.2022.073](#)]
- 165 **Yu Y**, Huang J, Chen X, Fu J, Wang X, Pu L, Gu C, Cai C. Efficacy and Safety of Diet Therapies in Children With Autism Spectrum Disorder: A Systematic Literature Review and Meta-Analysis. *Front Neurol* 2022; **13**: 844117 [PMID: [35359629](#) DOI: [10.3389/fneur.2022.844117](#)]
- 166 **Pruimboom L**, de Punder K. The opioid effects of gluten exorphins: asymptomatic celiac disease. *J Health Popul Nutr* 2015; **33**: 24 [PMID: [26825414](#) DOI: [10.1186/s41043-015-0032-y](#)]
- 167 **Trivedi MS**, Shah JS, Al-Mughairy S, Hodgson NW, Simms B, Trooskens GA, Van Crielinge W, Deth RC. Food-derived opioid peptides inhibit cysteine uptake with redox and epigenetic consequences. *J Nutr Biochem* 2014; **25**: 1011-1018 [PMID: [25018147](#) DOI: [10.1016/j.jnutbio.2014.05.004](#)]
- 168 **Stewart PA**, Hyman SL, Schmidt BL, Macklin EA, Reynolds A, Johnson CR, James SJ, Manning-Courtney P. Dietary Supplementation in Children with Autism Spectrum Disorders: Common, Insufficient, and Excessive. *J Acad Nutr Diet* 2015; **115**: 1237-1248 [PMID: [26052041](#) DOI: [10.1016/j.jand.2015.03.026](#)]
- 169 **Piwoarczyk A**, Horvath A, Łukasik J, Pisula E, Szajewska H. Gluten- and casein-free diet and autism spectrum disorders in children: a systematic review. *Eur J Nutr* 2018; **57**: 433-440 [PMID: [28612113](#) DOI: [10.1007/s00394-017-1483-2](#)]
- 170 **Quan L**, Xu X, Cui Y, Han H, Hendren RL, Zhao L, You X. A systematic review and meta-analysis of the benefits of a gluten-free diet and/or casein-free diet for children with autism spectrum disorder. *Nutr Rev* 2022; **80**: 1237-1246 [PMID: [34617108](#) DOI: [10.1093/nutrit/nuab073](#)]
- 171 **Obih C**, Wahbeh G, Lee D, Braly K, Giefer M, Shaffer ML, Nielson H, Suskind DL. Specific carbohydrate diet for pediatric inflammatory bowel disease in clinical practice within an academic IBD center. *Nutrition* 2016; **32**: 418-425 [PMID: [26655069](#) DOI: [10.1016/j.nut.2015.08.025](#)]
- 172 **Barnhill K**, Devlin M, Moreno HT, Potts A, Richardson W, Schutte C, Hewitson L. Brief Report: Implementation of a Specific Carbohydrate Diet for a Child with Autism Spectrum Disorder and Fragile X Syndrome. *J Autism Dev Disord* 2020; **50**: 1800-1808 [PMID: [30076499](#) DOI: [10.1007/s10803-018-3704-9](#)]
- 173 **Żarnowska I**, Chrapko B, Gwizda G, Nocuń A, Mitosek-Szewczyk K, Gasior M. Therapeutic use of carbohydrate-restricted diets in an autistic child; a case report of clinical and 18FDG PET findings. *Metab Brain Dis* 2018; **33**: 1187-1192 [PMID: [29644487](#) DOI: [10.1007/s11011-018-0219-1](#)]
- 174 **Ābele**, Silvija, Meija, Laila, Folkmanis, Valdis and Tzivian, Lilian. "Specific Carbohydrate Diet (SCD/GAPS) and Dietary Supplements for Children with Autistic Spectrum Disorder" Proceedings of the Latvian Academy of Sciences. Section B. *Natural, Exact, and Applied Sciences* 2021; **75**: 417-425 [DOI: [10.2478/prolas-2021-0062](#)]
- 175 **Shaaban S**, Al-Beltagi M, El Rashidy O, Nassar M, El Gendy Y. Ketogenic diet in childhood epilepsy: clinical algorithm in a tertiary care center. *Front Pediatr* 2023; **11**: 1221781 [PMID: [37484774](#) DOI: [10.3389/fped.2023.1221781](#)]
- 176 **Li Q**, Liang J, Fu N, Han Y, Qin J. A Ketogenic Diet and the Treatment of Autism Spectrum Disorder. *Front Pediatr* 2021; **9**: 650624 [PMID: [34046374](#) DOI: [10.3389/fped.2021.650624](#)]
- 177 **Albers J**, Kraja G, Eller D, Eck K, McBrien D, Bain JM. Assessing the feasibility of using the ketogenic diet in autism spectrum disorder. *J Hum Nutr Diet* 2023; **36**: 1303-1315 [PMID: [36478324](#) DOI: [10.1111/jhn.13115](#)]
- 178 **Díaz Vargas D**, Leonario Rodríguez M. Effectiveness of nutritional interventions on behavioral symptomatology of autism spectrum disorder: a systematic review. *Nutr Hosp* 2022; **39**: 1378-1388 [PMID: [36454020](#) DOI: [10.20960/nh.04155](#)]
- 179 **Varesio C**, Grumi S, Zanaboni MP, Mensi MM, Chiappedi M, Pasca L, Ferraris C, Tagliabue A, Borgatti R, De Giorgis V. Ketogenic Dietary Therapies in Patients with Autism Spectrum Disorder: Facts or Fads? A Scoping Review and a Proposal for a Shared Protocol. *Nutrients* 2021; **13** [PMID: [34208488](#) DOI: [10.3390/nu13062057](#)]
- 180 **Vallamchetla SK**. Exploring the Therapeutic Potential of the Ketogenic Diet on Neurological Disorders: A Comprehensive Review. *J Neurol Neuromedicine* 2023; **7**: 1-8 [DOI: [10.29245/2572.942X/2023/1.1286](#)]

- 181 **Oselu S**, Ebere R, Arimi JM. Camels, Camel Milk, and Camel Milk Product Situation in Kenya in Relation to the World. *Int J Food Sci* 2022; 2022: 1237423 [PMID: 35299617 DOI: 10.1155/2022/1237423]
- 182 **Al-Ayadhi LY**, Elamin NE. Camel Milk as a Potential Therapy as an Antioxidant in Autism Spectrum Disorder (ASD). *Evid Based Complement Alternat Med* 2013; 2013: 602834 [PMID: 24069051 DOI: 10.1155/2013/602834]
- 183 **Mihic T**, Rainkie D, Wilby KJ, Pawluk SA. The Therapeutic Effects of Camel Milk: A Systematic Review of Animal and Human Trials. *J Evid Based Complementary Altern Med* 2016; 21: NP110-NP126 [PMID: 27432772 DOI: 10.1177/2156587216658846]
- 184 **Al-Ayadhi LY**, Halepoto DM, Al-Dress AM, Mitwali Y, Zainah R. Behavioral Benefits of Camel Milk in Subjects with Autism Spectrum Disorder. *J Coll Physicians Surg Pak* 2015; 25: 819-823 [PMID: 26577969]
- 185 **Kandeel M**, El-Deeb W. The Application of Natural Camel Milk Products to Treat Autism-Spectrum Disorders: Risk Assessment and Meta-Analysis of Randomized Clinical Trials. *Bioinorg Chem Appl* 2022; 2022: 6422208 [PMID: 35669459 DOI: 10.1155/2022/6422208]
- 186 **Shabo**, Yosef and Yagil, Reuven. "Etiology of autism and camel milk as therapy". *International Journal on Disability and Human Development* 2005; 4: 67-70 [DOI: 10.1515/IJDHD.2005.4.2.67]
- 187 **O'Leary F**, Samman S. Vitamin B12 in health and disease. *Nutrients* 2010; 2: 299-316 [PMID: 22254022 DOI: 10.3390/nu2030299]
- 188 **Fakhroo A**, Al-Hammadi M, Fakhroo L, Al-Ali F, Snobar R, Al-Beltagi M, Kamal A. The Effect of High-Dose Methyl Vitamin B12 Therapy on Epileptogenesis in Rats: An In Vivo Study. *Cureus* 2023; 15: e35929 [PMID: 37050999 DOI: 10.7759/cureus.35929]
- 189 **Bertoglio K**, Jill James S, Deprey L, Brule N, Hendren RL. Pilot study of the effect of methyl B12 treatment on behavioral and biomarker measures in children with autism. *J Altern Complement Med* 2010; 16: 555-560 [PMID: 20804367 DOI: 10.1089/acm.2009.0177]
- 190 **Hendren RL**, James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism. *J Child Adolesc Psychopharmacol* 2016; 26: 774-783 [PMID: 26889605 DOI: 10.1089/cap.2015.0159]
- 191 **James SJ**, Melnyk S, Fuchs G, Reid T, Jernigan S, Pavliv O, Hubanks A, Gaylor DW. Efficacy of methylcobalamin and folic acid treatment on glutathione redox status in children with autism. *Am J Clin Nutr* 2009; 89: 425-430 [PMID: 19056591 DOI: 10.3945/ajcn.2008.26615]
- 192 **Frye RE**, Melnyk S, Fuchs G, Reid T, Jernigan S, Pavliv O, Hubanks A, Gaylor DW, Walters L, James SJ. Effectiveness of methylcobalamin and folic acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status. *Autism Res Treat* 2013; 2013: 609705 [PMID: 24224089 DOI: 10.1155/2013/609705]
- 193 **Žigman T**, Petković Ramadža D, Šimić G, Barić I. Inborn Errors of Metabolism Associated With Autism Spectrum Disorders: Approaches to Intervention. *Front Neurosci* 2021; 15: 673600 [PMID: 34121999 DOI: 10.3389/fnins.2021.673600]
- 194 **Čorejová A**, Fazekas T, Jánošíková D, Repiský J, Pospíšilová V, Miková M, Rauová D, Ostatníková D, Kyselovič J, Hrabovská A. Improvement of the Clinical and Psychological Profile of Patients with Autism after Methylcobalamin Syrup Administration. *Nutrients* 2022; 14 [PMID: 35631176 DOI: 10.3390/nu14102035]
- 195 **Rossignol DA**, Frye RE. The Effectiveness of Cobalamin (B12) Treatment for Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *J Pers Med* 2021; 11 [PMID: 34442428 DOI: 10.3390/jpm11080784]
- 196 **Dighriri IM**, Alsubaie AM, Hakami FM, Hamithi DM, Alshekh MM, Khobrani FA, Dalak FE, Hakami AA, Alsueaadi EH, Alsaawi LS, Alshammari SF, Alqahtani AS, Alawi IA, Aljuaid AA, Tawhari MQ. Effects of Omega-3 Polyunsaturated Fatty Acids on Brain Functions: A Systematic Review. *Cureus* 2022; 14: e30091 [PMID: 36381743 DOI: 10.7759/cureus.30091]
- 197 **Dyall SC**. Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA. *Front Aging Neurosci* 2015; 7: 52 [PMID: 25954194 DOI: 10.3389/fnagi.2015.00052]
- 198 **Agostoni C**, Nobile M, Ciappolino V, Delvecchio G, Tesei A, Turolo S, Crippa A, Mazzocchi A, Altamura CA, Brambilla P. The Role of Omega-3 Fatty Acids in Developmental Psychopathology: A Systematic Review on Early Psychosis, Autism, and ADHD. *Int J Mol Sci* 2017; 18 [PMID: 29207548 DOI: 10.3390/ijms18122608]
- 199 **Bent S**, Bertoglio K, Hendren RL. Omega-3 fatty acids for autistic spectrum disorder: a systematic review. *J Autism Dev Disord* 2009; 39: 1145-1154 [PMID: 19333748 DOI: 10.1007/s10803-009-0724-5]
- 200 **Cheng YS**, Tseng PT, Chen YW, Stubbs B, Yang WC, Chen TY, Wu CK, Lin PY. Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: a meta-analysis of randomized controlled trials. *Neuropsychiatr Dis Treat* 2017; 13: 2531-2543 [PMID: 29042783 DOI: 10.2147/NDT.S147305]
- 201 **Mankad D**, Dupuis A, Smile S, Roberts W, Brian J, Lui T, Genore L, Zaghloul D, Iaboni A, Marcon PM, Anagnostou E. A randomized, placebo controlled trial of omega-3 fatty acids in the treatment of young children with autism. *Mol Autism* 2015; 6: 18 [PMID: 25798215 DOI: 10.1186/s13229-015-0010-7]
- 202 **Parra M**, Stahl S, Hellmann H. Vitamin B6 and Its Role in Cell Metabolism and Physiology. *Cells* 2018; 7 [PMID: 30037155 DOI: 10.3390/cells7070084]
- 203 **Obara T**, Ishikuro M, Tamiya G, Ueki M, Yamanaka C, Mizuno S, Kikuya M, Metoki H, Matsubara H, Nagai M, Kobayashi T, Kamiyama M, Watanabe M, Kakuta K, Ouchi M, Kurihara A, Fukuchi N, Yasuhara A, Inagaki M, Kaga M, Kure S, Kuriyama S. Potential identification of vitamin B6 responsiveness in autism spectrum disorder utilizing phenotype variables and machine learning methods. *Sci Rep* 2018; 8: 14840 [PMID: 30287864 DOI: 10.1038/s41598-018-33110-w]
- 204 **Khan F**, Rahman MS, Akhter S, Momen ABI, Raihan SG. Vitamin B6 and Magnesium on Neurobehavioral Status of Autism Spectrum Disorder: A Randomized, Double-Blind, Placebo Controlled Study. *Bangladesh Journal of Medicine* 2021; 32: 12-18 [DOI: 10.3329/bjbm.v32i1.51089]
- 205 **Nye C**, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database Syst Rev* 2005; 2005: CD003497 [PMID: 16235322 DOI: 10.1002/14651858.CD003497.pub2]
- 206 **Srinivasan P**. A review of dietary interventions in autism. *Ann Clin Psychiatry* 2009; 21: 237-247 [PMID: 19917213]
- 207 **Burrus CJ**. A biochemical rationale for the interaction between gastrointestinal yeast and autism. *Med Hypotheses* 2012; 79: 784-785 [PMID: 23021572 DOI: 10.1016/j.mehy.2012.08.029]
- 208 **Baker S**, Shaw W. Case Study: Rapid Complete Recovery From An Autism Spectrum Disorder After Treatment of Aspergillus With The Antifungal Drugs Itraconazole And Sporanox. *Integr Med (Encinitas)* 2020; 19: 20-27 [PMID: 33132781]
- 209 **Herman A**, Herman AP. Could Candida Overgrowth Be Involved in the Pathophysiology of Autism? *J Clin Med* 2022; 11 [PMID: 35054136 DOI: 10.3390/jcm11020442]
- 210 **Bibbò S**, Ianiro G, Giorgio V, Scaldaferrì F, Masucci L, Gasbarrini A, Cammarota G. The role of diet on gut microbiota composition. *Eur Rev Med Pharmacol Sci* 2016; 20: 4742-4749 [PMID: 27906427]
- 211 **Vargason T**, McGuinness DL, Hahn J. Gastrointestinal Symptoms and Oral Antibiotic Use in Children with Autism Spectrum Disorder:

- Retrospective Analysis of a Privately Insured U.S. Population. *J Autism Dev Disord* 2019; **49**: 647-659 [PMID: [30178105](#) DOI: [10.1007/s10803-018-3743-2](#)]
- 212 **Mari-Bauset S**, Llopis-González A, Zazpe I, Mari-Sanchis A, Suárez-Varela MM. Fat intake in children with autism spectrum disorder in the Mediterranean region (Valencia, Spain). *Nutr Neurosci* 2016; **19**: 377-386 [PMID: [26020227](#) DOI: [10.1179/1476830515Y.0000000029](#)]
- 213 **Kaviyarasan S**, Chung Sia EL, Retinasamy T, Arulsamy A, Shaikh MF. Regulation of gut microbiome by ketogenic diet in neurodegenerative diseases: A molecular crosstalk. *Front Aging Neurosci* 2022; **14**: 1015837 [PMID: [36313018](#) DOI: [10.3389/fnagi.2022.1015837](#)]
- 214 **Baspinar B**, Yardimci H. Gluten-Free Casein-Free Diet for Autism Spectrum Disorders: Can It Be Effective in Solving Behavioural and Gastrointestinal Problems? *Eurasian J Med* 2020; **52**: 292-297 [PMID: [33209084](#) DOI: [10.5152/eurasianjmed.2020.19230](#)]
- 215 **Bialek-Dratwa A**, Szymańska D, Grajek M, Krupa-Kotara K, Szczepańska E, Kowalski O. ARFID-Strategies for Dietary Management in Children. *Nutrients* 2022; **14** [PMID: [35565707](#) DOI: [10.3390/nu14091739](#)]
- 216 **Yang H**, Liu Y, Cai R, Li Y, Gu B. A narrative review of relationship between gut microbiota and neuropsychiatric disorders: mechanisms and clinical application of probiotics and prebiotics. *Ann Palliat Med* 2021; **10**: 2304-2313 [PMID: [33549028](#) DOI: [10.21037/apm-20-1365](#)]
- 217 **Abdellatif B**, McVeigh C, Bendriss G, Chaari A. The Promising Role of Probiotics in Managing the Altered Gut in Autism Spectrum Disorders. *Int J Mol Sci* 2020; **21** [PMID: [32532137](#) DOI: [10.3390/ijms21114159](#)]
- 218 **Davani-Davari D**, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, Berenjian A, Ghasemi Y. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. *Foods* 2019; **8** [PMID: [30857316](#) DOI: [10.3390/foods8030092](#)]
- 219 **Grimaldi R**, Gibson GR, Vulevic J, Giallourou N, Castro-Mejía JL, Hansen LH, Leigh Gibson E, Nielsen DS, Costabile A. A prebiotic intervention study in children with autism spectrum disorders (ASDs). *Microbiome* 2018; **6**: 133 [PMID: [30071894](#) DOI: [10.1186/s40168-018-0523-3](#)]
- 220 **Lu C**, Rong J, Fu C, Wang W, Xu J, Ju XD. Overall Rebalancing of Gut Microbiota Is Key to Autism Intervention. *Front Psychol* 2022; **13**: 862719 [PMID: [35712154](#) DOI: [10.3389/fpsyg.2022.862719](#)]
- 221 **Sanctuary MR**, Kain JN, Chen SY, Kalanetra K, Lemay DG, Rose DR, Yang HT, Tancredi DJ, German JB, Slupsky CM, Ashwood P, Mills DA, Smilowitz JT, Angkustsiri K. Pilot study of probiotic/colostrum supplementation on gut function in children with autism and gastrointestinal symptoms. *PLoS One* 2019; **14**: e0210064 [PMID: [30625189](#) DOI: [10.1371/journal.pone.0210064](#)]
- 222 **Kong XJ**, Liu J, Liu K, Koh M, Sherman H, Liu S, Tian R, Sukijthamapan P, Wang J, Fong M, Xu L, Clairmont C, Jeong MS, Li A, Lopes M, Hagan V, Dutton T, Chan SP, Lee H, Kendall A, Kwong K, Song Y. Probiotic and Oxytocin Combination Therapy in Patients with Autism Spectrum Disorder: A Randomized, Double-Blinded, Placebo-Controlled Pilot Trial. *Nutrients* 2021; **13** [PMID: [34062986](#) DOI: [10.3390/nu13051552](#)]
- 223 **Li N**, Chen H, Cheng Y, Xu F, Ruan G, Ying S, Tang W, Chen L, Chen M, Lv L, Ping Y, Chen D, Wei Y. Fecal Microbiota Transplantation Relieves Gastrointestinal and Autism Symptoms by Improving the Gut Microbiota in an Open-Label Study. *Front Cell Infect Microbiol* 2021; **11**: 759435 [PMID: [34737978](#) DOI: [10.3389/fcimb.2021.759435](#)]
- 224 **Kang DW**, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, Khoruts A, Geis E, Maldonado J, McDonough-Means S, Pollard EL, Roux S, Sadowsky MJ, Lipson KS, Sullivan MB, Caporaso JG, Krajmalnik-Brown R. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome* 2017; **5**: 10 [PMID: [28122648](#) DOI: [10.1186/s40168-016-0225-7](#)]
- 225 **Hadrich D**. Microbiome Research Is Becoming the Key to Better Understanding Health and Nutrition. *Front Genet* 2018; **9**: 212 [PMID: [29951086](#) DOI: [10.3389/fgene.2018.00212](#)]
- 226 **Johnson D**, Letchumanan V, Thurairajasingam S, Lee LH. A Revolutionizing Approach to Autism Spectrum Disorder Using the Microbiome. *Nutrients* 2020; **12** [PMID: [32635373](#) DOI: [10.3390/nu12071983](#)]

Gastrointestinal and nutritional care in pediatric neuromuscular disorders

Valeria Dipasquale, Rossella Morello, Claudio Romano

Specialty type: Nutrition and dietetics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Amornyotin S, Thailand; Kawabata H, Japan; Torres MRF, Brazil

Received: March 27, 2023

Peer-review started: March 27, 2023

First decision: June 14, 2023

Revised: July 4, 2023

Accepted: August 9, 2023

Article in press: August 9, 2023

Published online: September 9, 2023



Valeria Dipasquale, Rossella Morello, Claudio Romano, Department of Human Pathology in Adulthood and Childhood “G. Barresi”, University Hospital “G. Martino”, Messina 98124, Italy

Corresponding author: Valeria Dipasquale, MD, PhD, Doctor, Department of Human Pathology in Adulthood and Childhood “G. Barresi”, University Hospital “G. Martino”, Via Consolare Valeria 1, Messina 98124, Italy. dipasquale.valeria@libero.it

Abstract

Neuromuscular diseases (NMDs) affect the development and growth of the neuromuscular system in children. The pathology can occur anywhere along the neuromuscular pathway, from the brain to the nerves to the muscle fibers. These diseases have a profound impact on the quality of life not only of children but also of their families. The predominant manifestation in NMDs is hypotonia, which leads to muscle weakness and fatigue, reduced mobility, and decreased physical performance. However, multiple organ systems can be affected, with resulting orthopedic, cardiac, infectious, respiratory, and nutritional problems. Children with NMD present an increased risk for several dietary and feeding difficulties because of their neuromuscular diagnosis, presentation, and severity. These problems include chronic gastrointestinal issues (constipation, dysphagia, gastroesophageal reflux, and diarrhea), dysphagia, malnutrition, and body composition alterations. As a result, compared to the overall pediatric population, infants and children with NMD are more likely to be malnourished, ranging from failure to thrive to overweight or obesity. Disease-specific guidelines vary in level of detail and recommendations for dietary management. Overall, nutritional data available are sparse, with the exception of Duchenne muscular dystrophy, spinal muscular atrophy, and congenital muscular dystrophy. The purpose of this review is to describe the spectrum of nutritional challenges in children with NMD and to summarize the main dietary and gastrointestinal recommendations for each neuromuscular disorder to provide guidance for daily clinical practice.

Key Words: Neuromuscular disorders; Diet; Malnutrition; Overweight; Dysphagia; Gastrointestinal dysmotility; Gastrointestinal symptoms; Tube feeding

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Pediatric neuromuscular disorders (NMDs) can be associated with a range of nutritional issues, such as insufficient or excessive weight gain, difficulty in swallowing, constipation, diarrhea, vomiting, gastroesophageal reflux disease, and micronutrient deficiencies. We herein discuss the spectrum of nutritional challenges in children with NMD and summarize the currently available dietary and gastrointestinal recommendations for each neuromuscular disorder to provide guidance for daily clinical practice.

Citation: Dipasquale V, Morello R, Romano C. Gastrointestinal and nutritional care in pediatric neuromuscular disorders. *World J Clin Pediatr* 2023; 12(4): 197-204

URL: <https://www.wjgnet.com/2219-2808/full/v12/i4/197.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i4.197>

INTRODUCTION

Pediatric neuromuscular disorders (NMDs) include a variety of diseases where the peripheral nervous system is the main site of abnormalities or damage. These include disorders of the anterior horn cell (*i.e.*, spinal muscular atrophy, poliomyelitis, and amyotrophic lateral sclerosis), peripheral nerve (*i.e.*, Charcot-Marie-Tooth disease), neuromuscular junction (*i.e.*, congenital myasthenic syndrome), and musculature (*i.e.*, myopathies and muscular dystrophies)[1]. The main and most frequent symptom in NMDs is hypotonia, which leads to muscle weakness, fatigue, reduced mobility, and decreased physical performance. Furthermore, a deterioration of the quality of life for NMD patients and their families is frequently brought on by orthopedic, cardiac, infectious, and respiratory issues[2]. Nutritional and gastrointestinal complications are also frequent in NMDs, but they are sometimes underestimated[2]. Compared with the general pediatric population, infants and children with NMDs are at higher risk of malnutrition, ranging from failure to thrive to being overweight or obese (Table 1)[3,4].

Moreover, they present an increased risk of developing chronic gastrointestinal (GI) conditions such as constipation, gastroesophageal reflux disease (GERD), dysphagia, and delayed gastric emptying. Several aspects related to nutrition need to be considered when prolonging survival in patients with NMD, including the negative impact of overnutrition on glucose metabolism, mobility, respiratory, and cardiac function and the effects of undernutrition on muscle development and strength ventilation function. In addition, difficulty chewing and swallowing can lead to a higher risk of aspiration, which predisposes to infectious diseases and respiratory issues[2]. Micronutrient deficiencies, such as vitamin D and calcium deficiencies, can affect bone health, particularly in children with Duchenne muscular dystrophy (DMD) who receive steroids (side effects include bone loss and fractures)[4,5].

The importance of optimal nutritional and GI management lies in reducing complications and mortality and improving the quality of life in this group of patients[4,5]. A particular attention to these issues is required with an early and appropriate approach. The purpose of this review is to describe the spectrum of nutritional problems in children with NMD and to provide specific dietary and GI recommendations for each NMD.

MATERIALS AND METHODS

For this review, relevant studies published over the last 20 years were identified *via* a PubMed/Medline (<http://www.ncbi.nlm.nih.gov/pubmed/>) search using the following keywords or combinations of keywords: neuromuscular disorders, malnutrition, overnutrition, diet, GI symptoms, management, guidelines. All of the most common neuromuscular disorders were afterwards used as search terms to review literature data regarding the GI and nutritional issues. Particular emphasis was placed on evidence-based guidelines and all high-quality studies illustrating current management pathways. Additional papers were identified by reviewing reference lists of relevant publications. Non-English publications were excluded. A systematic approach to study selection was not implemented. Instead, data were extracted based on their relevance to the topic.

RESULTS

Duchenne muscular dystrophy

DMD is an X-linked recessive disorder caused by out-of-frame mutations in the dystrophin gene (DMD; locus Xp21.2). These mutations result in a deficiency or absence of the protein dystrophin, leading to progressive muscle degeneration and the loss of the ability to walk independently[6]. The type of mutation and how it affects dystrophin synthesis are the primary factors in the different phenotypic expression[6]. There are also milder allelic forms of the disease, such as intermediate muscular dystrophy and Becker muscular dystrophy, which result in loss of walking ability by ages 13-16 and over 16, respectively[7]. DMD affects 1 in 3600-6000 male births and is the most common pediatric muscular dystrophy[7]. Initial presentation ranges from motor delay, walking slowly, and difficulty getting up from the floor (Gower's sign) to loss of the ability to walk and use of a wheelchair for mobility (since adolescence) without treatment[8].

Table 1 Neuromuscular diseases and Neuromuscular disorder-related nutritional issues

NMD	Potential nutritional issue(s)
Spinal muscular atrophy	Dysphagia, weight loss ^a
Duchenne muscular dystrophy	Overweight/obesity, dysphagia, weight loss ^b
Myotonic dystrophy type 1	Weight loss/underweight, feeding difficulties
Congenital myopathies	Underweight/growth failure, feeding and swallowing difficulty
Charcot-Marie-Tooth disease	Unknown
Limb-Girdle muscular dystrophy	Unknown

^aEspecially spinal muscular atrophy type I and II.

^bIn later stages of Duchenne muscular dystrophy (due to progressive muscle weakness).

NMDs: Neuromuscular disorders.

Glucocorticoids (GCs) (prednisone 0.75 mg/kg/d as first-line unless otherwise indicated) are the only drugs that currently supports children with DMD in maintaining muscle strength and functionality[1]. GCs are relatively well tolerated, although significant weight gain and small height gains are commonly observed. Other (rare) serious side effects include hypertension, glycosuria, osteoporosis, GI lesions, and adrenal crisis[1].

To help multidisciplinary care teams manage this complex pathology, the US Centers for Disease Control and Prevention (CDC) selected a working group in 2018 to develop DMD care recommendations, including consideration of diet and GI health[9]. The most important goals in nutritional and gastrointestinal management include: (1) Optimization of macronutrient intake to avoid growth failure or obesity; (2) management of feeding and swallowing issues; (3) treatment of the GI symptoms; and (4) monitoring micronutrient intakes such as vitamin D and calcium[9]. Nutritional and GI evidence for DMD children is summarized in Table 2.

Nutritional management

The purpose of nutritional management is to prevent overweight or obesity and under- or malnutrition through regular assessment of growth and weight and the promotion of a healthy, balanced diet. A registered dietitian, an essential member of the multidisciplinary DMD care team, should record the patient's weight and height on growth charts[9].

Unlike other NMDs, specific growth curves are available for DMD. In a sample of 26 patients with DMD, Griffiths *et al* [10] estimated total muscle mass using 24-h urine creatinine excretion and discovered a 4% loss in muscle mass per year.

The authors developed a weight *vs* age curve for DMD that would determine the appropriate percentile by initially identifying the percentiles on a standard percentile height table. Recent studies have revealed that urinary creatinine excretion is not a reliable predictor of skeletal muscle mass in DMD, which challenges the logic of these charts based on [11]. Using recurrent growth measurements in a cohort of 513 DMD individuals aged 2 to 12 years from the Muscular Dystrophy Surveillance, Tracking, and Research Network, West *et al*[12] created growth curves specifically for DMD. Based on the CDC clinical growth charts, these curves demonstrated that male DMD patients were shorter than unaffected boys and tended to be overweight. The same team, later, visited the Muscular Dystrophy Surveillance, Tracking, and Research Network cohort to survey it, and they recently presented growth data in a cohort of 324 outpatients receiving GC therapy for at least 6 mo[13]. In contrast to untreated patients, this cohort had shorter stature, more weight, and a higher body mass index[9].

After a correct interpretation of the anthropometric measurements, the dietitian should offer a nutritional plan that includes recommendations for increasing, decreasing, or maintaining caloric intake and water requirement as well as suggestions for modifying food textures to promote secure and pleasurable chewing and swallowing[9].

In the case of DMD and other NMDs, patient obesity is often attributed to a reduction in calorie requirements coupled with a decrease in physical activity and resting energy expenditure. In addition, chronic treatment with steroids can increase appetite and promote excess caloric intake. Instead, patients in the late stages of the disease may be malnourished and underweight[2,9]. Muscle weakness and its sequelae (dysphagia, constipation, delayed gastric emptying, prolonged mealtimes, and dependent food intake) are the main causes of malnutrition, and the presence of respiratory failure can cause increased energy demands. The result of malnutrition and increased energy needs is a negative energy balance and progressive weight loss[9].

As the disease progresses, most patients begin to experience increasing difficulty with chewing and swallowing[14]. The onset of dysphagia symptoms can be gradual, and the impact of oral-pharyngeal dysphagia might be under-recognized and under-reported by patients[15]. Dysphagia may manifest as unintentional weight loss or a slowing of the normal age-related weight growth. Tube feeding *via* gastrostomy should be considered early in patients with DMD. In the absence of symptoms consistent with suspected GERD, a polymeric formula may be considered initially. Alternatively, bolus feeding with home-made foods can be suggested and effective in children with chronic constipation[9].

According to the 2018 DMD Care Considerations, serum calcium and 25-hydroxyvitamin D levels should be regularly monitored once a year as part of routine bone health management. Vitamin D and mineral supplementation should be considered in all children if levels cannot be maintained[15].

Table 2 Nutritional and gastrointestinal management in children with Duchenne muscular dystrophy

Issue	Evidence
Tube feeding	Low to high probability (based on the stage of the disease)
Energy needs	Meet DRI
Formula	No special diet or formula
ONS	Possible; consider a speech-language therapist evaluation
Gastroesophageal reflux	Proton pump inhibitors; consider hydrolyzed or natural food enteral formulas
Constipation	PEG; consider hydrolyzed or natural food enteral formulas
Delayed gastric emptying	Meet fiber and fluid needs; prokinetics may be used

DMD: Duchenne muscular dystrophy; DRI: Daily recommended intake; ONS: Oral nutrition supplements; PEG: Polyethylene glycol.

GI symptoms management

The most common GI symptoms in DMD patients are GERD and constipation. GER may be related to altered gastric smooth muscle cell emptying function. Treatment includes the early use of proton pump inhibitors. Regarding constipation, the use of polyethylene glycol after gastrostomy placement is recommended to prevent the use of high oral volumes, both of which are associated with the risk of bronchoaspiration[2]. Increasing fiber intake or using natural food enteral formulas could also be considered to treat constipation[16,17].

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease caused by a homozygous mutation or deletion in the survival motor neuron 1 (SMN1) gene. Defects in the SMN1 gene cause the selective destruction of alpha motor neurons in the anterior horn cells of the spinal cord and brainstem. Clinical manifestations include muscle atrophy and weakness, resulting in swallowing and feeding difficulties and respiratory complications. SMA affects approximately one in 6000-10000 newborns worldwide[18]. The classification of SMA consists of four subtypes based on age of onset and maximal functional ability: very weak infants unable to sit unsupported, onset < 6 mo of age (type 1), nonambulant patients able to sit independently, onset between 6 and 18 mo of age (type 2), ambulant patients with onset between 18 mo and 18 years (type 3), and adult onset SMA (type 4).

The SMA multidisciplinary care focuses on reducing complications and improving quality of life. Symptoms of GI dysfunction, including constipation, delayed gastric emptying, and GERD, are important determinants of mortality and morbidity, for example dysphagia and reflux can lead to pulmonary disease[19].

In 2007, a consensus statement was published by the International Conference on the Standard of Care for SMA. A two-part update of the topics covered in the prior recommendations was published in 2018 as a result of the more current data publications and more generally made advancements in the themes mentioned in the original version[20].

One of the nine topics included in this update focused on nutrition. The main nutritional goals, which are slightly different for each type of SMA, include weight control, swallowing and dysphagia management, and management of GI dysfunction. Regular growth checks are important for all SMA types. Growth and body composition are measured using a variety of methods, such as basic anthropometry, dual-energy X-ray absorptiometry, and bioelectrical impedance analysis[19,20].

Specific growth charts for SMA are not currently available. Due to modifying body composition in standardized SMA growth charts, it may be helpful to monitor growth trends rather than monitor weight. In contrast, children with SMA type III are prone to overeating and obesity from physical inactivity and have reduced energy needs due to lower basal metabolic rates[3].

For optimal care, a nutritionist assessment is recommended every 3-6 mo for younger children and annually for older children and adults[20]. In addition, a qualified dietician should also promote healthy nutrition and keep track of hydration, macronutrient, and micronutrient intake, particularly calcium and vitamin D intake for bone health. Calcium and vitamin D supplements are recommended if the levels are low. It's crucial to inquire and record the specifics of GI symptoms in all subjects, which could include GERD, constipation, use of bowel regulators, delayed gastric emptying, and vomiting.

Infants and children with SMA types I and II should receive gastrostomies in the first few months of life to avoid the risk of malnutrition. This approach is also recommended to reduce the risk of respiratory infections[20]. Nutritional and GI evidence for SMA children is summarized in Table 3.

Non-sitter patients

Some aspects of nutrition assessments and interventions can differ among non-sitters, sitters, and ambulant patients[20]. One of the most significant considerations to take into account for a non-sitting child is safe swallowing, as bulbar dysfunction can lead to aspiration and lung infections. Recent data suggest that children with SMA type 1 should have a

Table 3 Nutritional and gastrointestinal management in children with spinal muscular atrophy

Issue	Evidence
Tube feeding	High probability (type 1 and 2)
Energy needs	Meet DRI
Formula	No special diet or formula
ONS	Possible (type 3 and 4); consider a speech-language therapist evaluation
Gastroesophageal reflux	Proton pump inhibitors; consider hydrolyzed or natural food enteral formulas
Constipation	PEG; consider hydrolyzed or natural food enteral formulas
Delayed gastric emptying	Meet fiber and fluid needs; prokinetics may be used

DRI: Daily recommended intake; ONS: Oral nutrition supplements; PEG: Polyethylene glycol.

videofluoroscopic swallow examination soon after diagnosis and when there are clinical indications suggestive of dysphagia (weak sucking, fatigue, a wet voice, pneumonia) to assess bulbar function and prevent growth failure[21,22]. In type 1 patient, reduced caloric intake and the possibility of malnutrition are caused by respiratory issues, dysphagia, and weak masticatory muscles. In addition, tachypnea can increase energy expenditure and calorie needs, further increasing the risk of malnutrition[20].

Sitter patients

Sitter patients may have a higher risk of being overweight or obese as a result of reductions in physical activity due to weakness and altered body composition[3,23]. Obesity can lead to reduced mobility and increased risks for associated comorbidities, including the metabolic syndrome.

Walkers

Swallowing disorders and feeding problems are rare in walkers[20]. The main nutritional concern is the risk of obesity and overweight, as these conditions can impair mobility and raise the possibility of comorbidities like metabolic syndrome, hypertension, and diabetes[3,20].

CHARCOT-MARIE-TOOTH DISEASE

Charcot-Marie-Tooth disease (CMT) is the most common inherited NMD with an estimated prevalence of up to 40 in 100000 people, which corresponds to 200000 cases in the European Union[24]. The disease generally appears in the first two decades of life and progresses slowly over many years. It is a genetically heterogeneous disorder resulting from mutations in genes that encode proteins in various locations, which include compact and non-compact myelin, Schwann cells, and axons. These proteins are involved in a wide variety of functions, including myelin compaction and maintenance, formation of the cytoskeleton and axonal transport rich, as well as mitochondrial metabolism[25]. Since motor and sensory peripheral nerves are affected, CMT is also known as hereditary motor and sensory neuropathy. Distal weakness, hand and foot deformities, slow loss of sensory perception, and mild to moderate disability are the most common clinical phenotypes.

There is still no effective drug therapy for CMT. A multidisciplinary approach is necessary for therapeutic management; the neurologist should work closely with other professionals such as orthopedics for the surgical treatment of skeletal deformities and soft tissue anomalies[1,25].

There are no specific nutritional recommendations for this patient group, and the nutritional approach must be evaluated individually. Sometimes the use of oral nutritional supplements may be recommended. Skeletal deformities may be associated with an increased risk of GERD.

CONGENITAL MUSCULAR DYSTROPHIES

Congenital muscular dystrophies (CMD) are a group of genetic neuromuscular disorders defined by muscle weakness that appears at birth or in the first few months of life and the presence of dystrophic biopsies and/or increased creatine kinase, two markers that are diagnostic of a muscular dystrophy[26]. The identification of different CMD subtypes backed by precise gene identification has been made possible by developments in molecular genetics and histopathology techniques[27]. Despite rapid advances in basic research, clinical care for patients with CMD remains poor due to the rarity of this pathology and the difficulty of differentiating clinical phenotypes.

The International Standard of Care Committee for Congenital Muscular Dystrophy published a consensus statement in November 2009 on standards of medical care divided into 7 areas: Diagnosis, neurology, pulmonology, orthopedics,

gastroenterology and nutrition, speech, and oral care, cardiology, and palliative care[28]. Main topics are nutrition and growth, food intake, GI motility, and oral care[28]. There are no specific growth charts or data on the energy and nutritional needs of CMD children, and this makes monitoring nutrition and growth even more difficult[28]. Patients with CMD often have a growth trajectory that is below age, and one of the most typical childhood problems is malnutrition and poor weight gain. Instead, obesity should be considered in adults due to the limited mobility of these patients.

In this group of patients, special attention needs to be paid to feeding and swallowing problems, which should be evaluated regularly during routine clinic visits, asking about: (1) Length of meals; (2) frequency of meals; (3) frequency of lung infections; (4) difficulty chewing (choking and coughing); (5) change in the structure of food; (6) stress in the family or enjoyment of meals for the child and parents; and (7) ability to eat independently. Videofluoroscopy can reveal difficulties in the oral phase, a delay in pharyngeal swallowing, and increased risks with aspiration[28]. In the case of dysphagia and feeding problems, treatment strategies may include adjustments in standing positioning and sitting, support for self-feeding, which include adjustment of feeding utensils and devices, safe swallowing procedures, and texture modification. When symptomatic treatment is inadequate, the use of tube feeding must be considered.

GERD and GI dysmotility, *i.e.*, delayed gastric emptying and constipation, are common in CMD patients. In order to minimize the risk of gastroesophageal reflux and dysmotility, the frequency and volume of tube feeding should be adjusted and attention should be paid to adequate fluid intake, posture, and movement. Medical treatment includes use of proton pump inhibitors and treatment with antacids and laxatives for GERD and constipation, respectively[28]. Increasing fiber intake or using natural food enteral formulas could also be considered to treat constipation[16,17].

MYOTONIC DYSTROPHY

Myotonic dystrophy (MD) is the most common form of muscular dystrophy in adults, with an estimated prevalence of 1 in 8000[29]. Myotonia and muscular dystrophy were traditionally used to name this multisystem condition. Myotonic dystrophy type 1 (MD1, Steinert disease) is caused by a cytosine, thymine, and guanine repeat expansion in the 3rd untranslated region of the myotonic dystrophy protein kinase gene on chromosome 19[30]. MD1 patients range from asymptomatic or moderately severe, late adult onset to severe congenital variants, with an autosomal dominant inheritance pattern. In particular, congenital MD is the most severe form and may present prenatally with polyhydramnios and reduced fetal movements.

Respiratory failure, hypotension, feeding difficulty, weakness, and tented or fish-shaped upper lips are all frequent at birth[30]. Facial weakness, dysarthria, myotonia, low intellect, and cardiac conduction anomalies characterize the childhood-onset (1-10 years) phenotype[31]. Patients may gradually present with early cataracts, myotonia, muscle weakness or atrophy, fatigue, excessive daytime sleepiness, central or obstructive apnea, respiratory failure, cardiac arrhythmia, insulin resistance, dysphagia, GI dysmotility, cognitive impairment, cluster C personality traits, and/or mood swings.

No particular dietary risks are reported for MD patients, although each patient must be assessed on an individual basis. The major GI problems that arise during the course of the disease are dysphagia, postprandial bloating or abdominal pain, diarrhea, constipation, and/or fecal incontinence, and cholelithiasis[31]. Drug therapy for the treatment of GERD does not differ from that for other patient groups[32].

CONCLUSION

The management of children with NMDs, who frequently present with nutritional issues like inappropriate weight and body composition, difficulty swallowing and feeding, constipation, and GERD, places a high priority on nutritional care. Effective interdisciplinary management can considerably lower morbidity and mortality even though there is often no treatment available.

This present study is an unstructured, narrative review, so there are inherent limitations, such as the lack of direct comparison between studies. However, we described the methods for selecting and reviewing literature to make it possible to verify or replicate these results. Moreover, the heterogeneity of the published studies on the nutritional and GI care of pediatric patients with NMDs made it challenging to implement a systematic approach to study selection and interpretation. The aims of the present article were to report the spectrum of nutritional problems in children with NMD and to provide clinicians with specific dietary and GI directions for each NMD while highlighting the knowledge gaps in this topic. There are no specific nutritional and GI recommendations for all of the NMDs in the scientific literature currently available, especially in the pediatric age group. More nutritional and GI data are available for DMD and SMA. Future studies should focus on creating disease-specific treatment guidelines, including dietary recommendations based on age group, physical activity status, and swallowing problems. This patient population is at high nutritional risk, so a proactive attitude is recommended. The clinician should plan for the early use of tube feeding and the appropriate selection of the most appropriate formula, with a particular interest in enteral hydrolyzed formulas. In terms of GI symptoms, the greatest challenges lie in the treatment of GERD and chronic constipation. The use of drugs to inhibit acid secretion should be prompt. The possibility of increasing fiber intake or the use of natural food formulas in enteral feeding should also be considered to further assist in the management of constipation.

FOOTNOTES

Author contributions: Dipasquale V, Morello R and Romano C equally contributed to the article.

Conflict-of-interest statement: All the authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Italy

ORCID number: Valeria Dipasquale 0000-0003-3328-0734.

S-Editor: Liu JH

L-Editor: A

P-Editor: Yuan YY

REFERENCES

- 1 Dowling JJ, D Gonorazky H, Cohn RD, Campbell C. Treating pediatric neuromuscular disorders: The future is now. *Am J Med Genet A* 2018; **176**: 804-841 [PMID: 28889642 DOI: 10.1002/ajmg.a.38418]
- 2 Salera S, Menni F, Moggio M, Guez S, Sciacco M, Esposito S. Nutritional Challenges in Duchenne Muscular Dystrophy. *Nutrients* 2017; **9** [PMID: 28604599 DOI: 10.3390/nu9060594]
- 3 De Amicis R, Baranello G, Foppiani A, Leone A, Battezzati A, Bedogni G, Ravella S, Giaquinto E, Mastella C, Agosto C, Bertini E, D'Amico A, Pedemonte M, Bruno C, Wells JC, Fewtrell M, Bertoli S. Growth patterns in children with spinal muscular atrophy. *Orphanet J Rare Dis* 2021; **16**: 375 [PMID: 34481516 DOI: 10.1186/s13023-021-02015-9]
- 4 Chou E, Lindeback R, Sampaio H, Farrar MA. Nutritional practices in pediatric patients with neuromuscular disorders. *Nutr Rev* 2020; **78**: 857-865 [PMID: 31968103 DOI: 10.1093/nutrit/nuz109]
- 5 Chou E, Lindeback R, D'Silva AM, Sampaio H, Neville K, Farrar MA. Growth and nutrition in pediatric neuromuscular disorders. *Clin Nutr* 2021; **40**: 4341-4348 [PMID: 33551221 DOI: 10.1016/j.clnu.2021.01.013]
- 6 Brinkmeyer-Langford C, Kornegay JN. Comparative Genomics of X-linked Muscular Dystrophies: The Golden Retriever Model. *Curr Genomics* 2013; **14**: 330-342 [PMID: 24403852 DOI: 10.2174/13892029113149990004]
- 7 Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol* 2010; **9**: 77-93 [PMID: 19945913 DOI: 10.1016/S1474-4422(09)70271-6]
- 8 McDonald CM. Clinical approach to the diagnostic evaluation of hereditary and acquired neuromuscular diseases. *Phys Med Rehabil Clin N Am* 2012; **23**: 495-563 [PMID: 22938875 DOI: 10.1016/j.pmr.2012.06.011]
- 9 Brumbaugh D, Watne L, Gottrand F, Gulyas A, Kaul A, Larson J, Tomezsko J. Nutritional and Gastrointestinal Management of the Patient With Duchenne Muscular Dystrophy. *Pediatrics* 2018; **142**: S53-S61 [PMID: 30275249 DOI: 10.1542/peds.2018-0333G]
- 10 Griffiths RD, Edwards RH. A new chart for weight control in Duchenne muscular dystrophy. *Arch Dis Child* 1988; **63**: 1256-1258 [PMID: 3196052 DOI: 10.1136/adc.63.10.1256]
- 11 Franciotta D, Zanardi MC, Albertotti L, Orcesi S, Berardinelli A, Pichiecchio A, Uggetti C, Tagliabue A. Measurement of skeletal muscle mass in Duchenne muscular dystrophy: use of 24-h creatinine excretion. *Acta Diabetol* 2003; **40** Suppl 1: S290-S292 [PMID: 14618496 DOI: 10.1007/s00592-003-0089-8]
- 12 West NA, Yang ML, Weitzenkamp DA, Andrews J, Meaney FJ, Oleszek J, Miller LA, Matthews D, DiGuseppi C. Patterns of growth in ambulatory males with Duchenne muscular dystrophy. *J Pediatr* 2013; **163**: 1759-1763.e1 [PMID: 24103921 DOI: 10.1016/j.jpeds.2013.08.004]
- 13 Lamb MM, West NA, Ouyang L, Yang M, Weitzenkamp D, James K, Cialfoni E, Pandya S, DiGuseppi C; Muscular Dystrophy Surveillance, Research, and Tracking Network (MD STARnet). Corticosteroid Treatment and Growth Patterns in Ambulatory Males with Duchenne Muscular Dystrophy. *J Pediatr* 2016; **173**: 207-213.e3 [PMID: 27039228 DOI: 10.1016/j.jpeds.2016.02.067]
- 14 Toussaint M, Davidson Z, Bouvoie V, Evenepoel N, Haan J, Soudon P. Dysphagia in Duchenne muscular dystrophy: practical recommendations to guide management. *Disabil Rehabil* 2016; **38**: 2052-2062 [PMID: 26728920 DOI: 10.3109/09638288.2015.1111434]
- 15 Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol* 2010; **9**: 177-189 [PMID: 19945914 DOI: 10.1016/S1474-4422(09)70272-8]
- 16 Romano C, Pallio S, Cucinotta U, Accorsi P, Dipasquale V. Fibers in pediatric functional gastrointestinal disorders. Practical considerations from clinical cases. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 583-587 [PMID: 33522316 DOI: 10.1080/17474124.2021.1884543]
- 17 Dipasquale V, Diamanti A, Trovato CM, Elia D, Romano C. Real food in enteral nutrition for chronically ill children: overview and practical clinical cases. *Curr Med Res Opin* 2022; **38**: 831-835 [PMID: 35274578 DOI: 10.1080/03007995.2022.2052514]
- 18 D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. *Orphanet J Rare Dis* 2011; **6**: 71 [PMID: 22047105 DOI: 10.1186/1750-1172-6-71]
- 19 Moore GE, Lindenmayer AW, McConchie GA, Ryan MM, Davidson ZE. Describing nutrition in spinal muscular atrophy: A systematic review. *Neuromuscul Disord* 2016; **26**: 395-404 [PMID: 27241822 DOI: 10.1016/j.nmd.2016.05.005]

- 20 **Mercuri E**, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Qian Y, Sejersen T; SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord* 2018; **28**: 103-115 [PMID: 29290580 DOI: 10.1016/j.nmd.2017.11.005]
- 21 **Aton J**, Davis RH, Jordan KC, Scott CB, Swoboda KJ. Vitamin D intake is inadequate in spinal muscular atrophy type I cohort: correlations with bone health. *J Child Neurol* 2014; **29**: 374-380 [PMID: 23334077 DOI: 10.1177/0883073812471857]
- 22 **Berti B**, Fanelli L, de Sanctis R, Onesimo R, Palermo C, Leone D, Carnicella S, Norcia G, Forcina N, Coratti G, Giorgio V, Cerchiari A, Lucibello S, Finkel R, Pane M, Mercuri E. Oral and Swallowing Abilities Tool (OrSAT) for Type 1 SMA Patients: Development of a New Module. *J Neuromuscul Dis* 2021; **8**: 589-601 [PMID: 34024771 DOI: 10.3233/JND-200614]
- 23 **Sproule DM**, Montes J, Montgomery M, Battista V, Koenigsberger D, Shen W, Punyanitya M, De Vivo DC, Kaufmann P. Increased fat mass and high incidence of overweight despite low body mass index in patients with spinal muscular atrophy. *Neuromuscul Disord* 2009; **19**: 391-396 [PMID: 19427208 DOI: 10.1016/j.nmd.2009.03.009]
- 24 **Sivera R**, Sevilla T, Vilchez JJ, Martínez-Rubio D, Chumillas MJ, Vázquez JF, Muelas N, Bataller L, Millán JM, Palau F, Espinós C. Charcot-Marie-Tooth disease: genetic and clinical spectrum in a Spanish clinical series. *Neurology* 2013; **81**: 1617-1625 [PMID: 24078732 DOI: 10.1212/WNL.0b013e3182a9f56a]
- 25 **Pareyson D**, Marchesi C. Diagnosis, natural history, and management of Charcot-Marie-Tooth disease. *Lancet Neurol* 2009; **8**: 654-667 [PMID: 19539237 DOI: 10.1016/S1474-4422(09)70110-3]
- 26 **Bertini E**, D'Amico A, Gualandi F, Petrini S. Congenital muscular dystrophies: a brief review. *Semin Pediatr Neurol* 2011; **18**: 277-288 [PMID: 22172424 DOI: 10.1016/j.spen.2011.10.010]
- 27 **Fu XN**, Xiong H. Genetic and Clinical Advances of Congenital Muscular Dystrophy. *Chin Med J (Engl)* 2017; **130**: 2624-2631 [PMID: 29067961 DOI: 10.4103/0366-6999.217091]
- 28 **Wang CH**, Bonnemant CG, Rutkowski A, Sejersen T, Bellini J, Battista V, Florence JM, Schara U, Schuler PM, Wahbi K, Aloysius A, Bash RO, Bérout C, Bertini E, Bushby K, Cohn RD, Connolly AM, Deconinck N, Desguerre I, Eagle M, Estournet-Mathiaud B, Ferreira A, Fujak A, Goemans N, Iannaccone ST, Jouinot P, Main M, Melacini P, Mueller-Felber W, Muntoni F, Nelson LL, Rahbek J, Quijano-Roy S, Sewry C, Storhaug K, Simonds A, Tseng B, Vajsaar J, Vianello A, Zeller R; International Standard of Care Committee for Congenital Muscular Dystrophy. Consensus statement on standard of care for congenital muscular dystrophies. *J Child Neurol* 2010; **25**: 1559-1581 [PMID: 21078917 DOI: 10.1177/0883073810381924]
- 29 **Suominen T**, Bachinski LL, Auvinen S, Hackman P, Baggerly KA, Angelini C, Peltonen L, Krahe R, Udd B. Population frequency of myotonic dystrophy: higher than expected frequency of myotonic dystrophy type 2 (DM2) mutation in Finland. *Eur J Hum Genet* 2011; **19**: 776-782 [PMID: 21364698 DOI: 10.1038/ejhg.2011.23]
- 30 **Udd B**, Krahe R. The myotonic dystrophies: molecular, clinical, and therapeutic challenges. *Lancet Neurol* 2012; **11**: 891-905 [PMID: 22995693 DOI: 10.1016/S1474-4422(12)70204-1]
- 31 **Ho G**, Cardamone M, Farrar M. Congenital and childhood myotonic dystrophy: Current aspects of disease and future directions. *World J Clin Pediatr* 2015; **4**: 66-80 [PMID: 26566479 DOI: 10.5409/wjcp.v4.i4.66]
- 32 **Smith CA**, Gutmann L. Myotonic Dystrophy Type 1 Management and Therapeutics. *Curr Treat Options Neurol* 2016; **18**: 52 [PMID: 27826760 DOI: 10.1007/s11940-016-0434-1]



Retrospective Cohort Study

Accidental ingestion of foreign bodies/harmful materials in children from Bahrain: A retrospective cohort study

Hasan M Isa, Shaikha A Aldoseri, Aysha S Abduljabbar, Khaled A Alsulaiti

Specialty type: Pediatrics

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

P-Reviewer: Huang JG, Singapore; Osatakul S, Thailand

Received: April 28, 2023

Peer-review started: April 28, 2023

First decision: May 25, 2023

Revised: June 9, 2023

Accepted: July 7, 2023

Article in press: July 7, 2023

Published online: September 9, 2023



Hasan M Isa, Shaikha A Aldoseri, Aysha S Abduljabbar, Department of Pediatrics, Salmaniya Medical Complex, Manama 26671, Bahrain

Hasan M Isa, Department of Pediatrics, Arabian Gulf University, Manama 26671, Bahrain

Khaled A Alsulaiti, Department of Radiology, Salmaniya Medical Complex, Manama 26671, Bahrain

Corresponding author: Hasan M Isa, MBChB, Associate Professor, Consultant Physician-Scientist, Department of Pediatrics, Salmaniya Medical Complex, 2904, Manama 26671, Bahrain. halfaraj@hotmail.com

Abstract

BACKGROUND

Children like to discover their environment by putting substances in their mouths. This behavior puts them at risk of accidentally ingesting foreign bodies (FBs) or harmful materials, which can cause serious morbidities.

AIM

To study the clinical characteristics, diagnosis, complications, management, and outcomes of accidental ingestion of FBs, caustics, and medications in children.

METHODS

We conducted a retrospective cohort study of all children admitted for accidental ingestion to the Department of Pediatrics, Salmaniya Medical Complex, Bahrain, between 2011 and 2021. Demographic data, type of FB/harmful material ingested, and investigations used for diagnosis and management were recorded. The patients were divided into three groups based on the type of ingested material (FBs, caustics, and medications). The three groups were compared based on patient demographics, socioeconomic status (SES), symptoms, ingestion scenario, endoscopic and surgical complications, management, and outcomes. The FB anatomical location was categorized as the esophagus, stomach, and bowel and compared with respect to symptoms. The Fisher's exact, Pearson's χ^2 , Mann-Whitney *U*, and Kruskal-Wallis tests were used for comparison.

RESULTS

A total of 161 accidental ingestion episodes were documented in 153 children. Most children were boys ($n = 85$, 55.6%), with a median age of 2.8 (interquartile

range: 1.8-4.4) years. Most participants ingested FBs ($n = 108$, 70.6%), 31 (20.3%) ingested caustics, and the remaining 14 (9.2%) ingested medications. Patients with caustic ingestion were younger at the time of presentation ($P < 0.001$) and were more symptomatic ($n = 26/31$, 89.7%) than those who ingested medications ($n = 8/14$, 57.1%) or FBs ($n = 52/108$, 48.6%) ($P < 0.001$). The caustic group had more vomiting ($P < 0.001$) and coughing ($P = 0.029$) than the other groups. Most FB ingestions were asymptomatic ($n = 55/108$, 51.4%). In terms of FB location, most esophageal FBs were symptomatic ($n = 14/16$, 87.5%), whereas most gastric ($n = 34/56$, 60.7%) and intestinal FBs ($n = 19/32$, 59.4%) were asymptomatic ($P = 0.002$). Battery ingestion was the most common ($n = 49$, 32%). Unsafe toys were the main source of batteries ($n = 22/43$, 51.2%). Most episodes occurred while playing ($n = 49/131$, 37.4%) or when they were unwitnessed ($n = 78$, 57.4%). FBs were ingested more while playing ($P < 0.001$), caustic ingestion was mainly due to unsafe storage ($P < 0.001$), and medication ingestion was mostly due to a missing object ($P < 0.001$). Girls ingested more jewelry items than boys ($P = 0.006$). The stomach was the common location of FB lodgment, both radiologically ($n = 54/123$, 43.9%) and endoscopically ($n = 31/91$, 34%). Of 107/108 (99.1%) patients with FB ingestion, spontaneous passage was noted in 54 (35.5%), endoscopic removal in 46 (30.3%), laparotomy in 5 (3.3%) after magnet ingestion, and direct laryngoscopy in 2 (1.3%). Pharmacological therapy was required for 105 (70.9%) patients; 79/105 (75.2%) in the FB group, 22/29 (75.9%) in the caustic group, and 4/14 (28.8%) in the medication group ($P = 0.001$). Omeprazole was the commonly used ($n = 58$; 37.9%) and was used more in the caustic group ($n = 19/28$, 67.9%) than in the other groups ($P = 0.001$). Endoscopic and surgical complications were detected in 39/148 (26.4%) patients. The caustic group had more complications than the other groups ($P = 0.036$). Gastrointestinal perforation developed in the FB group only ($n = 5$, 3.4%) and was more with magnet ingestion ($n = 4$) than with other FBs ($P < 0.001$). In patients with FB ingestion, patients aged < 1 year ($P = 0.042$), those with middle or low SES ($P = 0.028$), and those with more symptoms at presentation ($P = 0.027$) had more complications. Patients with complications had longer hospital stays ($P < 0.001$) than those without.

CONCLUSION

Accidental ingestion in children is a serious condition. Symptomatic infants from middle or low SES families have the highest morbidity. Prevention through parental education and government legislation is crucial.

Key Words: Pediatric; Accidental ingestion; Foreign body; Caustic; Complication; Bahrain

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Foreign body (FB) or harmful material ingestion is common in pediatric patients. These accidents occur more frequently among boys. Toddlers are at a higher risk of accidental ingestion because of their exploratory behavior. Batteries are the most commonly ingested FBs. Many ingestion incidents have occurred while playing and because of unsafe storage. The stomach is the most common anatomical location of FB loosening on radiography and endoscopy. Caregiver education regarding preventive methods and governmental execution of safe manufacturing of toys, magnets, and batteries is essential to prevent FB ingestion and the complications that might occur.

Citation: Isa HM, Aldoseri SA, Abduljabbar AS, Alsulaiti KA. Accidental ingestion of foreign bodies/harmful materials in children from Bahrain: A retrospective cohort study. *World J Clin Pediatr* 2023; 12(4): 205-219

URL: <https://www.wjgnet.com/2219-2808/full/v12/i4/205.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i4.205>

INTRODUCTION

Children like to discover their environment by putting substances into their mouth[1]. Accidental ingestion of foreign bodies (FBs) or caustic materials is a common problem encountered by families with children. It is considered as one of the most common indications for emergency referral and hospital admission. There are diverse types of FBs or ingested materials that can be swallowed by children. Coins, toy parts, jewelry, button-type batteries, needles, and pins are the most frequently ingested materials[1].

Most ingested FBs pass spontaneously, and patients can be safely observed[2]. Although most ingestion incidents are insignificant in terms of consequences, a few can pose a challenging problem that may lead to serious life-threatening complications[2]. For example, numerous magnetic objects located at various sites in the bowel can attract one another, leading to pressure necrosis of the bowel wall and eventual perforation[1]. Furthermore, although batteries can pass easily through the digestive tract and are eliminated from the stool within a few days of ingestion, swallowing batteries is more dangerous than swallowing coins or other inert objects because of their electrochemical composition and high risk of local damage[3]. Moreover, batteries 20 mm or larger in size can affect the esophagus, especially in young children[3]. Strong exothermic reactions can lead to serious mucosal injuries that may appear as skin burns[3]. Caustic ingestion is also common in pediatric age groups, and most cases happen accidentally[4]. The seriousness of this ingestion is due to

the tissue injury and necrosis[4]. Tissue damage can start from the mucosa and extend to the muscular layers, causing multiple complications, such as burns, strictures, and perforations[4].

Prompt diagnosis of accidental ingestion, appropriate management, and a decision on whether the patient necessitates intervention are crucial for reducing morbidity[2]. The type of FB, anatomic location in which the FB is lodged, and clinical picture of the patient determine the timing of endoscopic removal of the swallowed FB[2,3]. In children with caustic ingestion, postoperative treatment remains controversial and includes entities such as antireflux therapy, antibiotic therapy, steroids, and interventions such as esophageal stenting[3]. Nonetheless, the implementation of preventive methods and safe storage of caustic materials is essential to avoid these accidents and their related consequences[4].

Although many studies on accidental ingestion in children have been published in several countries, no studies have been published on this issue in Bahrain. The aim of this study was to review the incidence, demographics, different types of FBs/harmful materials, diagnostic modalities, complications, and outcomes of accidental ingestion in a pediatric age group and compare patients with endoscopic or surgical complications with those without complications to identify the predicted risk factors.

MATERIALS AND METHODS

Study design, setting, and population

In this retrospective cohort study, all pediatric patients (aged < 18 years) who presented to the Department of Accident and Emergency with a history of accidental ingestion and were admitted to the Department of Pediatrics, Salmaniya Medical Complex, Bahrain from January, 2011 to August, 2021 were included. Patients who presented to the Department of Accident and Emergency and were subsequently discharged were excluded.

Data collection

Patient data were collected by reviewing electronic and paper-based medical records. Important missing data were retrieved through direct contact with the patients' parents or guardians *via* telephone. Demographic data, including year of admission, nationality, sex, age at presentation, and age at the time of the study, were collected. Data on families' socioeconomic status (SES) were collected, including paternal and maternal educational levels, occupation, number of children, and total family income. Accordingly, families were categorized into low-, middle-, and high-SES groups. Data on symptoms at presentation, including vomiting, abdominal pain, passing tarry stool, choking, dysphagia, drooling of saliva, shortness of breath, and coughing, were collected. Details related to accidental ingestion of FBs, including the type, number, and source of FBs, were collected. Additionally, the presence of witnesses at the time of accidental ingestion, time to presentation to the Department of Accident and Emergency, and spontaneous passage times were outlined. More details regarding the type of battery were collected from the patients who ingested batteries.

Radiological imaging findings, endoscopic findings, and extraction methods were also reviewed. Urgent endoscopy was considered if it was performed within 48 h of ingestion, whereas a longer time was considered a delayed endoscopy. Data on the patients' hospital management, including endoscopic removal and the use of medications, such as lactulose, enema, glycerin suppositories, and omeprazole, were gathered. Furthermore, data on patient outcomes, including length of stay, morbidity, mortality, and follow-up period, were assessed.

Statistical analysis

Patient data were initially collected and entered into an Excel sheet and then transferred to and analyzed using the Statistical Package for the Social Sciences Statistics ver. 21.0 (IBM Corp., Armonk, NY, United States). Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean and standard deviation or median and interquartile range (IQR), according to distribution normality using the Shapiro-Wilk test. To assess the trend of accidental ingestion episodes over the last 10-year period, the duration was divided into two periods of 5 years each (2012-2016 and 2017-2021), and the incidence of ingestion in both periods was compared. The incidence was calculated as the number of patients with accidental ingestion per year divided by the total pediatric population (less than 18 years), obtained from the Bahrain Health Statistics website (<https://www.moh.gov.bh/Ministry/Statistics?lang=en>). The patients were divided into three groups based on the type of ingested material (FBs, caustic chemicals, and medications). The three groups were compared based on patient demographics, family SES, clinical presentations, ingestion scenario, endoscopic and surgical complications, management, and outcomes. Based on radiological and endoscopic findings, the anatomical location of the FB was categorized into esophageal, stomach, and bowel locations and compared with regard to the presenting symptoms. Metallic FBs were divided into jewelry and other metal objects and compared based on sex. The Fisher's exact test or Pearson's chi-square test was used to compare categorical variables, while student's *t* test, Mann-Whitney *U* test, or Kruskal-Wallis's test was used to compare independent groups. Confidence interval (CI) was set to 95%. *P* < 0.05 was considered statistically significant.

Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki, and it was ethically approved by the Secondary Health Care Research Committee, Salmaniya Medical Complex, Government Hospitals, Kingdom of Bahrain (IRB number: 88300719, July 30, 2019).

RESULTS

During the study period, 161 accidental ingestion episodes were documented in 153 children admitted to the hospital, all of whom were included in this study. Eight (5.0%) patients had another episode of accidental ingestion following the initial episode; one of them had three episodes in total, and two patients ingested the same object (battery or hard food) during the two episodes. Of the eight patients with multiple ingestions, three (37.5%) had neuropsychiatric disorders, including autism, demyelination, and mild intellectual disability. The latter had iron-deficiency anemia associated with pica. The patient with three episodes had disc battery ingestion, followed by two repeated FB ingestions, and was referred to the child protection team because of suspected child neglect, as this patient also had repeated burn events.

The mean number of accidental ingestions was 13.9 ± 10.3 episodes per year. The annual incidence of accidental ingestion episodes is shown in [Figure 1](#). The incidence of accidental ingestion increased during the study period. In 2012-2016, the mean incidence was 3.3 ± 2.8 compared to 4.2 ± 2.4 episodes in 2017-2021. However, this increase was not statistically significant ($P = 0.610$, 95%CI: -4.6 to 2.9).

The demographic data and clinical presentations are shown in [Table 1](#). Most of the patients ingested FBs ($n = 108$, 70.6%), 31 (20.3%) ingested caustic chemicals, and the remaining 14 (9.2%) ingested medications. Most of the patients were boys ($n = 85$, 55.6%). Most patients were Bahraini children ($n = 118$, 77.1%), while non-Bahraini children accounted for 35 (22.9%) patients (10 from India, 5 from Saudi Arabia, 2 from Bangladesh and United States of America each, 1 from Egypt, Sri Lanka, Sudan, Yemen, and Syria each, while 8 patients had unspecified nationalities). The median age at presentation was 2.8 (IQR: 1.8-4.4) years, and the most frequent age group was 2-3 years old, accounting for 43.5%. Patients with caustic ingestion were younger than those who ingested medications or FBs at the time of presentation ($P < 0.001$). Most patients ($n = 119$, 77.8%) ingested one item, and most were symptomatic ($n = 86$, 57.3%). The most common symptom was vomiting ($n = 44$, 29.3%), followed by abdominal pain ($n = 25$, 16.7%). Patients with caustic ingestion ($n = 26/31$, 89.7%) were more symptomatic than those who ingested medications ($n = 8/14$, 57.1%) or FBs ($n = 52/108$, 48.6%) ($P < 0.001$). The caustic group had more vomiting ($P < 0.001$) and coughing ($P = 0.029$) than the other two groups. Most of patients with FB ingestion were asymptomatic ($n = 55/108$, 51.4%). Upon comparison of symptoms according to the location of FBs (esophagus, stomach, or bowel), most of the 16 patients with esophageal FBs were found to be symptomatic [14 (87.5%) *vs* 2 (12.5%)], while the majority of the 56 patients with gastric FBs [34 (60.7%) *vs* 22 (39.3%)] and the 32 patients with intestinal FBs [19 (59.4%) *vs* 13 (40.6%)] were asymptomatic ($P = 0.002$).

Five patients had underlying diseases that might have been related to accidental ingestion. Esophageal strictures after tracheoesophageal fistula repair were found in two patients with food bolus impaction; one patient had cerebral palsy with needle ingestion, one had mental retardation with coin ingestion, and one had autism with disc battery ingestion.

Out of 136 (88.9%) patients with available witness history, 58 (43.6%) were witnessed and 78 (57.4%) were unwitnessed. Of those witnessed, 55 (94.8%) patients had a known witness person, while 3 (5.2%) had an unknown witness. Three (5.2%) patients had more than one witness person. First degree relatives were witnesses in 47 (85.5%) patients, second degree relatives in 8 (14.6%), and unrelated people (teacher, housemaid, and family friend) in 3 (5.5%). The mother was the most frequent witness ($n = 27$, 49.1%), followed by other siblings [$n = 11$ (20%); seven of them were sisters and four were brothers] and fathers ($n = 7$, 12.7%).

There were no significant differences among the three groups with respect to sex, nationality, SES, maternal occupation, number of siblings, time to presentation, length of stay, number of ingested materials, or the presence of a witness.

The different types of ingested material are listed in [Table 2](#). Battery ingestion was the most frequent FB type ($n = 49$, 32%); 48 of them were disc batteries, and 1 was a finger type. The sharp objects included earring, screw, and nail/nail hanger ($n = 5$ each), key/keyring/keychain ($n = 4$), needle ($n = 3$), hair clip/pin and sharp pin ($n = 2$ each), gold chain, leg accessories, necklace, pepsi cap, and zipper piece ($n = 1$ each). The chemicals and corrosive solutions included alkaline corrosives ($n = 19$; Clorox in 11 patients, detergents or disinfectants in 3 each, and nonspecific corrosives in 2 patients), acid corrosives ($n = 5$; keratolytic agents in three and toilet cleaners in two patients), and other chemicals ($n = 6$). The medications included paracetamol ($n = 4$), antihypertensives ($n = 3$, coversyl in two and angiotensin-converting enzyme inhibitor in one patient), antihistamines, hypoglycemic agents, oral contraceptives, nitrite, multivitamins, methylphenidate, and multiple medications ($n = 1$ each).

Even though there was no significant difference between boys and girls in terms of the type of FBs ingested ($P = 0.217$), in metal object ingestions, girls were found to ingest more jewelry items than boys, with seven (70%) *vs* three (30%), respectively ($P = 0.006$). Of the 49 (32%) patients who ingested batteries, 43 (87.8%) patients had the source of battery data available. Unsafe toys were the main sources of batteries ($n = 22$, 51.2%), followed by light torches ($n = 10$, 23.3%), remote-control devices ($n = 2$, 4.7%), artificial candles, baskets, electronic walking aids, headphones, laser pens, on car seats, on tables, and from watches and weighing scales ($n = 1$ each, 2.3%).

The accidental ingestion scenarios are presented in [Table 3](#). Data regarding this scenario were available for 131 (85.6%) patients. Accidental ingestion mostly happened while the child was playing ($n = 53$, 40.5%). FBs were ingested more while playing ($P < 0.001$), caustic chemical ingestion was mainly due to unsafe storage ($P < 0.001$), and medication ingestion was mostly due to a missing object ($P < 0.001$).

Results of radiological imaging, including chest and abdominal radiography, were available for 123 (80.4%) patients: 108 (100%) for FB, 8 (25.8%) for caustic, and 7 (50%) for medication ingestion ($P < 0.001$) ([Table 4](#)). The remaining 30 (24.6%) patients with no radiological findings ingested either corrosives ($n = 23$, 76.7%) or medications ($n = 7$, 23.3%). The most common location of the ingested object was the stomach both radiologically ($n = 54/123$, 43.9%) and endoscopically ($n = 31/91$, 34%).

Table 1 Demographic data and clinical presentation of 153 children with accidental ingestion

Demographic data	Total, <i>n</i> = 153 (100)	FB, <i>n</i> = 108 (70.6)	Caustic, <i>n</i> = 31 (20.3)	Medication, <i>n</i> = 14 (9.2)	<i>P</i> value
Sex					0.513 ^a
Male	85 (55.6)	58 (53.7)	20 (64.5)	7 (50)	
Female	68 (44.4)	50 (46.3)	11 (35.5)	7 (50)	
Nationality					0.260 ^a
Bahraini	118 (77.1)	87 (80.6)	22 (71.0)	9 (64.3)	
Non-Bahraini	35 (22.9)	21 (19.4)	9 (29.0)	5 (35.7)	
Socioeconomic status (<i>n</i> = 95)					0.520 ^a
Low	32 (33.7)	26 (34.7)	3 (20.0)	3 (60.0)	
Middle	31 (32.6)	25 (33.3)	5 (33.3)	1 (20.0)	
High	32 (33.7)	24 (32.0)	7 (46.7)	1 (20.0)	
Working mother	33/95 (34.7)	28/75 (37.3)	4/15 (26.7)	1/5 (20.0)	0.568 ^a
Number of siblings, (<i>n</i> = 94)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	0.877 ^b
Age at presentation (yr), (<i>n</i> = 152)	2.8 (1.8-4.4)	3.4 (2.0-5.6)	1.8 (1.5-2.5)	2.6 (2.1-2.8)	< 0.001 ^b
Age categories (yr), (<i>n</i> = 152)					0.001 ^a
0-1	41 (27)	22 (20.6)	17 (54.8)	2 (14.3)	
2-3	66 (43.4)	45 (42.1)	11 (35.5)	10 (71.4)	
4-5	31 (20.4)	27 (25.2)	2 (6.5)	2 (14.3)	
≥ 6	14 (9.2)	13 (12.1)	1 (3.2)	0 (0.0)	
Time to presentation (h), (<i>n</i> = 139)	2.0 (1.0-6.0)	2.0 (1.0-6.0)	1.0 (0.3-5.0)	2.0 (1.0-4.0)	0.306 ^b
Length of stay (d)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-4.0)	1.0 (1.0-1.0)	0.063 ^b
Length of stay categories (d), (<i>n</i> = 146)					0.102 ^a
0-1	104 (71.2)	74 (71.8)	16 (55.2)	14 (100)	
2-3	20 (13.7)	15 (14.6)	5 (17.2)	0 (0.0)	
4-5	7.0 (4.8)	5 (4.9)	2 (6.9)	0 (0.0)	
≥ 6	15 (10.3)	9 (8.7)	6 (20.7)	0 (0.0)	
Number of ingested FBs/materials per patient					0.053 ^a
1	119 (77.8)	81 (75.0)	30 (96.8)	8 (57.1)	
2-5	23 (15.0)	19 (17.6)	1 (3.2)	3 (21.4)	
6-10	3.0 (2.0)	2 (1.9)	0 (0.0)	1 (7.1)	
> 10	8.0 (5.2)	6 (5.6)	0 (0.0)	2 (14.3)	
Clinical presentations (<i>n</i> = 150)					
Symptomatic ¹	86 (57.3)	52 (48.6)	26 (89.7)	8 (57.1)	< 0.001 ^a
Vomiting	44 (29.3)	23 (21.9)	18 (62.1)	3 (21.4)	< 0.001 ^a
Abdominal pain	25 (16.7)	21 (20.0)	2 (6.9)	2 (14.3)	0.240 ^a
Cough	13 (8.7)	7 (6.7)	6 (20.7)	0 (0.0)	0.029 ^a
Shortness of breath	11 (7.3)	6 (5.7)	5 (17.2)	0 (0.0)	0.060 ^a
Choking	11 (7.3)	8 (7.6)	3 (10.3)	0 (0.0)	0.475 ^a
Dysphagia/drooling of saliva	9 (6.0)	5 (4.6)	4 (12.9)	0 (0.0)	0.139 ^a
Convulsion	3.0 (2.0)	1 (0.9)	1 (3.2)	1 (7.1)	0.245 ^a

Others ²	16 (10.6)	11 (10.2)	4 (12.9)	1 (7.1)	0.831 ^a
Asymptomatic	64 (42.7)	55 (51.4)	3 (10.3)	6 (42.9)	< 0.001^a
Presence of witness (<i>n</i> = 136)	58 (43.6)	38 (40.4)	14 (50.0)	6 (42.9)	0.667 ^a

^aPearson's χ^2 test was used for categorical variables.

^bKruskal-Wallis's test was used for continuous variables.

¹Patients might have more than one symptom.

²Dizziness, chest pain, nausea, tarry stool, and throat discomfort, each in two patients; fever, fatigue, nose swelling, tongue and lips swelling, abdominal bloating, noisy breathing, cyanosis, drowsiness (chlorpheniramine ingestion), reduction in activity, and lip ulcer, each in one patient (two patients of them had two symptoms).

Boldface indicates a statistically significant difference with $P < 0.05$. Values are presented as number (%) or median (interquartile range). FB: Foreign body.

Table 2 Types of foreign bodies and harmful materials accidentally ingested by 153 children

Type	Patients, <i>n</i> (%)
Foreign bodies	108 (70.6) ¹
Battery	49 (32)
Metal/sharp object	31 (20.3)
Magnets	16 (10.5)
Coin	8 (5.2)
Others ²	5 (3.3)
Chemicals/corrosive solutions	31 (20.3)
Alkaline corrosives	19 (12.4)
Acid corrosives	5 (3.03)
Others ³	6 (3.9)
Medications	14 (9.2)

¹One patient ingested both magnet and disc battery.

²Marble (*n* = 2), intact grape, olive, and pistachio nut (*n* = 1 each).

³Kerosene in two, and comfor oil, mercury, car oil, and superglue in one patient each.

Values are presented as number (%).

Table 3 Scenario of foreign body/material ingestion in children (*n* = 131)

Ingestion scenario	Total, <i>n</i> = 131 ¹ (100)	FB, <i>n</i> = 90 (68.7)	Caustic, <i>n</i> = 27 (20.6)	Medication, <i>n</i> = 14 (10.7)	<i>P</i> value ^a
While playing	53 (40.5)	50 (55.6)	3 (11.1)	0 (0.0)	< 0.001 ^b
Unsafe storage	46 (35.1)	13 (14.4)	26 (96.3)	7 (50)	< 0.001 ^b
Missing objects	18 (13.7)	12 (13.3)	0 (0.0)	6 (42.9)	< 0.001 ^b
Told by patient/relative	13 (9.9)	12 (13.3)	0 (0.0)	1 (7.1)	0.118
Accidental ingestion	4 (3.1)	4 (4.4)	0 (0.0)	0 (0.0)	0.391
Incidental finding on X-ray	3 (2.3)	3 (3.3)	0 (0.0)	0 (0.0)	0.497
Food bolus impaction	3 (2.3)	3 (3.3)	0 (0.0)	0 (0.0)	0.497
Suicidal attempt	1 (0.07)	0 (0.0)	1 (3.7)	0 (0.0)	0.144

¹Some patients had more than one scenario.

^aPearson's χ^2 .

^bIndicating a statistically significant difference with $P < 0.05$.

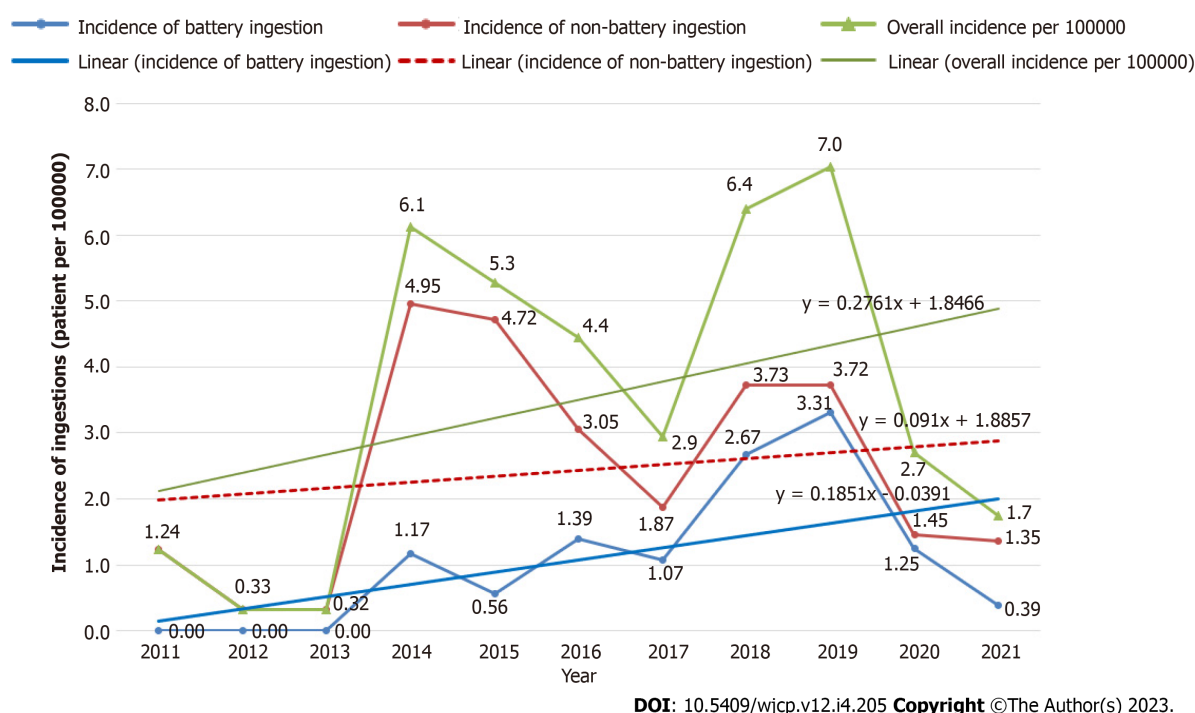
Data are presented as number (%). FB: Foreign body.

Table 4 Anatomical locations of ingested foreign bodies based on radiological and endoscopic findings

Foreign body location	On X-ray, <i>n</i> = 123/153 (80.4)	In endoscopy, <i>n</i> = 91/152 (59.9)
Esophagus	14 (11.4)	13 (14.3)
Stomach	54 (43.9)	31 (34.0)
Small intestine	18 (14.6)	22 (24.2)
Large intestine	16 (13.0)	1.0 (1.1)
Others ¹	2.0 (1.6)	0.0 (0.0)
Not seen/normal	19 (15.5)	24 (26.4)

¹Nose and throat (*n* = 1 each).

Data are presented as number (%).

**Figure 1 Incidence of accidental ingestion episodes among children admitted to Salmaniya Medical Complex, Bahrain in 2011-2021.**

Endoscopic procedures were performed in 91 (59.9%) of the 152 (99.4%) patients: 73/107 (68.2%) for FB ingestion, 18/31 (58.1%) for caustic ingestion, while no patient with medication ingestion underwent endoscopy ($P < 0.001$) (Table 4). Ninety patients (59.2%) underwent upper gastrointestinal endoscopy and one (0.7%) underwent colonoscopy. The common endoscopic location of the ingested objects was also the stomach ($n = 31$, 34%). The time from presentation to endoscopy was available for 81 (89%) patients; 78 (96.3%) of them had an emergency endoscopy (< 48 h), while 3 (3.7%) were delayed after 48 h. The first delayed patient was a 4-year-old girl who was brought by her parents with a history of fainting and vomiting streaks of blood after accidental ingestion of Clorox stored in a small water bottle. The second patient was an 8-year-old boy who ingested two attached magnets while playing a game. X-ray imaging revealed that the magnets had passed down to the large intestine. He was administered laxatives for 2 d without any progress; therefore, the magnets were removed endoscopically. The third patient was a 7-year-old boy who ingested a coin while playing, which was found to be in the stomach radiologically and remained there for 3 mo.

Data about the method of extraction were available in 107/152 (70.4%) patients with FB ingestion; spontaneous passage was noted in 54 (35.5%), endoscopic removal in 46 (30.3%), laparotomy in 5 (3.3%) (all after magnets ingestion), and direct laryngoscopy in 2 (1.3%); while in the remaining 45 (29.6%) patients nothing was removed as they ingested chemicals ($n = 31$, 20.4%) or medications ($n = 14$, 9.2%). Among patients who passed the FB spontaneously, 34 (59.7%) passed it within the first 24 h of admission, 13 (22.8%) passed it between 1 and 2 d, 10 (17.5%) passed it after 3 d, and one patient had missing data. Three patients underwent endoscopic removal of one FB and spontaneous passage of the other.

Pharmacological therapy was required for 105/148 (70.9%) patients; 79/105 (75.2%) in the FB group, 22/29 (75.9%) in the caustic group, and 4/14 (28.8%) in the medication group ($P = 0.001$). The commonest medication was omeprazole ($n = 58$; 37.9%), which was used more in the caustic group ($n = 19/28$, 67.9%) than in the FB ($n = 37/104$, 25.9%) and medi-

cation ($n = 2/14$, 14.3%) groups ($P = 0.001$). Phosphate/glycerin enemas, lactulose, and glycerin suppositories were used in 30 (19.6%), 28 (18.3%), and 24 (15.6%) patients, respectively. Laxatives and whole-bowel irrigation were administered to one patient who ingested mercury. Among the patients who ingested medication, two received gastric lavage, and two were given activated charcoal.

Seven types of endoscopic and surgical complications were detected in 39 (26.4%) out of 148 patients with available data (Table 5). Some patients experienced more than one complication. Overall, patients who ingested caustics had more complications than those in the other groups ($P = 0.036$) in the form of mucosal erythema ($P = 0.005$) and strictures ($P = 0.019$). Gastrointestinal perforation developed in the FB group only ($n = 5$, 3.4%) and was more with magnet ingestion (4 patients) than with other FB types (one with battery and none with others) ($P < 0.001$). Examples of complications caused by battery and magnet bead ingestion are shown in Figures 2 and 3, respectively. Patients who ingested the medications showed no endoscopic or surgical complications. Data from follow-up out-patient visits were available for 49 (32%) patients. Median follow-up period was 2 (IQR = 1.7-6.2) wk.

A comparison between the FB and caustic groups with respect to the presence or absence of endoscopic and surgical complications is shown in Table 6. In patients with FB ingestion, patients aged < 1 year ($P = 0.042$), those with middle or low SES ($P = 0.028$), and those with more symptoms at presentation ($P = 0.027$) had more complications. Both the FB and caustic groups with complications had longer hospital stays ($P < 0.001$) than those without. There were no significant differences in sex, nationality, maternal occupation, number of siblings, presence of witnesses, time to presentation, number and type of ingested FBs, or anatomical location.

DISCUSSION

This study observed an increasing trend in the incidence of accidental ingestion among children. This may be attributed to the increasing number of battery-powered electronic devices and the increased incidence of disc battery ingestion over the past several years[2,5].

The present study showed a male predominance among children with accidental ingestions, where boys accounted for 55.7%. Some accidental ingestion patterns may also be related to sex[6]. In fact, there was a consensus among all the reviewed studies that boys form the majority of children with accidental ingestion (Table 7)[2,4,6-17]. However, there were some variations in percentages. For instance, Dereci *et al*[13] from Turkey showed that boys accounted for 56%, which is similar to our study. However, Diaconescu *et al*[14] reported a male predominance, but with a lower percentage (52.45%), while Chan *et al*[9] reported a higher proportion of boys (80%). This finding may be explained by the fact that boys are more active and explore more[16]. However, some FBs are more accessible to girls than to boys and *vice versa*[6]. For instance, girls frequently consume jewelry and hair products[6]. This finding was confirmed in the present study. In a study by Orsagh-Yentis *et al*[6], girls were 2.5 times more likely to swallow jewelry than boys. Speidel *et al*[4] also found that girls were at higher risk of sharp object ingestion.

The current study found that the median age at presentation was 2.8 years, and the most frequent age group was between 2-3 years old, accounting for 43.4%. This finding is consistent with several other studies showing that the toddler age group is the most frequent risk factor for accidental ingestion[2,4,6-10,14,17]. This high prevalence of accidental ingestion in younger age groups can be attributed to the exploratory habits of these children[14]. Furthermore, children in the oral phase are prone to ingesting objects while crawling and playing[7]. Several studies have attributed the high prevalence of FB ingestion to the accessibility of FBs in a child's environment, especially because this age group has the desire to explore their surroundings[1,6,16,18]. However, few studies have reported older age groups up to adulthood[11, 13,15,16,18].

In the current study, we evaluated families' SES as a risk factor for the increased incidence of accidental ingestion, as the child might be left alone at home unwitnessed by the parents/caregivers owing to their work obligations, as stated by Kalra *et al*[16]. Despite that, we did not observe an overall significant difference between families of different SES. However, in patients who ingested FBs, families with middle or low SES had more endoscopic and surgical complications than those with higher SES families ($P = 0.028$).

In this study, 57.3% (86/150) of the patients were symptomatic at presentation. This is comparable to the studies by Speidel *et al*[4] and Khorana *et al*[17], where the percentages of symptomatic patients were 51.6% and 55.67%, respectively. However, studies by Uba *et al*[7] and Diaconescu *et al*[14] reported higher percentages of symptomatic patients (85% and 70.5%, respectively). In contrast, Chan *et al*[9] and Lee *et al*[10] reported very low percentages of symptomatic patients, with 12% and 9.2%, respectively. This variation in the percentage of symptomatic patients who ingested FBs or other materials can be attributed to the differences in the time from ingestion to presentation and the shape, type, location, and amount of the ingested object[14,15].

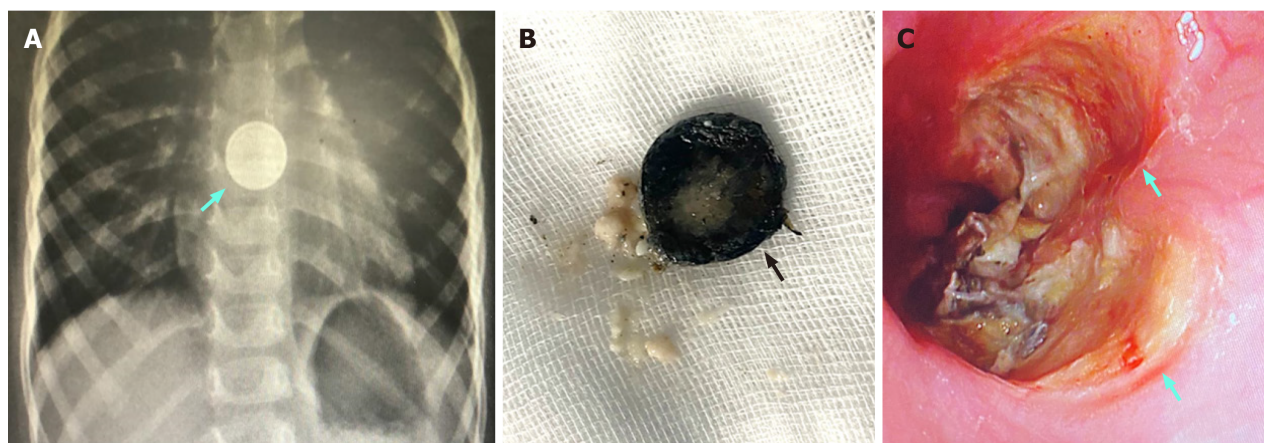
Overall, the most frequent presenting symptom in our study was vomiting (29.3%). In the literature review, we found variations in the presenting symptoms depending on the type of FBs/materials ingested or the site of the FB impaction [15]. In terms of the type of ingestion, caustic materials exhibited the highest percentage of symptoms (89.7%) in this study. A lower percentage of symptomatic patients who ingested cleansers was reported by Speidel *et al*[4] (53.4%). In the FB group, 48.6% of our patients were symptomatic, and 21.9% had vomiting as the most common symptom. Khorana *et al* [17] reported a higher percentage of symptomatic patients with FB ingestion (55.67%), and vomiting was also the commonest presenting symptom (23.2%). Moreover, Diaconescu *et al*[14] reported symptoms in 70.5% of their patients with FB ingestion, yet they mainly presented with abdominal pain (55.73%), followed by vomiting (34.42%). Upon comparison of symptoms according to the lodgment site, most patients with esophageal FBs were symptomatic in our study (87.5%). This was comparable to the percentage reported by Uba *et al*[7] in patients with esophageal FBs (85%).

Table 5 Endoscopic and surgical complications in children with accidental ingestion based on type of ingested materials (n = 153)

Complication	Total, n = 148 ¹ (96.7)	FB, n = 104 (70.3)	Caustic, n = 30 (20.3)	Medication, n = 14 (9.6)	P value ^a
Erythema	16 (10.8)	8 (7.7)	8 (26.7)	0 (0.0)	0.005 ^b
Ulcer	14 (9.5)	10 (9.6)	4 (13.3)	0 (0.0)	0.369
Mucosal erosions	9 (6.1)	9 (8.7)	0 (0.0)	0 (0.0)	0.132
Hemorrhage	6 (4.1)	6 (5.8)	0 (0.0)	0 (0.0)	0.266
Perforation	5 (3.4)	5 (4.8)	0 (0.0)	0 (0.0)	0.335
Airway edema	5 (3.4)	2 (1.9)	3 (10.0)	0 (0.0)	0.074
Stricture	2 (1.4)	0 (0.0)	2 (6.7)	0 (0.0)	0.019 ^b
Total	39 (26.4)	28 (26.9)	11 (36.7)	0 (0.0)	0.036 ^b

¹Some patients had more than one complication.^aPearson's χ^2 .^bIndicating a statistically significant difference with $P < 0.05$.

Data are presented as number and percentage. FB: Foreign body.



DOI: 10.5409/wjcp.v12.i4.205 Copyright ©The Author(s) 2023.

Figure 2 Disc battery ingestion in children. A: Plain chest X-ray revealing the double hallow shadow of a disc battery impacted in the esophagus; B: Rusted and friable disc battery after endoscopic removal; C: Endoscopic picture of the esophagus showing two large kissing mucosal ulcers at the site of the disc battery impaction.

Drooling of saliva and dysphagia are the main symptoms in patients with esophageal FBs[8,13], while abdominal pain and vomiting are the main symptoms in patients with FBs found in the stomach[14,15]. Diaconescu *et al*[14] explained the wide variation in presenting symptoms among different studies based on the shape of the FB, duration between the ingestion event and time to presentation, and age of the patient.

In the current study, 42.7% of the children who ingested FBs, caustics, or medications were asymptomatic. This is comparable to the study by Speidel *et al*[4], who also included the three types of ingested materials, where the percentage of asymptomatic patients was 48.4%. Moreover, Lee *et al*[10] reported that most of the 76 patients with FB ingestions were asymptomatic (90.8%), which was also the case in our study, but at a lower rate (51.4%). Chan *et al*[9] also documented that most of the 25 patients with button battery ingestion were asymptomatic (88%). This high percentage of asymptomatic patients is of concern, as it may lead to delayed diagnosis in many cases, putting these children at risk of a higher rate of complications. Preventing complications and missed diagnoses, particularly in high-risk objects, such as batteries, is important. Early detection of an incident by parents leads to faster presentation, diagnosis, and intervention[3,19]. Nevertheless, doctors should consider FB ingestion scenarios in young patients who present with vague symptoms, such as abdominal pain and vomiting[3,19].

In this study, the majority of the ingestion scenarios were during the playing time (40.5%) and were unwitnessed (57.4%). Ingestion episodes while playing were also documented by Dereci *et al*[13] but at a higher rate (72%). Unwitnessed events were also found in other studies, such as those illustrated by Litovitz *et al*[19] who reported a comparable percentage to our study (56.2%). In contrast, most of accidental ingestions reported by Lin *et al*[15] were witnessed (89%). However, Kalra *et al*[16] found a low percentage of witnessed accidental ingestions (19%). The presence of a witness during the child's play is important for the early detection of ingestion episodes and might hasten medical management.

Table 6 Predictors of complications in children with accidental ingestion based on type of ingested materials (foreign body or caustic material)

Variable	FB complications, <i>n</i> = 104		<i>P</i> value	Caustic complications, <i>n</i> = 31		<i>P</i> value
	Yes, <i>n</i> = 28 (26.9)	No, <i>n</i> = 76 (73.1)		Yes, <i>n</i> = 11 (35.5)	No, <i>n</i> = 20 (64.5)	
Sex			0.661 ^a			1.000 ^a
Male	16 (57.1)	39 (51.3)		7 (63.6)	13 (68.4)	
Female	12 (42.9)	37 (48.7)		4 (36.4)	6 (31.6)	
Nationality			0.775 ^a			0.199 ^a
Bahraini	24 (85.7)	61 (80.3)		10 (90.9)	12 (63.2)	
Non-Bahraini	4 (14.3)	15 (19.7)		1 (9.1)	7 (36.8)	
Socioeconomic status (<i>n</i> = 74)			0.028 ^b			0.059 ^b
Low	9 (42.9)	16 (30.2)		2 (28.6)	1 (12.5)	
Medium	10 (47.6)	15 (28.3)		4 (57.1)	1 (12.5)	
High	2 (9.5)	22 (41.5)		1 (14.3)	6 (75.0)	
Working mother (<i>n</i> = 74)	4/21 (19.0)	24/53 (45.3)	0.061 ^a	1/7 (14.3)	3/8 (37.5)	0.569 ^a
Number of siblings, (<i>n</i> = 74)	3 (2-4)	3 (2-4)	0.355 ^c	3 (1-5)	3 (3-4)	0.779 ^c
Age at presentation (yr), (<i>n</i> = 103)	2.8 (1.5-4.2)	3.4 (2.2-5.7)	0.069 ^c	1.5 (0.9-2.5)	1.9 (1.6-2.7)	0.185 ^c
Age group (yr) (<i>n</i> = 103)			0.042 ^b			0.181 ^b
0-1	11 (39.3)	11 (14.7)		8 (72.7)	9 (47.4)	
2-3	9 (32.1)	35 (46.7)		2 (18.2)	8 (42.1)	
4-5	4 (14.3)	20 (26.7)		0 (0.0)	2 (10.5)	
≥ 6	4 (14.3)	9 (12.0)		1 (9.1)	0 (0.0)	
Presence of ingestion witness (<i>n</i> = 93)	12/27 (44.4)	25/66 (37.9)	0.643 ^a	4/10 (40)	10 (55.6)	0.695 ^a
Time to presentation (h), (<i>n</i> = 96)	3 (1-8.5)	2 (1-5)	0.325 ^c	1 (0.3-3.0)	2 (0.5-6.0)	0.155 ^c
Length of stay (d), (<i>n</i> = 102)	2 (1-4)	1 (0-1)	< 0.001 ^c	7 (2-12)	1 (0-2)	< 0.001 ^c
Number of ingested FBs/materials per patient ^c			0.372 ^b			1.000 ^b
1	18 (64.3)	60 (78.9)		11 (100)	18 (94.7)	
2-5	6 (21.4)	12 (15.8)		0 (0.0)	1 (5.3)	
6-10	1 (3.6)	1 (1.3)		0 (0.0)	0 (0.0)	
> 10	3 (10.7)	3 (3.9)		0 (0.0)	0 (0.0)	
Type of FBs			0.384 ^b	NA	NA	NA
Battery	15 (53.6)	34 (44.7)	0.508 ^a	NA	NA	NA
Metal/sharp object	6 (21.4)	23 (30.3)	0.464 ^a	NA	NA	NA
Magnets	6 (21.4)	9 (11.8)	0.224 ^a	NA	NA	NA
Coin	1 (3.6)	7 (9.2)	0.679 ^a	NA	NA	NA
Food bolus ¹	0 (0.0)	3 (3.9)	0.562 ^a	NA	NA	NA
Anatomical location			0.682 ^b	NA	NA	NA
Esophagus	3 (11.1)	13 (17.3)	0.550 ^a	NA	NA	NA
Stomach	16 (59.3)	38 (50.7)	0.504 ^a	NA	NA	NA
Bowel	8 (29.6)	23 (30.7)	1.000 ^a	NA	NA	NA
Clinical presentations			0.027 ^a			1.000 ^a
Symptomatic	19 (67.9)	32 (42.1)		9 (90)	17 (89.5)	

Asymptomatic	9 (32.1)	44 (57.9)	1 (10)	2 (10.5)
--------------	----------	-----------	--------	----------

^aFisher's exact test was used for categorical variables.

^bPearson's χ^2 test was used for categorical variables.

^cMann-Whitney *U* test was used for continuous variables.

¹Intact grape, olive, and pistachio nut (*n* = 1 each).

Boldface indicates a statistically significant difference with *P* < 0.05. Data are presented as number (%) or median (interquartile range). FB: Foreign body; NA: Not applicable.

Table 7 Summary of foreign body ingestion in children from neighboring counties and worldwide

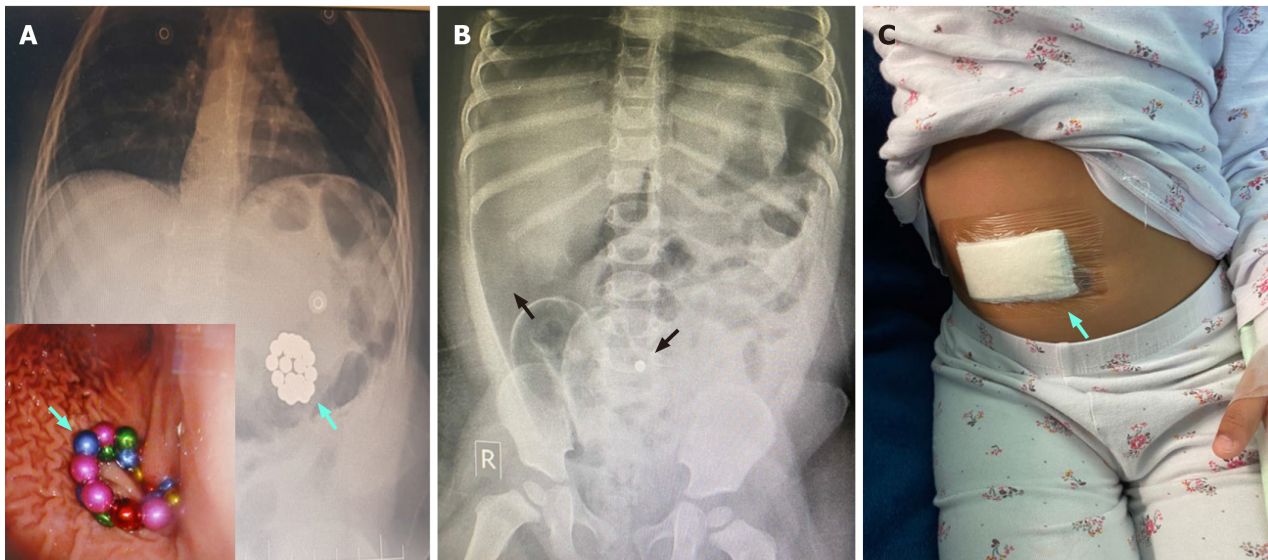
Ref.	Country	<i>n</i>	Age (yr) ¹	Sex	Two most common FBs (%)	Two most common symptoms (%)	Two most common sites of FB (%)
Our study	Bahrain ²	153	2.8 (1.8-4.4)	M > F	Battery (32), metals/sharps (21)	Vomiting (29), abdominal pain (16)	Stomach (44), small intestine (15)
Al-Salem <i>et al</i> [11], 1995	Kingdom of Saudi Arabia	40	8.5 (5 mo-8)	M > F	Coins (43), metallic dog toy	NR	Esophagus (60), stomach (38)
Dereci <i>et al</i> [13], 2015	Turkey	64	5.7 ± 4.6	M > F	Coin (37), pin (8)	Dysphagia (24), cough (8)	Esophagus (56), stomach (16)
Kalra <i>et al</i> [16], 2022	India	100	5.0 ± 14.4	M > F	Coin (65), battery cell (13)	FB sensation (55), vomiting (54)	Just below the cricopharynx (89)
Lee <i>et al</i> [10], 2016	Korea	76	3.1 ± 3.1	M > F	Coins (22), button battery (16)	Chest discomfort, abdominal pain (9)	FBs: Stomach (40), unknown (28). Batteries: Duodenum (50), stomach (42)
Chan <i>et al</i> [9], 2002	Taiwan	25	2.6 ± 1.8	M > F	Button battery	Abdominal pain (8), dyspnea (4)	Stomach (52), small intestine (8)
Lin <i>et al</i> [15], 2007	Taiwan	87	3.4 (6 mo-13)	M > F	Coins (57), button battery (22)	Odynophagia, cough (84)	Esophagus (51), stomach (45)
Khorana <i>et al</i> [17], 2019	Thailand	194	43.5 (21-72) mo	M > F	Coin (41), button battery (17)	Vomiting (45), dysphagia (27)	Esophagus (37), stomach (29)
Uba <i>et al</i> [7], 2002	Nigeria	108	3.0 ± 0.8	M > F	Coins (80), bottle caps (7)	Drooling (34), regurgitation (17)	Esophagus (52), hypopharynx (33)
Adedeji <i>et al</i> [12], 2013	Nigeria	28	32.1 (2-75)	M > F	Alkali (79), acid (14)	NR	NR
Diaconescu <i>et al</i> [14], 2016	Romania	61	3.3 ± 4.7	M > F	Coins (26), metals (13)	Abdominal pain (56), vomiting (34)	NR
Antoniou and Christopoulos-Geroulanos[2], 2011	Greece	675	3.3 (4 mo-14)	M > F	Coins (32), safety pins (21)	Retrosternal pain, drooling	Stomach (58), bowel (33)
Speidel <i>et al</i> [4], 2020	Germany	1199	3.3 ± 3.2	M > F	Coin (19), metal (16)	Retching and vomiting (30), coughing (8)	NR
Little <i>et al</i> [8], 2006	United States	555	3.2 (2 mo-19)	M > F	Coins (88), round batteries	Dysphagia (37), drooling (31)	Esophagus (99)
Orsagh-Yentis <i>et al</i> [6], 2019	United States	29893	< 6	M > F	Coins (62), toys (10)	NR	NR

¹Age is presented as either median (range) or the mean ± SD.

²The present study.

FB: Foreign body; NR: No record; M: Male; F: Female.

In our study, the most frequently ingested FBs were batteries (32%), followed by chemical solutions (20.3%). The main source of ingested batteries was unsafe toys (51.2%). Unsafe toys are a source of danger, particularly if their batteries are not locked. This may be due to the ease of swallowing these objects and/or being within reach of the children. However, our findings are not compatible with those of many other studies on the most commonly ingested FBs. Most studies have reported that coins are the most common[2,6-8,10,11,13,14]. This can be explained by the strict inclusion criteria of our study, in which patients were admitted to the hospital for observation and for the inclusion of possible endoscopic procedures. Most patients who ingested coins at our hospital were seen in the Department of Emergency, and if the coin was in the stomach or beyond, the patient was discharged if he or she was asymptomatic. Because a significant number of patients with accidental ingestion present to the hospital without any symptoms, the implementation of specific investig-



DOI: 10.5409/wjcp.v12.i4.205 Copyright ©The Author(s) 2023.

Figure 3 Magnet bead ingestion in children. A: Plain chest and abdominal X-ray of a 13-mo-old girl who ingested multiple beads of magnet which shows a shadow of magnet beads that were found to be adherent to the gastric mucosa and were removed endoscopically; B: Plain post-endoscopy abdominal X-ray showing signs of gastric perforation (free air in the peritoneum) and one remaining magnet bead; C: A picture of the child's abdomen post laparotomy.

ations and diagnostic modalities, such as erect chest radiography, technetium-labelled sucalfate scan, and early esophago-gastroduodenoscopy, is important to establish any anatomical-internal injuries[4]. The decision to perform an endoscopic procedure to remove a FB depends on the time since ingestion, FB location, size, and shape, as well as the patient's age, symptoms, and complications[10]. In our study, both radiologically and endoscopically, FBs were mostly found in the stomach, followed by the small bowel, and then the esophagus, with 37.7%, 19.7%, and 14.7%, respectively. However, the study by Lin *et al*[15], which was conducted on 87 patients who underwent an endoscopic procedure, showed that the most common lodgment site of FBs was the esophagus (51.4%), followed by the stomach (44.6%) and finally the duodenum (4%).

Fortunately, most of our patients did not develop complications (73.6%). However, 26.4% had endoscopic and surgical complications, 10.8% developed mucosal erythema, 9.5% had ulcer, 6.1% had erosions, and 3.4% had gastrointestinal perforation ($n = 5$). Uba *et al*[7] illustrated that the most common comorbidities were hemorrhage (15%), perforation (3.7%), and aspiration pneumonitis (2.8%).

In our study, 38.2% ($n = 58$) of the patients had a spontaneous passage of the FBs. However, higher rates of spontaneous passage have been documented. Chan *et al*[9] and Khorana *et al*[17] reported percentages of spontaneous passages that reached 92% and 60.31%, respectively. Accordingly, it was thought that the actual number of ingested FBs in children was higher than the documented number, since many cases had uneventful and symptomless spontaneous passage without the recognition and witnessing of the parents[13]. In our study, 30.3% of children underwent endoscopic procedures either to remove the FB or for the assessment/management of any complications. However, Dereci *et al*[13] reported a higher percentage of endoscopic procedures ($n = 55$, 85%). Fortunately, the overall need for surgical intervention reported in the literature is relatively low. In our study, five (3.3%) cases needed surgical intervention. Speidel *et al*[4] showed an even lower percentage ($n = 4$; 0.3%).

Limitations

This study had several limitations. As this was a retrospective study, missing data, such as patient contact number, presence of a witness, and details of the ingestion scenario, were expected. One of the limitations of this study was that we included only those who had been admitted to the hospital, excluding those who attended the Departments of Accident and Emergency and were discharged home, especially asymptomatic patients and those who ingested metallic coins found in the stomach or beyond. Moreover, the ingestion scenario of some patients was gathered *via* telephone calls to the child's parents/guardians after the ingestion episode, which was subject to recall bias. Some parents did not provide consent for endoscopy, especially for children who ingested corrosives, which made the assessment of local injury and gastrointestinal complications difficult. The ingestion of glass is a real challenge because it is radiolucent, and nothing was seen on the X-ray to determine the location. Despite these limitations, this study had many strengths. It is the first study from Bahrain to focus on accidental ingestion in children. This covered all types of accidental ingestion, unlike most other studies, which included the ingestion of only one type of hazardous material. The findings of this study are particularly important for health care providers dealing with this group of patients. They are also valuable for policy-makers as prevention guidelines and legislation are crucial for protecting children from avoidable risks.

CONCLUSION

Accidental ingestion of FBs/harmful materials in children is a serious problem. Our study showed that boys and toddlers were at a higher such risk. Most children were symptomatic at presentation, with vomiting being the predominant symptom. Batteries were the most commonly ingested materials, followed by metals and chemicals. Most accidents occur while children playing games unwitnessed. Patients who ingested chemicals had higher endoscopic morbidity than the FB or drug group. In patients with FB ingestion, younger age (less than 1 year), those from middle- and low-SES families, and those with more symptoms at presentation, were more prone to complications. Gastrointestinal perforation developed in the FB group only, and mainly after magnet ingestion. Further studies are required to assess the impact of parental education, government legislation, and ensuring a safe environment to prevent such serious accidents in children.

ARTICLE HIGHLIGHTS

Research background

Accidental ingestion of foreign bodies (FBs) or harmful materials is a common problem in families with children because of their exploratory behavior. This behavior puts them at risk and can cause serious morbidities.

Research motivation

While many studies on accidental ingestion in children have been published from several countries worldwide, no study has been published on this issue in Bahrain. This knowledge gap motivated us to study this health problem in Bahrain.

Research objectives

To evaluate the incidence, demographics, types of FBs/harmful materials ingested, diagnostic methods, management, complications, and outcomes of accidental ingestion in pediatric patients at the main tertiary hospital in Bahrain and compare patients with endoscopic or surgical complications with those without to identify the predicted risk factors.

Research methods

We retrospectively reviewed and collected the demographic data, clinical presentations, radiological and endoscopic findings, treatments, complications, and outcomes of accidental ingestions in children admitted to the Department of Pediatrics at the Salmaniya Medical Complex, Kingdom of Bahrain, from medical records between 2011 and 2021.

Research results

In total, 161 accidental ingestion episodes were documented in 153 children. Male predominance was noted ($n = 85$, 55.6%). The median age at presentation was 2.8 (interquartile range: 1.8-4.4) years. Most participants ingested FBs ($n = 108$, 70.6%), followed by caustic chemicals ($n = 31$, 20.3%) or medications ($n = 14$, 9.2%). Most patients were symptomatic ($n = 86$, 57.3%); vomiting was the common symptom ($n = 44$, 29.3%), followed by abdominal pain ($n = 25$, 16.7%). Batteries were the most commonly ingested FBs ($n = 49$, 32%). Unsafe toys were the main source of batteries ($n = 22/43$, 51.2%). Most episodes occurred while playing ($n = 49/131$, 37.4%) or unwitnessed ($n = 78$, 57.4%). Stomach was the common location of FB lodgment, both radiologically ($n = 54/123$, 43.9%) and endoscopically ($n = 31/91$, 34%). Of 107/108 (99.1%) patients with FB ingestions, spontaneous passage was noted in 54 (35.5%), endoscopic removal in 46 (30.3%), laparotomy in 5 (3.3%), and direct laryngoscopy in 2 (1.3%). Pharmacological therapy was required in 105 (70.9%) patients. Complications were detected in 39 (26.4%) patients, five of whom had gastrointestinal perforation. Patients who ingested FBs before the age of one year ($P = 0.042$), those with middle or low socioeconomic status ($P = 0.028$), and those with more symptoms at presentation ($P = 0.027$) had more complications.

Research conclusions

Accidental ingestion in children is a serious health problem. Symptomatic infants from families with middle or low families have the highest morbidity. Prevention through parental education and government legislation is crucial.

Research perspectives

Additional research is required to evaluate the influence of parental awareness, authority regulations, and the provision of safe environments to prevent such serious incidents.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge all health care providers taking care of children with accidental ingestion in the Department of Pediatrics and Pediatric Surgery Division at Salmaniya Medical Complex, Manama, Bahrain.

FOOTNOTES

Author contributions: Isa HM was the main contributor in study conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, original draft writing, and manuscript review and editing; Aldoseri SA, Abduljabbar AS, and Alsulaiti KA were responsible for literature review, data collection, and manuscript drafting and revision; and all the authors have read and approved the final manuscript.

Institutional review board statement: This study was conducted in accordance with the principles of the Declaration of Helsinki, and it was ethically approved by the Secondary Health Care Research Committee, Salmaniya Medical Complex, Government Hospitals, Kingdom of Bahrain (IRB number: 88300719, July 30, 2019).

Informed consent statement: Consent was not needed as the study was retrospective without exposure to the patients' data.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Data are available upon reasonable request.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Bahrain

ORCID number: Hasan M Isa 0000-0001-6022-5576; Shaikha A Aldoseri 0000-0001-5533-7119; Aysha S Abduljabbar 0000-0002-6028-9198; Khaled A Alsulaiti 0000-0002-3057-3833.

S-Editor: Wang JJ

L-Editor: Wang TQ

P-Editor: Wang JJ

REFERENCES

- 1 Sahin C, Alver D, Gulcin N, Kurt G, Celayir AC. A rare cause of intestinal perforation: ingestion of magnet. *World J Pediatr* 2010; **6**: 369-371 [PMID: 21080149 DOI: 10.1007/s12519-010-0237-5]
- 2 Antoniou D, Christopoulos-Geroulanos G. Management of foreign body ingestion and food bolus impaction in children: a retrospective analysis of 675 cases. *Turk J Pediatr* 2011; **53**: 381-387 [PMID: 21980840]
- 3 Marom T, Goldfarb A, Russo E, Roth Y. Battery ingestion in children. *Int J Pediatr Otorhinolaryngol* 2010; **74**: 849-854 [PMID: 20538351 DOI: 10.1016/j.ijporl.2010.05.019]
- 4 Speidel AJ, Wölfl L, Mayer B, Posovszky C. Increase in foreign body and harmful substance ingestion and associated complications in children: a retrospective study of 1199 cases from 2005 to 2017. *BMC Pediatr* 2020; **20**: 560 [PMID: 33339520 DOI: 10.1186/s12887-020-02444-8]
- 5 Brumbaugh DE, Colson SB, Sandoval JA, Karrer FM, Bealer JF, Litovitz T, Kramer RE. Management of button battery-induced hemorrhage in children. *J Pediatr Gastroenterol Nutr* 2011; **52**: 585-589 [PMID: 21502830 DOI: 10.1097/MPG.0b013e3181f98916]
- 6 Orsagh-Yentis D, McAdams RJ, Roberts KJ, McKenzie LB. Foreign-Body Ingestions of Young Children Treated in US Emergency Departments: 1995-2015. *Pediatrics* 2019; **143** [PMID: 30979810 DOI: 10.1542/peds.2018-1988]
- 7 Uba AF, Sowande AO, Amusa YB, Ogundoyin OO, Chinda JY, Adeyemo AO, Adejuyigbe O. Management of oesophageal foreign bodies in children. *East Afr Med J* 2002; **79**: 334-338 [PMID: 12638825 DOI: 10.4314/eamj.v79i6.8855]
- 8 Little DC, Shah SR, St Peter SD, Calkins CM, Morrow SE, Murphy JP, Sharp RJ, Andrews WS, Holcomb GW 3rd, Ostlie DJ, Snyder CL. Esophageal foreign bodies in the pediatric population: our first 500 cases. *J Pediatr Surg* 2006; **41**: 914-918 [PMID: 16677882 DOI: 10.1016/j.jpedsurg.2006.01.022]
- 9 Chan YL, Chang SS, Kao KL, Liao HC, Liaw SJ, Chiu TF, Wu ML, Deng JF. Button battery ingestion: an analysis of 25 cases. *Chang Gung Med J* 2002; **25**: 169-174 [PMID: 12022737]
- 10 Lee JH, Lee JH, Shim JO, Eun BL, Yoo KH. Foreign Body Ingestion in Children: Should Button Batteries in the Stomach Be Urgently Removed? *Pediatr Gastroenterol Hepatol Nutr* 2016; **19**: 20-28 [PMID: 27066446 DOI: 10.5223/pghn.2016.19.1.20]
- 11 Al-Salem AH, Qaisarrudin S, Murugan A, Hammad HA, Talwalker V. Swallowed foreign bodies in children: Aspects of management. *Ann Saudi Med* 1995; **15**: 419-421 [PMID: 17590624 DOI: 10.5144/0256-4947.1995.419]
- 12 Adedeji TO, Tobih JE, Olaosun AO, Sogebi OA. Corrosive oesophageal injuries: a preventable menace. *Pan Afr Med J* 2013; **15**: 11 [PMID: 23898360 DOI: 10.11604/pamj.2013.15.11.2495]
- 13 Dereci S, Koca T, Serdaroglu F, Akcam M. Foreign body ingestion in children. *Turk Pediatri Ars* 2015; **50**: 234-240 [PMID: 26884693 DOI: 10.5152/TurkPediatriArs.2015.3164]
- 14 Diaconescu S, Gimiga N, Sarbu I, Stefanescu G, Olaru C, Ioniuc I, Ciongradi I, Burlea M. Foreign Bodies Ingestion in Children: Experience of 61 Cases in a Pediatric Gastroenterology Unit from Romania. *Gastroenterol Res Pract* 2016; **2016**: 1982567 [PMID: 26949384 DOI: 10.1155/2016/1982567]

- 15 **Lin CH**, Chen AC, Tsai JD, Wei SH, Hsueh KC, Lin WC. Endoscopic removal of foreign bodies in children. *Kaohsiung J Med Sci* 2007; **23**: 447-452 [PMID: [17766213](#) DOI: [10.1016/S1607-551X\(08\)70052-4](#)]
- 16 **Kalra V**, Yadav SPS, Ranga R, Moudgil H, Mangla A. Epidemiological, Clinical and Radiological Profile of Patients with Foreign Body Oesophagus: A Prospective Study. *Indian J Otolaryngol Head Neck Surg* 2022; **74**: 443-448 [PMID: [36514420](#) DOI: [10.1007/s12070-021-02553-5](#)]
- 17 **Khorana J**, Tantivit Y, Phiuphong C, Pattapong S, Siripan S. Foreign Body Ingestion in Pediatrics: Distribution, Management and Complications. *Medicina (Kaunas)* 2019; **55** [PMID: [31615117](#) DOI: [10.3390/medicina55100686](#)]
- 18 **Litovitz T**, Whitaker N, Clark L. Preventing battery ingestions: an analysis of 8648 cases. *Pediatrics* 2010; **125**: 1178-1183 [PMID: [20498172](#) DOI: [10.1542/peds.2009-3038](#)]
- 19 **Litovitz T**, Whitaker N, Clark L, White NC, Marsolek M. Emerging battery-ingestion hazard: clinical implications. *Pediatrics* 2010; **125**: 1168-1177 [PMID: [20498173](#) DOI: [10.1542/peds.2009-3037](#)]



Retrospective Study

Safety and efficacy of intravitreal anti vascular endothelial growth factor for severe posterior retinopathy of prematurity with flat fibrovascular proliferation

Puja Maitra, Subramaniam Prema, Venkatapathy Narendran, Parag K Shah

Specialty type: Ophthalmology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Chen X, United States;
Wongwai P, Thailand

Received: May 5, 2023

Peer-review started: May 5, 2023

First decision: June 19, 2023

Revised: June 26, 2023

Accepted: July 7, 2023

Article in press: July 7, 2023

Published online: September 9, 2023



Puja Maitra, Subramaniam Prema, Venkatapathy Narendran, Parag K Shah, Pediatric Retina and Ocular Oncology, Aravind Eye Hospital and Postgraduate Institute of Ophthalmology, Coimbatore 641014, Tamil Nadu, India

Corresponding author: Parag K Shah, DNB, Professor, Pediatric Retina & Ocular Oncology, Aravind Eye Hospital, Avinashi Road, Coimbatore 641014, Tamil Nadu, India.

drshahpk2002@yahoo.com

Abstract

BACKGROUND

Intravitreal anti-vascular endothelial growth factor (IVA) injection is known to cause contraction of fibrovascular proliferation (FVP), when present in severe retinopathy of prematurity (ROP).

AIM

To assess the structural outcomes of IVA injection in the treatment of severe posterior ROP with significant FVP.

METHODS

It was a retrospective study in which 36 eyes of 18 preterm babies who developed > 4 clock hours of FVP in zone I or posterior zone II, were treated with either intravitreal 0.625 mg bevacizumab or intravitreal 0.2 mg of ranibizumab. Favorable structural outcome included resolution of plus disease and FVP without the development of tractional retinal detachment. Secondary outcome measure included either full retinal maturation at follow-up or development of recurrent disease requiring additional treatment. Adverse outcomes included progression to retinal detachment.

RESULTS

The mean gestational age of the 18 preterm babies was 30 wk (range 27-36), and mean birth weight was 1319 g (range 650-1980 g). Mean post-menstrual age (PMA) at the time of primary treatment was 35.5 wk (range 31-41 wk). All eyes showed regression of plus disease and FVP. 5 eyes of 3 babies showed reactivation of disease and were treated with repeat IVA ($n = 2$ eyes) or peripheral laser photocoagulation ($n = 3$ eyes) respectively. 16 out of 36 (44%) reached retinal vascular maturation at final follow up at 5 years.

CONCLUSION

There was good resolution of severe posterior ROP with FVP with IVA, with retinal maturity of 44% at 5 year follow-up and a reactivation rate of 13.8%. When the IVA injection is given prior to 37 wk PMA, while disease is in phase 2, it is less likely to cause contracture of pre-existing FVP.

Key Words: Retinopathy of prematurity; Anti-vascular endothelial growth factor injection; Contraction; Crunch phenomenon

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This is a retrospective study to evaluate if anti-vascular endothelial growth factor injection could cause contraction of preexisting fibrovascular proliferation when present in severe retinopathy of prematurity.

Citation: Maitra P, Prema S, Narendran V, Shah PK. Safety and efficacy of intravitreal anti vascular endothelial growth factor for severe posterior retinopathy of prematurity with flat fibrovascular proliferation. *World J Clin Pediatr* 2023; 12(4): 220-229

URL: <https://www.wjgnet.com/2219-2808/full/v12/i4/220.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i4.220>

INTRODUCTION

Since the first description of retinopathy of prematurity (ROP) by Terry in 1942, the understanding of the disease has evolved vastly, especially over that last decade with wider armamentarium of treatment options[1,2]. There has been an increase in the popularity of intravitreal anti-vascular endothelial growth factor (IVA) injection as a treatment modality especially with the landmarks trails such as Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) and Ranibizumab *vs* laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW), proving their safety and efficacy[3,4]. IVA injection has become the treatment of choice in aggressive and posterior diseases. Although dramatic effects are often noted after IVA injections, minimizing need for laser and related effects such as high myopia and peripheral field defect, reactivations are not uncommon and many of them may need re-treatment[5]. Therefore a through close follow up for these babies is mandatory. In cases associated with flat fibrovascular proliferation (FVP), there is often a risk of development or worsening of anteroposterior traction- also known as crunch phenomenon, especially in babies with higher post menstrual age[6,7]. The current study aims to show the safety and effectiveness of IVA injection in the treatment of severe type 1 ROP with more than 4 clock hours of flat FVP in zone I and posterior zone II.

MATERIALS AND METHODS

It is a retrospective study of babies with severe type 1 ROP as defined by the early treatment for retinopathy of prematurity study[8] with significant flat FVP in zone 1 or posterior zone II, who were treated with IVA injections between December 2013 to December 2016 and followed up for five years. The study was approved by the Ethics committee and the Institutional Review Board and adhered to the tenets of declaration of Helsinki. Significant FVP was defined as FVP spanning more than 4 clock hours. Relevant data of the baseline characteristics like gestational age, birth weight, post conceptional age at treatment, date of injection were collected from the electronic medical records. Zone of the disease and stage of the disease was defined as per the latest ICROP guidelines[9]. Informed consent was obtained from all the parents prior to the IVA, and the parents of the babies were offered to choose either Bevacizumab (Avastin; Genentech Inc, South San Francisco, CA, United States) or Ranibizumab (Accentrix; Novartis pharma Stein AG) after they were explained the possible side- effects, need for long follow up, and off label use. Dosage administered was 0.625mg of bevacizumab or 0.2 mg of ranibizumab given under aseptic precaution in operation theatre under topical anesthesia using 30 gauge needle about 1.5 mm from limbus. Two ophthalmologist reviewed fundus images pre and post injection. Documentation was done by taking images using 130 degrees lens using the Retcam 3 (Clarity Medical Systems, Pleasanton CA, United States).

All the babies were treated within 2 days of presentation. Concurrent bilateral injection were given under aseptic precautions for each eye separately, using drugs with different batch numbers for the two eyes. Patients were followed up weekly for two months, two weekly for next two months, monthly till 6 months, two monthly till 12 months and six monthly till 5 years of age.

Patients who demonstrated peripheral avascular retina (PAR), were followed up as per schedule and examination under anesthesia was performed wherever necessary. Reactivation was treated with either repeat IVA injection or peripheral laser photocoagulation depending on the location of the disease and family's preference. Rescue vitrectomy was planned in case of development of tractional retinal detachment/crunch phenomenon.

Primary outcome was measured in terms of regression of plus disease and absence of FVP. Secondary outcome was measured in terms of absence of reactivation of disease and vessels reaching maturity at the end of 1 year, which was considered as the minimum follow up period. Safety profile was assessed by lack of development of anteroposterior traction or crunch phenomenon. The results were tabulated in Microsoft excel version 2206, in which mean and percentages were calculated.

RESULTS

Thirty-six eyes of 18 infants were included in the study. The mean gestational age of the 18 preterm babies was 30 wk (range 27-36), and mean birth weight was 1319 g (range 650-1980g). Mean post-menstrual age (PMA) at the time of IVA was 35 wk (range 31-41 wk). 22 eyes (61.1%) had aggressive ROP (AROP) in zone I, 6 eyes (16.66%) had AROP in posterior zone II. Two eyes had stage 3 in zone I and 6 eyes had stage 3 in posterior zone II. Thirty two eyes (89%) received 0.625 mg of intravitreal bevacizumab and 4 eyes (11%) received 0.2 mg of intravitreal ranibizumab (0.2 mg). All eyes showed regression of plus disease and FVP. In 10 eyes (27%) this regression was within a week of IVA and in additional 25 (69%) eyes it occurred within a month and only in 1 eye regression occurred by 2 mo post IVA. Figures 1 and 2 show pre injection (Figure 1A and B) and post IVA regression of plus disease and FVP (Figure 1C and D). 2 eyes of 2 patients (5.5%) developed vitreous hemorrhage within one week post IVA, which showed resolution within a month. The neovascularization of iris (in 4 eyes) regressed within a week of injection. The regression of disease activity after IVA for each case is shown in Table 1.

In 14 out of 36 (39%) eyes the retinal vessels reached maturity uneventfully without intervention. In 4 eyes (11%) the vessels matured by 4 months, in 6 eyes (33%) by six months and in another 6 eyes (33%) by one year. Among the 20 (55.5%) eyes that did not reach maturation, recurrence of disease was seen in 5 eyes (13.8%). The mean time of recurrence was 10 weeks in our study (6 weeks for ranibizumab eyes and 12 wk for bevacizumab eyes). An additional dose of IVA was given in 2 eyes of 1 patient (post ranibizumab) at one and half months after initial injection. 3 eyes of 2 patients required peripheral laser photocoagulation. In 15 of 36 eyes, although there was no recurrence of ROP, babies were kept under follow-up with immature vessels/peripheral avascular retina in zone II or III. All eyes were followed up for a minimum period of 1 year at our centre. 12 out of 18 babies (24 eyes) (66%) completed 3 years follow up, and 11 out of 18 babies (22 eyes) (61%) completed 5 years.

At final follow up, vascular maturity was noted in 16 (44%) eyes, PAR was noted in 17(47%) eyes and peripheral laser scars in 3 (8%) eyes. Development of disc pallor was noted in 2 eyes. 4 eyes of 2 babies developed white without pressure in the area of PAR and 2 eyes of 1 baby additionally developed lattice degeneration in the PAR at 5 years follow up. Babies who were lost to follow up at our center due to the emergence of coronavirus disease 2019 outbreak, were followed up over telephonic conversation and directed to the closest ophthalmic center for follow up to rule out the possibility of development of any sight threatening ROP.

None of the babies developed anteroposterior traction or tractional retinal detachment or required rescue vitrectomy at any time until the last follow up. None of developed any systemic complications.

DISCUSSION

In this study we attempted to show the effectiveness of IVA in severe posterior type 1 ROP with over 4 clock hours of FVP. Trials such as the BEAT ROP[3] study has showed the effectiveness of bevacizumab in ROP in posterior disease, and the RAINBOW trial has showed the outcomes of ranibizumab *vs* laser in ROP[3,4]. However, its effectiveness in presence of flat FVP is not studied. The fate of the retinal vessels following bevacizumab follow certain scalloped pattern described by Chen *et al*[10] as having one of the following fate; vascular arrest alone with peripheral non perfusion in 43%, vascular arrest with persistent tortuosity in 38%, reactivated ROP in 18%, and full vascular maturation (by 60 week PMA) in 3%. [10] Although in our cohort we did not look into these patterns, 11% of the eyes had vascular maturation within 4 months post IVA, which appears to be greater than reported by them, and finally 39% eyes reached maturation in 1 year. Even in the RAINBOW trial, full peripheral vascularization (which they assessed only by indirect ophthalmoscopy) occurred in 32% by day 169 in both the combined ranibizumab groups[4].

It is known and has been emphasized even in landmark trails that the retinal vessels advance to the point at which the vascular precursors have ceased migration, with differentiation of the underlying retina, in case of IVA injection monotherapy[3]. Therefore a PAR is expected in majority of these cases. The rate of reactivation was 13.8% in our patients, which was low considering that presence of FVP is not the typical cohort of choice for IVA in most of the studies conducted. Infact, before the widespread use of IVA injections, early vitrectomy was recommended for such cases[11].

The timing of recurrence is influenced by the half-life of the drug in the vitreous cavity. For Ranibizumab, which is a 48 kDa Fab antibody fragment, the serum half-life is much lesser than bevacizumab, which is a 149 kDa monoclonal antibody. Therefore, an earlier recurrence is expected in Ranibizumab eyes[4]. The mean time of recurrence was 10 week in our study (6 week for ranibizumab eyes and 12 week for bevacizumab eyes). These results were similar to the recurrence at 16 week for bevacizumab in BEAT-ROP trial[3]. In the RAINBOW trial the median time to recurrence was 8 week for ranibizumab[4]. Reactivation have been reported with bevacizumab occurring upto 69 weeks after injection and there have been reports of very late reactivations, even as late as 2.5 years of age with tractional retinal detachment (TRD) after bevacizumab for AROP[12,13]. TRD in proliferative diseases like diabetic retinopathy[14] can worsen after IVA injection and studies have showed that similar phenomenon can also occur in advanced ROP, described as crunch effect

Table 1 Regression of disease activity after intravitreal anti vascular endothelial growth factor

S. No	Eye	GA	BW	PMA	Features	Follow up after IVA								
						1 wk	1 mo	2 mo	3-4 mo	6 mo	8 mo	12 mo	3 yr	5 yr
1	OD	30	1200	35	Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	Zone II stage 3 – Lasered	Stable	Stable	Stable	Stable	Stable (lasered)
	OS				Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	Zone II stage 3 – Lasered	Stable	Stable	Stable	Stable	Stable (lasered)
2	OD	32	1200	38	Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	Mature	Mature	Mature	Stable
	OS				Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	Mature	Mature	Mature	Stable
3	OD	30	950	35	Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	Mature	Mature	Mature	Mature	Stable
	OS				Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	Mature	Mature	Mature	Mature	Stable
4	OD	28	1235	36	Zone 1 AROP	Regressing FVP	Complete FVP regression	Zone II stage 3-repeat -R	PAR	PAR	PAR	Mature	Mature	Stable, disc pallor
	OS				Zone 1 AROP	Regressing FVP	Complete FVP regression	Zone II stage 3-repeat -R	PAR	PAR	PAR	Mature	Mature	Stable, disc pallor
5	OD	36	1800	41	Zone II P AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone II P AROP	Regressing FVP	Complete FVP regression	PAR	Zone II stage 3 – lasered	PAR	PAR	Stable (Lasered)	FU elsewhere	FU elsewhere
6	OD	35	1700	41	Zone II P AROP	Regressing FVP	Complete FVP regression	PAR	PAR	Mature	Stable	Stable	stable	FU elsewhere
	OS				Zone II P AROP	Regressing FVP	Complete FVP regression	PAR	PAR	Mature	Stable	Stable	Stable	FU elsewhere
7	OD	28	1200	34	Zone II stage 3 P +	Regressing FVP	Complete FVP regression	PAR	Mature	Stable	Stable	Stable	Stable	Stable
	OS				Zone II stage 3 P +	Regressing FVP	Complete FVP regression	PAR	Mature	Stable	Stable	Stable	Stable	Stable
8	OD	32	1980	36	Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone 1 AROP	Complete FVP regression		PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere

9	OD	29	2050	35	Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone 1 AROP	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
10	OD	28	1300	34	Zone 1 AROP (hge)	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	Mature	Mature	Mature
	OS				Zone 1 AROP (hge)	Regressing FVP	Complete FVP regression	PAR	PAR	PAR	PAR	Mature	Mature	Mature
11	OD	29	1265	34	Zone II stage 3 P+	Regressing FVP	Complete FVP regression	PAR	PAR	Mature	Mature	Mature	Mature	Mature
	OS				Zone II stage 3 P+	Regressing FVP	Complete FVP regression	PAR	PAR	Mature	Mature	Mature	Mature	Mature
12	OD	29	1750	33	Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR, lattice, WWOP	PAR, lattice, WWOP
	OS				Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR, lattice, WWOP	PAR, lattice, WWOP
13	OD	27	650	33	NVI, Zone 1 Stage 3 +	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR, WWOP	PAR, WWOP
	OS				NVI, Zone 1 Stage 3 +	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR WWOP	PAR, WWOP
14	OD	30	1300	35	Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone 1 AROP	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
15	OD	28	1500	31	Zone 1 AROP	Regressing	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
	OS				Zone 1 AROP	Regressing	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
16	OD	28	1060	35	NVI, Zone II P AROP	regressing	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR	PAR
	OS				NVI, Zone II P AROP	Regressing	Inomplete FVP regression	Complete FVP regression	PAR	PAR	PAR	PAR	PAR	PAR
17	OD	29	1450	33	Zone II stage 3 P+	Regressing	Complete FVP regression	PAR	Mature	Mature	Mature	Mature	Mature	Mature
	OS				Zone II stage 3 P+	Regressing	Complete FVP regression	PAR	Mature	Mature	Mature	Mature	Mature	Mature
18	OD	29	1260	34	Zone II AROP	Regressing	Complete FVP	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere

OS	Zone II AROP	regressing	regression	PAR	PAR	PAR	PAR	PAR	FU elsewhere	FU elsewhere
			Complete FVP regression							

GA: Gestational age; OD: Right eye; OS: Left eye; BW: Birth weight; PMA: Post menstrual age; PAR: Peripheral avascular retina; FU: Follow up; AROP: Aggressive retinopathy of prematurity; FVP: Fibrovascular proliferation; NVI: Neovascularization of iris; WWOP: White without pressure.

[7].

Crunch effect is the term given to accelerated posterior/prepapillary fibrosis and contraction as one of the characteristic patterns of TRD which may occur following intravitreal injection of anti-vascular endothelial growth factor (VEGF) therapies in acute ROP, with 49% of detachments occurring within 4 week of the treatment, with older infants (by PMA) at higher risk[7].

In this American Academy of Ophthalmology 2019 interview[15], Dr. Capone Jr. describes his experience with crunch detachment where he states an inverse relationship of PMA with pace of developing detachment - older children are at a greater risk of crunch detachments because they typically have pre-existing fibrosis and an increased chance of abrupt contraction. He also described 2 unique types of crunch – arcuate and prepaillary contraction. Thus, the presence of extensive FVP presents a dilemma in treating zone 1 or posterior zone II disease with anti-VEGF injection. All babies in our study had no clinical evidence of antero-posterior traction unlike described by Honda *et al*[6] where avastin given to baby with stage 4A resulted in acute contracture of proliferative membrane resulting in worsening of the disease. A similar study by Kychenthal *et al*[16] showed that bevacizumab given in eyes with extensive neovascular tissue showed higher chances of development of fibrosis. However they also recruited cases with stages 4A and B, which already have established antero-posterior traction.

In a study by Wu *et al*[17], bevacizumab was injected for stages 3, 4A and stage 5 patients. 33% of eyes with 4A regressed after bevacizumab alone without the requirement of vitrectomy. Many studies have shown the outcomes of use of intravitreal bevacizumab prior to vitrectomy, where reduced vascularity not only aided the surgery but also induced contracture of proliferative membrane indicating earlier surgical intervention[18,19].

This phenomenon is likely to be secondary to a shift in the cytokine signalplex, with exacerbation of the unopposed activity of profibrotic cytokines such as transforming growth factor-beta (TGF- β); TGF- β , an antagonist of VEGF, rises in systemic and intravitreal concentration between 36 and 40 wk PMA, the time period during which many of these premature infants are being treated with anti-VEGF[20]. No contracture of FVP was seen in any of our cases, rather in 75% eyes there was disappearance of FVP within a month of injection, earliest being within a week.

In the attempted normal physiological vascularization in a preterm, various risk factors interrupt this process to and assist in the pathogenesis of ROP. In the Phase 1 or vaso-obliterative phase, there is a low level of VEGF as well as declining levels of circulating insulin like growth factor 1 (IGF-1) from the maternal source. With the maturation of the liver of the premature baby, IGF-1 production starts and its levels rise. This, along with the rise in VEGF levels in phase 2 of pathogenesis of ROP, aids in development of treatable ROP[21-24]. A late component of phase 2 can be described as Phase 3, which is the phase of development of fibrosis and TRD[25]. Increased VEGF activates plasminogen activators which converts plasminogen to plasmin which in turn activates transforming growth factor beta 1 (TGF- β 1) which downregulates VEGF and promote fibrosis leading to excessive scarring in stages 4 and 5 ROP[26]. As the baby matures, the liver is able to produce the factors such as TGF- β 1, and this allows exaggerated effects of the VEGF and subsequently the development of fibrous component, providing a scaffold for the high levels of VEGF to act and cause a contracture. This is why crunch phenomenon is often seen in babies with higher PMA[15].

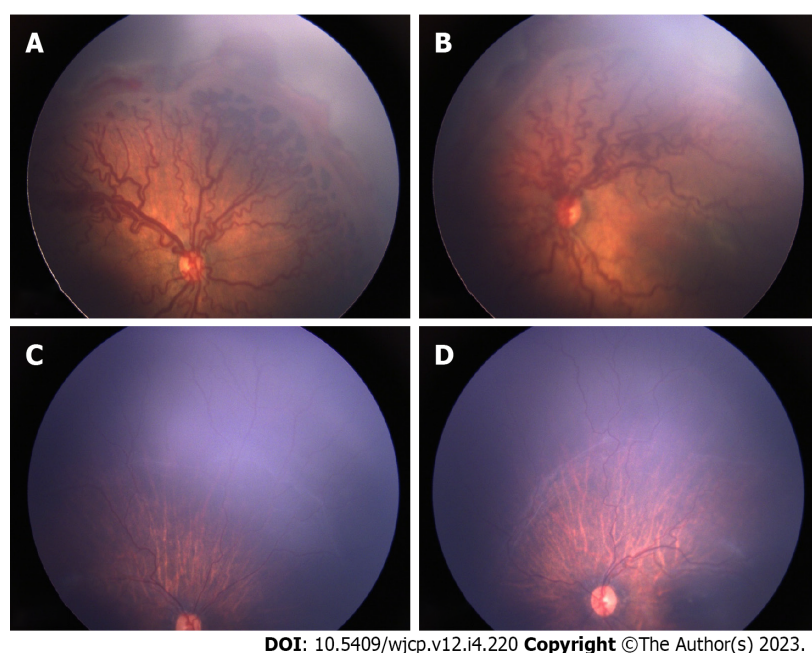


Figure 1 Pre and post intravitreal anti-vascular endothelial growth factor injection fundus pictures showing disease regression. A: Fundus picture of right eye and; B: Fundus picture of left eye showing severe Zone 1 Aggressive retinopathy of prematurity with extensive fibro vascular proliferation; C: Fundus picture of right eye and; D: Fundus picture of left eye taken 4 months following anti-vascular endothelial growth factor injection showing marked resolution of disease with minimal residual fibrous tissue.

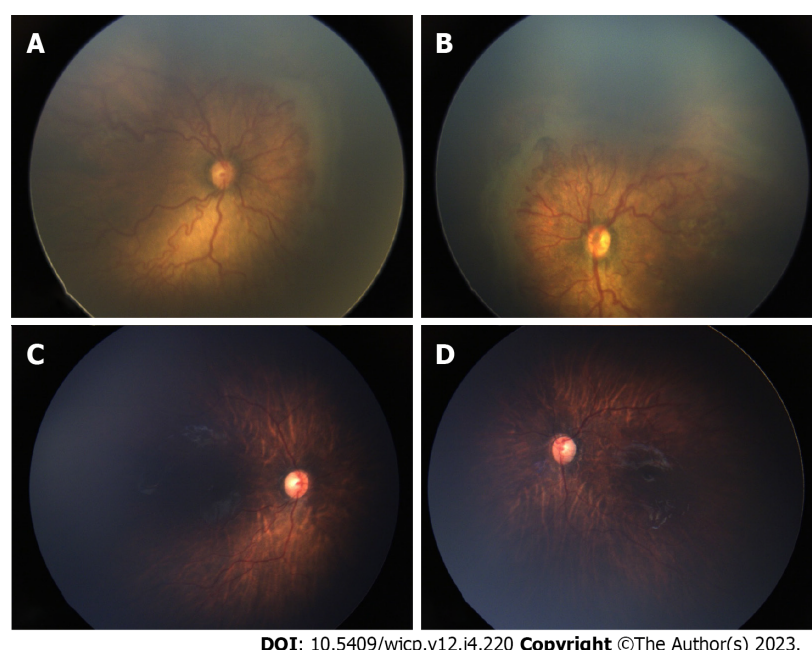


Figure 2 Pre and post intravitreal anti-vascular endothelial growth factor injection fundus pictures showing disease regression. A: Fundus picture of right eye and; B: Fundus picture of left eye showing severe Zone 1 Aggressive retinopathy of prematurity with extensive fibro vascular proliferation; C: Fundus picture of right eye and; D: Fundus picture of left eye taken 3 months following anti-vascular endothelial growth factor injection showing marked resolution of disease.

The mean PMA at the time of injection in our cases was 35.1 week which explains the resolution of FVP in our series. In most of the reported cases of crunch phenomenon, the IVA has been given between 37-42 wk[6,27,28]. Thus, we can assume when the anti- VEGF injection given prior 37 week PMA, the baby is believed to be in phase 2 where the vascular component predominates and no contracture of FVP occurs. On the contrary, if anti-VEGF injection is given near or at term, then the disease is already in Phase 3 and anti-VEGF would hasten the already set-in fibrosis leading to contracture with progression of disease to stages 4b and 5. Although determining an exact cut off requires studies with larger sample size, it may still lack direct evidence to establish such a cut off, due to prior knowledge of crunch phenomenon in older babies and ethical considerations. However, it must be kept in mind that the timing of IVA is key and it is unlikely to

cause a contracture of pre-existing FVP prior to 37 week PMA, as per indirect evidence.

The effect of systemic absorption of IVA and effect on the other eye has been noted by the development of crunch effect in the fellow eye[28]. Theoretically a shorter acting IVA is preferred due to lesser suppression of systemic VEGF and we feel it could be preferred in cases with significant FVP as well, as this would limit the development of contracture or atleast shorten the critical time when contracture is likely to occur. In our cohort however, the choice of IVA was as per the patient's preference which in turn was mostly influenced by the cost of the injection. The drawback of this study includes comparison across different anti VEGF that are known to have different half-life in the vitreous cavity. Also, we included babies with significant FVP (> 4 clock hours) treated with IVA injections, without performing ultrasound B scan to rule out anteroposterior traction.

CONCLUSION

The subset of severe posterior ROP with FVP pose therapeutic dilemma. This study shows favorable outcomes when treated with IVA injections, in babies with PMA < 37 weeks. The present study also shows the importance of extended period of follow up post IVA injections, as we found a high percentage (55.5%) of babies having incomplete vascular maturity at 1 year follow up. However, none of the babies developed anteroposterior traction or tractional retinal detachment or required rescue vitrectomy at any time until the last follow up 5 years post IVA. But we advise caution, especially in a setting without vitreoretinal surgery back up, and recommend a multi-center prospective study with a larger sample size.

ARTICLE HIGHLIGHTS

Research background

There is always a dilemma whether or not intravitreal anti-vascular endothelial growth factor (IVA) injections can be given in severe retinopathy of prematurity (ROP) with fibro vascular proliferation (FVP).

Research motivation

The outcome of laser alone in treating severe posterior ROP with FVP is poor. Hence we wanted to test if IVA injections could be a better option for these subset of cases.

Research objectives

To test if early IVA injections in severe posterior ROP with FVP would cause worsening of the disease.

Research methods

It is a retrospective study which included 36 eyes of 18 babies, which were given IVA injections for severe posterior ROP with FVP and followed up till 5 years of age.

Research results

There was no contraction of the FVP in any of the eyes after the IVA injections. All eyes showed very good regression. The mean post menstrual age of injection was 35.5 wk. Five eyes showed disease reactivation on follow up which was treated by laser in 3 eyes and repeat IVA injections in 2 eyes.

Research conclusions

IVA injections can be tried as an initial treatment in severe posterior ROP with FVP, if the post menstrual age at the time of injection is < 37 wk.

Research perspectives

IVA injections could be used as a first line treatment in the management of severe posterior ROP with FVP.

FOOTNOTES

Author contributions: Shah PK and Narendran V designed the research study; Maitra P and Prema S performed the research; Narendran V contributed towards analytic tools; Maitra P, Prema S and Shah PK analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Aravind Eye Hospital Institutional Ethics Committee (Approval No. RET201300423).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at email address: drshahpk2002@yahoo.com. Participants gave informed consent for data sharing.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: India

ORCID number: Venkatapathy Narendran [0000-0001-7436-6783](https://orcid.org/0000-0001-7436-6783); Parag K Shah [0000-0002-5014-6599](https://orcid.org/0000-0002-5014-6599).

S-Editor: Liu JH

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- 1 Terry TL. Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Infants Born Prematurely: II. Report of Cases-Clinical Aspects. *Trans Am Ophthalmol Soc* 1942; **40**: 262-284 [PMID: [16693285](https://pubmed.ncbi.nlm.nih.gov/16693285/)]
- 2 Hansen ED, Hartnett ME. A review of treatment for retinopathy of prematurity. *Expert Rev Ophthalmol* 2019; **14**: 73-87 [PMID: [31762784](https://pubmed.ncbi.nlm.nih.gov/31762784/) DOI: [10.1080/17469899.2019.1596026](https://doi.org/10.1080/17469899.2019.1596026)]
- 3 Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011; **364**: 603-615 [PMID: [21323540](https://pubmed.ncbi.nlm.nih.gov/21323540/) DOI: [10.1056/NEJMoa1007374](https://doi.org/10.1056/NEJMoa1007374)]
- 4 Stahl A, Lepore D, Fielder A, Fleck B, Reynolds JD, Chiang MF, Li J, Liew M, Maier R, Zhu Q, Marlow N. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet* 2019; **394**: 1551-1559 [PMID: [31522845](https://pubmed.ncbi.nlm.nih.gov/31522845/) DOI: [10.1016/S0140-6736\(19\)31344-3](https://doi.org/10.1016/S0140-6736(19)31344-3)]
- 5 Wu AL, Wu WC. Anti-VEGF for ROP and Pediatric Retinal Diseases. *Asia Pac J Ophthalmol (Phila)* 2018; **7**: 145-151 [PMID: [29633587](https://pubmed.ncbi.nlm.nih.gov/29633587/) DOI: [10.22608/APO.201837](https://doi.org/10.22608/APO.201837)]
- 6 Honda S, Hirabayashi H, Tsukahara Y, Negi A. Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol* 2008; **246**: 1061-1063 [PMID: [18320201](https://pubmed.ncbi.nlm.nih.gov/18320201/) DOI: [10.1007/s00417-008-0786-7](https://doi.org/10.1007/s00417-008-0786-7)]
- 7 Yonekawa Y, Wu WC, Nitulescu CE, Chan RVP, Thanos A, Thomas BJ, Todorich B, Drenser KA, Trese MT, Capone A Jr. Progressive retinal detachment in infants with retinopathy of prematurity treated with intravitreal bevacizumab or ranibizumab. *Retina* 2018; **38**: 1079-1083 [PMID: [28471890](https://pubmed.ncbi.nlm.nih.gov/28471890/) DOI: [10.1097/IAE.0000000000001685](https://doi.org/10.1097/IAE.0000000000001685)]
- 8 Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003; **121**: 1684-1694 [PMID: [14662586](https://pubmed.ncbi.nlm.nih.gov/14662586/) DOI: [10.1001/archophth.121.12.1684](https://doi.org/10.1001/archophth.121.12.1684)]
- 9 Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, Binenbaum G, Blair M, Peter Campbell J, Capone A Jr, Chen Y, Dai S, Ellis A, Fleck BW, Good WV, Elizabeth Hartnett M, Holmstrom G, Kusaka S, Kychenthal A, Lepore D, Lorenz B, Martinez-Castellanos MA, Özdek Ş, Ademola-Popoola D, Reynolds JD, Shah PK, Shapiro M, Stahl A, Toth C, Vinekar A, Visser L, Wallace DK, Wu WC, Zhao P, Zin A. International Classification of Retinopathy of Prematurity, Third Edition. *Ophthalmology* 2021; **128**: e51-e68 [PMID: [34247850](https://pubmed.ncbi.nlm.nih.gov/34247850/) DOI: [10.1016/j.ophtha.2021.05.031](https://doi.org/10.1016/j.ophtha.2021.05.031)]
- 10 Chen TA, Shields RA, Bodnar ZH, Callaway NF, Schachar IH, Moshfeghi DM. A Spectrum of Regression Following Intravitreal Bevacizumab in Retinopathy of Prematurity. *Am J Ophthalmol* 2019; **198**: 63-69 [PMID: [30312578](https://pubmed.ncbi.nlm.nih.gov/30312578/) DOI: [10.1016/j.ajo.2018.09.039](https://doi.org/10.1016/j.ajo.2018.09.039)]
- 11 Micelli Ferrari T, Furino C, Lorusso VV, Dammacco R, Sborgia G, Sborgia L, Besozzi G. Three-port lens-sparing vitrectomy for aggressive posterior retinopathy of prematurity: early surgery before tractional retinal detachment appearance. *Eur J Ophthalmol* 2007; **17**: 785-789 [PMID: [17932856](https://pubmed.ncbi.nlm.nih.gov/17932856/) DOI: [10.1177/112067210701700516](https://doi.org/10.1177/112067210701700516)]
- 12 Hu J, Blair MP, Shapiro MJ, Lichtenstein SJ, Galasso JM, Kapur R. Reactivation of retinopathy of prematurity after bevacizumab injection. *Arch Ophthalmol* 2012; **130**: 1000-1006 [PMID: [22491394](https://pubmed.ncbi.nlm.nih.gov/22491394/) DOI: [10.1001/archophth.2012.592](https://doi.org/10.1001/archophth.2012.592)]
- 13 Snyder LL, Garcia-Gonzalez JM, Shapiro MJ, Blair MP. Very Late Reactivation of Retinopathy of Prematurity After Monotherapy With Intravitreal Bevacizumab. *Ophthalmic Surg Lasers Imaging Retina* 2016; **47**: 280-283 [PMID: [26985803](https://pubmed.ncbi.nlm.nih.gov/26985803/) DOI: [10.3928/23258160-20160229-12](https://doi.org/10.3928/23258160-20160229-12)]
- 14 Arevalo JF, Maia M, Flynn HW Jr, Saravia M, Avery RL, Wu L, Eid Farah M, Pieramici DJ, Berrocal MH, Sanchez JG. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008; **92**: 213-216 [PMID: [17965108](https://pubmed.ncbi.nlm.nih.gov/17965108/) DOI: [10.1136/bjo.2007.127142](https://doi.org/10.1136/bjo.2007.127142)]
- 15 Park DW III, Capone A Jr. In: AAO Interviews [Internet]. San Francisco: 2019. Available from: <https://www.aao.org/education/interview/crunch-detachment-after-anti-vegf-therapy-rop>
- 16 Kychenthal A, Dorta P. Vitrectomy after intravitreal bevacizumab (Avastin) for retinal detachment in retinopathy of prematurity. *Retina* 2010; **30**: S32-S36 [PMID: [20224474](https://pubmed.ncbi.nlm.nih.gov/20224474/) DOI: [10.1097/IAE.0b013e3181ca146b](https://doi.org/10.1097/IAE.0b013e3181ca146b)]
- 17 Wu WC, Yeh PT, Chen SN, Yang CM, Lai CC, Kuo HK. Effects and complications of bevacizumab use in patients with retinopathy of prematurity: a multicenter study in taiwan. *Ophthalmology* 2011; **118**: 176-183 [PMID: [20673589](https://pubmed.ncbi.nlm.nih.gov/20673589/) DOI: [10.1016/j.ophtha.2010.04.018](https://doi.org/10.1016/j.ophtha.2010.04.018)]
- 18 Sun HJ, Choi KS, Lee SJ. Adjunctive effect of intravitreal bevacizumab prior to lens-sparing vitrectomy in aggressive posterior retinopathy of prematurity: a case report. *Jpn J Ophthalmol* 2012; **56**: 476-480 [PMID: [22843138](https://pubmed.ncbi.nlm.nih.gov/22843138/) DOI: [10.1007/s10384-012-0141-8](https://doi.org/10.1007/s10384-012-0141-8)]

- 19 **Xu Y**, Zhang Q, Kang X, Zhu Y, Li J, Chen Y, Zhao P. Early vitreoretinal surgery on vascularly active stage 4 retinopathy of prematurity through the preoperative intravitreal bevacizumab injection. *Acta Ophthalmol* 2013; **91**: e304-e310 [PMID: [23647944](#) DOI: [10.1111/aos.12055](#)]
- 20 **Connor TB Jr**, Roberts AB, Sporn MB, Danielpour D, Dart LL, Michels RG, de Bustros S, Enger C, Kato H, Lansing M. Correlation of fibrosis and transforming growth factor-beta type 2 levels in the eye. *J Clin Invest* 1989; **83**: 1661-1666 [PMID: [2708527](#) DOI: [10.1172/JCI114065](#)]
- 21 **Carroll L**, Owen LA. Current evidence and outcomes for retinopathy of prematurity prevention: insight into novel maternal and placental contributions. *Explor Med* 2020; **1**: 4-26 [PMID: [32342063](#) DOI: [10.37349/emed.2020.00002](#)]
- 22 **Smith LE**. IGF-1 and retinopathy of prematurity in the preterm infant. *Biol Neonate* 2005; **88**: 237-244 [PMID: [16210846](#) DOI: [10.1159/000087587](#)]
- 23 **Hellstrom A**, Perruzzi C, Ju M, Engstrom E, Hard AL, Liu JL, Albertsson-Wikland K, Carlsson B, Niklasson A, Sjödel L, LeRoith D, Senger DR, Smith LE. Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells: direct correlation with clinical retinopathy of prematurity. *Proc Natl Acad Sci U S A* 2001; **98**: 5804-5808 [PMID: [11331770](#) DOI: [10.1073/pnas.101113998](#)]
- 24 **Lofqvist C**, Chen J, Connor KM, Smith AC, Aderman CM, Liu N, Pintar JE, Ludwig T, Hellstrom A, Smith LE. IGFBP3 suppresses retinopathy through suppression of oxygen-induced vessel loss and promotion of vascular regrowth. *Proc Natl Acad Sci U S A* 2007; **104**: 10589-10594 [PMID: [17567756](#) DOI: [10.1073/pnas.0702031104](#)]
- 25 **Hartnett ME**. Pathophysiology and mechanisms of severe retinopathy of prematurity. *Ophthalmology* 2015; **122**: 200-210 [PMID: [25444347](#) DOI: [10.1016/j.ophtha.2014.07.050](#)]
- 26 **Capone A Jr**, Trese MT. Evolution of stage 4 retinopathy of prematurity. In: Hartnett ME, Trese MT, Capone A Jr, Keats BJB, Caputo G, eds. *Pediatric Retina*. 2nd ed. Philadelphia: Wolters Kluwer, 2014: 568-572
- 27 **Zepeda-Romero LC**, Liera-Garcia JA, Gutiérrez-Padilla JA, Valtierra-Santiago CI, Avila-Gómez CD. Paradoxical vascular-fibrotic reaction after intravitreal bevacizumab for retinopathy of prematurity. *Eye (Lond)* 2010; **24**: 931-933 [PMID: [19557020](#) DOI: [10.1038/eye.2009.156](#)]
- 28 **Wood EH**, Rao P, Moysidis SN, Dedania VS, Elman MJ, Drenser KA, Capone A Jr, Trese MT. Fellow Eye Anti-VEGF 'Crunch' Effect in Retinopathy of Prematurity. *Ophthalmic Surg Lasers Imaging Retina* 2018; **49**: e102-e104 [PMID: [30222828](#) DOI: [10.3928/23258160-20180907-16](#)]



Retrospective Study

Radiation dose analysis of computed tomography coronary angiography in Children with Kawasaki disease

Mahesh Chandra Bhatt, Manphool Singhal, Rakesh Kumar Pania, Subhash Chand Bansal, Niranjana Khandelwal, Pankaj Gupta, Surjit Singh

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Ng HY, China; Zeng C, United States

Received: May 17, 2023

Peer-review started: May 17, 2023

First decision: July 4, 2023

Revised: July 12, 2023

Accepted: August 9, 2023

Article in press: August 9, 2023

Published online: September 9, 2023



Mahesh Chandra Bhatt, Manphool Singhal, Subhash Chand Bansal, Niranjana Khandelwal, Pankaj Gupta, Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Rakesh Kumar Pania, Surjit Singh, Pediatric Allergy Immunology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Manphool Singhal, MD, DNB, FICR, FSCCT, FSCMR, Professor, Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Madhya Marg, Sector 12, Chandigarh 160012, India. drmsinghal74@gmail.com

Abstract

BACKGROUND

There is evolving role of computed tomography coronary angiography (CTCA) in non-invasive evaluation of coronary artery abnormalities in children with Kawasaki disease (KD). Despite this, there is lack of data on radiation dose in this group of children undergoing CTCA.

AIM

To audit the radiation dose of CTCA in children with KD.

METHODS

Study (December 2013-February 2018) was performed on dual source CT scanner using adaptive prospective electrocardiography-triggering. The dose length product (DLP in milligray-centimeters-mGy.cm) was recorded. Effective radiation dose (millisieverts-mSv) was calculated by applying appropriate age adjusted conversion factors as per recommendations of International Commission on Radiological Protection. Radiation dose was compared across the groups (0-1, 1-5, 5-10, and > 10 years).

RESULTS

Eighty-five children (71 boys, 14 girls) with KD underwent CTCA. The median age was 5 years (range, 2 mo-11 years). Median DLP and effective dose was 21 mGy.cm, interquartile ranges (IQR) = 15 (13, 28) and 0.83 mSv, IQR = 0.33 (0.68, 1.01) respectively. Mean DLP increased significantly across the age groups. Mean effective dose in infants (0.63 mSv) was significantly lower than the other age

groups (1-5 years 0.85 mSv, 5-10 years 1.04 mSv, and > 10 years 1.38 mSv) ($P < 0.05$). There was no significant difference in the effective dose between the other groups of children. All the CTCA studies were of diagnostic quality. No child required a repeat examination.

CONCLUSION

CTCA is feasible with submillisievert radiation dose in most children with KD. Thus, CTCA has the potential to be an important adjunctive imaging modality in children with KD.

Key Words: Computed tomography coronary angiography; Coronary artery abnormalities; Dual source computed tomography; Kawasaki disease; Radiation exposure

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Dual source computed tomography (CT) scanners by virtue of high temporal resolution, faster gantry rotation, electrocardiography triggered tube current modulation, large area coverage, body adaptive automatic selection of tube current modulation and iterative reconstruction algorithm have largely addressed the issue of high radiation exposure when subjecting children with Kawasaki disease (KD) to CT coronary angiography. It is now possible to evaluate these patients using submillisievert radiation exposure. This is a significant advance in management of KD.

Citation: Bhatt MC, Singhal M, Pilia RK, Bansal SC, Khandelwal N, Gupta P, Singh S. Radiation dose analysis of computed tomography coronary angiography in Children with Kawasaki disease. *World J Clin Pediatr* 2023; 12(4): 230-236

URL: <https://www.wjgnet.com/2219-2808/full/v12/i4/230.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i4.230>

INTRODUCTION

Kawasaki disease (KD) is a common childhood medium vessel vasculitis with special propensity for coronary arteries. It typically affects children below 5, however, older children and young adults can also be affected. Diagnosis of KD is based on constellation of clinical features, and there are no pathognomonic laboratory tests. Children with KD fulfilling the epidemiological case definition are known as complete KD. Incomplete and atypical forms of disease can constitute up to 50% of patients with KD[1-4]. Coronary artery abnormalities (CAAs) represent the major contributors to both acute as well as long term morbidity and mortality related to KD[4-8]. Timely treatment of KD reduces the CAAs incidence from 25% to < 5%. Timely and precise evaluation of CAAs is important for management of patients with KD[4]. 2D-echocardiography (ECHO) has hitherto been the first line imaging modality for evaluation of CAAs. However, it has some inherent limitations. These include operator dependency, poor acoustic window and lack of visualization of middle and distal segments of coronary arteries[6]. Further, it is difficult to visualize the coronaries in older children who have thick chest walls[9,10]. Catheter angiography (CA) is the gold standard imaging modality but has the disadvantages of being invasive and is associated with high radiation exposure[11-13].

Recently, multi-detector CT (MDCT) and dual source CT (DSCT) platforms have allowed imaging of coronary arteries at any heart rate with attempts at radiation optimization[14-18], which otherwise is a serious concern in children[19,20]. There are limited studies that to with small sample size on radiation dose in children with KD undergoing CTCA on DSCT (Table 1). Radiation dose in these studies was either more or comparable to our study. This study enumerates various methods to optimize the radiation exposure on CTCA in children with KD, an audit of the radiation dose and show that radiation exposure can be reduced to 1mSv or less in majority of children.

MATERIALS AND METHODS

Study design

Review of records was carried out during the period December 2013-February 2018. The manuscript has been approved by Departmental Publication Review Board (RDG/EC/Pub/27 dated July 03, 2020). Written informed consent was obtained from parents prior to CTCA.

Patient population

Children with KD who underwent CTCA were either at presentation or on regular follow-up with CAAs on ECHO were included in the analysis. As per International Commission on Radiological Protection-103 (ICRP 103) recommendations, children were grouped as per age into infants (< 1 year), 1-5 years, 5-10 years, > 10 years. System generated radiation exposure dose length product (DLP in milligray-centimeters-mGy.cm) was recorded and effective radiation dose (millisieverts-mSv) was calculated by applying age adjusted conversion factors recommended by ICRP 103[21] and analysis of

Table 1 Comparison of effective radiation dose on dual source computed tomography coronary angiography platforms in patients with Kawasaki disease

Ref.	Country	Number of cases	Platform	ECG triggering	Age	Radiation dose	Remarks
Duan <i>et al</i> [27], 2012	China	19	DSCT	Prospective	Range: 3 mo-5 yr	ED (mean $\pm$ SD): 0.36 $\pm$ 0.06 mSv	
Kim and Goo [28], 2013	Korea	51	DSCT: (1) 64-Slice: $n = 49$; and (2) 128-Slice: $n = 2$	Retrospective in most of the patients	Mean (range): 13.2 (1-24) yr	ED (mean $\pm$ SD): (1) 64-Slice: 2.6 $\pm$ 2.7 mSv; and (2) 128-Slice: 2.1 $\pm$ 0.6 mSv	ED was only 0.6 $\pm$ 0.5 mSv in 5 children < 2 yr of age, who underwent prospective ECG-triggering
Ghoshhajra <i>et al</i> [29], 2014	United States	52	DSCT: (1) 64-Slice: $n = 16$; and (2) 128-Slice: $n = 36$	Prospective	Range: 0-18 yr	Median (IQR) ED: (1) 64-Slice: 2.9 (0.9-4.1) mSv; and (2) 128-Slice: 1.0 (0.6-2.0) mSv	ED significantly reduced compared to 16 and 64-Slice Scanner platforms
Kantarci <i>et al</i> [30], 2019	Turkey	17	128-Slice DSCT	Details NA	Mean (range): 3 yr (2 mo-11.3 yr)	ED range: 1.2-4.3 mGy depending on the patient's body weight	
van Stijn <i>et al</i> [26], 2020	Netherlands	70	DSCT: (1) 2 $\times$ 192-Slice: $n = 56$; and (2) Other CT scanners (64/128/320-Slice): $n = 14$	Prospective	Median (range): 15.1 (0.5-59.5) yr	Median (range) ED: (1) 2 $\times$ 192-Slice: 1.5 (0.3-9.4) mSv; and (2) Other CT scanner: 3.8 (1.7-20.0) mSv	This is the only study on 3 rd generation DSCT platform
Borhanuddin <i>et al</i> [31], 2022	Malaysia	52	64-slice DSCT	Retrospective	Median (range): 5 (1-18) yr	Median (range) ED: 0.81 (0.4-5.8)	
Present study, Chandigarh	India	85	128-Slice DSCT	Prospective	Median (range): 5 yr (2 mo-11 yr)	Median (IQR) ED: 0.83 (0.68-1.01)	Largest study on 128-Slice platform which provides data that CTCA can be performed in sub-millisevert doses

CTCA: Computed tomography coronary angiography; DSCT: Dual source computed tomography; ED: Effective radiation dose; IQR: Interquartile range.

radiation exposure across groups was done (Table 2).

CTCA technique

CTCA was carried out on a second generation DSCT 128-slice scanner (Somatom Definition Flash, Siemens, Erlangen, Germany) using non-ionic contrast (Omnipaque 350, GE Healthcare, Ireland) with the following parameters: Temporal resolution- 75 milliseconds, gantry rotation time-0.28 s, slice thickness-0.6 mm. The scan was conducted in a craniocaudal direction from floor of carina to the diaphragm (till base of heart). CTCA was carried out with adaptive prospective electrocardiography (ECG) triggered sequence (CorAdSeq) tube current modulation to minimize radiation exposures without compromising image quality. With this technique the CT X-ray tube is switched on at the predefined range of R-R interval of ECG (in our study 30%-80% R-R interval) and provides images in systolic and diastolic phases.

Scanning parameters were customized to ensure minimal radiation exposure. Volume CT dose index (CTDIvol) was taken as adjusted by the CT scanner according to body-size adapted protocols-CARE Dose4D (Siemens, Erlangen, Germany). With this tube current-time product (mA.s) is automatically calculated for optimal automatic exposure depending on body weight and cross-sectional area. Automatic CARE kV was switched off and adjusted to 80 kilovolt (kVp) in all children. These modifications, along with CARE-Dose 4D tube current modulation, enabled us to further reduce the effective radiation dose. Lowest kVp and mAs values ensured optimal image quality with minimum possible radiation exposure. The current-time product ranged between 32-154 mA.s.

Statistical analysis

Parameters showing normal distribution were depicted as mean and standard deviation, while variables with skewed distribution were expressed as median and interquartile ranges (IQR). A P value of < 0.05 was regarded as significant. Statistical analysis was accomplished using SPSS statistical software version 20.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Demographic characteristics

CTCA of 85 patients [71 (84%) boys; 14 (16%) girls] with KD were acquired. Median age of our cohort was 5 years [IQR: 5

Table 2 Conversion factors for chest in different age groups at 80 kV according to recent International Commission on Radiological Protection recommendations (20)

S.No.	Age group	Tube voltage (kV)	Conversion factor
1	< 1 yr	80	0.0823
2	> 1 - < 5 yr	80	0.0525
3	> 5 - < 10 yr	80	0.0344
4	≥ 10 yr	80	0.0248

(7, 2)]; range: 2 mo-11 years. As per ICRP 103 recommendations, children were grouped as per age into infants (< 1 year) (n-10; 12%), 1-5 years (n-29; 34%), 5-10 years (n-38; 45%), > 10 years (n-8; 9%).

Radiation dose

The median DLP and effective dose of all 85 patients in our study were 21.0 mGy.cm, IQR = 15 (13, 28) and 0.83 mSv, IQR = 0.33(0.68, 1.01), respectively. Details of DLP and effective CT radiation dose for children in study group are given in Table 3.

The mean DLP in infants, 1-5 years, 5-10 years, and > 10 years was 9.19, 18.82, 31.76, and 55.67 mGy.cm, respectively. The mean effective dose in infants, 1-5 years, 5-10 years, and > 10 years was 0.63, 0.83, 1.04, and 1.38 mSv. The DLP showed significant increase with increasing age. The difference in the DLP was statistically significant across all age groups (*P* value for infants *vs* 1-5 years, 1-5 years *vs* 5-10 years, and 5-10 years > 10 years; < 0.001, < 0.001, and 0.01, respectively). The mean effective dose in infants (0.63 mSv) was significantly lower than the other age groups (1-5 years 0.85 mSv, 5-10 years 1.04 mSv, and > 10 years 1.38 mSv) (*P* < 0.05). There was no significant difference in the effective dose among children in the other groups.

All the CTCA studies were of diagnostic quality. No child required a repeat examination.

DISCUSSION

We performed CTCA on 128-DSCT scanner with radiation optimized protocols (CorAdSeq tube current modulation, body-size adapted protocols and reduced tube kilovoltage settings at 80 kVp) to minimize radiation exposures. In total 85 children with median age of 5 years [IQR: 5 (7, 2)]; (range: 2 mo-11 years) were scanned. The mean effective radiation dose was 0.83 mSv with radiation exposure significantly lower in infants (0.63 mSv) as compared to other age groups. CTCA can visualize CAAs along the entire course of coronary arteries[6].

KD is a medium vessels vasculitis with special predilection for involvement of coronary arteries[1-4]. ECHO has hitherto been considered the imaging modality of choice for diagnosis and follow-up of CAAs in patients with KD, but with many limitations related to comprehensive evaluation of coronary arteries. CA is the gold standard, but is associated with inordinate radiation exposure, is invasive and cannot be repeated often for follow-up. Moreover, mural abnormalities cannot be depicted on CA[9,22].

With the advent of new high MDCT and DSCT scanners, imaging of coronary arteries is possible. However, until recently the risk of high radiation exposure had precluded the use of CTCA in children with KD. This was probably the limiting factor that prevented its application in pediatrics when cardiac CT on single source 64-slice was made possible. CTCA with single source 64-Slice CT is associated with radiation exposure as high as 3.0-5.7 mSv[23]. Moreover, this technique resulted in sub-optimal image quality due to inability to acquire images at high heart rates in children. Though there are no criteria to define limits of radiation dose in children, authors are of the opinion that this is clearly unacceptable in children and every possible method should be used to reduce radiation exposure in children as per ALARA (as low as reasonably achievable) principle[24]. Higher slice and dual source CT scanners with improvised technologies have emerged as promising platforms for CTCA with possibility for radiation optimization providing a promising imaging modality for assessment of CAAs of KD vis-a-vis CA.

Various dose-saving strategies that can be adopted during CTCA on DSCT are body size-adapted protocols including low tube voltage techniques, ECG-controlled and attenuation-based tube current modulations, and prospectively ECG-triggered scanning[14-18]. Lowering the KVp values (to 80) results in a significant dose reduction with acceptable image quality[25]. We have used adaptive prospective ECG-triggered sequence with tube current modulation, lower tube voltage (80 kVp) and optimized system calculated tube current using CARE-Dose 4D for radiation reduction. Iterative reconstruction algorithm that was used in our protocol in addition provides excellent quality images even at low exposure.

van Stijn *et al*[26] recently published a study on coronary artery assessment in patients with KD using 3rd generation DSCT platform (2 × 192-Slice CT scanner) on 70 children. The authors achieved a radiation exposure of 1.5 mSv (range 0.3-9.4 mSv)[26]. The radiation dose in our cohort was lower. Median effective dose of radiation 0.83 mSv (0.68-1.01) in our study is amongst the lowest achieved so far on DSCT platform using 128-Slice CT scanner. Further, cohort sizes in the previously published studies have been much smaller than ours[26-31] (Table 1). Having achieved such low radiation exposures and given the fidelity of images acquired on these platforms, it may not be long before CTCA on a DSCT platform becomes the imaging modality of choice for detailed evaluation of CAAs in children with KD.

Table 3 Effective computed tomography radiation exposure according to age in adaptive prospective electrocardiography-triggered sequence computed tomography coronary angiography on 128-dual source computed tomography platform

S.No.	Age group	Mean DLP (mGy.cm)	Mean effective radiation dose (mSv)
1	0-1 yr (<i>n</i> = 10)	9.19 ± 2.21	0.63 ± 0.16
2	1-5 yr (<i>n</i> = 29)	18.82 ± 8.48	0.85 ± 0.41
3	5-10 yr (<i>n</i> = 38)	31.79 ± 14.14	1.04 ± 0.37
4	> 10 yr (<i>n</i> = 8)	55.67 ± 19.39	1.38 ± 0.48

DLP: Dose length product; mSv: Millisievert.

We recognize several limitations to our study. The data in the current study comes from a single center and more such studies are required for further validation of our results. Further, there were fewer children in individual age groups. The cumulative impact of radiation dose in children who may require follow up CTCA is not known. Though, all the scans were of diagnostic quality, it is desirable to assess image quality along with radiation dose. However, our study was not tailored to assess the image quality.

CONCLUSION

In conclusion, DSCT scanners by virtue of high temporal resolution, faster gantry rotation, ECG triggered tube current modulation, large field of view, body adaptive automatic selection of tube current modulation and iterative reconstruction algorithm have largely addressed the issue of high radiation exposure when subjecting children with KD to CTCA. It is now possible to evaluate these patients using submillisievert radiation exposure. This is a significant advance in management of KD.

ARTICLE HIGHLIGHTS

Research background

There is evolving role of computed tomography coronary angiography (CTCA) in non-invasive evaluation of coronary artery abnormalities in children with Kawasaki disease (KD). Despite this, there is lack of data on radiation dose in this group of children undergoing CTCA.

Research motivation

There is paucity of literature on radiation exposure in children with KD undergoing CTCA for coronary artery assessment.

Research objectives

To estimate the radiation dose exposure in children with KD undergoing CTCA for coronary artery assessment.

Research methods

Children with KD who underwent CTCA were either at presentation or on regular follow were included in the analysis. System generated radiation exposure dose length product (DLP in milligray-centimeters-mGy.cm) was recorded and effective radiation dose (millisieverts-mSv) was calculated by applying age adjusted conversion factors.

Research results

Total 85 children with median age of 5 years were scanned. Mean effective radiation dose was 0.83 mSv with radiation exposure significantly lower in infants (0.63 mSv) as compared to other age groups. CTCA demonstrated coronary artery abnormalities along the entire course of coronary arteries.

Research conclusions

CTCA is feasible with submillisievert radiation dose in most children with KD.

Research perspectives

CTCA has the potential to be an important adjunctive imaging modality in children with KD. To confirm our results multicentric study with larger sample size would be required.

FOOTNOTES

Author contributions: Bhatt MC and Singhal M contributed to the data interpretation, writing of first draft, review of literature, editing of manuscript and critical revision of manuscript at all stages; Pilania RK contributed to the patient management, data interpretation, writing of first draft, review of literature, editing of manuscript and critical revision of manuscript at all stages; Bansal SC, Khandelwal N, and Gupta P contributed to the review of literature and editing of manuscript; Singh S contributed to the patient management, review of literature, editing of manuscript, critical revision of manuscript at all stages; Bhatt MC and Singhal M contributed equally; Singhal M finally approved the manuscript.

Institutional review board statement: The manuscript has been approved by Departmental Publication Review Board (RDG/EC/Pub/27 dated July 03, 2020), No. NK/1837/Res/2890.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The author(s) declare(s) that they had full access to all of the data in this study and the author(s) take(s) complete responsibility for the integrity of the data and the accuracy of the data analysis.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: India

ORCID number: Manphool Singhal 0000-0002-1311-7203; Rakesh Kumar Pilania 0000-0002-9015-1704; Niranjana Khandelwal 0000-0002-8326-5164; Pankaj Gupta 0000-0003-3914-3757; Surjit Singh 0000-0002-8738-4582.

S-Editor: Fan JR

L-Editor: A

P-Editor: Yuan YY

REFERENCES

- Lo MS. A framework for understanding Kawasaki disease pathogenesis. *Clin Immunol* 2020; **214**: 108385 [PMID: 32173601 DOI: 10.1016/j.clim.2020.108385]
- Friedman KG, Jone PN. Update on the Management of Kawasaki Disease. *Pediatr Clin North Am* 2020; **67**: 811-819 [PMID: 32888683 DOI: 10.1016/j.pcl.2020.06.002]
- Jindal AK, Pilania RK, Prithvi A, Guleria S, Singh S. Kawasaki disease: characteristics, diagnosis, and unusual presentations. *Expert Rev Clin Immunol* 2019; **15**: 1089-1104 [PMID: 31456443 DOI: 10.1080/1744666X.2019.1659726]
- Singh S, Jindal AK, Pilania RK. Diagnosis of Kawasaki disease. *Int J Rheum Dis* 2018; **21**: 36-44 [PMID: 29131549 DOI: 10.1111/1756-185X.13224]
- Pilania RK, Jindal AK, Bhattarai D, Naganur SH, Singh S. Cardiovascular Involvement in Kawasaki Disease Is Much More Than Mere Coronary Arteritis. *Front Pediatr* 2020; **8**: 526969 [PMID: 33072669 DOI: 10.3389/fped.2020.526969]
- Singhal M, Pilania RK, Jindal AK, Gupta A, Sharma A, Guleria S, Johnson N, Maralakunte M, Vignesh P, Suri D, Sandhu MS, Singh S. Distal coronary artery abnormalities in Kawasaki disease: experience on CT coronary angiography in 176 children. *Rheumatology (Oxford)* 2023; **62**: 815-823 [PMID: 35394488 DOI: 10.1093/rheumatology/keac217]
- Pilania RK, Singhal M, Singh S. Dense calcifications of giant coronary aneurysms in an 11-year-old girl with Kawasaki disease. *Rheumatology (Oxford)* 2021; **60**: 4441-4442 [PMID: 33404660 DOI: 10.1093/rheumatology/keaa907]
- Chakraborty R, Singhal M, Pandiarajan V, Sharma A, Pilania RK, Singh S. Coronary arterial abnormalities detected in children over 10 years following initial Kawasaki disease using cardiac computed tomography. *Cardiol Young* 2021; **31**: 998-1002 [PMID: 33504398 DOI: 10.1017/S1047951121000020]
- Singhal M, Gupta P, Singh S, Khandelwal N. Computed tomography coronary angiography is the way forward for evaluation of children with Kawasaki disease. *Glob Cardiol Sci Pract* 2017; **2017**: e201728 [PMID: 29564349 DOI: 10.21542/gcsp.2017.28]
- Pilania RK, Bhattarai D, Singh S. Controversies in diagnosis and management of Kawasaki disease. *World J Clin Pediatr* 2018; **7**: 27-35 [PMID: 29456929 DOI: 10.5409/wjcp.v7.i1.27]
- Bakalyar DM, Castellani MD, Safian RD. Radiation exposure to patients undergoing diagnostic and interventional cardiac catheterization procedures. *Cathet Cardiovasc Diagn* 1997; **42**: 121-125 [PMID: 9328690 DOI: 10.1002/(sici)1097-0304(199710)42:2<121::aid-ccd4>3.0.co;2-f]
- van de Putte S, Verhaegen F, Taeymans Y, Thierens H. Correlation of patient skin doses in cardiac interventional radiology with dose-area product. *Br J Radiol* 2000; **73**: 504-513 [PMID: 10884747 DOI: 10.1259/bjr.73.869.10884747]
- Bacher K, Bogaert E, Lapere R, De Wolf D, Thierens H. Patient-specific dose and radiation risk estimation in pediatric cardiac catheterization. *Circulation* 2005; **111**: 83-89 [PMID: 15611374 DOI: 10.1161/01.CIR.0000151098.52656.3A]
- Khan A, Khosa F, Nasir K, Yassin A, Clouse ME. Comparison of radiation dose and image quality: 320-MDCT versus 64-MDCT coronary angiography. *AJR Am J Roentgenol* 2011; **197**: 163-168 [PMID: 21701026 DOI: 10.2214/AJR.10.5250]

- 15 Sun Z, Choo GH, Ng KH. Coronary CT angiography: current status and continuing challenges. *Br J Radiol* 2012; **85**: 495-510 [PMID: 22253353 DOI: 10.1259/bjr/15296170]
- 16 Danad I, Ó Hartaigh B, Min JK. Dual-energy computed tomography for detection of coronary artery disease. *Expert Rev Cardiovasc Ther* 2015; **13**: 1345-1356 [PMID: 26549789 DOI: 10.1586/14779072.2015.1102055]
- 17 Sabarudin A, Sun Z. Coronary CT angiography: Diagnostic value and clinical challenges. *World J Cardiol* 2013; **5**: 473-483 [PMID: 24392192 DOI: 10.4330/wjcv.v5.i12.473]
- 18 Singhal M, Singh S, Gupta P, Sharma A, Khandelwal N, Burns JC. Computed Tomography Coronary Angiography for Evaluation of Children With Kawasaki Disease. *Curr Probl Diagn Radiol* 2018; **47**: 238-244 [PMID: 29203262 DOI: 10.1067/j.cpradiol.2017.09.013]
- 19 Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 2007; **357**: 2277-2284 [PMID: 18046031 DOI: 10.1056/NEJMr072149]
- 20 National Research Council 2006. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington DC: The National Academies Press, 2006
- 21 The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. *Ann ICRP* 2007; **37**: 1-332 [PMID: 18082557 DOI: 10.1016/j.icrp.2007.10.003]
- 22 Tsuda E, Singhal M. Role of imaging studies in Kawasaki disease. *Int J Rheum Dis* 2018; **21**: 56-63 [PMID: 29115035 DOI: 10.1111/1756-185X.13210]
- 23 Fink C, Krissak R, Henzler T, Lechel U, Brix G, Takx RA, Nance JW, Abro JA, Schoenberg SO, Schoepf UJ. Radiation dose at coronary CT angiography: second-generation dual-source CT versus single-source 64-MDCT and first-generation dual-source CT. *AJR Am J Roentgenol* 2011; **196**: W550-W557 [PMID: 21512044 DOI: 10.2214/AJR.10.5153]
- 24 Ogbale GI. Radiation dose in paediatric computed tomography: risks and benefits. *Ann Ib Postgrad Med* 2010; **8**: 118-126 [PMID: 25161479 DOI: 10.4314/aipm.v8i2.71823]
- 25 Leschka S, Stolzmann P, Schmid FT, Scheffel H, Stinn B, Marincek B, Alkadhi H, Wildermuth S. Low kilovoltage cardiac dual-source CT: attenuation, noise, and radiation dose. *Eur Radiol* 2008; **18**: 1809-1817 [PMID: 18392829 DOI: 10.1007/s00330-008-0966-1]
- 26 van Stijn D, Planken RN, Groenink M, Streekstra GJ, Kuijpers TW, Kuipers IM. Coronary artery assessment in Kawasaki disease with dual-source CT angiography to uncover vascular pathology. *Eur Radiol* 2020; **30**: 432-441 [PMID: 31428828 DOI: 10.1007/s00330-019-06367-6]
- 27 Duan Y, Wang X, Cheng Z, Wu D, Wu L. Application of prospective ECG-triggered dual-source CT coronary angiography for infants and children with coronary artery aneurysms due to Kawasaki disease. *Br J Radiol* 2012; **85**: e1190-e1197 [PMID: 22932064 DOI: 10.1259/bjr/18174517]
- 28 Kim JW, Goo HW. Coronary artery abnormalities in Kawasaki disease: comparison between CT and MR coronary angiography. *Acta Radiol* 2013; **54**: 156-163 [PMID: 23482350 DOI: 10.1258/ar.2012.120484]
- 29 Ghoshhajra BB, Lee AM, Engel LC, Celeng C, Kalra MK, Brady TJ, Hoffmann U, Westra SJ, Abbata S. Radiation dose reduction in pediatric cardiac computed tomography: experience from a tertiary medical center. *Pediatr Cardiol* 2014; **35**: 171-179 [PMID: 23872908 DOI: 10.1007/s00246-013-0758-5]
- 30 Kantarcı M, Güven E, Ceviz N, Oğul H, Sade R. Vascular imaging findings with high-pitch low-dose dual-source CT in atypical Kawasaki disease. *Diagn Interv Radiol* 2019; **25**: 50-54 [PMID: 30644368 DOI: 10.5152/dir.2018.18092]
- 31 Borhanuddin BK, Abdul Latiff H, Mohamed Yusof AK. CT coronary angiogram in children with Kawasaki patients: experience in 52 patients. *Cardiol Young* 2022; **32**: 1994-1998 [PMID: 35707919 DOI: 10.1017/S1047951122000154]



Transient hyperphosphatasemia in a toddler with COVID-19 infection: A case report and literature review

Pemiga Sukhupanyarak, Voraluck Phatarakijirund

Specialty type: Pediatrics

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Aydin S, Turkey;
Giacomelli L, Italy

Received: March 6, 2023

Peer-review started: March 6, 2023

First decision: May 9, 2023

Revised: May 25, 2023

Accepted: June 9, 2023

Article in press: June 9, 2023

Published online: September 9, 2023



Pemiga Sukhupanyarak, Voraluck Phatarakijirund, Division of Endocrinology, Department of Pediatrics, Phramongkutklao College of Medicine, Bangkok 10400, Thailand

Pemiga Sukhupanyarak, Division of Endocrinology, Department of Pediatrics, Buddhachinaraj Hospital, Phitsanulok 6500, Thailand

Corresponding author: Voraluck Phatarakijirund, MD, Assistant Professor, Division of Endocrinology, Department of Pediatrics, Phramongkutklao College of Medicine, No. 315 Ratchawithi Road, Phayathai, Ratchathewi, Bangkok 10400, Thailand.

phatara.voraluck@gmail.com

Abstract

BACKGROUND

Transient hyperphosphatasemia (TH) is a condition characterized by elevated serum alkaline phosphatase (ALP) in the clinical setting with no evidence of bone or liver disease among children under the age of 5. Typically, it will resolve spontaneously in a few months in the majority of cases. TH has been found to be associated with viral infections. Two cases of TH associated with coronavirus disease 2019 (COVID-19) infection in toddlers have been previously reported.

CASE SUMMARY

A previously healthy 2-year-old boy presented with fever and positive real-time polymerase chain reaction for COVID-19. Prior to his illness, the patient had been in close contact with his grandfather, who later developed COVID-19. The physical examination on admission was unremarkable. He remained asymptomatic throughout 7 d of hospitalization. On the 5th day of his illness, blood tests showed markedly elevated serum ALP (4178 U/L). Results from the simultaneous testing of the remaining liver profiles and metabolic bone panels were normal. Two months after discharge from the hospital, the patient continued to thrive well. The skeletal surveys revealed no significant abnormalities. The serum ALP declined into the normal range adjusted for his age. This evidence is consistent with the diagnosis of TH.

CONCLUSION

TH can occur in COVID-19-infected toddlers. Serial measurements of ALP levels have been shown to gradually decline into the normal range within a few months. Therefore, being aware of this transient abnormality will help clinicians to avoid additional unnecessary investigations.

Key Words: Alkaline phosphatase; Coronavirus; Pediatric endocrinology; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Transient hyperphosphatasemia (TH) is an unrecognized condition among children under the age of 5. The only abnormality demonstrated is markedly elevated serum alkaline phosphatase (ALP) without evidence of bone or hepatic disease and spontaneous resolution occurring in several months. Numerous reports have identified various viral infections as contributing factors to the etiology of this condition. TH should be considered in coronavirus disease 2019 -infected toddlers exhibiting isolated high serum ALP. Awareness of this condition will help to avoid unnecessary investigations.

Citation: Sukhupanyarak P, Phatarakijirund V. Transient hyperphosphatasemia in a toddler with COVID-19 infection: A case report and literature review. *World J Clin Pediatr* 2023; 12(4): 237-243

URL: <https://www.wjgnet.com/2219-2808/full/v12/i4/237.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i4.237>

INTRODUCTION

Transient hyperphosphatasemia (TH) is a benign and self-limiting condition characterized by a marked increase in serum alkaline phosphatase (ALP) in the absence of liver or bone disease[1]. The elevated serum ALP level usually declines into the normal range within a few months[1,2]. TH is observed in either sick or healthy infants and children under the age of 5 by finding incidentally elevated serum ALP on routine laboratory investigation for other purposes[3-8]. Although its etiology remains unclear, the propensity of TH associated with various conditions, such as post organ transplantation, hematologic malignancy, rheumatologic disease[9-11], and, in particular, infectious diseases, has been reported in the literature[5,12,13].

Coronavirus disease 2019 (COVID-19) infection is a highly contagious infection that quickly became a global pandemic disease. Endocrinopathies associated with COVID-19 infection in children, such as thyroid diseases (subacute thyroiditis, hypothyroidism, hyperthyroidism), adrenal insufficiency, diabetes mellitus, vitamin D deficiency and hypopituitarism, had been previously reported[14,15]. TH observed with COVID-19 infection in toddlers is a new discovery that was recently described in two cases[16,17]. Here, we report a case of a 2-year-old boy who developed TH associated with COVID-19 infection.

CASE PRESENTATION

Chief complaints

A previously healthy 2-year-old boy was admitted to our hospital with an acute febrile illness of 4 d duration.

History of present illness

There was a history of the patient being in close contact with his grandfather, who was later diagnosed with symptomatic COVID-19 infection. The patient had a positive test of real-time reverse transcription polymerase chain reaction for severe acute respiratory syndrome coronavirus 2.

History of past illness

He was a full-term baby with a birth weight of 2800 g, requiring no medication since his birth.

Personal and family history

No special notes.

Physical examination

The physical examination upon admission revealed that the patient was in good general condition, with no sign of respiratory distress or dehydration, body temperature 37.6°C, pulse rate 90/min, respiratory rate 22/min and O₂ saturation in room air 99%. His weight and height were 12.1 kgs (-0.7 SDS) and 86.5 cm (+0.7 SDS), respectively. The skeletal examination revealed no wrist joint swelling, rachitic rosary, knock knee or abnormal gait to suggest definite skeletal disease. There were no clinical findings of jaundice or hepato-splenomegaly to indicate hepatobiliary disease.

Laboratory examinations

The initial laboratory results showed hemoglobin 13.3 g/dL, white blood cell 10100/μL with 61.6% lymphocytes and platelet count 196000/μL. Chest X-ray revealed no infiltration. The liver function test (LFT) on the 5th day of his illness

showed a markedly elevated serum ALP of 4178 U/L (normal range: 111-277). Additionally, the occurrence of bone or hepatobiliary disease was assessed, and the results were normal as follows: Blood urea nitrogen 12.4, Cr. 0.3, calcium 9.9, phosphate 4, magnesium 2.2 mg/dL, intact-PTH 21.3 pg/mL, 25-OHD 33.6 ng/mL and gamma-glutamyl transferase 12 U/L (Table 1). The serum ALP was repeated 4 d following the initial study. It remained elevated at 4662 U/L, but the rest of the LFT was normal.

Table 1 Laboratory tests of our patient during coronavirus disease 2019 infection and follow-up

Parameters	At admission		Follow-up after illness	
	5 th day of illness	9 th day of illness	2 nd month	6 th month
ALP (U/L)	4178	4662	252	229
AST (U/L)	35.8	30.8	37.7	29.3
ALT (U/L)	17	15.9	16.5	18.8
TP (g/dL)	7.1	6.8	6.7	6.8
Alb (g/dL)	4.9	4.8	4.6	4.6
TB/DB (g/dL)	0.25/0.12	0.17/0.11	0.37/0.12	0.24/0.11
GGT (U/L)	12	-	-	-
Cr (mg/dL)	0.3	-	-	-
Ca (mg/dL)	9.9	-	9.7	-
P (mg/dL)	4.0	-	4.9	-
Mg (mg/dL)	2.2	-	2.26	-
iPTH (pg/mL)	21.3	-	26.4	-
25-OHD (ng/mL)	33.6	-	23.4	-

ALP: Alkaline phosphatase (normal range: 111-277 U/L; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TP: Total protein; Alb: Albumin; TB: Total bilirubin; DB: Direct bilirubin; GGT: Gamma-glutamyl transferase; Ca: Calcium; P: Phosphate; Mg: Magnesium; iPTH: Intact parathyroid hormone.

Imaging examinations

No special notes.

FINAL DIAGNOSIS

At this point, the diagnosis of TH was strongly considered. The entire 7 d of his hospital course was uneventful without fever, diarrhea or respiratory tract symptoms.

TREATMENT

The management was symptomatic and supportive care with oral antipyretic, anti-emesis and oral rehydration solution.

OUTCOME AND FOLLOW-UP

Two months after discharge, the patient was re-evaluated at the outpatient endocrine clinic. His physical examination was normal. Serum ALP became normal at 252 U/L. The other investigations, including LFT, calcium, phosphorus, magnesium, 25-OHD and skeletal survey radiography, were completely normal. A six-month follow-up study with the same parameters as the 2-month follow-up study revealed that everything remained within the normal range (Table 2).

Table 2 Clinical characteristics and laboratory tests in hyperphosphatasemia associated with coronavirus disease 2019 infection: our patient and previous reports

Clinical characteristics	Our patient	Erat <i>et al</i> [16], 2020	Tchidjou <i>et al</i> [17], 2020
Ethnicity	Thai	Turkish	French
Gender	M	F	M
Age (mo)	26	16	9
Symptom of COVID-19 infection			
Fever	Yes	Yes	Yes
Upper respiratory tract symptom	No	Yes (Cough, oropharyngeal hyperemia)	Yes (Rhinitis)
Lower respiratory tract symptom	No	No	No
Gastrointestinal symptom	No	Yes (Nausea, diarrhea)	No
Laboratory tests			
Peak ALP (U/L)	4662 (Normal: 111-277)	1860 (Normal: 145-420)	3384 (Normal: 46-116)
ALP ratio ^a	16.8	4.4	29
Cr (mg/dL)	0.21	0.22	0.43
AST (U/L)	36	34	37
ALT (U/L)	17	14	39
GGT (U/L)	12	13	8
Ca (mg/dL)	9.9	9.8	NA
P (mg/dL)	4	5.5	6.8
iPTH (pg/mL)	21.3	28.1	NA
25-OHD (ng/mL)	33.6	32	NA
Resolution of TH			
Time turned to normal ALP level	Two months	One month	One month
ALP (U/L)	252	254	371

^aALP ratio: The measured ALP level divided by the upper limit of normal. ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; Ca: Calcium; COVID-19: Coronavirus disease 2019; P: Phosphate; Mg: Magnesium; iPTH: Intact parathyroid hormone; TH: Hyperphosphatasemia; NA: Not available.

DISCUSSION

ALP is a membrane-bound phosphomonoesterase enzyme consisting of four isoenzymes, three tissue-specific ALPs (intestinal, placental and germ cell) and the tissue-nonspecific ALP (TNSALP)[18]. TNSALP is abundant in the bone, liver and kidney and accounts for 95% of total ALP activity in serum[19]. Therefore, abnormally high ALP levels are an important marker for skeletal and hepatobiliary diseases.

TH is a benign self-limited condition that reportedly has a prevalence from 1.1% to 3.5% among infants aged 2-24 mo and affects both sexes equally[20,21]. This condition was first described in 1954 by Bach[22]. In 1985, Kraut *et al*[2] established the criteria for the diagnosis of TH in infancy and children, defined as an age group below 5 years, no evidence of bone or liver disease on physical examination or laboratory test, elevation of both bone and liver ALP isoenzymes and a return to normal serum AP values within 4 mo. Although the specific cutoff value of ALP level for diagnosis of TH had not been identified by the original criteria, recent studies have suggested that TH is considered when serum ALP is above 800[5,13], 1000 (6, 11, 21) or 2000 U/L[23]. However, the peak serum ALP of TH was distinctively higher than the serum ALP levels of other bone and hepatic diseases. In a review of 733 TH patients, the mean ALP level was 9 times above the upper limit of the normal range, and 71% of these patients had the highest ALP > 5 times above the upper limit of the reference value[4].

Numerous reports have identified various viral infections as contributing factors to the etiology of TH (Table 3)[13,23-27]. Suzuki *et al*[28] identified antibodies against enteroviruses, such as ECHO 22, entero-71 and coxsackie B4, in the serum of 50 TH children. Among these viruses, ECHO 22 antibody was most frequent, accounting for 32% of TH cases. Additionally, few but not all studies reported clusters of TH during the fall and winter seasons, which supported the assumption of the viral etiology[3,12,21].

Table 3 Viral infections associated with hyperphosphatasemia [13,23-27]

Respiratory syncytial virus
Influenza virus
Epstein-Barr virus
Adenovirus
Bocavirus
Cytomegalovirus
Rotavirus

The mechanism of TH is obscure. Several hypotheses have been postulated, including increased activities of ALP in plasma, increased production and impaired clearance of ALP. The most likely mechanism is decreased hepatic clearance due to the high sialic acid content of ALP, but the mechanism involved in excessive sialic acid content of the molecule is unknown[29]. Increased bone ALP production is thought to be a result of increased bone resorption triggered by virus infection, consequently increasing osteoblast activities and bone formation and hence increasing bone turnover. This was supported by evidence of transiently increased urinary hydroxyproline (bone resorption marker) excretion[30]. In contrast, the study by Kutilek *et al*[8] in 2012 showed a lack of elevated iPTH, Beta-CrossLaps and osteocalcin in TH patients. As such, the hypothesis of increased bone turnover leading to elevated ALP in TH remains controversial.

TH typically resolves without any treatment. A reduction in ALP level to the normal range occurs between 2 wk and 4 years with a median of 10 wk[4]. In 80% of cases, ALP returns to the normal level in 16 wk[4].

Our patient, who was confirmed to have an active COVID-19 infection, exhibited typical clinical features of TH, including high serum ALP levels and no clinical or laboratory evidence of bone or hepatic disease. His biochemical markers of bone metabolism were normal, including calcium, vitamin D and intact PTH. ALP isoenzyme assays were not available at our facility, nor were the other more specific tests for bone turnover markers. The markedly elevated ALP in our patient became normal within 3 mo of follow-up and remained stable at the 6-month follow-up. Given the reports of TH associated with other viral infections, we concluded that our patient developed TH related to COVID-19 infection. Recently, two cases of TH associated with COVID-19 infection in children have been reported[16,17]. All 3 cases, including ours, were aged under 3 years, in accordance with the preponderance (82%) of TH in patients aged < 36 mo in a previous report[4]. The peak level of ALP appears to have no association with the severity of the illness. In our patient, the peak ALP was at 4, 662 U/L (16.8 times to upper normal range), while his symptoms were mild only with low-grade fever. However, the other 2 previous cases had additional clinical symptoms of the upper respiratory tract and gastrointestinal symptoms, but peak levels of ALP appeared to be lower (Table 2). Nonetheless, the serum ALP levels of all 3 cases were similar to those in previous case reports, ranging from 805 to 16814 U/L[3,5,8]. Our patient had the serum ALP return to the normal range of 252 U/L at 2 mo after the acute illness, which is similar to most of the TH cases. In the 2 previous cases of TH associated with COVID-19 infection, their ALP levels declined to the normal range within a month (Table 2). This can be explained by their early schedule testing compared to ours.

In summary, we demonstrated a typical case of TH in a toddler who had been confirmed to have acute COVID-19. It is likely that a rising number of TH cases will be observed along with continuation of the COVID-19 pandemic.

CONCLUSION

Transient hyperphosphatasemia is a benign and self-limiting condition that occurs mainly in infants and children under the age of 5. This condition can be found in toddlers with COVID-19 who exhibit an isolated high level of serum ALP without evidence of bone or hepatic disease based on physical examination and laboratory testing. Therefore, follow-up monitoring of serum ALP levels to confirm the resolution of hyperphosphatasemia without additional extensive investigation and treatment is recommended.

ACKNOWLEDGEMENTS

We are grateful to Dr. Ruenrudee Suwannasri for suggesting and review of manuscript and would like to thank the patient and family participated in this study.

FOOTNOTES

Author contributions: Sukhupanyarak P and Phatarakijirund V contributed to manuscript writing and editing, data collection and final approval of the version of the article to be published

Informed consent statement: Subjects and legally authorized representative gave their written and verbal informed consent prior to study inclusion.

Conflict-of-interest statement: All authors state that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Thailand

ORCID number: Pemiga Sukhupanyarak 0000-0001-7441-7608; Voraluck Phatarakijirund 0000-0002-0955-083X.

S-Editor: Liu JH

L-Editor: A

P-Editor: Liu JH

REFERENCES

- 1 Root AW, Levine MA. Abnormalities of mineral homeostasis in the newborn, infant, child and adolescent. In: Sperling MA, Majzoub JA, Menon RK, Stratakis CA (eds). *Pediatric endocrinology*. 5th ed. Philadelphia: Elsevier. 2020; 768-813 [DOI: 10.1016/B978-0-323-62520-3.00020-8]
- 2 Kraut JR, Metrick M, Maxwell NR, Kaplan MM. Isoenzyme studies in transient hyperphosphatasemia of infancy. Ten new cases and a review of the literature. *Am J Dis Child* 1985; **139**: 736-740 [PMID: 4014098 DOI: 10.1001/archpedi.1985.02140090098042]
- 3 Behúlová D, Bzdúch V, Holesová D, Vasilenková A, Ponc J. Transient hyperphosphatasemia of infancy and childhood: study of 194 cases. *Clin Chem* 2000; **46**: 1868-1869 [PMID: 11067838]
- 4 Gualco G, Lava SA, Garzoni L, Simonetti GD, Bettinelli A, Milani GP, Provero MC, Bianchetti MG. Transient benign hyperphosphatasemia. *J Pediatr Gastroenterol Nutr* 2013; **57**: 167-171 [PMID: 23539049 DOI: 10.1097/MPG.0b013e3182922807]
- 5 Dori N, Levi L, Stam T, Sukhotnik I, Shaoul R. Transient hyperphosphatasemia in children revisited. *Pediatr Int* 2010; **52**: 866-871 [PMID: 21029252 DOI: 10.1111/j.1442-200X.2010.03265.x]
- 6 Teitelbaum JE, Laskowski A, Barrows FP. Benign transient hyperphosphatasemia in infants and children: a prospective cohort. *J Pediatr Endocrinol Metab* 2011; **24**: 93-95 [PMID: 21528824 DOI: 10.1515/jpem.2011.077]
- 7 Eymann A, Cacchiarelli N, Alonso G, Llera J. Benign transient hyperphosphatasemia of infancy. A common benign scenario, a big concern for a pediatrician. *J Pediatr Endocrinol Metab* 2010; **23**: 927-930 [PMID: 21175092 DOI: 10.1515/jpem.2010.148]
- 8 Kutilek S, Cervickova B, Bebova P, Kmonickova M, Nemec V. Normal bone turnover in transient hyperphosphatasemia. *J Clin Res Pediatr Endocrinol* 2012; **4**: 154-156 [PMID: 22664360 DOI: 10.4274/jcrpe.680]
- 9 Kutilek S, Skálová S, Vethamuthu J, Geier P, Feber J. Transient hyperphosphatasemia in pediatric renal transplant patients--is there a need for concern and when? *Pediatr Transplant* 2012; **16**: E5-E9 [PMID: 20819182 DOI: 10.1111/j.1399-3046.2010.01379.x]
- 10 Neto A, Costa M, Branco JC, Mourão AF. Benign transient hyperphosphatasemia in Juvenile Idiopathic Arthritis: a case report. *Acta Reumatol Port* 2019; **44**: 317-319 [PMID: 32281964]
- 11 Massey GV, Dunn NL, Heckel JL, Chan JC, Russell EC. Benign transient hyperphosphatasemia in children with leukemia and lymphoma. *Clin Pediatr (Phila)* 1996; **35**: 501-504 [PMID: 8902328 DOI: 10.1177/000992289603501004]
- 12 Carroll AJ, Coakley JC. Transient hyperphosphatasemia: an important condition to recognize. *J Paediatr Child Health* 2001; **37**: 359-362 [PMID: 11532055 DOI: 10.1046/j.1440-1754.2001.00686.x]
- 13 Kutilek S, Bayer M. Transient hyperphosphatasemia of infancy and early childhood--clinical and laboratory data of 52 patients. *J Paediatr Child Health* 2003; **39**: 157 [PMID: 12603811 DOI: 10.1046/j.1440-1754.2003.t01-1-00121.x]
- 14 Memar EHE, Mohsenipour R, Sadrosadat ST, Rostami P. Pediatric endocrinopathies related to COVID-19: an update. *World J Pediatr* 2022; **1-12** [PMID: 36480134 DOI: 10.1007/s12519-022-00662-x]
- 15 Esmaeilzadeh A, Elahi R, Siahmansouri A, Maleki AJ, Moradi A. Endocrine and metabolic complications of COVID-19: lessons learned and future prospects. *J Mol Endocrinol* 2022; **69**: R125-R150 [PMID: 35900847 DOI: 10.1530/JME-22-0036]
- 16 Erat T, Atar M, Kontbay T. Transient benign hyperphosphatasemia due to COVID-19: the first case report. *J Pediatr Endocrinol Metab* 2021; **34**: 385-387 [PMID: 33577728 DOI: 10.1515/jpem-2020-0503]
- 17 Tchidjou HK, Caron F, Ferec A, Braun K, Hery L, Castelain S, Romeo B. Severe hyperphosphatasemia and severe acute respiratory syndrome coronavirus 2 infection in children. *Blood Coagul Fibrinolysis* 2020; **31**: 575-577 [PMID: 32897891 DOI: 10.1097/MBC.0000000000000954]
- 18 Whyte MP. Physiological role of alkaline phosphatase explored in hypophosphatasia. *Ann N Y Acad Sci* 2010; **1192**: 190-200 [PMID: 20392236 DOI: 10.1111/j.1749-6632.2010.05387.x]
- 19 Bianchi ML, Bishop NJ, Gunahe N, Hofmann C, Jakob F, Roux C, Zillikens MC; Rare Bone Disease Action Group of the European Calcified Tissue Society. Hypophosphatasia in adolescents and adults: overview of diagnosis and treatment. *Osteoporos Int* 2020; **31**: 1445-1460 [PMID: 32162014 DOI: 10.1007/s00198-020-05345-9]
- 20 Asanti R, Hultin H, Visakorpi JK. Serum alkaline phosphatase in healthy infants. Occurrence of abnormally high values without known cause. *Ann Paediatr Fenn* 1966; **12**: 139-142 [PMID: 5914305]

- 21 **Huh SY**, Feldman HA, Cox JE, Gordon CM. Prevalence of transient hyperphosphatasemia among healthy infants and toddlers. *Pediatrics* 2009; **124**: 703-709 [PMID: [19620198](#) DOI: [10.1542/peds.2008-3093](#)]
- 22 **BACH U**. [Behavior of serum alkaline phosphatase in prematurity, rickets and spasmophilia]. *Z Kinderheilkd* 1954; **74**: 593-609 [PMID: [13227160](#)]
- 23 **Sakurai Y**, Higashiguchi T. Transient hyperphosphatasemia: Possible association with pediatric acute respiratory infection. *Pediatr Investig* 2021; **5**: 94-98 [PMID: [34179704](#) DOI: [10.1002/ped4.12265](#)]
- 24 **Koike Y**, Aoki N. Benign transient hyperphosphatasemia associated with Epstein-Barr virus infection. *Pediatr Int* 2013; **55**: 667-668 [PMID: [24134761](#) DOI: [10.1111/ped.12173](#)]
- 25 **Ng PC**, Cheung CK, Tam JS, Li CK. Benign transient hyperphosphatasemia associated with adenovirus infection. *J Paediatr Child Health* 1995; **31**: 561-562 [PMID: [8924313](#) DOI: [10.1111/j.1440-1754.1995.tb00885.x](#)]
- 26 **Akcaboy M**, Zorlu P, Acoglu EA, Acar M, Oguz MM, Senel S. Human Bocavirus Infection Associated Transient Benign Hyperphosphatasemia in an Infant. *Indian J Pediatr* 2016; **83**: 902-903 [PMID: [27246826](#) DOI: [10.1007/s12098-016-2156-5](#)]
- 27 **Marrali V**, Cutaia A, Zarbo C, Meli G, Fragapane D, Mandini A. [Transient idiopathic hyperphosphatasemia in a rotavirus infection]. *Minerva Pediatr* 1990; **42**: 559-560 [PMID: [2087231](#)]
- 28 **Suzuki M**, Okazaki T, Nagai T, Törö K, Sétonyi P. Viral infection of infants and children with benign transient hyperphosphatasemia. *FEMS Immunol Med Microbiol* 2002; **33**: 215-218 [PMID: [12110484](#) DOI: [10.1111/j.1574-695X.2002.tb00593.x](#)]
- 29 **Crofton PM**. What is the cause of benign transient hyperphosphatasemia? A study of 35 cases. *Clin Chem* 1988; **34**: 335-340 [PMID: [3342506](#)]
- 30 **Stepan JJ**, Kutilek S, Bayer M. Transient hyperphosphatasemia in infancy associated with an increased urinary hydroxyproline excretion. *Clin Chim Acta* 1995; **233**: 115-118 [PMID: [7758199](#) DOI: [10.1016/0009-8981\(94\)05956-s](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2023 December 9; 12(5): 244-364



Contents

Quarterly Volume 12 Number 5 December 9, 2023

FRONTIER

- 244 Comments by opponents on the British Medical Association's guidance on non-therapeutic male circumcision of children seem one-sided and may undermine public health
Moreton S, Cox G, Sheldon M, Bailis SA, Klausner JD, Morris BJ

OPINION REVIEW

- 263 Prediabetes in children and adolescents: An updated review
Ng HY, Chan LTW

REVIEW

- 273 Pre-autism: What a paediatrician should know about early diagnosis of autism
Al-Beltagi M
- 295 Renal calcification in children with renal tubular acidosis: What a paediatrician should know
Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R, Hasan S, Hamza MB

ORIGINAL ARTICLE

Case Control Study

- 310 Brain metabolic profile assessed by magnetic resonance spectroscopy in children with Down syndrome: Relation to intelligence quotient
El Feil NS, Elmahdy HS, Elmahdy RA, Aboelezz AAE, Dawoud HS, Al-Beltagi M

Retrospective Study

- 319 Clinical factors predicting rotavirus diarrhea in children: A cross-sectional study from two hospitals
Indrawan M, Chendana J, Handoko TGH, Widjaja M, Octavius GS

SYSTEMATIC REVIEWS

- 331 Migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion: A systematic literature review and meta-analysis
Ghritlaharey RK
- 350 Warburg effect mimicking inborn errors of metabolism in childhood hematologic malignancies: A case-based systematic review
Permtawee K, Tengsujaritkul M, Choed-Amphai C, Chanthong S, Mankhemthong K, Sathitsamitphong L, Natesirinilkul R, Charoenkwan P

CASE REPORT

- 359 Situs inversus totalis in an asymptomatic adolescent - importance of patient education: A case report
Hayashi LC, Acharya R

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Pediatrics*, Luca Giacomelli, PhD, Director, Polistudium SRL, 20121, Milan, Italy. luca.giacomelli@polistudium.it

AIMS AND SCOPE

The primary aim of the *World Journal of Clinical Pediatrics* (WJCP, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCP mainly publishes articles reporting research results and findings obtained in the field of pediatrics and covering a wide range of topics including anesthesiology, cardiology, endocrinology, gastroenterology, hematology, immunology, infections and infectious diseases, medical imaging, neonatology, nephrology, neurosurgery, nursing medicine, perinatology, pharmacology, respiratory medicine, and urology.

INDEXING/ABSTRACTING

The WJCP is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The WJCP's CiteScore for 2022 is 1.7 and Scopus CiteScore rank 2022: Pediatrics, perinatology and child health is 176/306.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xiang-Di Zhang*; Production Department Director: *Xiang Li*; Editorial Office Director: *Xu Guo*.

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2219-2808/editorialboard.htm>

PUBLICATION DATE

December 9, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Comments by opponents on the British Medical Association's guidance on non-therapeutic male circumcision of children seem one-sided and may undermine public health

Stephen Moreton, Guy Cox, Mark Sheldon, Stefan A Bailis, Jeffrey D Klausner, Brian J Morris

Specialty type: Pediatrics

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

P-Reviewer: Anaya-Prado R, Mexico; Cassell III AK, Liberia; Shalaby MN, Egypt

Received: June 30, 2023

Peer-review started: June 30, 2023

First decision: August 24, 2023

Revised: September 7, 2023

Accepted: September 25, 2023

Article in press: September 25, 2023

Published online: December 9, 2023



Stephen Moreton, CircFacts, Warrington WA5 1HY, Cheshire, United Kingdom

Guy Cox, Australian Centre for Microscopy & Microanalysis and School of Aeronautical, Mechanical and Mechatronic Engineering, University of Sydney, Sydney 2006, New South Wales, Australia

Mark Sheldon, Medical Humanities and Bioethics Program, Feinberg School of Medicine, Northwestern University, Chicago, IL 60661, United States

Stefan A Bailis, Cornerstone Therapy & Recovery Center, St. Paul, MN 55101, United States

Jeffrey D Klausner, Department of Medicine, Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, United States

Brian J Morris, School of Medical Sciences, University of Sydney, Sydney 2006, New South Wales, Australia

Corresponding author: Brian J Morris, DSc, PhD, Professor Emerita, School of Medical Sciences, University of Sydney, Building F13, Eastern Avenue, Sydney 2006, New South Wales, Australia. brian.morris@sydney.edu.au

Abstract

The British Medical Association (BMA) guidance on non-therapeutic circumcision (NTMC) of male children is limited to ethical, legal and religious issues. Here we evaluate criticisms of the BMA's guidance by Lempert *et al.* While their arguments promoting autonomy and consent might be superficially appealing, their claim of high procedural risks and negligible benefits seem one-sided and contrast with high quality evidence of low risk and lifelong benefits. Extensive literature reviews by the American Academy of Pediatrics and the United States Centers for Disease Control and Prevention in developing evidence-based policies, as well as risk-benefit analyses, have found that the medical benefits of infant NTMC greatly exceed the risks, and there is no reduction in sexual function and pleasure. The BMA's failure to consider the medical benefits of early childhood NTMC may partly explain why this prophylactic intervention is discouraged in the United Kingdom. The consequence is higher prevalence of preventable infections, adverse medical conditions, suffering and net costs to the UK's National Health Service for treatment of these. Many of the issues and contradictions in the BMA

guidance identified by Lempert *et al* stem from the BMA's guidance not being sufficiently evidence-based. Indeed, that document called for a review by others of the medical issues surrounding NTMC. While societal factors apply, ultimately, NTMC can only be justified rationally on scientific, evidence-based grounds. Parents are entitled to an accurate presentation of the medical evidence so that they can make an informed decision. Their decision either for or against NTMC should then be respected.

Key Words: Circumcision, Male; Child; Infections; Risk; Policy; Public health

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This article assesses arguments by circumcision opponents Lempert *et al* criticizing the British Medical Association (BMA)'s guidance on non-therapeutic male circumcision (NTMC) for failing to consider all of the issues. We find that the BMA's focus on non-medical issues expose it to such claims by NTMC opponents. Indeed, the medical evidence, as used for evidence-based NTMC policies in the United States, does not support their claims. The lifetime benefits of early infant NTMC greatly exceed the risks, and the procedure has no adverse effect on sexual function or pleasure. The neonatal period is the optimal time for parent approved NTMC.

Citation: Moreton S, Cox G, Sheldon M, Bailis SA, Klausner JD, Morris BJ. Comments by opponents on the British Medical Association's guidance on non-therapeutic male circumcision of children seem one-sided and may undermine public health. *World J Clin Pediatr* 2023; 12(5): 244-262

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/244.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.244>

INTRODUCTION

In 2019 the BMA released practical guidance for doctors on non-therapeutic male circumcision (NTMC) of boys[1]. This stated that it “abhors the harassment of individual doctors through intimidating and threatening behaviour on the basis of their involvement in the provision of NTMC”. As with vaccination, NTMC attracts criticism from activists. Opponents argue that NTMC of a nonconsenting child violates their human rights to genital integrity and that circumcision should be delayed until they are old enough to make the decision for themselves. There are, however, sound scientific reasons why early NTMC is beneficial to the child's health. These include protection against infections in infancy and infections, including sexually transmitted ones, disease and other adverse medical conditions over the lifespan. Reduced risk of penile[2-4] and possibly prostate[5,6] cancer is greatest the earlier the NTMC is performed, being particularly strong (40% lower) in Black men[6]. Risk was lower in men circumcised after age 36 years in the Canadian study[6]. In the current “post-truth era”, in which individuals and lobby groups dispute scientific evidence by way of on-line rhetoric, threats and intimidation using social media and protests to promote their views, the challenge for scientists and society is considerable[7-15]. As with other decisions by parents made in what they consider to be the best interest of the child, such as vaccination, lobbying by opponents can involve inappropriate pressuring of parents to reconsider their decision to have their sons circumcised.

The most recent reviews by the American Academy of Pediatrics (AAP)[16] and the United States (US) Centers for Disease Control and Prevention (CDC)[17] concluded that the health benefits of NTMC exceeded the risks and recommended the procedure for parents who choose it (Table 1).

NTMC opponents responded by denouncing the new policies. The claims were evaluated by the AAP, CDC, and academic authorities and found not to be consistent with the consensus of scientific evidence (Table 2).

Selective citation, obfuscation and denial of scientific evidence are features of anti-NTMC arguments. Most of these and the evaluation of each publication by medical authorities can be found in a systematic review[18].

The BMA guidance attracted the attention of NTMC opponents Antony Lempert, Chair of the Secular Medical Forum which advises the United Kingdom's National Secular Society, in an article with ethicist Brian Earp as author for correspondence, and two others[19]. The aim of the present article is to evaluate their arguments.

ANTI-NTMC SENTIMENTS BY OTHER MEDICAL BODIES

Lempert *et al*[19] support particular statements in the BMA's guidance[1] disfavoring NTMC. They refer to negative NTMC policies by Dutch (Kindermishandeling en huselijk geweld [KNMG]: Royal Dutch Medical Association), Danish and Finnish medical bodies. Then refer to the Finnish Medical Association as being “more forward in their approach, offering a clear medical-ethical stance for consideration”. They argue that “mainstream, non-partisan, national-level professional societies that have formally studied the issue”, with the exception of those in the United States, “have concluded that NPC [NTMC] of children cannot be justified on medical grounds in the sense of conferring a net health

Table 1 Conclusions and recommendations by the American Academy of Pediatrics in its non-therapeutic male circumcision policy statement

The AAP Systematic evaluation of English-language peer-reviewed literature from 1995 through 2010 indicates that preventive health benefits of elective circumcision of male newborns outweigh the risks of the procedure
Benefits include significant reductions in the risk of urinary tract infection in the first year of life and, subsequently, in the risk of heterosexual acquisition of HIV and the transmission of other sexually transmitted infections
The procedure is well tolerated when performed by trained professionals under sterile conditions with appropriate pain management. Complications are infrequent; most are minor, and severe complications are rare. Male circumcision performed during the newborn period has considerably lower complication rates than when performed later in life
Although health benefits are not great enough to recommend routine circumcision for all male newborns, the benefits of circumcision are sufficient to justify access to this procedure for families choosing it and to warrant third-party payment for circumcision of male newborns. It is important that clinicians routinely inform parents of the health benefits and risks of male newborn circumcision in an unbiased and accurate manner
Parents ultimately should decide whether circumcision is in the best interests of their male child. They will need to weigh medical information in the context of their own religious, ethical, and cultural beliefs and practices. The medical benefits alone may not outweigh these other considerations for individual families. Findings from the systematic evaluation are available in the accompanying technical report. The American College of Obstetricians and Gynecologists has endorsed this statement

HIV: Human immunodeficiency virus.

Table 2 Nontherapeutic male circumcision policy statements showing arguments by opponents (left column) and responses to each (right column)

2012 AAP policy on NTMC[16,67]	
Frisch <i>et al</i> [95], 2013	AAP Task Force[15], 2013
Svoboda & Van Howe[96], 2013	Morris <i>et al</i> [99], 2014
Jenkins[97], 2014	Morris <i>et al</i> [100], 2014
Darby[98], 2014	Morris[170], 2014
Darby[171], 2015	Morris <i>et al</i> [101], 2016
Svoboda <i>et al</i> [172], 2016	Brady[102], 2016; Morris <i>et al</i> [103], 2017
2014 CDC MC draft policy[17,88]	
Earp[150], 2015	Morris[151], 2015
Adler[173], 2016	Rivin <i>et al</i> [174], 2016
Frisch <i>et al</i> [175], 2018	Morris <i>et al</i> [177], 2017; CDC[153], 2018
Van Howe[177], 2015	CDC[178], 2018
2015 CPS policy on NTMC[27]	
Sorokan <i>et al</i> [27], 2015	Morris <i>et al</i> [70], 2016
Robinson <i>et al</i> [180], 2017	Morris <i>et al</i> [180], 2017
RACP policy on NTMC[183], 2010	
RACP[181], 2010	Morris <i>et al</i> [182], 2012
Forbes[183], 2012	Morris <i>et al</i> [184], 2012
Jansen[185], 2016	Wodak <i>et al</i> [186], 2017

AAP: American Academy of Pediatrics; CDC: Centers for Disease Control and Prevention; CPS: Canadian Paediatric Society; NTMC: Non-therapeutic male circumcision; RACP: Royal Australasian College of Physicians.

benefit". Infant NTMC was endorsed in high human immunodeficiency virus (HIV) settings by various bodies combatting the HIV epidemic. According to a recent editorial[20], however, the World Health Organization (WHO) no longer endorses NTMC of infants in its voluntary medical male circumcision (VMMC) program. Reasons likely include immediate cost-effectiveness of NTMC for men in combatting the HIV epidemic, as opposed to the long lag that would occur between infant NTMC and its potential benefit for HIV risk reduction. Another factor may be reports of adverse events by inadequately skilled and over-stretched providers.

In a 2017 report, the CDC recommended routine infant NTMC for HIV prevention in 12 high priority countries[21]. Various local bodies fighting the epidemic have also endorsed the procedure[21-26]. But presumably Lempert *et al*[19] had in mind socio-economically advantaged countries such as the UK and North America that have a relatively low HIV prevalence. The negative Canadian Paediatric Society policy nevertheless concluded that in Canada “there may be a benefit [from NTMC] for some boys in high-risk populations and circumstances”[27].

Lempert *et al*[19] quote the KNMG as saying “it is reasonable to put off circumcision until the age at which [the] boy himself can decide about the intervention or can opt for any available alternatives”. But this disregards the fact that, in early infancy, risk is minimized, and lifetime health benefits are maximized by NTMC. By postponing the procedure until the “boy himself can decide”, the boy is deprived of the early benefits, such as a 10-fold reduction in risk of urinary tract infection (UTI)[28], as well as reduced risk of inflammatory and physical problems during childhood. Since procedural risk is lowest for NTMC performed in early infancy[29], delay also means an increased risk of harm to the boy from an adverse event. Thus, the longer the delay the lower will be the benefit to risk ratio.

The benefits of neonatal NTMC (and % affected based on population prevalence of uncircumcised males and of the medical condition) are: (1) A 90% decreased risk of UTI at age 0–1 years (with 1.3% affected), 85% lower risk at 1–16 years (2.7% affected), 70% reduced risk at > 16 years (28% affected), as found in a meta-analysis of males of all ages[28]; (2) almost complete elimination of risk of phimosis, with an observational study finding 12% of uncircumcised British males still have phimosis by the age of 18 years[30]; (3) a 68% decreased risk of balanitis (10% being affected), as found in a meta-analysis of 8 studies[31]; (4) 60% decreased risk of candidiasis (thrush; with 10% affected)[31]; (5) a 70% decreased risk of HIV infection during heterosexual sex or insertive anal intercourse (with 0.1% affected), as found in a meta-analysis[32]; (6) a 53%–65% decreased risk of high-risk human papillomavirus (HPV) infection (4%–10% affected) according to meta-analyses[33–35]; (7) a 30% decreased risk of herpes simplex virus type 2 infection (with 4% being affected) based on randomized controlled trial (RCT) findings[36–39]; (8) a 50% decreased risk of genital ulcer disease (with approximately 1% affected), based on observational studies[40–42] and a meta-analysis[43]; (9) a 40%–55% decreased risk of syphilis infection (with 1% affected) based on the findings of a meta-analysis[43] and observational studies[44,45]; (10) a 50% decreased risk of *Trichomonas vaginalis* infection (with 1% affected), according to a RCT[46]; (11) a 40% decreased risk of *Mycoplasma genitalium* infection (with 0.5% affected) as revealed by RCT findings[47]; (12) a 50% decreased risk of chancroid (with < 1% affected), according to a meta-analysis[43]; (13) a 67%–99% decreased lifetime risk of penile cancer (with 0.11%–0.15% affected), as found in the most recent meta-analysis[4] and observational studies[48–50]; and (14) 10% decreased risk of prostate cancer (with 1% being affected), as determined by meta-analyses[51–53].

A common cause of inflammatory foreskin conditions such as balanitis can be poor hygiene, medications (such as antibiotics), allergens (including latex condoms, propylene glycol in lubricants), some spermicides, and corticosteroids. Ammonia released from urine by bacterial hydrolysis of urea can cause inflammation of the glans and foreskin. Frequent washing with soaps containing topical allergens or irritants is another common cause of contact dermatitis. Microorganisms are often responsible.

No adverse effect on sexual function or pleasure was found in multiple systematic reviews and meta-analyses[54–58]. The most recent found pain during intercourse and erectile dysfunction were significantly lower in circumcised men[57].

A drawback of NTMC includes risk of a minor adverse event, which affects 0.4% in infancy, 8% at age 1–10 years, and 4% at ages ≥ 10 years[29]. Risk of a major complication is extremely low. Another is cost, which can be substantial if the procedure is not covered by third party insurance. In the UK the National Health Service (NHS) covers medical MC, but not NTMC. If either is performed later, the time taken for the procedure and for the immediate recovery period will mean disruption of daily activities, including employment and school attendance. If the mature male is sexually active, then abstinence from sexual activities will be required during the healing period, which is generally 6 weeks.

PROCEDURAL RISKS MISUNDERSTOOD

The suggestion by Lempert *et al*[19] that procedural risks are similar “between infants and adults” is not the case. A US study of 1.4 million NTMCs by CDC researchers found risk of adverse events is 10–20 times higher after the neonatal period[29].

At “age 2–18” circumcision is often for treatment of medical problems, usually phimosis, excessive foreskin and lichen sclerosus, which would have been prevented by NTMC in early infancy. Lempert *et al*[19] ignore many key issues, such as those associated with UTIs that are 10-fold higher in uncircumcised infants. These include the excruciating pain of UTI, the need for blood collection, lumbar puncture, hospitalization for intravenous antibiotic administration, and risk of sepsis, death, and treatment challenges from burgeoning antibiotic resistance[59–62]. Early NTMC also means immediate and lifetime abatement of risk of numerous other adverse medical conditions that have varying degrees of morbidity, and, for some, a risk of mortality. Various clinical experts have likened NTMC to a “surgical vaccine”[63,64]. In contrast, the overwhelming majority of procedural complications from NTMC in early infancy are minor, and easily and fully resolvable[29].

MEDICAL NEED VERSUS PREVENTION

Lempert *et al*[19] state that “circumcision is rarely required for medical reasons”, citing studies that reported the need for surgery in 1.7%–2.5% of boys < 18 years[65,66]. These figures do not, however, include the much greater number who will develop a foreskin-related problem (mostly phimosis) that infant NTMC would have prevented. Nor do they include

infections and diseases that will occur over the lifetime of uncircumcised males with a healthy foreskin. As well, some will require therapeutic circumcision to treat a medical condition at ages > 18 years. The benefits of circumcision when indicated for treatment include treatment of the devastating foreskin inflammatory condition lichen sclerosus, for paraphimosis when emergency intervention must be performed to prevent ischemia and gangrene, as a cure for intractable phimosis that has failed to respond to other interventions such as steroid treatment, and for treatment of cancerous tissue which frequently involves the foreskin of penile cancer patients.

The potential benefits of foreskin retention are its potential use as a skin graft during surgical repair of hypospadias, or to treat burns or other injuries in some specific areas of the body. There may be cultural reasons for retaining the foreskin, in which having the same general genital appearance as other males in non-circumcising cultures may help the boy or man fit in. This was recognized by the AAP in its recommendation that parents “will need to weigh the medical information in the context of their own religious, ethical, and cultural reasons and practices” [16,67]. Another is the requirement of a foreskin in the uncommon sexual practice of “docking” [68].

Health authorities have provided advice on care of an uncircumcised penis [69]: Gently, not forcefully, pull the foreskin away from the tip of the penis. Rinse the tip of the penis and the inside part of the foreskin with soap and water. Return the foreskin back over the tip of the penis.

As calculated in risk-benefit analyses for Anglophone countries [70-72], including the United Kingdom [73], approximately half of British males will likely experience a medical condition during their lifetime that NTMC might have protected against. Men can be reluctant to see a medical practitioner when they have a medical problem, especially when it involves their genitalia or sexual dysfunction.

COMPARISON WITH LABIAPLASTY

Lempert *et al* [19] argue that if “the ‘better in infancy’ view applied with equal force to ‘infant labiaplasty’”, and that “even if the data were unambiguous ... the presumable consensus of Western medical ethicists and legal experts would be that such data are irrelevant” [19], citing Reis *et al* [74]. But data *are* relevant, and it is far from clear that the consensus would be otherwise. Evidence-based medicine is held in high regard by professionals for good reason – it works. The ethics (and legality) of a medical procedure must be guided by the best available scientific data, or else incorrect decisions, adverse outcomes and bad laws can result. In the case of labiaplasty the science is clear – it has no significant benefits, so there is no rational justification for performing it on a minor in the absence of a clear medical indication. NTMC, in contrast, does have clear benefits established by a very large body of scientific research data, and the optimal time is early infancy, as supported by the data. NTMC is thus unequivocally evidence based. The reference [74] used by Lempert *et al* [19] to support their argument is to an opinion piece about surgery on intersex infants. This is a poor analogy as intersex is a complex set of conditions. These may be associated with hormonal imbalances in the womb, or chromosomal abnormalities, and patients have a high risk of later identifying with a gender other than the one decided for them in infancy by a surgeon.

ETHICS

Because NTMC involves surgery on the healthy tissue of a child who is too young to give his consent (consent instead being given by his parents or guardians), and the health benefits during infancy and early childhood are modest (although high over the lifetime), individuals such as Lempert *et al* [19] argue that childhood NTMC is unethical. Public health ethics attempts to be practical by seeking decisions that will likely produce the greatest net benefit. Well-informed public health authorities might logically be persuaded by the strong evidence favoring NTMC. The extensive reviews by the AAP and CDC led these major authorities to conclude that since the benefits of infant NTMC exceed the risks, parents have a right to choose NTMC for a child. It has been argued that NTMC is justifiable as a public health necessity [75].

The Brussels Collaboration on Genital Integrity (BCGI) [76] decided that an intervention to alter a bodily state should be regarded as a medical necessity when the bodily state poses a threat to the person's well-being. While absence of NTMC may not pose a “threat” at the time at which NTMC is usually performed, the scientific evidence shows that if not circumcised early in life, approximately half of uncircumcised males will suffer an adverse medical condition over their lifetime because of their uncircumcised state [70-73]. Given the degree and breadth of benefits conferred by NTMC, performing infant and childhood NTMC appears consistent with the BCGI's statement.

Given the wide-ranging protection afforded by NTMC against diverse medical conditions and infections in infancy and childhood, including sexually transmitted infections (STIs) in sexually active adolescent males, it has been argued that it would be unethical not to circumcise boys early in childhood [77,78]. Article 24 of the United Nations Convention on the Rights of the Child [79] contains the statement:

“States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health ... States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services”.

Article 24 states that the definition of health includes preventative health. Thus, not advising parents of benefits and risk of NTMC may violate the rights of the child. Logically, Article 24 might be seen as mandating NTMC, since not circumcising boys poses a threat to their health [78].

Article 5 is also noteworthy. The text reads: “States Parties shall respect the responsibilities, rights and duties of parents or, where applicable, the members of the extended family or community as provided for by local custom, legal guardians or other persons legally responsible for the child, to provide, in a manner consistent with the evolving capacities of the

child, appropriate direction and guidance in the exercise by the child of the rights recognized in the present Convention" [79].

Should NTMC be delayed until later, the BMA guidance advises in "card 2, Ten good practice points" that "3. Children who are able to express views about NTMC should be involved in the decision-making process. 4. Where a child (with or without competence) refuses NTMC, the BMA cannot envisage a situation in which it will be in a child's best interests to perform circumcision, irrespective of the parents' wishes." Curiously, item 5 states: "It is the parents' responsibility to explain and justify requests for circumcision, in terms of the individual factors in relation to a particular child's best interests." In contrast, the AAP guidance states: "It is important that clinicians routinely inform parents of the health benefits and risks of male newborn circumcision in an unbiased and accurate manner".

THE "DELAY UNTIL THE MALE CAN DECIDE FOR HIMSELF" ARGUMENT

The policy of deferring early NTMC until an age of consent is reached involves an appeal to "autonomy". Whilst superficially and emotionally appealing, it is not consistent with evidence and thus appears to be misplaced as we will now explain. The argument fails to consider a more valid concern about beneficence or the best interests of the infant, and a fairer allocation of resources in society. In high-HIV settings, where striving for as high an uptake of NTMC as possible is vital to curb the HIV epidemic, a policy of deferring the procedure would mean fewer circumcisions and hence more infections, increased pressure on health systems, as well as higher health care costs (because later NTMC is more expensive), suffering, social costs and deaths. Even without the risk of HIV infection, deferring infant NTMC would still mean higher incidence of medical conditions that NTMC protects against, and thus higher morbidity, mortality, and costs. We therefore question if that is ethical?

Lempert *et al* [19] assert that "only a small minority of non-circumcised men report 'ever' wishing that they 'had been' circumcised—even in the United States, where infant circumcision remains a dominant cultural practice". As support they cite two articles by their article's co-author Earp. The first [80] cites a YouGov poll that found 10% of circumcised US men wished they had not been circumcised. But Lempert *et al* [19] ignore the same poll's finding that 29% of uncircumcised US men wished they were circumcised. Twenty-nine percent is not a "small" minority, as claimed. Their second citation [81] is to a survey of Amazon Mechanical Turk cohort participants. These were described in their first citation [80]. In the latter article, 15.9% of uncircumcised men wished they were circumcised, whereas 13.6% of circumcised men wished they were not [81]. Thus, slightly more uncircumcised than circumcised men were unsatisfied (1 in 6 *vs* 1 in 7). Since both surveys showed higher dissatisfaction amongst uncircumcised men, and the percentages are not small, the references cited by Lempert *et al* [19] do not support their claim.

Lempert *et al* [19] reference an article by Earp & Darby that states that "nontherapeutic circumcisions are rarely sought by adults with intact genitals, even in cultures in which circumcision is common and normative" [80]. A footnote on page 43 of that article cites a US study of men-who-have-sex-with-men (MSM) that found most were unwilling to have NTMC to prevent HIV. But a single study asking just MSM a hypothetical question is not representative of the majority view. In contrast, a systematic review of over 40 studies across multiple countries and cultures found that when all men are properly informed about NTMC they usually respond positively, and are more positive the better informed they are [82]. The VMMC program to combat the African HIV epidemic resulted in circumcision of almost 30 million men by 2020 [20], and men continue to queue in some African countries to obtain the procedure. This does not support the critics' "rarely sought" statement. That many uncircumcised men outside of high-HIV settings (or circumcising cultures) do not wish or seek circumcision may reflect their lack of motive (low HIV risk), lack of free availability, or lack of education about the procedure's benefits.

Lempert *et al* [19] go on to argue that men who wish to be circumcised at least have the option of undergoing the procedure, unlike those circumcised as infants, who cannot reverse the decision. Whilst true, this overlooks the barriers to adults seeking the procedure. Lempert *et al* [19] acknowledge that there will be "certain costs and inconveniences". But their argument downplays the broad spectrum of barriers (Table 3).

CDC researchers conducted a study of adverse procedural events involving 1.4 million medical NTMCs in the US across all ages [29]. Amongst the 1.3 million infant NTMCs, adverse event frequency was 0.4%. The CDC referred to these findings in its 2018 policy statement [17]. Of the 1400920 reimbursement claims, 95.3% were for males aged ≤ 1 year, 2.0% were for ages 1–9 years, and 2.7% were for ages ≥ 10 years and above. Compared with infancy, adverse events were 20-times higher in boys aged 1–9 years, and 10-times higher in those aged ≥ 10 years [29]. The most common risks were minor bleeding, post-operative clearing of adhesions and removal of excess foreskin [29]. Such adverse events are easily and quickly resolved with no lasting effect. An exception is very rare fatal hemorrhage as a result of undiagnosed hemophilia and botched circumcision by poorly trained or negligent operators. In a large California study, frequency of complications was 0.5% in neonates, but in non-neonates was 18.5 times greater [17]. A United Kingdom study found complications were 1% amongst boys aged 3–16 years receiving therapeutic MC [83]. All were minor and there were no major complications.

A risk-benefit analysis for the United Kingdom [104] found benefits exceeded risks by $> 100:1$ and estimated that if not circumcised early a large proportion of males would be at risk of an adverse medical condition during their lifetime from a condition attributable to foreskin retention.

In settings where the procedure is freely and readily available, many men who would like to have a circumcision are nevertheless deterred by barriers such as fear of pain, need for sexual abstinence during the healing process, loss of earnings, inconvenience, embarrassment, and various psychosocial factors, as demonstrated by a voluminous literature (see review [84]). In developed countries, a man wanting to be circumcised, but who does not have a medical indication

Table 3 The advantages of non-therapeutic male circumcision in neonates compared with older boys and men

Neonatal non-therapeutic male circumcision	Non-therapeutic male circumcision of older boys and men
Is a simple surgical procedure for a well-trained competent medical practitioner	More complex
No psychological considerations	Possibility of adverse peer pressure, especially in societies such as the UK where MC is uncommon
Quick: Takes several minutes	Takes 30 min or more
Cost is lower	Much more expensive and often unaffordable
Low risk of adverse events (0.4%), and almost all are minor	Higher risk of adverse events (4%–8%)
Any bleeding is minimal and easily stopped	Bleeding is more common, requiring cautery or other interventions
Sutures not needed	Sutures or tissue glue are needed
Convenient since the baby sleeps most of the day	Inconvenient owing to need for time off school or work
Local anesthesia used if the infant is less than 2 mo of age	General anesthesia for age 2 mo to age 9 yr. For men local anesthesia may be used, although general anesthesia is sometimes preferred by the surgeon
Healing is fast (less than 2 weeks)	Healing takes 6 weeks or more
Cosmetic outcome usually good	If stitches are used, stitch marks may be visible permanently
No long-term memory of the procedure, or anxiety in anticipation	May be a source of fear in the boy or man of undergoing an operation
Does not disrupt breast-feeding or other activities	Abstinence from sexual intercourse required for the healing period of 6 or more weeks

MC: Male circumcision; UK: United Kingdom.

for circumcision, would have to attend a private clinic. In the UK, the cost of an elective adult NTMC is approximately £2259[85], which would be unaffordable to many. In contrast, the cost of an infant NTMC by a private provider is about 10-times lower[86,87]. One might wonder whether the “delay until the male is old enough to decide for himself” argument is used by NTMC opponents such as Lempert *et al*[19] to reduce the likelihood of NTMC ever happening. The multiple advantages of infant NTMC over adult NTMC have been highlighted in multiple reviews[16,17,71–73,88–90] (Table 3).

A systematic review of arguments opposing NTMC found that these were supported mostly by low-quality evidence and opinion and were contradicted by strong scientific evidence[18,91]. Many of those arguments have been stated above. Others included in the first systematic review[18] were that opponents appear to favor waiting until an adverse medical condition arises and then treating it by methods other than circumcision. However, such methods tend to be only partially effective, require prolonged intervention, and may have side effects. Steroids to treat phimosis is an example. In the meantime, the male will continue to suffer. Circumcision can not only be the definitive choice up front – but will provide at least partial protection against the elevated risk of the array of other adverse medical conditions over the lifetime of the uncircumcised male. Although penile cancer affects only about 0.1% of males over their lifetime[4,90,92], the consequences are devastating. Since childhood NTMC may provide almost complete protection against this cancer, that patient may regret his parents’ failure to have him circumcised. Sexual function and pleasure are often referred to by opponents, likely because problems with these may not be discussed by men affected. A later section is devoted to this issue.

AN ALTERNATIVE TO NTMC FOR JEWISH FAMILIES

Just as is true of the BMA guidance document, Lempert *et al*[19] see NTMC as mostly a religious practice. They point out the existence of Jewish groups that reject NTMC. Those groups instead practice “Brit Shalom” (Covenant of Peace), a “gender-inclusive welcoming ceremony for children of Jewish parents” who prefer not to have their male children circumcised[93]. Brit Shalom arose in recent decades. It provides ritual options for families not affiliated with a synagogue and who may question NTMC. Instead of NTMC, the ceremony may involve cutting a pomegranate instead of a foreskin, and mainly focuses on naming the baby and welcoming him (or her) into the Jewish faith[93]. The reasons for replacing Brit Milah with Brit Shalom by some families appear to be respect for gender equality, response to local culture, acceptance of the arguments of NTMC opponents, perception of stigma being associated with circumcision, and Jewish feminism[93]. But Lempert *et al*[19] fail to acknowledge that the practice of Brit Shalom is by a very small minority within Judaism[93]. Orthodox Jews reject such alternatives to Brit Milah. The fastest growing section of the Jewish community, at least in Israel, is the Ultra-Orthodox[94] who would never relinquish NTMC on the eighth day of life. In addition, the Reform and Conservative movements, which essentially represent mainstream Judaism, continue their support and

practice of Brit Milah. The following is a statement provided to author Mark Sheldon by Rabbi Mark Cooper, Director of the National Organization of American Mohalim (NOAM) and Brit Milah Program of Report Judaism, a program under the auspices of the Hebrew Union College (HUC), Jewish Institute of Religion (JIR):

"Brit Milah, or Jewish ritual or ceremonial circumcision, is widely endorsed in the American Jewish community for Jewish families of various configurations. The Reform Movement of Judaism, under the academic supervision of HUC-JIR in Los Angeles, has sponsored the Brit Milah Program since 1984, with the aim of recruiting, training, and supporting physicians who wish to serve their communities as mohalim. Graduates of the program, currently numbering over 100 physicians and nurse midwives, belong to NOAM. The Conservative Movement of Judaism, under the organizational supervision of the Rabbinical Assembly, likewise sponsors its Brit Kodesh program, with a similar aim. Both movements are committed to perpetuating Brit Milah as Judaism's oldest continuously practiced ritual and enduring symbol of an unyielding commitment to the continuity of the Jewish way of life".

Lempert *et al*'s statement that "Children do not always grow up to share the religious or metaphysical beliefs, nor the associated cultural values, of their parents" is a valid point, and is one reason why infant NTMC can only be rationally justified on scientific, evidence-based grounds[19].

EVIDENCE-BASED VS NON-EVIDENCE BASED

Unlike the BMA's guidance and European position statements on NTMC of boys, those of the AAP[16,67] and CDC[17, 88] are evidence-based and were supported by comprehensive reviews of the best data available at the time. Contrary to these are ones, such as Dutch and Scandinavian, cited by Lempert *et al*[19], that ignore most of the literature concerning the established benefits of the procedure, and focus instead on issues of ethics, human rights, consent, and legalities, making them essentially ideological positions rather than scientific evidence-based ones.

Lempert *et al*[19] disparage the AAP's infant NTMC policy statement, saying it "was met with unprecedented criticism from international experts for falling short of its usual scientific standards and exhibiting strong evidence of cultural bias" [95-98]. However, they fail to acknowledge the detailed rebuttals that those claims attracted[15,99-103] (Table 2). The "cultural bias" argument by Frisch and his mostly northern European (in particular Scandinavian) co-authors[95] was rebutted by the AAP Task Force on circumcision as applying more logically to northern Europe, where NTMC is rare, than to the US where the proportion of circumcised and uncircumcised males is more equal[15]. In response to the AAP, Earp & Darby argued that in Western medicine the bias is "against medically unnecessary surgeries performed on nonconsenting minors"[80]. But, unlike the anti-NTMC position, Western medicine might be seen as having a "bias" that is in favor of evidence-based medicine. Two of the most highly rated clinical practice guidelines for NTMC[104] were found by Canadian authors, who could be regarded as non-partisans in the debate, to be the evidence-based policy recommendations by the AAP and CDC.

Lempert *et al*[19] point out that all AAP policy statements automatically "expire" after 5 years, thus implying that the AAP's infant NTMC policy is no longer valid. It nevertheless remains the most up-to-date, evidence-based statement by a pediatric body to date. The AAP is, moreover, the world's largest pediatric body.

QUESTIONABLE ASSERTIONS ABOUT PROTECTION AGAINST HIV

Lempert *et al*[19] claim that there is no evidence anywhere in the world that NTMC of infants or children reduces the risk of HIV transmission, whether to males or to females. That is not true. Some of the observational studies in Africa that identified the connection between lack of NTMC and risk of HIV were in countries where NTMC of infants and children is the norm[105,106]. And studies in Asia and the developed world where NTMC is usually performed in infancy or childhood have found the same[107,108]. The evidence favoring childhood NTMC for HIV risk reduction has been reviewed recently[134].

Lempert *et al*[19] refer to "recent evidence from United Kingdom-comparable epidemiological environments within the Global North, including Canada and Denmark" that show NTMC does not protect against HIV. In support, they cite a Canadian study by Nayan *et al*[109] that found a non-significant 2% lower HIV prevalence amongst circumcised men. But a detailed analysis of those data by one of the present authors showed that the apparent lack of a significant effect stemmed from the disproportionately high prevalence of HIV infections amongst MSM, the majority of whom adopt the receptive role during anal intercourse, a sexual practice in which being circumcised affords no protection against HIV infection[110,111]. Circumcised men in the study who engaged in heterosexual intercourse or who were MSM practicing insertive anal intercourse were at 70% lower risk of HIV infection ($P = 7.2 \times 10^{-10}$)[110,111], just as found in the most recent meta-analysis of all studies globally[112]. Nayan *et al*[113] agreed with those calculations[110].

The same problem of failing to consider MSM in the analyses affected findings in the Danish study cited by Lempert *et al*[19] of HIV and other STIs amongst men who had undergone NTMC in childhood[114]. This was pointed out in a brief critique[115], and in much more detail in a comprehensive critique that also identified multiple other problems with the Danish study[111].

Lempert *et al*[19] also assert that "there is no evidence of a benefit to female partners of circumcised men, whether in Africa or elsewhere". This is untrue. Systematic reviews have found that NTMC protects the female partners of circumcised men indirectly by reducing the likelihood that a sexual partner will become infected[116,117]. Furthermore, the studies cited by Lempert *et al*[19] do not support their claim. Two[118,119] were general discussions that predate by up to a decade the data-based studies we cite above. The other[120] was to a trial in which some HIV-infected men

ignored advice and resumed sex before their circumcision wounds were fully healed, leading to infection of some female partners, a situation that may not have arisen had they been circumcised in infancy.

SEXUAL FUNCTION AND PLEASURE

Lempert *et al*[19] criticize the BMA's guidance for failing to address this topic. In common with assertions by other NTMC opponents, Lempert *et al*[19] claim that "the foreskin is the most sensitive part of the penis to light-touch sensation both to light touch stimulation and sensations of warmth" and "is a potential source of pleasure in its own right"[19]. In support, they cite a weak study[121] critiqued previously[122]. That study[121] appeared as a chapter in a 2006 book by NTMC opponents. They also cite a 2007 San Francisco study funded by NOCIRC (an anti-circumcision organization) of sensitivity to light touch[123], but not the critique pointing out flaws in the study's statistical analyses, methodology and recruitment[124]. In contrast, a Canadian study by Bossio *et al*[125] tested touch, pain, warmth and heat pain, finding that the foreskin is not the most sensitive part of the adult penis across all sensation types examined. Lempert *et al*[19] ignored the latter study and its findings that tactile sensation of the foreskin was similar to a control point on the forearm, and that there were no differences in sensitivity of other penile sites between circumcised and uncircumcised men.

The "light-touch sensation" Lempert *et al*[19] focus on involves Meissner's corpuscles. The histological data confirms the physiological data by showing that the foreskin has no role in sexual sensation or pleasure. Histologically, the neuroreceptors responsible for sexual sensation and thus pleasure have been described as genital corpuscles which are concentrated in the highly innervated coronal ridge of the glans and the underside of the distal shaft of the penis, thus ruling out the foreskin as a histological source of sexual pleasure[126]. Meissner's corpuscles, which are mechanoreceptors, are the most abundant sensory corpuscles in the glabrous skin of the prepuce, and are identical in structure to Meissner's corpuscles in fingers[127]. Whatever the neurological origins of erogenous sensation may be, it is not Meissner's corpuscles. Thus, the fixation on the light-touch sensation type in publications opposing NTMC is irrelevant. The BMA was right to disregard it in its guidance.

There is abundant high-quality evidence from randomized controlled trials, cohort and case-control studies, and large, well-designed cross-sectional surveys, that medical NTMC has no adverse effect on sexual function, pleasure or satisfaction in men, as summarized in all systematic reviews[54,56,57,128] and meta-analyses[55,57]. Significantly, three of these were not by individuals often involved in the NTMC debate and were from non-circumcising countries (Denmark and China, although one author of the Danish study was of Jewish heritage).

Systematic reviews found women, including those from non-circumcising cultures, overwhelmingly prefer a circumcised penis for sexual activity[154,155]. Across countries, cultures and sexual preference, a majority of men too regard being circumcised as esthetically pleasing and more sexually desirable to women[129-135]. While esthetics is clear-cut, sexual pleasure may be purely physical, or could be influenced by psychological factors. Women may have a valid perception of better hygiene and lower risk of STIs if their male partner is circumcised.

Lempert *et al*[19] quote from a recent review by Tye *et al*[136] that speculated about the inability of circumcised men to experience the phenomena of "gliding", "rocking", "rolling" or "moving" of the foreskin, and their supposed need for lubrication during sexual intercourse. But they failed to acknowledge that Tye & Sardi's review stressed that there are no data supporting such phenomena. A recent article examined the claims made by Tye & Sardi and found no evidence that any were of importance[122]. When asked which were the most erogenous parts of the penis, men put the glans first, and the foreskin last[137].

INAPPROPRIATE ANALOGIES

Lempert *et al*[19] wondered why NTMC should be legal whereas "female genital mutilation" (FGM) "is illegal in the United States and most other developed countries". But this is a false analogy. Most forms of FGM are anatomically dissimilar to MC. FGM confers no medical benefits, only risks. In contrast, NTMC confers a wide range of benefits that greatly exceed risks, especially when performed early in infancy. The two are therefore not comparable, and thus represent separate issues. A FGM case in the United Kingdom, in which the presiding magistrate was Sir James Munby, was misconstrued by NTMC opponents[138]. The latter failed to reveal that items 72 and 73 of the judgement recognized substantial health benefits of childhood NTMC that differentiated it from FGM[139]. A critical evaluation of the judgement can be found in McAlister[140].

The female equivalent of MC is "hoodectomy" – the removal or reduction of the clitoral hood (female prepuce). It may be done for medical reasons – such as inflammation – the female equivalent of balanitis[141] but can be chosen by women for perceived improvement in sexual function. A number of clinics in the UK offer the procedure. This is not remotely equivalent to the mutilations practised in some North African countries, so to bundle these all together as FGM is unhelpful.

The Lempert *et al*[19] critique referred to tattooing as being "analogous" to NTMC of minors. But they failed to state whether tattooing confers medical, sexual, or hygienic benefits. For an analogy to be valid, the two must be comparable. Tattooing is not a prophylactic procedure, and we are unaware of it having any proven health benefits. NTMC would appear unique as far as benefits are concerned. Childhood vaccination has some parallels but does not involve removing body parts. Tooth extraction – for example when teeth cause overcrowding of the mouth – comes to mind, but then an overcrowded mouth is a pre-existing problem that can be serious in that it may lead to impacted molars. Various procedures commonly performed on minors and that attract little criticism include cosmetic surgery, such as the removal

of birthmarks, or straightening of crooked teeth. But it is curious to us that removal of the foreskin, a well-known haven for bacteria and other microorganisms that play varying degrees of responsibility in the etiology of UTI, HIV, oncogenic HPV genotypes and some other STIs, inflammatory dermatological conditions, physical problems, penile cancer, and prostate cancer in uncircumcised men, and an increased risk of cervical cancer and several STIs in female partners, is a topic of derision by particular minority groups who oppose NTMC of children.

UNTRAINED PRACTITIONERS

Lempert *et al*[19] raise concerns about NTMC being carried out by untrained practitioners. We share these concerns insofar as the procedure should only be carried out by those who are well-trained and who abide by accepted clinical practice guidelines. This should not preclude a well-trained Jewish mohel, for example, from carrying out the procedure. Research both in developing and developed world settings has shown that, if properly trained and provided with adequate resources, nurses, midwives and physician assistants can perform the procedure to just as high a standard as doctors and surgeons[142-146]. Consistent with the studies cited, the BMA guidance states "Male infant circumcision does not require a medical professional"[1]. This contradicts Lempert *et al*[19], who claim the BMA guidance states: "Male infant circumcision does not require medical expertise". Their misquote is somewhat out of context. The only place in the BMA guidance where the word "expertise" is used is in the preamble, entitled "About this toolkit" on the second page, which states, "We note that there is no requirement in law for these practitioners to have proven expertise, although there are standards that some practitioners ascribe to set by external collectives, associations and societies." The BMA's guidance goes on to acknowledge that there have been rare cases of serious injury or death caused by "non-doctor practitioners" and "urge parents who are considering having their child circumcised, to ensure that the practitioner who carries out the circumcision has undergone relevant training and has proven experience and competence in the practice", a caution the guidance repeats two pages later.

Clearly the BMA was aware of the problem of inadequately trained practitioners causing harm and urge parents to seek trained and experienced providers. We share Lempert *et al*'s concern that there is no legal requirement in the United Kingdom for a provider to have appropriate training in NTMC, or to abide by particular standards. It is right and proper to draw attention to this issue[19].

LEGAL CONCERNS BY THE CRITICS

In part (1) of their 2nd table, Lempert *et al*[19] state that NTMC "has been ruled to amount to 'significant harm' within the meaning of the Children Act 1989 by the High Court (Family Division) in the context of care", and in part (2) that it "has been held, again by the High Court, to amount to greater harm than at least some of WHO Types 1, 2, and/or 4 FGM which are agreed to be unethical and unlawful procedures"[19]. Each is followed by a footnote ("p"), which discusses the ruling by Lord Justice Munby in 2015[139] in which Lempert *et al*[19] point out that Munby decided that NTMC constituted "significant harm" on the grounds that it was more invasive than some forms of FGM which were already considered "significant harm" in law. We disagree. Munby set out to decide whether a case of FGM amounted to "significant harm" and agreed that it did. In item 69 Munby states "In my judgment, if FGM Type IV amounts to significant harm, as in my judgment it does, then the same must be so of male circumcision." Then in item 73, Munby states "there is a very clear distinction between FGM and male circumcision. FGM in any form will suffice to establish 'threshold' in accordance with section 31 of the Children Act 1989; male circumcision without more will not." Lempert *et al*[19] therefore appear to have misrepresented Munby's judgement.

Sir William Patrick Dean, a High Court Judge (and former Governor General of Australia), stated in a 1992 case that NTMC, "for perceived hygienic – or even religious – reasons...plainly lies within the authority of parents of an incapable child to authorize surgery on the basis of medical advice"[147]. It should be noted that at that time the medical evidence favoring NTMC was not as strong as it is today.

Thus, our evaluation of much of the legal evidence referred to by Lempert *et al*[19] shows that they have ignored key statements by judges and authoritative organizations that contradict their stance that is opposed to NTMC of boys[19].

As an aside, in relation to FGM, it seems to us difficult to comprehend how the mildest forms of FGM, which may be no more than a prick or scratch, can be construed as "significant harm." An accidental scratch, cut, or bruise that heals fully within a week or two should not be considered "significant harm", even though it may damage more skin, cause more pain, and shed more blood than type IV FGM. The definition of "significant harm" is too broad here. There is unarguably a temporary harm in NTMC as the wound heals, but once healed (a process which is much faster in the neonate than the 6-8 weeks required for post-circumcision healing in an adult) there is no harm, as indicated by the multiple studies referred to above showing that sexual function, pleasure, and satisfaction are unimpaired, even improved following the procedure. The "significant harm" assertion was also heavily criticised by a British Law postgraduate[140]. Lempert *et al*[19] ignored this. They also ignored items 72 and 73 of Munby's judgement which recognized health benefits of boyhood circumcision that distinguish it from FGM.

Lempert *et al*'s 2nd table, part (e)[19], states that "Under English criminal law, the imposition of [NTMC] on a non-consenting adult certainly amounts to the criminal offence of Actual Bodily Harm, and very likely amounts to the offence of Grievous Bodily Harm"[148]. But does it? This comment refers the reader to their footnote "s" which states: "See Crown Prosecution Service, Code for Crown Prosecutors, 'Offences against the Person, incorporating the Charging Standard' [available at [cps.gov.uk/Legal-guidance/offences-against-person-incorporating-charging-standard](https://www.cps.gov.uk/legal-guidance/offences-against-person-incorporating-charging-standard)]." Since the

word “circumcision” does not appear in that document, the reference fails to support Lempert *et al*'s argument[19].

The authors go on to suggest that “Either ‘minor’ forms of FGM will have to be allowed, as prominent defenders of child [NTMC] are increasingly proposing or [NTMC] of minors will have to be brought into closer alignment with existing standards applied to other practices”. We would, however, question whether the authors of the 9 references they cite are “prominent defenders” of NTMC. If having just a few publications on the topic of NTMC makes one a “prominent” defender of NTMC, one wonders what Lempert *et al*[19] would make of authors with a prolific publication record, whose findings agree with the medical evidence supporting NTMC. We are, moreover, unaware of any prominent defender of NTMC who also defends any version of FGM. The “prominent defenders” that Lempert *et al*[19] refer to do not defend FGM on “medical grounds” but recognize the existence of cultural issues.

At the end of their article, Lempert *et al*[19] provide Notes to their Table 3, where their item marked “I” states: “A subsequent report by the U.S. Centers for Disease Control, apparently produced in coordination with the AAP, was met with similar international criticism[149]. For further discussion of the specific problems with these American analyses by one of us see Ref.[151]” Lempert *et al*[19] ignore the responses to those criticisms[151]. They cite a criticism by Kupferschmid *et al*[149], which was just one of many submissions to the CDC that followed release of the CDC's draft policy in 2014[17,151]. The Kupferschmid web reference is now unobtainable. The CDC reviewed and provided answers addressing virtually all of the various objections in a separate document in 2018[153]. Their “by one of us” article cited in Lempert *et al*'s quote above was by Earp[150] (the author for correspondence on the Lempert *et al* article[19]). They do not, however, cite the co-published rebuttal[151] of Earp's article.

SUMMARY OF THE CRITICISMS BY LEMPERT *ET AL*.

The basic tenets of Lempert *et al*'s criticisms of the BMA's guidance are encapsulated in their statement: “More generally, we find that selective quotes and evidence, where discussed, operate throughout the guidance in the direction of minimizing problems with [NTMC] and downplaying reasons to object to it, while alluding to unproven or intangible (e.g. prophylactic or psychosocial) benefits of the practice.” Lempert *et al*[19] can be accused of doing the same, but in the opposite direction. Thus, their article appears to be projection.

Many of the issues and contradictions in the BMA guidance identified by Lempert *et al*[19] stem from the BMA's statement not being sufficiently evidence-based. Ultimately, NTMC can only be justified rationally on scientific, evidence-based grounds. Religious circumcision may, however, have had a sound practical basis. The reason for Jewish circumcision is lost in the mists of time, although, if we believe Genesis, Abraham was unable to father a child by his wife Sara until he was circumcised. Islamic circumcision is not a command from on high but part of a whole suite of recommendations for practical health and hygiene, which make sense in the scientific era of today. Modern bathing facilities may have improved on some Islamic cleanliness recommendations, but the health and hygiene benefits of circumcision are unchanged. Many children and adults who drift away from their birth religion understand this and continue to favor circumcision. Although, as Lempert *et al*[19] correctly point out, there is no guarantee that the infant will continue to follow religious traditions when they grow up. Moreover, performing the procedure for religious and cultural reasons may not be accepted by some individuals outside of those traditions and may even be vehemently rejected.

CLAIMS BY OTHER NTMC OPPONENTS IN THE UK

London urologists Matthew Deacon and Gordon Muir recently published a review[155] examining pros and cons of infant NTMC. Although not addressing the BMA's statement directly, being UK-based, their review is relevant to the BMA's guidance, so it would be remiss not to mention it here. Several of the present authors examined it and found it was selective with the literature, misleading and contradictory[155].

Deacon *et al*'s reply[156] was also problematic. Their complaint about self-citing by their critics was *ad hominem*. Self-citing shows that an author has published copiously on a topic, it says nothing about the quality of their work. Besides, some on the negative side of the NTMC debate also extensively cite their own and each other's publications[81]. Deacon & Muir ignored a systematic review and meta-analysis of all 27 studies of meatal stenosis[157], instead “cherry picking” an outlier study by an anti-NTMC activist, ignoring the strong criticism it attracted[158]. They complain that risk-benefit analyses by the present last author and colleagues have not been replicated but no one has tried. They dismissed criticism of their claim that NTMC may increase the need for antibiotics as getting “lost in a statistical debate”, but their claim was based on a gross over-estimate of post-procedural infections, and a false assumption that all such infections require antibiotics. They also misunderstood evidence that circumcision protects against HIV during vaginal intercourse by heterosexual men[108,110,111,159,160] and insertive anal intercourse by MSM[110,111,161,162] in developed countries. Deacon & Muir exaggerate perceived pain from NTMC by including “Minimal pain” and “Acceptable pain” responses in a study on parent's perception of procedural pain from NTMC, arriving at 70.7%, instead of the more realistic 3.7% for “More than acceptable”, or “Much more pain” in their infant child. Finally, they persist in misunderstanding that it is erogenous sensation, not light touch or heat, that matters during sexual intercourse, and that erogenous sensation is concentrated around the glans and distal shaft, not the foreskin[126,136,137]. In short, Deacon *et al*'s reply failed to properly address the original criticisms[155].

An article by Sutton *et al*[163] argued that general practitioners (GPs) in the United Kingdom were guilty of referring too many uncircumcised males with foreskin problems to their regional pediatric surgery clinic. A critique pointed out that “circumcision as soon as a problem becomes apparent is by far the most cost-effective solution”[164]. In a reply to the

criticisms, the article's co-authors Corbett *et al* [165] cited dated guidelines in 2006 by the British Association of Pediatric Urologists that has a disclaimer that "this statement is not evidence based" [166]. Instead, they refuse to circumcise – even 16-year-old boys who are unable to consummate sexual relations – if they regard their phimosis as "physiological", that is foreskin constriction without evidence of pathology. The tendency to conserve the foreskin ignores the fact that 50% of cases of lichen sclerosis are only discovered after circumcision, when clinical assessment is conducted [167]. Those authors then complained that health care providers lack education about foreskin health in children and that many "would welcome further educational resources." We hope the present article will address this need. Their claim that on average a GP working in the NHS has an annual caseload of "1700 thousand" patients, is a figure three orders of magnitude higher than the likely actual caseload. Corbett *et al* [165] ended by promoting their own website [168], which makes the curious claim that "Your penis produces smegma to help keep it lubricated and prevent dryness".

TAKING AN EVIDENCE-BASED POSITION

As scientists and professionals, we take a strictly evidence-based approach. If infant NTMC is favored by both risk-benefit and cost-benefit analyses, which the present article affirms, then a logical, evidence-based case can be made independently of religious and cultural considerations. As should be apparent from the evidence presented, such a case can be made, and indeed has been made, by several professional bodies, such as the AAP [16,66], the CDC [17,87], and the Circumcision Academy of Australia [71]. Opponents of the procedure are welcome to debate these assessments. That is how science proceeds, but to date the contributions to such debates by opponents have been marred by poor science.

Based on high quality scientific evidence, NTMC has minimal or no adverse effect on sexual function, pleasure, or satisfaction [53-57] – if anything, as shown by the most recent meta-analysis, it reduces sexual dysfunction (less pain, less erectile dysfunction, and more favorable intravaginal ejaculatory latency time) [56]. This does not by itself justify the procedure, but it does refute one of the main objections by NTMC opponents, namely that NTMC reduces sexual function and pleasure. NTMC also confers a range of medical, health, sexual and practical benefits, and those benefits are maximal and the risks minimal if the procedure is carried out during the neonatal period. If, as the cumulative evidence strongly suggests is the case, neonatal NTMC is favored based on risk-benefit analyses and is cost saving with minimal harm to the recipient, then it is in the male child's best interests to be provided with the procedure. As a corollary, it would be unethical to deny infant NTMC to parents who want their sons to be circumcised. It also follows that religious or cultural NTMC, provided it is performed to a high clinical standard, is simply doing a medically beneficial procedure for non-medical reasons, so neutralizing the ethical objections Lempert *et al* [19] raise against it.

NTMC is a one-off procedure that is most conveniently performed in early infancy using local anesthesia. In early infancy it is simpler, safer, quicker, cheaper, more convenient, cosmesis is optimum, and healing is faster than later circumcision which presents multiple other challenges, as listed in Table 3. The BMA guidance recognizes the need for the procedure to "be in the child's best interests". This should prioritize the child's immediate and long-term health, and its medical benefits to the United Kingdom population as a whole, rather than merely appeasing the religious and cultural requirements of minorities. Medical practitioners, nurses and other health professionals in the United Kingdom have an ethical duty to present clear and unbiased information to parents of boys and to men regarding the diversity of benefits afforded by NTMC, the net level of lifetime protection against these, the low prevalence of procedural risks, that are especially low for neonatal NTMC, and that, unless otherwise indicated, circumcision will be performed using local anesthesia at that age. If the medical practitioner is unable or unwilling to perform the procedure, she or he should direct parents to a medical practitioner who is competent, experienced, and willing.

Given the evidence, infant NTMC might be considered in a similar manner to childhood vaccination. Vaccination is also an early intervention providing considerable benefits, with low risks. Denial of vaccination by medical professionals is unethical. Infant NTMC confers cost-savings to health systems and individuals [169].

A recent evaluation by Canadian researchers of 13 clinical practice guidelines for NTMC in different countries [103] found the best included those by the CDC and the Canadian Urological Association, followed by the AAP. These were chosen because of the thorough reviews of the medical literature each had performed in developing their NTMC policies. The BMA's guidance was not amongst the 13 chosen.

Alignment of medical thinking in the United Kingdom – that seems to have changed little over the years – with current high-quality scientific evidence and evidence-based policy statements in the US would better inform practitioners, health authorities, policy makers and governments in the United Kingdom. The outcome would likely be improvements in public health, cost coverage by the NHS, as well as long-term cost savings for the NHS and the United Kingdom taxpayer by reducing the case load of infections and diseases that NTMC protects against.

CONCLUSION

The present review finds that extensive criticism of the BMA's guidance on NTMC by a member of the United Kingdom's National Secular Society and his co-authors does not stand up to scrutiny. Their opinions are at odds with widely available high-quality scientific evidence and evidence-based policies by major medical bodies such as the CDC and AAP.

FOOTNOTES

Author contributions: Moreton S and Morris BJ conceived the study, Moreton S and Morris BJ prepared the initial draft of the manuscript, Moreton S, Cox G, Sheldon M, Bailis SA, Klausner JD and Morris BJ provided input to successive drafts. All authors have read and approve the final manuscript.

Conflict-of-interest statement: Stephen Moreton is an editor of, and contributor to <http://www.circfacts.org>, an online facility that provides evidence-based information on male circumcision. Brian J Morris is a member of the Circumcision Academy of Australia, a not-for-profit, government registered, medical society that provides evidence-based information on male circumcision to parents, practitioners and others, as well as contact details of doctors who perform the procedure. Research performed by Brian Morris is supported by U.S. National Institutes of Health Center of Biomedical Research Excellence grant 1P20GM125526-01A1 but was not used for the present publication. None of the authors receive income from their affiliations or work related to circumcision.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United Kingdom

ORCID number: Stephen Moreton 0000-0003-1918-800X; Guy Cox 0000-0002-3719-1109; Mark Sheldon 0000-0003-2256-2365; Stefan A Bailis 0000-0002-4376-5615; Jeffrey D Klausner 0000-0002-6922-7364; Brian J Morris 0000-0003-2468-3566.

Corresponding Author's Membership in Professional Societies: Circumcision Academy of Australia.

S-Editor: Liu JH

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- 1 **British Medical Association.** Non-therapeutic male circumcision of children toolkit. 2019. (accessed Dec 29, 2022). Available from: <https://www.bma.org.uk/advice/employment/ethics/children-and-young-people/non-therapeutic-male-circumcision-of-children-ethics-toolkit>
- 2 **Tsen HF,** Morgenstern H, Mack T, Peters RK. Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). *Cancer Causes Control* 2001; **12**: 267-277 [PMID: 11405332 DOI: 10.1023/a:1011266405062]
- 3 **Daling JR,** Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, Carter JJ, Porter PL, Galloway DA, McDougall JK, Krieger JN. Penile cancer: importance of circumcision, human papillomavirus and smoking in situ and invasive disease. *Int J Cancer* 2005; **116**: 606-616 [PMID: 15825185 DOI: 10.1002/ijc.21009]
- 4 **Larke NL,** Thomas SL, dos Santos Silva I, Weiss HA. Male circumcision and penile cancer: a systematic review and meta-analysis. *Cancer Causes Control* 2011; **22**: 1097-1110 [PMID: 21695385 DOI: 10.1007/s10552-011-9785-9]
- 5 **Wright JL,** Lin DW, Stanford JL. Circumcision and the risk of prostate cancer. *Cancer* 2012; **118**: 4437-4443 [PMID: 22411189 DOI: 10.1002/cncr.26653]
- 6 **Spence AR,** Rousseau MC, Karakiewicz PI, Parent MÉ. Circumcision and prostate cancer: a population-based case-control study in Montréal, Canada. *BJU Int* 2014; **114**: E90-E98 [PMID: 24655933 DOI: 10.1111/bju.12741]
- 7 **Enfield N.** Giving advice in a post-truth world. *Acuity magazine*. May 21, 2018. (accessed Jan 11, 2022). Available from: <https://www.acuitymag.com/opinion/giving-advice-in-a-post-truth-world>
- 8 **Zaliznyak M,** Masterson JM, Duel B. YouTube as a source for information on newborn male circumcision: Is YouTube a reliable patient resource? *J Pediatr Urol* 2022; **18**: 678.e1-678.e7 [PMID: 35985919 DOI: 10.1016/j.jpuro.2022.07.011]
- 9 **Cheng JW,** Fernandez N, Shnorhavorian M, Merguerian PA, Kieran K. Engagement of common pediatric urologic conditions on social media. *J Pediatr Urol* 2022; **18**: 236.e1-236.e7 [PMID: 35125286 DOI: 10.1016/j.jpuro.2021.12.003]
- 10 **Vosoughi S,** Roy D, Aral S. The spread of true and false news online. *Science* 2018; **359**: 1146-1151 [PMID: 29590045 DOI: 10.1126/science.aap9559]
- 11 **Hoffman BL,** Felter EM, Chu KH, Shensa A, Hermann C, Wolynn T, Williams D, Primack BA. It's not all about autism: The emerging landscape of anti-vaccination sentiment on Facebook. *Vaccine* 2019; **37**: 2216-2223 [PMID: 30905530 DOI: 10.1016/j.vaccine.2019.03.003]
- 12 **Ucar T,** Culpan M, Caskurlu T, Karaman Mİ, Silay MS. The activity and discussion points of #Circumcision through Twitter; a microblogging platform. *Int J Impot Res* 2018; **30**: 249-252 [PMID: 30104670 DOI: 10.1038/s41443-018-0058-y]
- 13 **Johnson NF,** Leahy R, Restrepo NJ, Velasquez N, Zheng M, Manrique P, Devkota P, Wuchty S. Hidden resilience and adaptive dynamics of the global online hate ecology. *Nature* 2019; **573**: 261-265 [PMID: 31435010 DOI: 10.1038/s41586-019-1494-7]
- 14 **Stern MJ.** How circumcision broke the Internet. *Slate* Sep 18, 2013. (accessed Feb 26, 2023). Available from: http://www.slate.com/articles/health_and_science/medical_examiner/2013/09/intactivists_online_a_fringe_group_turned_the_internet_against_circumcision.html
- 15 **Task Force on Circumcision.** Cultural bias and circumcision: the AAP Task Force on circumcision responds. *Pediatrics* 2013; **131**: 801-804 [PMID: 23509171 DOI: 10.1542/peds.2013-0081]
- 16 **American Academy of Pediatrics Task Force on Circumcision.** Male circumcision. *Pediatrics* 2012; **130**: e756-e785 [PMID: 22926175 DOI: 10.1542/peds.2012-1990]
- 17 **Centers for Disease Control and Prevention.** Background, Methods, and Synthesis of Scientific Information Used to Inform "Information for Providers to Share with Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, Sexually Transmitted

- Infections, and other Health Outcomes" 2018. (accessed Dec 29, 2022). Available from: <https://stacks.cdc.gov/view/cdc/58457>
- 18 **Morris BJ**, Moreton S, Krieger JN. Critical evaluation of arguments opposing male circumcision: A systematic review. *J Evid Based Med* 2019; **12**: 263-290 [PMID: [31496128](#) DOI: [10.1111/jebm.12361](#)]
 - 19 **Lempert A**, Chegwidden J, Steinfeld R, Earp BD. Non-therapeutic penile circumcision of minors: current controversies in UK law and medical ethics. *Clin Ethics* 2022; **18**: 36-54 [DOI: [10.1177/14777509221104703](#)]
 - 20 **Davis SM**, Bailey RC. Can the ShangRing bring us closer to endorsing early infant male circumcision in sub-Saharan Africa? *Lancet Glob Health* 2022; **10**: e1377-e1378 [PMID: [36113516](#) DOI: [10.1016/S2214-109X\(22\)00380-1](#)]
 - 21 **Hines JZ**, Ntsuape OC, Malaba K, Zegeye T, Serrem K, Odoyo-June E, Nyirenda RK, Msungama W, Nkanaunena K, Come J, Canda M, Nhaguiombe H, Shihepo EK, Zemburuka BLT, Mutandi G, Yoboka E, Mbayiha AH, Maringa H, Bere A, Lawrence JJ, Lija GJI, Simbeye D, Kazaura K, Mwiru RS, Talisuna SA, Lubwama J, Kabuye G, Zulu JE, Chituwo O, Mumba M, Xaba S, Mandisarisa J, Baack BN, Hinkle L, Grund JM, Davis SM, Toledo C. Scale-Up of Voluntary Medical Male Circumcision Services for HIV Prevention - 12 Countries in Southern and Eastern Africa, 2013-2016. *MMWR Morb Mortal Wkly Rep* 2017; **66**: 1285-1290 [PMID: [29190263](#) DOI: [10.15585/mmwr.mm6647a2](#)]
 - 22 **Clearing House on Male Circumcision**. Cost and Impact of Scaling Up EIMC in Southern and Eastern Africa using the DMPPT 2.0 Model. 2014. (accessed Feb 19, 2023). Available from: <https://www.malecircumcision.org/resource/cost-and-impact-scaling-eimc-southern-and-eastern-africa-using-dmppt-20-model>
 - 23 **Amuri M**, Msemo G, Plotkin M, Christensen A, Boyee D, Mahler H, Phafoli S, Njozi M, Hellar A, Mlangi E, Yansaneh A, Njeuhmeli E, Lija J. Bringing Early Infant Male Circumcision Information Home to the Family: Demographic Characteristics and Perspectives of Clients in a Pilot Project in Tanzania. *Glob Health Sci Pract* 2016; **4** Suppl 1: S29-S41 [PMID: [27413081](#) DOI: [10.9745/GHSP-D-15-00210](#)]
 - 24 **Kikaya V**, Kakaire R, Thompson E, Ramokhele M, Adamu T, Curran K, Njeuhmeli E. Scale-Up of Early Infant Male Circumcision Services for HIV Prevention in Lesotho: A Review of Facilitating Factors and Challenges. *Glob Health Sci Pract* 2016; **4** Suppl 1: S87-S96 [PMID: [27413087](#) DOI: [10.9745/GHSP-D-15-00231](#)]
 - 25 **Luo C**. Sustaining Gains Made in Voluntary Medical Male Circumcision. *Glob Health Sci Pract* 2016; **4** Suppl 1: S1-S2 [PMID: [27413079](#) DOI: [10.9745/GHSP-D-16-00106](#)]
 - 26 **Mangenah C**, Mavhu W, Hatzold K, Biddle AK, Ncube G, Mugurungi O, Ticklay I, Cowan FM, Thirumurthy H. Comparative Cost of Early Infant Male Circumcision by Nurse-Midwives and Doctors in Zimbabwe. *Glob Health Sci Pract* 2016; **4** Suppl 1: S68-S75 [PMID: [27413085](#) DOI: [10.9745/GHSP-D-15-00201](#)]
 - 27 **Sorokan ST**, Finlay JC, Jefferies AL; Canadian Paediatric Society, Fetus and Newborn Committee, Infectious Diseases and Immunization Committee. Newborn male circumcision. *Paediatr Child Health* 2015; **20**: 311-320 [PMID: [26435672](#) DOI: [10.1093/pch/20.6.311](#)]
 - 28 **Morris BJ**, Wiswell TE. Circumcision and lifetime risk of urinary tract infection: a systematic review and meta-analysis. *J Urol* 2013; **189**: 2118-2124 [PMID: [23201382](#) DOI: [10.1016/j.juro.2012.11.114](#)]
 - 29 **El Beheraoui C**, Zhang X, Cooper CS, Rose CE, Kilmarx PH, Chen RT. Rates of adverse events associated with male circumcision in U.S. medical settings, 2001 to 2010. *JAMA Pediatr* 2014; **168**: 625-634 [PMID: [24820907](#) DOI: [10.1001/jamapediatrics.2013.5414](#)]
 - 30 **Osmond TE**. Is routine circumcision advisable? *J R Army Med Corps* 1953; **99**: 254 [PMID: [13097540](#)]
 - 31 **Ferris JA**, Richters J, Pitts MK, Shelley JM, Simpson JM, Ryall R, Smith AM. Circumcision in Australia: further evidence on its effects on sexual health and wellbeing. *Aust N Z J Public Health* 2010; **34**: 160-164 [PMID: [23331360](#) DOI: [10.1111/j.1753-6405.2010.00501.x](#)]
 - 32 **Lei JH**, Liu LR, Wei Q, Yan SB, Yang L, Song TR, Yuan HC, Lv X, Han P. Circumcision Status and Risk of HIV Acquisition during Heterosexual Intercourse for Both Males and Females: A Meta-Analysis. *PLoS One* 2015; **10**: e0125436 [PMID: [25942703](#) DOI: [10.1371/journal.pone.0125436](#)]
 - 33 **Albero G**, Castellsagué X, Giuliano AR, Bosch FX. Male circumcision and genital human papillomavirus: a systematic review and meta-analysis. *Sex Transm Dis* 2012; **39**: 104-113 [PMID: [22249298](#) DOI: [10.1097/OLQ.0b013e3182387abd](#)]
 - 34 **Larke N**, Thomas SL, Dos Santos Silva I, Weiss HA. Male circumcision and human papillomavirus infection in men: a systematic review and meta-analysis. *J Infect Dis* 2011; **204**: 1375-1390 [PMID: [21965090](#) DOI: [10.1093/infdis/jir523](#)]
 - 35 **Shapiro SB**, Laurie C, El-Zein M, Franco EL. Association between male circumcision and human papillomavirus infection in males and females: a systematic review, meta-analysis, and meta-regression. *Clin Microbiol Infect* 2023; **29**: 968-978 [PMID: [37011808](#) DOI: [10.1016/j.cmi.2023.03.028](#)]
 - 36 **Tobian AA**, Ssempijja V, Kigozi G, Oliver AE, Serwadda D, Makumbi F, Nalugoda FK, Iga B, Reynolds SJ, Wawer MJ, Quinn TC, Gray RH. Incident HIV and herpes simplex virus type 2 infection among men in Rakai, Uganda. *AIDS* 2009; **23**: 1589-1594 [PMID: [19474649](#) DOI: [10.1097/QAD.0b013e32832d4042](#)]
 - 37 **Tobian AA**, Charvat B, Ssempijja V, Kigozi G, Serwadda D, Makumbi F, Iga B, Laeyendecker O, Riedesel M, Oliver A, Chen MZ, Reynolds SJ, Wawer MJ, Gray RH, Quinn TC. Factors associated with the prevalence and incidence of herpes simplex virus type 2 infection among men in Rakai, Uganda. *J Infect Dis* 2009; **199**: 945-949 [PMID: [19220138](#) DOI: [10.1086/597074](#)]
 - 38 **Sobngwi-Tambekou J**, Taljaard D, Lissouba P, Zarca K, Puren A, Lagarde E, Auvert B. Effect of HSV-2 serostatus on acquisition of HIV by young men: results of a longitudinal study in Orange Farm, South Africa. *J Infect Dis* 2009; **199**: 958-964 [PMID: [19220143](#) DOI: [10.1086/597208](#)]
 - 39 **Mehra SD**, Moses S, Agot K, Maclean I, Odoyo-June E, Li H, Bailey RC. Medical male circumcision and herpes simplex virus 2 acquisition: posttrial surveillance in Kisumu, Kenya. *J Infect Dis* 2013; **208**: 1869-1876 [PMID: [23901089](#) DOI: [10.1093/infdis/jit371](#)]
 - 40 **Nasio JM**, Nagelkerke NJ, Mwatha A, Moses S, Ndinya-Achola JO, Plummer FA. Genital ulcer disease among STD clinic attenders in Nairobi: association with HIV-1 and circumcision status. *Int J STD AIDS* 1996; **7**: 410-414 [PMID: [8940669](#) DOI: [10.1258/0956462961918374](#)]
 - 41 **Mehra SD**, Moses S, Parker CB, Agot K, Maclean I, Bailey RC. Circumcision status and incident herpes simplex virus type 2 infection, genital ulcer disease, and HIV infection. *AIDS* 2012; **26**: 1141-1149 [PMID: [22382150](#) DOI: [10.1097/QAD.0b013e328352d116](#)]
 - 42 **Aslam M**, Kropp RY, Jayaraman G, Dinner K, Wong T, Steben M. Genital herpes in Canada: Deciphering the hidden epidemic. *Can J Infect Dis Med Microbiol* 2012; **23**: e6-e9 [PMID: [23450170](#) DOI: [10.1155/2012/386329](#)]
 - 43 **Weiss HA**, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. *Sex Transm Infect* 2006; **82**: 101-9; discussion 110 [PMID: [16581731](#) DOI: [10.1136/sti.2005.017442](#)]
 - 44 **Pintye J**, Baeten JM, Manhart LE, Celum C, Ronald A, Mugo N, Mujugira A, Cohen C, Were E, Bukusi E, Kiarie J, Heffron R; Partners PrEP Study Team. Association between male circumcision and incidence of syphilis in men and women: a prospective study in HIV-1 serodiscordant heterosexual African couples. *Lancet Glob Health* 2014; **2**: e664-e671 [PMID: [25442691](#) DOI: [10.1016/S2214-109X\(14\)70315-8](#)]

- 45 **Otieno-Nyunya B**, Bennett E, Bunnell R, Dadabhai S, Gichangi A A, Mugo N, Wanyungu J, Baya I, Kaiser R; Kenya AIDS Indicator Survey Study Team. Epidemiology of syphilis in Kenya: results from a nationally representative serological survey. *Sex Transm Infect* 2011; **87**: 521-525 [PMID: 21917697 DOI: 10.1136/sextrans-2011-050026]
- 46 **Sobngwi-Tambekou J**, Taljaard D, Nieuwoudt M, Lissouba P, Puren A, Auvert B. Male circumcision and *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*: observations after a randomised controlled trial for HIV prevention. *Sex Transm Infect* 2009; **85**: 116-120 [PMID: 19074928 DOI: 10.1136/sti.2008.032334]
- 47 **Mehta SD**, Gaydos C, Maclean I, Odoyo-June E, Moses S, Agunda L, Quinn N, Bailey RC. The effect of medical male circumcision on urogenital *Mycoplasma genitalium* among men in Kisumu, Kenya. *Sex Transm Dis* 2012; **39**: 276-280 [PMID: 22421693 DOI: 10.1097/OLQ.0b013e318240189c]
- 48 **Schoen EJ**, Oehrli M, Colby Cd, Machin G. The highly protective effect of newborn circumcision against invasive penile cancer. *Pediatrics* 2000; **105**: E36 [PMID: 10699138 DOI: 10.1542/peds.105.3.e36]
- 49 **Christakis DA**, Harvey E, Zerr DM, Feudtner C, Wright JA, Connell FA. A trade-off analysis of routine newborn circumcision. *Pediatrics* 2000; **105**: 246-249 [PMID: 10617731 DOI: 10.1542/peds.105.S2.246]
- 50 **Wingo PA**, Tong T, Bolden S. Cancer statistics, 1995. *CA Cancer J Clin* 1995; **45**: 8-30 [PMID: 7528632 DOI: 10.3322/canjclin.45.1.8]
- 51 **Pabalan N**, Singian E, Jarjanazi H, Paganini-Hill A. Association of male circumcision with risk of prostate cancer: a meta-analysis. *Prostate Cancer Prostatic Dis* 2015; **18**: 352-357 [PMID: 26215783 DOI: 10.1038/pcan.2015.34]
- 52 **Li YD**, Teng Y, Dai Y, Ding H. The Association of Circumcision and Prostate Cancer: A Meta-Analysis. *Asian Pac J Cancer Prev* 2016; **17**: 3823-3827 [PMID: 27644623]
- 53 **Morris BJ**, Matthews JG, Pabalan N, Moreton S, Krieger JN. Male circumcision and prostate cancer: a meta-analysis revisited. *Can J Urol* 2021; **28**: 10768-10776 [PMID: 34378513]
- 54 **Morris BJ**, Krieger JN. Does male circumcision affect sexual function, sensitivity, or satisfaction?--a systematic review. *J Sex Med* 2013; **10**: 2644-2657 [PMID: 23937309 DOI: 10.1111/jsm.12293]
- 55 **Tian Y**, Liu W, Wang JZ, Wazir R, Yue X, Wang KJ. Effects of circumcision on male sexual functions: a systematic review and meta-analysis. *Asian J Androl* 2013; **15**: 662-666 [PMID: 23749001 DOI: 10.1038/aja.2013.47]
- 56 **Shabanzadeh DM**, Clausen S, Maigaard K, Fode M. Male Circumcision Complications - A Systematic Review, Meta-Analysis and Meta-Regression. *Urology* 2021; **152**: 25-34 [PMID: 33545206 DOI: 10.1016/j.urology.2021.01.041]
- 57 **Yang Y**, Wang X, Bai Y, Han P. Circumcision does not have effect on premature ejaculation: A systematic review and meta-analysis. *Andrologia* 2018; **50** [PMID: 28653427 DOI: 10.1111/and.12851]
- 58 **Morris BJ**, Krieger JN. The Contrasting Evidence Concerning the Effect of Male Circumcision on Sexual Function, Sensation, and Pleasure: A Systematic Review. *Sex Med* 2020; **8**: 577-598 [PMID: 33008776 DOI: 10.1016/j.esxm.2020.08.011]
- 59 **Fasugba O**, Gardner A, Mitchell BG, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired *Escherichia coli* urinary tract infections: a systematic review and meta-analysis of observational studies. *BMC Infect Dis* 2015; **15**: 545 [PMID: 26607324 DOI: 10.1186/s12879-015-1282-4]
- 60 **Bryce A**, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ* 2016; **352**: i939 [PMID: 26980184 DOI: 10.1136/bmj.i939]
- 61 **Morris BJ**, Tobian AA. Legal threat to infant male circumcision. *JAMA Pediatr* 2013; **167**: 890-891 [PMID: 23979448 DOI: 10.1001/jamapediatrics.2013.2761]
- 62 **Looke DF**, Gottlieb T, Jones CA, Paterson DL. Gram-negative resistance: can we combat the coming of a new "Red Plague"? *Med J Aust* 2013; **198**: 243-244 [PMID: 23496385 DOI: 10.5694/mja13.10190]
- 63 **Schoen EJ**. Circumcision as a lifetime vaccination with many benefits. *J Men's Hlth Gender* 2007; **382**: 306-311 [DOI: 10.1016/j.jmhg.2007.05.005]
- 64 **Ben KL**, Xu JC, Lu L, Lü NQ, Cheng Y, Tao J, Liu DK, Min XD, Cao XM, Li PS. [Male circumcision is an effective "surgical vaccine" for HIV prevention and reproductive health]. *Zhonghua Nan Ke Xue* 2009; **15**: 395-402 [PMID: 19514549]
- 65 **Sneppen I**, Thorup J. Foreskin Morbidity in Uncircumcised Males. *Pediatrics* 2016; **137** [PMID: 27244821 DOI: 10.1542/peds.2015-4340]
- 66 **Rickwood AM**. Medical indications for circumcision. *BJU Int* 1999; **83** Suppl 1: 45-51 [PMID: 10349414 DOI: 10.1046/j.1464-410x.1999.0830s1045.x]
- 67 **American Academy of Pediatrics Task Force on Circumcision**. Circumcision policy statement. *Pediatrics* 2012; **130**: 585-586 [PMID: 22926180 DOI: 10.1542/peds.2012-1989]
- 68 **Allan JA**. The spectre of docking in circumcision debates. *Sexualities* 2023; Online ahead of print [DOI: 10.1177/1363460723119940]
- 69 **Johns Hopkins Medicine**. Care of the uncircumcised penis in teens. 2023. (accessed Sep 2, 2023). Available from: <https://www.hopkinsmedicine.org/health/wellness-and-prevention/care-of-the-uncircumcised-penis>
- 70 **Morris BJ**, Klausner JD, Krieger JN, Willcox BJ, Crouse PD, Pollock N. Canadian Pediatrics Society position statement on newborn circumcision: a risk-benefit analysis revisited. *Can J Urol* 2016; **23**: 8495-8502 [PMID: 27705739]
- 71 **Morris BJ**, Bailis SA, Wiswell TE. Circumcision rates in the United States: rising or falling? *Mayo Clin Proc* 2014; **89**: 677-686 [PMID: 24702735 DOI: 10.1016/j.mayocp.2014.01.001]
- 72 **Morris BJ**, Katelaris A, Blumenthal NJ, Hajoona M, Sheen AC, Schrieber L, Lumbers ER, Wodak AD, Katelaris P. Evidence-based circumcision policy for Australia. *J Mens Health* 2022; **18** [PMID: 36034719 DOI: 10.31083/j.jomh1806132]
- 73 **Morris BJ**, Krieger JN. Non-therapeutic male circumcision. *Paediatr Child Health (UK)* 2020; **30**: 102-107. Available from: [https://www.paediatricsandchildhealthjournal.co.uk/article/S1751-7222\(19\)30263-X/pdf](https://www.paediatricsandchildhealthjournal.co.uk/article/S1751-7222(19)30263-X/pdf)
- 74 **Reis E**, Reis-Dennis S. The Irrelevance of Data to the Ethics of Intersex Surgery. *J Pediatr Ethics* 2021; **1**: 162-164
- 75 **Vawda YA**, Maqutu LN. Neonatal circumcision - violation of children's rights or public health necessity? *S Afr J Bioethics Law* 2011; **4**: 36-42
- 76 **Brussels Collaboration on Bodily Integrity**. Medically Unnecessary Genital Cutting and the Rights of the Child: Moving Toward Consensus. *Am J Bioeth* 2019; **19**: 17-28 [PMID: 31557092 DOI: 10.1080/15265161.2019.1643945]
- 77 **Bates MJ**, Ziegler JB, Kennedy SE, Wodak AD, Zoloth LS, Tobian AA, Morris BJ. Recommendation by a law body to ban infant male circumcision has serious worldwide implications for pediatric practice and human rights. *BMC Pediatr* 2013; **13**: 136 [PMID: 24010685 DOI: 10.1186/1471-2431-13-136]
- 78 **Jacobs AJ**. The ethics of circumcision of male infants. *Isr Med Assoc J* 2013; **15**: 60-65 [PMID: 23484246]

- 79 United Nations Human Rights Office of the High Commissioner for Human Rights, Convention on the Rights of the Child. 44/25. Nov 20, 1989. (accessed Dec 21, 2022). Available from: <http://www.ohchr.org/en/professionalinterest/pages/crc.aspx>
- 80 **Earp BD**, Darby R. Circumcision, sexual experience, and harm. *U Penn J Int Law* 2017; **37**: 1-56. Available from: https://www.researchgate.net/publication/315763686_Circumcision_Sexual_Experience_and_Harm
- 81 **Earp BD**, Sardi LM, Jellison WA. False beliefs predict increased circumcision satisfaction in a sample of US American men. *Cult Health Sex* 2018; **20**: 945-959 [PMID: 29210334 DOI: 10.1080/13691058.2017.1400104]
- 82 Moreton S. Do false beliefs predict increased circumcision satisfaction in men? *Adv Sex Med* 2020; **10**: 42-55 [DOI: 10.4236/asm.2020.102003]
- 83 **Hung YC**, Chang DC, Westfal ML, Marks IH, Masiakos PT, Kelleher CM. A Longitudinal Population Analysis of Cumulative Risks of Circumcision. *J Surg Res* 2019; **233**: 111-117 [PMID: 30502236 DOI: 10.1016/j.jss.2018.07.069]
- 84 **Jones P**, Rooney H, Hawary A. Pediatric Circumcision in the 21st Century National Health Service: A Snapshot of Practice in a United Kingdom Center. *Surg J (N Y)* 2020; **6**: e188-e191 [PMID: 33335988 DOI: 10.1055/s-0040-1721430]
- 85 **Carrasco MA**, Wilkinson J, Kasdan B, Fleming P. Systematic review of barriers and facilitators to voluntary medical male circumcision in priority countries and programmatic implications for service uptake. *Glob Public Health* 2019; **14**: 91-111 [PMID: 29695201 DOI: 10.1080/17441692.2018.1465108]
- 86 **Private Health Care UK**. How much does a private circumcision cost in the UK? 2021. (accessed Feb 22, 2023). Available from: <https://www.privatehealth.co.uk/conditions-and-treatments/circumcision/costs/>
- 87 **Integral Medical Co (IMC)**. Circumcision prices. 2022. (accessed Feb 22, 2023). Available from: <https://www.privatehealth.co.uk/conditions-and-treatments/circumcision/costs/>
- 88 **Centers for Disease Control and Prevention**. Information for providers counseling male patients and parents regarding male circumcision and the prevention of HIV infection, STIs, and other health outcomes. 2018. (accessed Dec 29, 2022). Available from: <https://stacks.cdc.gov/view/cdc/58456>
- 89 **Tobian AA**, Kacker S, Quinn TC. Male circumcision: a globally relevant but under-utilized method for the prevention of HIV and other sexually transmitted infections. *Annu Rev Med* 2014; **65**: 293-306 [PMID: 24111891 DOI: 10.1146/annurev-med-092412-090539]
- 90 **Morris BJ**, Kennedy SE, Wodak AD, Mindel A, Golovsky D, Schrieber L, Lumbers ER, Handelsman DJ, Ziegler JB. Early infant male circumcision: Systematic review, risk-benefit analysis, and progress in policy. *World J Clin Pediatr* 2017; **6**: 89-102 [PMID: 28224100 DOI: 10.5409/wjcp.v6.i1.89]
- 91 **Morris BJ**, Moreton S, Bailis SA, Cox G, Krieger JN. Critical evaluation of contrasting evidence on whether male circumcision has adverse psychological effects: A systematic review. *J Evid Based Med* 2022; **15**: 123-135 [PMID: 35785439 DOI: 10.1111/jebm.12482]
- 92 **Kochen M**, McCurdy S. Circumcision and the risk of cancer of the penis. A life-table analysis. *Am J Dis Child* 1980; **134**: 484-486 [PMID: 7377156 DOI: 10.1001/archpedi.1980.02130170034012]
- 93 **DuBoff M**, Davis DS. B'rit shalom: a Jewish ritual alternative to newborn male circumcision. *Int J Impot Res* 2023; **35**: 324-327 [PMID: 36042355 DOI: 10.1038/s41443-022-00607-y]
- 94 **Winer S**. Haredi population growing twice as fast as overall Israeli population — report. *Times of Israel* Dec 31, 2020. (accessed Nov 23, 2022). Available from: <https://www.timesofisrael.com/haredi-population-growing-twice-as-fast-as-total-israeli-population-report/>
- 95 **Frisch M**, Aigrain Y, Barauskas V, Bjarnason R, Boddy SA, Czauderna P, de Gier RP, de Jong TP, Fasching G, Fetter W, Gahr M, Graugaard C, Greisen G, Gunnarsdottir A, Hartmann W, Havranek P, Hitchcock R, Huddart S, Janson S, Jaszczak P, Kupferschmid C, Lahdes-Vasama T, Lindahl H, MacDonald N, Markestad T, Märtson M, Nordhov SM, Pälve H, Petersons A, Quinn F, Qvist N, Rosmundsson T, Saxen H, Söder O, Stehr M, von Loewenich VC, Wallander J, Wijnen R. Cultural bias in the AAP's 2012 Technical Report and Policy Statement on male circumcision. *Pediatrics* 2013; **131**: 796-800 [PMID: 23509170 DOI: 10.1542/peds.2012-2896]
- 96 **Svoboda JS**, Van Howe RS. Out of step: fatal flaws in the latest AAP policy report on neonatal circumcision. *J Med Ethics* 2013; **39**: 434-441 [PMID: 23508208 DOI: 10.1136/medethics-2013-101346]
- 97 **Jenkins I**. Bias and male circumcision. *Mayo Clin Proc* 2014; **89**: 1588 [PMID: 25444492 DOI: 10.1016/j.mayocp.2014.09.001]
- 98 **Darby R**. To avoid circumcision complications, avoid circumcision. *Can Urol Assoc J* 2014; **8**: 231 [PMID: 25210542 DOI: 10.5489/cuaj.1709]
- 99 **Morris BJ**, Tobian AA, Hankins CA, Klausner JD, Banerjee J, Bailis SA, Moses S, Wiswell TE. Veracity and rhetoric in paediatric medicine: a critique of Svoboda and Van Howe's response to the AAP policy on infant male circumcision. *J Med Ethics* 2014; **40**: 463-470 [PMID: 23955288 DOI: 10.1136/medethics-2013-101614]
- 100 **Morris BJ**, Bailis SA, Wiswell TE. In reply--Bias and male circumcision. *Mayo Clin Proc* 2014; **89**: 1588-1589 [PMID: 25444491 DOI: 10.1016/j.mayocp.2014.09.002]
- 101 **Morris BJ**, Krieger JN, Klausner JD. Critical evaluation of unscientific arguments disparaging affirmative infant male circumcision policy. *World J Clin Pediatr* 2016; **5**: 251-261 [PMID: 27610340 DOI: 10.5409/wjcp.v5.i3.251]
- 102 **Brady MT**. Newborn Male Circumcision with Parental Consent, as Stated in the AAP Circumcision Policy Statement, Is Both Legal and Ethical. *J Law Med Ethics* 2016; **44**: 256-262 [PMID: 27338601 DOI: 10.1177/1073110516654119]
- 103 **Morris BJ**, Krieger JN, Klausner JD, Rivin BE. The ethical course is to recommend infant male circumcision – Arguments disparaging American Academy of Pediatrics affirmative policy do not withstand scrutiny. *J Law Med Ethics* 2017; **45**: 647-663 [DOI: 10.1177/1073110517750603]
- 104 **Pokarowski M**, Kim JK, Milford K, Yadav P, Koyle M, Mahood Q, Santos JD, Rickard M, Lorenzo A, Chua M. Examining Clinical Practice Guidelines for Male Circumcision: A Systematic Review and Critical Appraisal Using AGREE II. *J Pediatr* 2022; **244**: 186-193.e6 [PMID: 35063471 DOI: 10.1016/j.jpeds.2021.12.073]
- 105 **Addanki KC**, Pace DG, Bagasra O. A practice for all seasons: male circumcision and the prevention of HIV transmission. *J Infect Dev Ctries* 2008; **2**: 328-334 [PMID: 19745498 DOI: 10.3855/jidc.192]
- 106 **Bailey RC**, Plummer FA, Moses S. Male circumcision and HIV prevention: current knowledge and future research directions. *Lancet Infect Dis* 2001; **1**: 223-231 [PMID: 11871509 DOI: 10.1016/S1473-3099(01)00117-7]
- 107 **Kenyon CR**. HIV prevalence correlated with circumcision prevalence and high-risk sexual behavior in India's states: an ecological study. *FI000Res* 2019; **8**: 60 [PMID: 31316754 DOI: 10.12688/fi000research.17807.2]
- 108 **Chemtob D**, Op de Coul E, van Sighem A, Mor Z, Cazein F, Semaille C. Impact of Male Circumcision among heterosexual HIV cases: comparisons between three low HIV prevalence countries. *Isr J Health Policy Res* 2015; **4**: 36 [PMID: 26244087 DOI: 10.1186/s13584-015-0033-8]

- 109 **Nayan M**, Hamilton RJ, Juurlink DN, Austin PC, Jarvi KA. Circumcision and Risk of HIV among Males from Ontario, Canada. *J Urol* 2022; **207**: 424-430 [PMID: [34551593](#) DOI: [10.1097/JU.0000000000002234](#)]
- 110 **Morris BJ**, Krieger JN. Circumcision and Risk of HIV among Males from Ontario, Canada. Letter. *J Urol* 2022; **207**: 479 [PMID: [34779237](#) DOI: [10.1097/JU.0000000000002337](#)]
- 111 **Morris BJ**, Moreton S, Krieger JN, Klausner JD. Infant Circumcision for Sexually Transmitted Infection Risk Reduction Globally. *Glob Health Sci Pract* 2022; **10** [PMID: [36041835](#) DOI: [10.9745/GHSP-D-21-00811](#)]
- 112 **Sharma SC**, Raison N, Khan S, Shabbir M, Dasgupta P, Ahmed K. Male circumcision for the prevention of human immunodeficiency virus (HIV) acquisition: a meta-analysis. *BJU Int* 2018; **121**: 515-526 [PMID: [29232046](#) DOI: [10.1111/bju.14102](#)]
- 113 **Nayan M**, Hamilton RJ, Juurlink DN, Austin PC, Jarvi KA. Circumcision and Risk of HIV among Males from Ontario, Canada. Reply. *J Urol* 2022; **207**: 479-480 [PMID: [34779238](#) DOI: [10.1097/JU.0000000000002338](#)]
- 114 **Frisch M**, Simonsen J. Non-therapeutic male circumcision in infancy or childhood and risk of human immunodeficiency virus and other sexually transmitted infections: national cohort study in Denmark. *Eur J Epidemiol* 2022; **37**: 251-259 [PMID: [34564796](#) DOI: [10.1007/s10654-021-00809-6](#)]
- 115 **Meyrowitsch DW**, Andersen LS, Lohse N, von Euler-Chelpin M, Hankins C. Re: Frisch & Simonson. Non-therapeutic male circumcision in infancy or childhood and risk of human immunodeficiency virus and other sexually transmitted infections: national cohort study in Denmark. *Eur J Epidemiol* 2022; **37**: 651-652 [PMID: [35723808](#) DOI: [10.1007/s10654-022-00872-7](#)]
- 116 **Grund JM**, Bryant TS, Jackson I, Curran K, Bock N, Toledo C, Taliano J, Zhou S, Del Campo JM, Yang L, Kivumbi A, Li P, Pals S, Davis SM. Association between male circumcision and women's biomedical health outcomes: a systematic review. *Lancet Glob Health* 2017; **5**: e1113-e1122 [PMID: [29025633](#) DOI: [10.1016/S2214-109X\(17\)30369-8](#)]
- 117 **Morris BJ**, Hankins CA, Banerjee J, Lumbers ER, Mindel A, Klausner JD, Krieger JN. Does Male Circumcision Reduce Women's Risk of Sexually Transmitted Infections, Cervical Cancer, and Associated Conditions? *Front Public Health* 2019; **7**: 4 [PMID: [30766863](#) DOI: [10.3389/fpubh.2019.00004](#)]
- 118 **Berer M**. Male circumcision for HIV prevention: perspectives on gender and sexuality. *Reprod Health Matters* 2007; **15**: 45-48 [PMID: [17512373](#) DOI: [10.1016/S0968-8080\(07\)29304-8](#)]
- 119 **Berer M**. Male circumcision for HIV prevention: what about protecting men's partners? *Reprod Health Matters* 2008; **16**: 171-175 [PMID: [19027633](#) DOI: [10.1016/S0968-8080\(08\)32418-5](#)]
- 120 **Wawer MJ**, Makumbi F, Kigozi G, Serwadda D, Watya S, Nalugoda F, Buwembo D, Ssemplijja V, Kiwanuka N, Moulton LH, Sewankambo NK, Reynolds SJ, Quinn TC, Opendi P, Iga B, Ridzon R, Laeyendecker O, Gray RH. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet* 2009; **374**: 229-237 [PMID: [19616720](#) DOI: [10.1016/S0140-6736\(09\)60998-3](#)]
- 121 **Ball PJ**. A survey of subjective foreskin sensation in 600 intact men. In: Bodily Integrity and the Politics of Circumcision, Denniston GC, Grassi-Varo-Gallo P, Hodges FM, Milos MF, Viviani F, Editors. 2006, Springer: New York. 177-188 [DOI: [10.1007/978-1-4020-4916-3_16](#)]
- 122 **Bailis S**, Moreton S, Krieger JN, Morris BJ. Tye & Sardi's psychological, psychosocial, and psychosexual aspects of penile circumcision. *Adv Sex Med* 2022; **12**: 65-83 [DOI: [10.4236/asm.2022.123006](#)]
- 123 **Sorrells ML**, Snyder JL, Reiss MD, Eden C, Milos MF, Wilcox N, Van Howe RS. Fine-touch pressure thresholds in the adult penis. *BJU Int* 2007; **99**: 864-869 [PMID: [17378847](#) DOI: [10.1111/j.1464-410X.2006.06685.x](#)]
- 124 **Waskett JH**, Morris BJ. Fine-touch pressure thresholds in the adult penis. *BJU Int* 2007; **99**: 1551-1552 [PMID: [17537227](#) DOI: [10.1111/j.1464-410X.2007.06970_6.x](#)]
- 125 **Bossio JA**, Pukall CF, Steele SS. Examining Penile Sensitivity in Neonatally Circumcised and Intact Men Using Quantitative Sensory Testing. *J Urol* 2016; **195**: 1848-1853 [PMID: [26724395](#) DOI: [10.1016/j.juro.2015.12.080](#)]
- 126 **Cox G**, Krieger JN, Morris BJ. Histological Correlates of Penile Sexual Sensation: Does Circumcision Make a Difference? *Sex Med* 2015; **3**: 76-85 [PMID: [26185672](#) DOI: [10.1002/sm2.67](#)]
- 127 **García-Mesa Y**, García-Piqueras J, Cobo R, Martín-Cruces J, Suazo I, García-Suárez O, Feito J, Vega JA. Sensory innervation of the human male prepuce: Meissner's corpuscles predominate. *J Anat* 2021; **239**: 892-902 [PMID: [34120333](#) DOI: [10.1111/joa.13481](#)]
- 128 **Tian Y**, Wazir R, Wang K. Male circumcision decreases penile sensitivity as measured in a large cohort. *BJU Int* 2013; **112**: E2-E3 [PMID: [23759015](#) DOI: [10.1111/bju.12234_4](#)]
- 129 **Young MR**, Odoyo-June E, Nordstrom SK, Irwin TE, Ongong'a DO, Ochomo B, Agot K, Bailey RC. Factors associated with uptake of infant male circumcision for HIV prevention in western Kenya. *Pediatrics* 2012; **130**: e175-e182 [PMID: [22711723](#) DOI: [10.1542/peds.2011-2290](#)]
- 130 **Gonzales FA**, Zea MC, Reisen CA, Bianchi FT, Betancourt Rodriguez CF, Aguilar Pardo M, Poppen PJ. Popular perceptions of circumcision among Colombian men who have sex with men. *Cult Health Sex* 2012; **14**: 991-1005 [PMID: [22917475](#) DOI: [10.1080/13691058.2012.712719](#)]
- 131 **Plotkin M**, Castor D, Mziray H, Küver J, Mupya E, Luvanda PJ, Hellar A, Curran K, Lukobo-Durell M, Ashengo TA, Mahler H. "Man, what took you so long?" Social and individual factors affecting adult attendance at voluntary medical male circumcision services in Tanzania. *Glob Health Sci Pract* 2013; **1**: 108-116 [PMID: [25276521](#) DOI: [10.9745/GHSP-D-12-00037](#)]
- 132 **Feldblum PJ**, Odoyo-June E, Obiero W, Bailey RC, Combes S, Hart C, Jou Lai J, Fischer S, Cherutich P. Safety, effectiveness and acceptability of the PrePex device for adult male circumcision in Kenya. *PLoS One* 2014; **9**: e95357 [PMID: [24788898](#) DOI: [10.1371/journal.pone.0095357](#)]
- 133 **Sokal DC**, Li PS, Zulu R, Awori QD, Agot K, Simba RO, Combes S, Lee RK, Hart C, Lai JJ, Zyambo Z, Goldstein M, Feldblum PJ, Barone MA. Field study of adult male circumcision using the ShangRing in routine clinical settings in Kenya and Zambia. *J Acquir Immune Defic Syndr* 2014; **67**: 430-437 [PMID: [25162816](#) DOI: [10.1097/QAI.0000000000000321](#)]
- 134 **Mavhu W**, Hatzold K, Ncube G, Fernando S, Mangenah C, Chatora K, Mugurungi O, Ticklay I, Cowan FM. Perspectives of Parents and Health Care Workers on Early Infant Male Circumcision Conducted Using Devices: Qualitative Findings From Harare, Zimbabwe. *Glob Health Sci Pract* 2016; **4** Suppl 1: S55-S67 [PMID: [27413084](#) DOI: [10.9745/GHSP-D-15-00200](#)]
- 135 **Wirth KE**, Semo BW, Ntsuape C, Ramabu NM, Otlhomile B, Plank RM, Barnhart S, Ledikwe JH. Triggering the decision to undergo medical male circumcision: a qualitative study of adult men in Botswana. *AIDS Care* 2016; **28**: 1007-1012 [PMID: [26754167](#) DOI: [10.1080/09540121.2015.1133797](#)]
- 136 **Tye MC**, Sardi LM. Psychological, psychosocial, and psychosexual aspects of penile circumcision. *Int J Impot Res* 2023; **35**: 242-248 [PMID: [35347302](#) DOI: [10.1038/s41443-022-00553-9](#)]
- 137 **Claeys W**, Bronselaer G, Lumen N, Hoebeke P, Spinoit AF. The self-assessment of genital anatomy, sexual function, and genital sensation (SAGASF-M) questionnaire in a Belgian Dutch-speaking male population: A validating study. *Andrology* 2023; **11**: 489-500 [PMID: [35347302](#) DOI: [10.1038/s41443-022-00553-9](#)]

- 36426587 DOI: [10.1111/andr.13348](https://doi.org/10.1111/andr.13348)]
- 138 **Fox M**, Thomson M, Warburton J. Non-therapeutic male genital cutting and harm: Law, policy and evidence from U.K. hospitals. *Bioethics* 2019; **33**: 467-474 [PMID: [30511772](https://pubmed.ncbi.nlm.nih.gov/30511772/) DOI: [10.1111/bioe.12542](https://doi.org/10.1111/bioe.12542)]
 - 139 **Royal Courts of Justice**. Sir James Munby. In the matter of B and G (Children) (No 2), Neutral Citation number: [2015] EWFC 3, Case Number LJ13C00295, 14 January 2015. 2015. (accessed Dec 27, 2022). Available from: https://www.judiciary.gov.uk/wp-content/uploads/2015/01/BandG_2_.pdf
 - 140 **Mcalister RD**. A Dangerous muddying of the waters? The 'significant harm' of RE B and G (Children) (Care Proceedings)[2015] EWFC 3. *Med Law Rev* 2016; **24**: 259-267 [PMID: [27273918](https://pubmed.ncbi.nlm.nih.gov/27273918/) DOI: [10.1093/medlaw/fwv039](https://doi.org/10.1093/medlaw/fwv039)]
 - 141 **Mcdonald CF**. Circumcision of the female. *GP* 1958; **18**: 98-99 [PMID: [13574328](https://pubmed.ncbi.nlm.nih.gov/13574328/)]
 - 142 **Davis SM**, Baker H, Gross JM, Leslie SL, Chasokela CMZ, Samuelson J, Toledo C. The Role of Nurses and Midwives in Expanding and Sustaining Voluntary Medical Male Circumcision Services for HIV Prevention: A Systematic and Policy Review. *J Assoc Nurses AIDS Care* 2021; **32**: 3-28 [PMID: [33298685](https://pubmed.ncbi.nlm.nih.gov/33298685/) DOI: [10.1097/JNC.0000000000000222](https://doi.org/10.1097/JNC.0000000000000222)]
 - 143 **Giramonti KM**, Kogan BA. Pediatric penile surgery by a nurse practitioner in the operating room. *J Pediatr Urol* 2018; **14**: 573-576 [PMID: [30185376](https://pubmed.ncbi.nlm.nih.gov/30185376/) DOI: [10.1016/j.jpuro.2018.07.027](https://doi.org/10.1016/j.jpuro.2018.07.027)]
 - 144 **Onywerea H**, Williamson AL, Ponomarenko J, Meiring TL. The Penile Microbiota in Uncircumcised and Circumcised Men: Relationships With HIV and Human Papillomavirus Infections and Cervicovaginal Microbiota. *Front Med (Lausanne)* 2020; **7**: 383 [PMID: [32850898](https://pubmed.ncbi.nlm.nih.gov/32850898/) DOI: [10.3389/fmed.2020.00383](https://doi.org/10.3389/fmed.2020.00383)]
 - 145 **Colón-Sánchez K**, Middleton T, Ellsworth P. Experience and outcomes for PAs in a neonatal circumcision clinic. *JAAPA* 2020; **33**: 40-43 [PMID: [32976234](https://pubmed.ncbi.nlm.nih.gov/32976234/) DOI: [10.1097/01.JAA.0000697252.63695.3f](https://doi.org/10.1097/01.JAA.0000697252.63695.3f)]
 - 146 **Uimonen M**, Kuitunen I, Seikkula H, Mattila VM, Ponkilainen V. Healthcare lockdown resulted in a treatment backlog in elective urological surgery during COVID-19. *BJU Int* 2021; **128**: 33-35 [PMID: [33893701](https://pubmed.ncbi.nlm.nih.gov/33893701/) DOI: [10.1111/bju.15433](https://doi.org/10.1111/bju.15433)]
 - 147 **High Court of Australia**. Department of Health and Community Services v JWB and SMB (Marion's Case). [1992] HCA 15; 175 CLR 218 96, May 1992. (accessed Dec 28, 2021). Available from: http://www.austlii.edu.au/cgi-bin/sinodisp/au/cases/cth/high_ct/175clr218.html?stem=0&synonyms=0&query=title
 - 148 **Code for Crown Prosecutors**. Offences against the Person, incorporating the Charging Standard. 2022. (accessed Aug 28, 2023). Available from: <https://www.cps.gov.uk/legal-guidance/offences-against-person-incorporating-charging-standard>
 - 149 **Kupferschmid C**, Barauskas V, Bjarnason R, Boddy SA, Czauderna P, Fasching G, Wijnen R. Comment submitted to the CDC in response to Recommendations for Providers Counseling Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, STIs, and Other Health Outcomes". Atlanta, GA: U.S. Centers for Disease Control and Prevention. 2015
 - 150 **Earp BD**. Do the Benefits of Male Circumcision Outweigh the Risks? A Critique of the Proposed CDC Guidelines. *Front Pediatr* 2015; **3**: 18 [PMID: [25853108](https://pubmed.ncbi.nlm.nih.gov/25853108/) DOI: [10.3389/fped.2015.00018](https://doi.org/10.3389/fped.2015.00018)]
 - 151 **Morris BJ**. Commentary: Do the Benefits of Male Circumcision Outweigh the Risks? A Critique of the Proposed CDC Guidelines. *Front Pediatr* 2015; **3**: 88 [PMID: [26528459](https://pubmed.ncbi.nlm.nih.gov/26528459/) DOI: [10.3389/fped.2015.00088](https://doi.org/10.3389/fped.2015.00088)]
 - 152 **Centers for Disease Control and Prevention**. [Docket No. CDC-2014-0012-0002] Recommendations for Providers Counseling Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, STIs, and Other Health Outcomes. 2014. (accessed Dec 29, 2022). Available from: <http://www.regulations.gov/#!documentDetail;D=CDC-2014-0012-0002>
 - 153 **Centers for Disease Control and Prevention**. Summary of Public Comments and CDC Responses to Public Comments for Information for Providers Counseling Male patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, Sexually Transmitted Infections, and Other Health Outcomes. 2018. (accessed Dec 29, 2022). Available from: <https://www.cdc.gov/hiv/pdf/risk/MC-HISA-Public-Comments-and-Responses.pdf>
 - 154 **Deacon M**, Muir G. What is the medical evidence on non-therapeutic child circumcision? *Int J Impot Res* 2023; **35**: 256-263 [PMID: [34997197](https://pubmed.ncbi.nlm.nih.gov/34997197/) DOI: [10.1038/s41443-021-00502-y](https://doi.org/10.1038/s41443-021-00502-y)]
 - 155 **Morris BJ**, Moreton S, Krieger JN, Klausner JD, Cox G. Re: The medical evidence on non-therapeutic circumcision of infants and boys-setting the record straight. *Int J Impot Res* 2023; **35**: 264-266 [PMID: [35790855](https://pubmed.ncbi.nlm.nih.gov/35790855/) DOI: [10.1038/s41443-022-00579-z](https://doi.org/10.1038/s41443-022-00579-z)]
 - 156 **Deacon M**, Muir G. Reply to Morris *et al.* re: 'The medical evidence on non-therapeutic circumcision of infants and boys-setting the record straight'. *Int J Impot Res* 2023; **35**: 267-268 [PMID: [36261537](https://pubmed.ncbi.nlm.nih.gov/36261537/) DOI: [10.1038/s41443-022-00631-y](https://doi.org/10.1038/s41443-022-00631-y)]
 - 157 **Morris BJ**, Krieger JN. Does Circumcision Increase Meatal Stenosis Risk?-A Systematic Review and Meta-analysis. *Urology* 2017; **110**: 16-26 [PMID: [28826876](https://pubmed.ncbi.nlm.nih.gov/28826876/) DOI: [10.1016/j.urology.2017.07.027](https://doi.org/10.1016/j.urology.2017.07.027)]
 - 158 **Schoen EJ**. Meatal stenosis following neonatal circumcision. *Clin Pediatr (Phila)* 2007; **46**: 86 [PMID: [17164518](https://pubmed.ncbi.nlm.nih.gov/17164518/) DOI: [10.1177/0009922806289836](https://doi.org/10.1177/0009922806289836)]
 - 159 **Warner L**, Ghanem KG, Newman DR, Macaluso M, Sullivan PS, Erbeling EJ. Male circumcision and risk of HIV infection among heterosexual African American men attending Baltimore sexually transmitted disease clinics. *J Infect Dis* 2009; **199**: 59-65 [PMID: [19086815](https://pubmed.ncbi.nlm.nih.gov/19086815/) DOI: [10.1086/595569](https://doi.org/10.1086/595569)]
 - 160 **Sansom SL**, Prabhu VS, Hutchinson AB, An Q, Hall HI, Shrestha RK, Lasry A, Taylor AW. Cost-effectiveness of newborn circumcision in reducing lifetime HIV risk among U.S. males. *PLoS One* 2010; **5**: e8723 [PMID: [20090910](https://pubmed.ncbi.nlm.nih.gov/20090910/) DOI: [10.1371/journal.pone.0008723](https://doi.org/10.1371/journal.pone.0008723)]
 - 161 **Wysong CS**, Kongnyuy EJ, Shey M, Muula AS, Navti OB, Akl EA, Lo YR. Male circumcision for prevention of homosexual acquisition of HIV in men. *Cochrane Database Syst Rev* 2011; CD007496 [PMID: [21678366](https://pubmed.ncbi.nlm.nih.gov/21678366/) DOI: [10.1002/14651858.CD007496.pub2](https://doi.org/10.1002/14651858.CD007496.pub2)]
 - 162 **Templeton DJ**, Jin F, Mao L, Prestage GP, Donovan B, Imrie J, Kippax S, Kaldor JM, Grulich AE. Circumcision and risk of HIV infection in Australian homosexual men. *AIDS* 2009; **23**: 2347-2351 [PMID: [19752714](https://pubmed.ncbi.nlm.nih.gov/19752714/) DOI: [10.1097/QAD.0b013e32833202b8](https://doi.org/10.1097/QAD.0b013e32833202b8)]
 - 163 **Sutton G**, Fryer S, Rimmer G, Melling CV, Corbett HJ. Referrals from primary care with foreskin symptoms: Room for improvement. *J Pediatr Surg* 2023; **58**: 266-269 [PMID: [36428185](https://pubmed.ncbi.nlm.nih.gov/36428185/) DOI: [10.1016/j.jpedsurg.2022.10.046](https://doi.org/10.1016/j.jpedsurg.2022.10.046)]
 - 164 **Cox G**, Morris BJ. Letter to Editor regarding: Referrals from primary care with foreskin symptoms: Is there really room for improvement? *J Pediatr Surg* 2023; **58**: 1018 [PMID: [36658076](https://pubmed.ncbi.nlm.nih.gov/36658076/) DOI: [10.1016/j.jpedsurg.2022.12.012](https://doi.org/10.1016/j.jpedsurg.2022.12.012)]
 - 165 **Corbett HJ**, Melling CV, Kenny SE. Response to Letter to the Editor regarding: Referrals from Primary Care with Foreskin Symptoms: Is there Really Room for Improvement? *J Pediatr Surg* 2023; **58**: 1220 [PMID: [36898879](https://pubmed.ncbi.nlm.nih.gov/36898879/) DOI: [10.1016/j.jpedsurg.2023.02.001](https://doi.org/10.1016/j.jpedsurg.2023.02.001)]
 - 166 **British Association of Paediatric Urologists**. Management of foreskin conditions. 2006. (accessed 11 Mar 2023). Available from: <http://www.baps.org.uk/content/uploads/2017/03/MANAGEMENT-OF-FORESKINCONDITIONS.pdf>
 - 167 **Nguyen ATM**, Holland AJA. Balanitis xerotica obliterans: an update for clinicians. *Eur J Pediatr* 2020; **179**: 9-16 [PMID: [31760506](https://pubmed.ncbi.nlm.nih.gov/31760506/) DOI: [10.1007/s00131-020-02400-0](https://doi.org/10.1007/s00131-020-02400-0)]

- 10.1007/s00431-019-03516-3]
- 168 **4-skin Health.** Information for patients, parents and healthcare professionals. 2023. (accessed 11 Mar 2023). Available from: <https://4skin-health.alderhey.nhs.uk/>
- 169 **Kacker S, Frick KD, Gaydos CA, Tobian AA.** Costs and effectiveness of neonatal male circumcision. *Arch Pediatr Adolesc Med* 2012; **166**: 910-918 [PMID: 22911349 DOI: 10.1001/archpediatrics.2012.1440]
- 170 **Morris BJ.** Scientific evidence dispels false claims about circumcision. *Can Urol Assoc J* 2014; **8**: 396-397 [PMID: 25553151 DOI: 10.5489/cuaj.2490]
- 171 **Darby R.** Risks, benefits, complications and harms: neglected factors in the current debate on non-therapeutic circumcision. *Kennedy Inst Ethics J* 2015; **25**: 1-34 [PMID: 25843118 DOI: 10.1353/ken.2015.0004]
- 172 **Svoboda JS, Adler PW, Van Howe RS.** Circumcision Is Unethical and Unlawful. *J Law Med Ethics* 2016; **44**: 263-282 [PMID: 27338602 DOI: 10.1177/1073110516654120]
- 173 **Adler PW.** The draft CDC circumcision recommendations: Medical, ethical, legal, and procedural concerns. *Int J Child Rights* 2016; **24**: 237-262 [DOI: 10.1163/15718182-02402001]
- 174 **Rivin BE, Diekema DE, Mastroianni AC, Krieger JN, Klausner JD, Morris BJ.** Critical evaluation of Adler's challenge to the CDC's male circumcision recommendations. *Int J Child Rights* 2016; **24**: 265-303 [DOI: 10.1163/15718182-02402004]
- 175 **Frisch M, Earp BD.** Circumcision of male infants and children as a public health measure in developed countries: A critical assessment of recent evidence. *Glob Public Health* 2018; **13**: 626-641 [PMID: 27194404 DOI: 10.1080/17441692.2016.1184292]
- 176 **Morris BJ, Krieger JN, Klausner JD.** CDC's Male Circumcision Recommendations Represent a Key Public Health Measure. *Glob Health Sci Pract* 2017; **5**: 15-27 [PMID: 28351877 DOI: 10.9745/GHSP-D-16-00390]
- 177 **Van Howe RS.** A CDC-requested, evidence-based critique of the Centers for Disease Control and Prevention 2014 draft on male circumcision: How ideology and selective science lead to superficial, culturally-biased recommendations by the CDC. 2015. (accessed Dec 22, 2022). Available from: http://www.academia.edu/10553782/A_CDC-requested_Evidence-based_Critique_of_the_Centers_for_Disease_Control_and_Prevention_2014_Draft_on_Male_Circumcision_How_Ideology_and_Selective_Science_Lead_to_Superficial_Culturally-biased_Recommendations_by_the_CDC
- 178 **Centers for Disease Control and Prevention.** Peer Review Comments and CDC Responses for Information for Providers Counseling Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV infection, Sexually Transmitted Infections, and other Health Outcomes* and Background, Methods, and Synthesis of Scientific Information Used to Inform "Information for Providers to Share with Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, Sexually Transmitted Infections, and other Health Outcomes" 2018. (accessed Dec 29, 2022). Available from: <https://www.cdc.gov/hiv/pdf/risk/MC-HISA-Round-1-Peer-Review-Comments-and-Responses.pdf>
- 179 **Robinson JL, Jefferies A, Lacaze T.** Letter to the Editor - Re: Canadian Pediatrics Society position statement on newborn circumcision: a risk-benefit analysis revisited. *Can J Urol* 2017; **24**: 8684-8687 [PMID: 28263139]
- 180 **Morris BJ, Klausner JD, Krieger JN, Willcox BJ, Crouse PD, Pollock N.** Reply by Authors - Re: Canadian Pediatrics Society position statement on newborn circumcision: a risk-benefit analysis revisited. *Can J Urol* 2017; **24**: 8687-8692 [PMID: 28263140]
- 181 **Royal Australasian College of Physicians, Paediatrics & Child Health Division.** Circumcision of infant males. 2010. (accessed Dec 23, 2022). Available from: <http://www.racp.edu.au/index.cfm?objectid=65118B16-F145-8B74-236C86100E4E3E8E>
- 182 **Morris BJ, Wodak AD, Mindel A, Schrieber L, Duggan KA, Dilley A, Willcourt RJ, Lowy M, Cooper DA.** The 2010 Royal Australasian College of Physicians' policy statement 'Circumcision of infant males' is not evidence based. *Intern Med J* 2012; **42**: 822-828 [PMID: 22805686 DOI: 10.1111/j.1445-5994.2012.02823.x]
- 183 **Forbes D.** Evidence-based policy: circumcision of infant males. *Intern Med J* 2012; **42**: 1278-9 [PMID: 23157534 DOI: 10.1111/j.1445-5994.2012.02913.x]
- 184 **Morris BJ, Wodak AD, Mindel A, Schrieber L, Duggan KA, Dilly A, Willcourt RJ, Cooper DA.** Reply to Forbes: Evidence-based policy: circumcision of infant males. *Intern Med J* 2012; 1279-1280
- 185 **Jansen M.** Routine circumcision of infant boys: It's time to make progress through the common ground. *J Paediatr Child Health* 2016; **52**: 477-479 [PMID: 27329900 DOI: 10.1111/jpc.13224]
- 186 **Wodak AD, Ziegler JB, Morris BJ.** Infant circumcision: Evidence, policy, and practice. *J Paediatr Child Health* 2017; **53**: 93 [PMID: 28070947 DOI: 10.1111/jpc.13420]

Prediabetes in children and adolescents: An updated review

Hak Yung Ng, Louis Tsz Wang Chan

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Gaman MA, Romania; Pop TL, Romania

Received: July 25, 2023

Peer-review started: July 25, 2023

First decision: August 31, 2023

Revised: October 5, 2023

Accepted: October 16, 2023

Article in press: October 16, 2023

Published online: December 9, 2023



Hak Yung Ng, Louis Tsz Wang Chan, Department of Paediatrics and Adolescent Medicine, Tseung Kwan O Hospital, Hong Kong, China

Corresponding author: Hak Yung Ng, MBChB, DCH, PgDipPD, MSc, FHKCPaed, FHKAM, FRCP, FRCPC, Department of Paediatrics and Adolescent Medicine, Tseung Kwan O Hospital, No. 2 Po Ning Lane, Hang Hau, Tseung Kwan O, Hong Kong, China. nghypatrick@gmail.com

Abstract

Prediabetes, the precursor of type 2 diabetes mellitus, is an intermediate stage between normal glucose homeostasis and overt diabetes. This asymptomatic metabolic state is increasingly prevalent in pediatric population and is very difficult to detect without appropriate screening. Studies have shown that a certain proportion of children with prediabetes will develop diabetes in a few years. Even more alarming is the evidence that youth-onset diabetes has a more aggressive clinical course with progressive beta-cell decline and accelerated end-organ damage. Despite its importance, several aspects involving prediabetes in childhood are disputed or unknown. This review presents the latest insights into this challenging entity and outlines a simplified screening approach to aid clinical practice. In summary, childhood prediabetes is an important clinical condition indicating the need for proper screening and timely intervention.

Key Words: Prediabetes; Screening; Diagnosis; Management; Obesity; Type 2 diabetes mellitus; Children

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Prediabetes, an intermediate stage before type 2 diabetes mellitus, has increased in parallel with the growing burden of pediatric obesity worldwide. However, child health practitioners are struggling with the definition, significance, diagnostic approach, trajectories, implications, outcomes, and management of prediabetes. This review aims to provide pediatricians and primary care providers with an updated overview of this important, yet controversial, condition.

Citation: Ng HY, Chan LTW. Prediabetes in children and adolescents: An updated review. *World J Clin Pediatr* 2023; 12(5): 263-272

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/263.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.263>

INTRODUCTION

Childhood obesity has long been a public health challenge worldwide and has emerged as one of the most significant concerns. It poses an enormous health burden. The prevalence of childhood obesity has increased exponentially in recent years. This is further exacerbated by the novel coronavirus disease 2019 (COVID-19) pandemic, which negatively impacted the lifestyle and nutritional habits of children[1-3].

Prediabetes is a prominent clinical condition characterized by asymptomatic prodromal phase before the onset of diabetes mellitus. In adult population, prediabetes is considered a precursor to type 2 diabetes mellitus (T2DM)[4]. It is therefore tempting to infer a dramatic rise in prediabetes among pediatric population, given the increase in the prevalence of both obesity and T2DM in childhood[5]. A recent systematic review and meta-analysis showed a rapid increase in the prevalence of prediabetes in children globally. The pooled prevalence of 48 community-based studies was up to 8.84%[6]. Notably, prediabetes in children is associated with youth-onset T2DM, which is regarded as a more aggressive entity with increased cardiovascular and metabolic risk[7,8]. Significant damage to beta-cells may also occur prior to the development of dysglycemia[9]. The various adverse health effects in adulthood can be traced to prediabetes in childhood[10]. Fortunately, the occurrence and progression of dysglycemia in T2DM is more insidious compared with type 1 diabetes mellitus (T1DM) allowing more time for prevention and intervention.

Early diagnosis and management *via* screening represents a unique opportunity to intervene and is both logical and appealing. However, our current understanding of childhood prediabetes is mainly based on studies involving adult population and is poorly characterized[10]. The diagnosis and management of this important clinical condition is still imperfect, and is often disputed and debated. Thus, the need for a literature review to identify the latest evidence, insight and knowledge gaps cannot be overstated.

With this background, a comprehensive literature search was conducted in an effort to provide an overview of current understanding regarding prediabetes. It covers the latest epidemiology, diagnostic means, related controversies, and the need for future research. The span of our review is limited to articles published within the last 10 years in an effort to provide pediatricians and primary care providers with recent updates of this complex yet important condition.

LITERATURE SEARCH

For this narrative review, a literature search was conducted using MEDLINE, EMBASE, RCA, and Google Scholar databases. Search terms included “prediabetes”, “hyperglycemia”, “dysglycemia”, “abnormal glucose homeostasis”, “children”, and “adolescents”. Articles published between January 2013 to March 2023 were considered with the exception of landmark studies or articles. Additional publications were also retrieved by snowballing.

Specifically, articles reporting prediabetic children younger than 18 years old were reviewed, with full-text available in English. Exclusion criteria included T1DM (autoimmune β -cell destruction), gestational diabetes mellitus (GDM), and other specific types of diabetes, such as monogenic diabetes syndromes, pancreatogenic diabetes, and drug-induced diabetes[11].

CHILDHOOD OBESITY

Childhood obesity has evolved into a major public health crisis both in developed and developing countries[12-14]. Globally, studies showed a high level of obesity and a rising trend particularly in low-and middle-income countries[15]. The United Nations Children’s Fund estimated that 380 million children below 19 years of age were overweight, with the rate increasing to 18% in 2018 from 10% in 2000 among 5- to 19-year-old individuals[16].

The situation is further complicated by the unprecedented public health challenge due to coronavirus disease 2019 (COVID-19) pandemic. Response to global COVID-19 pandemic by decision-makers had a further impact on the obesity landscape as more than 80% of children worldwide experienced school closures, movement restrictions, physical inactivity, and drastic changes to their way of life[13,17,18]. These changes in lifestyle, daily routines, and nutritional habits contributed to weight gain[3]. Consequently, a significant rise in childhood obesity is imminent and inevitable[19, 20].

Recently, two systemic reviews and meta-analyses demonstrated a significant increase in weight gain, body mass index (BMI), and prevalence of obesity in children during the COVID-19 pandemic[21,22]. In another study evaluating the net impact of the COVID-19 Lockdown, Dietz[23] reported that the changes in obesity prevalence among children aged below 12 years were 28- to 37-fold higher than the annual expected changes observed in the National Health and Nutrition Examination Survey of United States. Particularly, the highest weight gain observed among youth with severe obesity was a cause for serious concern[24]. As the obesity rates and levels continue to rise in childhood, the prevalence of prediabetes and diabetes in children also increases rapidly with alarming trends worldwide[6].

TYPE 2 DIABETES MELLITUS

In brief, the pathophysiology of T2DM involves insulin resistance (IR) accompanied by insufficient insulin release[8,9,25]. Clinical signs suggesting insulin resistance, such as acanthosis nigricans, are risk factors indicated in various guidelines. Acanthosis nigricans is closely associated with insulin resistance and provides a prominent visual cue that can aid in early intervention[25-28]. Although the underlying risk for IR is not completely understood, genetic and environmental factors are largely implicated[8,25].

Youth-onset T2DM is a more aggressive disease with rapid deterioration of beta-cell function and poor response to treatment. Eventually, it progresses to complications more rapidly and earlier than in adult-onset T2DM, impacting the most productive years of life[29-33]. A substantial number of patients with youth-onset T2DM exhibit micro-vascular and macro-vascular complications in the early stages of the disease, suggesting prior ongoing vascular damage[34]. In an observational study of 500 cases of youth-onset T2DM conducted over 10 years, the cumulative incidence of hypertension, dyslipidemia, retinal disease, and diabetic kidney disease recorded exceeded 50%. Among these participants who were diagnosed with diabetes for 13.3 years (mean), 28.4% carried more than two diabetes complications at a mean age of 26.4 years[35]. At the time of first diagnosis, youth-onset T2DM often presents with comorbidities, including but not limited to hypertension, dyslipidemia, and hepatosteatorosis[36]. Given this grim threat, early identification of youth who are at-risk is imperative.

PREDIABETES

Prediabetes is a condition that is characterized by dysregulated glucose homeostasis[25]. Advocating prediabetes as a distinct pathological condition is controversial despite its recent inclusion in the ICD-10 coding[37,38]. While some authors caution against medicalization of prediabetes[39,40], others believe that it is essential and helpful to encourage positive lifestyle changes[41,42]. Emerging evidence suggests that individuals with prediabetes have pathophysiological changes in organs that are traditionally affected by diabetes, further validating it as a distinct disease entity[37].

Prevalence

For decades, the global prevalence of prediabetes in children was largely unknown. A recent systematic review and meta-analysis of 6630296 participants from 48 community-based pediatric studies found that the pooled prevalence of childhood prediabetes was 8.84% [95%CI (6.74, 10.95)] using a random-effects model. However, these data should be interpreted with caution given the heterogeneity of included studies, potential publication bias, and limited comparability based on different definitions and study designs[6]. Generally, the prevalence of prediabetes is substantially higher in the cohort targeting children with obesity. In an Italian study, the prevalence was 21.1%[43]. Our group demonstrated a prevalence of 15.4% in 879 Chinese pediatric patients from Hong Kong[44]. Another study conducted in German-speaking countries reported a prevalence of 11.9%[45]. Prevalence rate increases with age or deteriorating weight status [43,44].

Natural history

Despite the large number of studies involving T2DM in children, little is known about the natural history of prediabetes, which is an intermediate stage along the continuum of normal glucose regulation to overt diabetes[10,46-48]. Using data from a cohort of White Canadian children with a parental history of obesity, Harnois-Leblanc *et al*[49] reported that 73% of children with prediabetes at baseline (8-10 years of age) reverted to normoglycemia by the end of adolescence. In contrast, only 53% of children with prediabetes detected at 10-12 years of age reverted to normoglycemia at 15-17 years of age. However, it should be noted that their complete cohort (with complete 7-year data covering the three evaluations) consisted of 350 children, including those with normal weight. Hence, the prevalence of dysglycemia was only 10% at baseline and first evaluation. Indeed, what is more alarming is that one in five children (21%) in their cohort, recruited based on parental history of obesity, developed prediabetes or diabetes over 7 years.

In another multiethnic, prospective observational study carried out in the United States, 526 adolescents with obesity completed two evaluations with a median follow-up of 2.9 years. Galderisi, Giannini[50] reported that 65% adolescents with dysglycemia at baseline ($n = 162$) reverted to normal glycemia. Notably, the remaining 27% showed persistent dysglycemia and 8% progressed to T2DM. One of the strengths of their study was confirmation of T2DM with a second oral glucose tolerance test to eliminate any reproducibility issue. Although it was an observational study, the standard of care during follow-up included dietary assessment and advice every 6 mo, suggestion to limit sugary drinks and screen time, and promotion of physically active lifestyle.

A recent search of PubMed/ MEDLINE and the Cochrane Library for articles published through May 3, 2021 by the United States Preventive Services Task Force (USPSTF) revealed few studies suggesting that 22% to 52% children and adolescents with prediabetes returned to normal glycemia without intervention over 6 mo to 2 years[51].

Understanding the natural history of disease is critical to recognizing and responding to preventive efforts. It offers a framework to conceptualize the illness and preventive strategies. In a strict sense, the natural history of a disease refers to the natural progression over time without any treatment or intervention. In modern medicine, this is constructed from multiple sources to form a composite clinical picture of underlying disease dynamics[41].

Outlining the real natural progression of prediabetes in children is of great interest to clinicians. However, children with prediabetes are mostly asymptomatic and cannot usually be identified. If they are screened due to obesity, health care providers are obligated to provide appropriate advice regarding dietary and lifestyle intervention. Even in a research

setting, children and family are not blinded to their blood test results because it is not ethical to do so. Under such circumstances, they may exert substantial efforts to prevent further progression[34]. Simply informing participants of their abnormal results, even without intervention, can improve their dysglycemia[52]. This argument is supported by a retrospective cohort study in United States. Using data from the Children's Hospital of Philadelphia Primary Care Network, Vajravelu *et al*[53] found a stable BMI Z-score trajectory in all adolescents screened for prediabetes comparing with unscreened individuals. The improvement was even more striking among youth testing positive for prediabetes, suggesting that screening may have an important role in motivating the youth to take appropriate measures to diminish the risk. Indeed, screening and education about prediabetes can improve follow-up rates[54]. Therefore, caution is necessary when interpreting and extrapolating clinical research findings. Also, participants included in the analysis of the "natural course" of disease are those attended follow-up, and with complete data available. It is well known that a large number of children and adolescents are lost to follow-up, even after they are diagnosed with T2DM[36,55,56]. It is inaccurate or misleading to assume that more than half of these dysglycemic children will revert to normal glycemia eventually.

Screening of prediabetes, strategies and limitations

Early detection and timely intervention of dysglycemia can delay or prevent microvascular complications in adults[48]. While screening for prediabetes and T2DM in adults is considered cost-effective, it is highly complicated in children[57-60]. The latest USPSTF concluded that evidence to recommend screening for prediabetes in asymptomatic children and adolescents is unavailable[61]. Explicitly, their position is neither for nor against screening prediabetes. Pediatricians and health care providers should continue to use their clinical judgement in deciding whether or not screening is warranted [61,62].

Going back to year 2000, a consensus group of expert representatives from American Academy of Pediatrics (AAP) and the American Diabetes Association (ADA) first recommended screening of asymptomatic youth carrying at least two risk factors[63,64]. In view of persistent surge in prevalence and incidence of prediabetes, the ADA expanded its recommendation to include youth with only one risk factor in 2018[65]. In the latest publication, ADA continuously recommends screening of high-risk children and adolescents. Screening should be carefully considered in children and youth with overweight or obesity who have at least one of the following risk factors: maternal diabetes or GDM; family history of T2DM; vulnerable race or ethnicity; and signs or conditions associated with insulin resistance. Screening should be started when they turn 10 years of age, or after the onset of puberty, whichever occurs first. Testing should be repeated in cases of deteriorating BMI or risk factor profiles, or at a minimum of 3-year intervals[11]. Currently, the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends risk-based screening, which is largely similar to the one recommended by ADA[48,66]. By adopting such strategy, it is hoped that early diagnosis can enable early interventions to slow down or prevent disease progression[57,67,68]. In a recent study, the prevalence of dysglycaemia was found to be 23% with individuals carrying only one risk factor referred for assessment in an academic center, suggesting that a single risk factor is sufficient to warrant screening[69].

Despite most authorities proposing risk-based screening, the optimal or the best strategy remains a matter of debate[43, 62]. According to the latest ADA and ISPAD recommendations, fasting plasma glucose (FPG), 2-h plasma glucose level measured during oral glucose tolerance test (OGTT), and hemoglobin A1c (HbA1c) can be used to diagnose prediabetes and diabetes in childhood and adolescence[48,70]. Notably, studies reveal an overlap among the subgroups using different diagnostic tests and criteria. The three different tests cannot identify consistently the same group of individuals [43,71]. Indeed, it is now believed that each individual test may analyze different components of glucose metabolism[7, 72]. This may complicate the understanding and comparison of this condition in different clinical studies[73]. The prevalence of prediabetes will differ largely if disparate test combinations are used[6,62], and the discussion is further complicated by the different impaired fasting glucose cutoffs adopted by international organizations[73-76]. Additionally, the cutoff thresholds used are derived and adopted from adult studies instead of longitudinal prospective studies involving children and adolescents. The suitability of these criteria will remain a matter of debate for years to come[48, 62].

In accordance with ADA, prediabetes should be viewed as risk factor for developing diabetes and cardiovascular disease. The risk starts below the lower end of the reference range and increases largely toward the higher end of the range, and is continuous[75]. Despite its reversibility in some children, prediabetes suggests that the beta-cell function is at its maximal capacity, predisposing to future failure[77].

HbA1c: According to ADA, an HbA1c value of 5.7%-6.4% has been used to define prediabetes in children[75]. It is an indicator of the average blood glucose concentration over the past three months. This test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program to minimize bias[78]. It has the advantages of being stable at room temperature, without the need for fasting, and is associated with minimal day-to-day variations. Nonetheless, ethnic, racial, and age differences in levels of HbA1c exist. Medical conditions, such as anemia, hemoglobinopathies, malaria, and post transfusion, which affect red cell turnovers can affect its validity. Various medications and supplements may also interfere with the assay and alter the value[72,79,80]. It is also noteworthy that the use of HbA1c in children remains controversial[79,81]. The recommendation in adult population is based on epidemiological studies[75]. Some pediatric studies using adult cutoff underestimated the prevalence of diabetes and prediabetes [79,82]. In a study involving Caribbean and African-American children with obesity, investigators found that HbA1c alone, using adult cutoff value, is not a good differentiator of dysglycemia[83]. In recent studies from different countries and jurisdictions, various HbA1c values had been suggested[81,82,84]. This is not surprising as HbA1c is known to depend on age, race, and ethnicity. Further, in a large cohort of ethnically and racially diverse youth ($n = 4603$) who have normal weight and are otherwise healthy, researchers found that 2.2% have HbA1c values exceeding ADA cutoff, which

prompted clinicians to apply and adopt the cutoff value cautiously[48,85]. In sum, the optimal operational HbA1c cutoff in children remains uncertain and requires further study.

FPG and OGTT: FPG has been included as a screening test for dysglycemia in a majority of guidelines regarding management of youth with obesity[86]. It requires a single blood test and is easily available in all laboratories. However, it requires fasting and the result is affected by illness, stress, and time of the day[62,87]. Besides, it is not capable of detecting impaired glucose tolerance (IGT), which is common in children with prediabetes.

OGTT has been considered the “gold standard” for many decades although it has disadvantages of fasting requirement, complicated testing logistics, and reproducibility issues[72,85,88,89]. Although not ideal, it is the only test to assess post-prandial hyperglycemia[77]. Clinically, some individuals may have hyperglycemia only if challenged with a glucose load[48]. If OGTT is not done, half of children with prediabetes were missed in a Korean study[81]. We also demonstrated that 73% of children with prediabetes or diabetes were left out in a large cohort of Chinese Hong Kong Children. IGT is related to insulin resistance in the muscle and defective insulin secretion[90]. This phenotype was found to be associated with a worse cardiometabolic profile[91-93] and a high risk of developing T2DM and cardiovascular disease[57,62,93]. Contrary to usual belief, OGTT was well tolerated in our cohort of children and adolescents with more than 99.8% success rate[44]. Accordingly, it is suggested as the preferred screening method by some experts[94].

Additional parameters, or morphological features, can be obtained during OGTT at the expense of multiple venipunctures. These include but not limited to 1-hour glucose concentration, glucose response curve, and time to glucose peak. They are being investigated as a tool for prediabetes risk stratification. Nevertheless, further research and longitudinal studies are needed before their clinical utility can be considered[62,94-96].

Alternative tests or approaches: Instead of using OGTT, various studies have attempted to use a combination of blood tests or parameters, in an attempt to detect prediabetes. Combining fasting glucose with homeostatic model assessment of insulin resistance (HOMA-IR) cutoff of 3.4, van der Aa, Fazeli Farsani[97] detected all cases of diabetes while missing 36% of IGT. Poon *et al*[98] derived a clinical pathway using family history, HbA1c, and alanine transaminase. They omitted 50% of OGTTs, but 18.3% of children with dysglycemia were overlooked. Alternative glycemic markers, such as 1,5-anhydroglucitol, glycated albumin, and fructosamine, have been studied as screening tools. However, relevant and meaningful cutoff values associated with long-term risk and complications are still under investigation in pediatric population[62,99]. With the advent of diabetes technology, continuous glucose monitoring (CGM) is more capable of capturing detailed information and parameters of glucose fluctuations. There has been a growing interest in applying CGM technology in non-diabetic individuals[100]. However, its use in predicting prediabetes is still exploratory and preliminary[101].

Screening algorithms

Even though some management algorithms are reported in the literature, there is no consensus on the optimal screening approach for prediabetes and diabetes in children with obesity[10]. Magge *et al*[80] proposed a management algorithm for screening of high-risk youth. However, it is based on the definition of high risk as two or more risk factors instead of the 2018 ADA recommendation of a single risk factor or more. Nonetheless, it is complicated for daily clinical use. In a recent review article, Garonzi *et al*[62] proposed a flowchart based on the strengths and weaknesses of different screening tests, suggesting screening of children and adolescents with overweight or obesity using FPG and HbA1c. In case of abnormal findings, OGTT was suggested. Likewise, OGTT was recommended for high-risk children (with one or more risk factors).

To further simplify and streamline the screening process, we suggest a fasting glucose-based approach for overweight and obese children. An OGTT-based approach is warranted in the presence of risk factors suggested by the ADA. HbA1c is considered optional in both approaches as there is no evidence-based operational cutoff value. Limited data support the use of HbA1c in children and adolescents. Figure 1 outlines the simplified framework, as a starting point, for laboratory assessment.

MANAGEMENT OF PREDIABETES

Presumably, early identification of children at risk enables practitioners to intervene and interrupt the progression toward diabetes[102]. In the absence of consensus regarding optimal management of children with prediabetes, lifestyle interventions are still the cornerstone in this population[7,28]. A balanced diet consisting of adequate fruits and vegetables, less sugar and processed foods is key. Home-cooked meals are preferred to dining out. Regular daily exercise with limitation of screen time should be reinforced. Innovative strategies for patient education should be explored so that knowledge can be translated into behavioral changes[8,103,104].

Currently, there is no United States Food and Drug Administration (FDA)-approved pharmacologic agent for prediabetes in children. Nevertheless, metformin has been used off-label in pediatric weight-management programs for children with prediabetes and insulin resistance. It is relatively well tolerated with gastrointestinal intolerance being the most common side effect[34,55]. Lactic acidosis is rare and can be monitored during treatment[34,105]. Proponents suggest metformin as a second-line management in those refractory to lifestyle interventions[34]. Liraglutide, a glucagon-like peptide-1 receptor agonist, was approved by the FDA in 2019 for use in childhood T2DM[106]. It may improve beta-cell mass and function and represents a potential treatment for prediabetes in future[56,107].

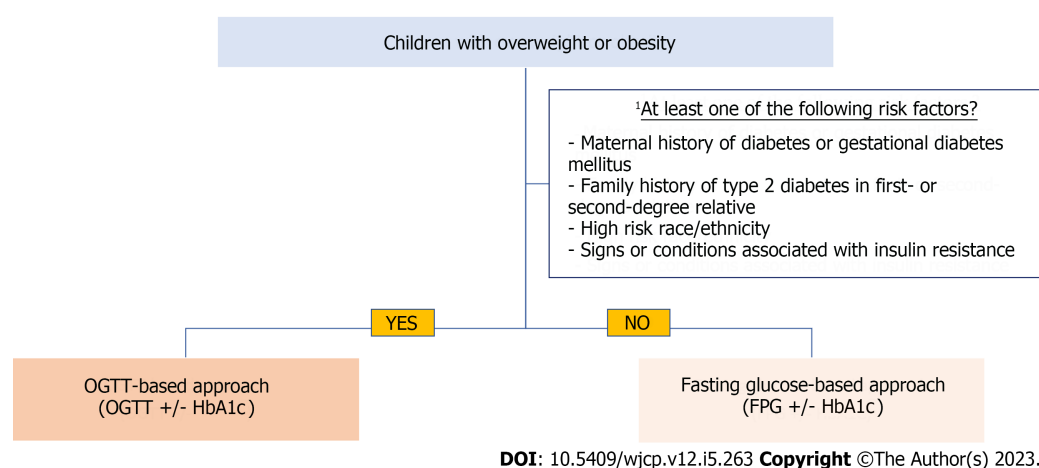


Figure 1 Simplified approach for risk-based dysglycemia screening in asymptomatic children and adolescents. ¹Risk factors adopted from American Diabetes Association[75]. OGTT: Oral glucose tolerance test; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c.

FUTURE PERSPECTIVES

The recent USPSTF attempted to search for direct evidence supporting screening of asymptomatic children for prediabetes and T2DM to improve health outcomes. However, their commissioned review found insufficient evidence to assess any benefits or harms of screening, mainly, due to a lack of studies[51,60,61]. The lack of prospective long-term longitudinal data to inform evidence-based practice for disease prevention and complication avoidance is the real challenge and major gap in pediatric prediabetes research. Clinical trials of pharmaceutical agents face the challenge of inadequate number of participants[108]. Further, the use of different screening tests and cutoff values in studies has led to discrepant results in different race and ethnicity. A “one-size-fits-all” approach may not be the best, suggesting the need for further validation[72]. Additionally, randomized controlled trials are urgently needed to evaluate the effectiveness of various preventive and management options in prediabetes[109].

CONCLUSION

Prediabetes is increasingly common in childhood and frequently goes unnoticed. It remains a challenging entity facing child health practitioners. Traditionally, it is diagnosed using adult criteria, which may not be readily applicable for children. This extrapolation of adult data is problematic and results in controversial and questionable approaches to prognosis, diagnostic criteria, investigation strategies, and management. The latest AAP guideline alerts pediatricians and healthcare providers to be aware of the pros and cons of each test based on clinical context, patient preferences, and accessibility issues[110]. Apparently, until effective prevention measures for childhood obesity can be found, managing and reversing the growing crisis of diabetes and prediabetes is still a major challenge.

FOOTNOTES

Author contributions: Ng HY reviewed the literature, wrote the manuscript, revised it and approved the final version; Chan LTW reviewed the literature, revised it and approved the final version.

Conflict-of-interest statement: All the authors report no conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Hak Yung Ng 0000-0002-4213-5574; Louis Tsz Wang Chan 0000-0003-2259-8165.

S-Editor: Liu JH

L-Editor: A

P-Editor: Cai YX

REFERENCES

- 1 **Al-Agailat L**, Littlejohn E. Emerging Pediatric Obesity Epidemic with the COVID-19 Pandemic as an Influence. *Pediatr Ann* 2023; **52**: e48-e50 [PMID: 36779879 DOI: 10.3928/19382359-20230102-03]
- 2 **Browne NT**, Snethen JA, Greenberg CS, Frenn M, Kilanowski JF, Gance-Cleveland B, Burke PJ, Lewandowski L. When Pandemics Collide: The Impact of COVID-19 on Childhood Obesity. *J Pediatr Nurs* 2021; **56**: 90-98 [PMID: 33293199 DOI: 10.1016/j.pedn.2020.11.004]
- 3 **Palermi S**, Vecchiato M, Pennella S, Marasca A, Spinelli A, De Luca M, De Martino L, Fernando F, Sirico F, Biffi A. The Impact of the COVID-19 Pandemic on Childhood Obesity and Lifestyle-A Report from Italy. *Pediatr Rep* 2022; **14**: 410-418 [PMID: 36278553 DOI: 10.3390/pediatric14040049]
- 4 **Xu XY**, Leung AYM, Smith R, Wong JYH, Chau PH, Fong DYT. The relative risk of developing type 2 diabetes among individuals with prediabetes compared with individuals with normoglycaemia: Meta-analysis and meta-regression. *J Adv Nurs* 2020; **76**: 3329-3345 [PMID: 33009836 DOI: 10.1111/jan.14557]
- 5 **Perng W**, Conway R, Mayer-Davis E, Dabelea D. Youth-Onset Type 2 Diabetes: The Epidemiology of an Awakening Epidemic. *Diabetes Care* 2023; **46**: 490-499 [PMID: 36812420 DOI: 10.2337/dci22-0046]
- 6 **Han C**, Song Q, Ren Y, Chen X, Jiang X, Hu D. Global prevalence of prediabetes in children and adolescents: A systematic review and meta-analysis. *J Diabetes* 2022; **14**: 434-441 [PMID: 35790502 DOI: 10.1111/1753-0407.13291]
- 7 **Serbis A**, Giapros V, Kotanidou EP, Galli-Tsinopoulou A, Siomou E. Diagnosis, treatment and prevention of type 2 diabetes mellitus in children and adolescents. *World J Diabetes* 2021; **12**: 344-365 [PMID: 33889284 DOI: 10.4239/wjd.v12.i4.344]
- 8 **Valaiyapathi B**, Gower B, Ashraf AP. Pathophysiology of Type 2 Diabetes in Children and Adolescents. *Curr Diabetes Rev* 2020; **16**: 220-229 [PMID: 29879890 DOI: 10.2174/1573399814666180608074510]
- 9 **Esquivel Zuniga R**, DeBoer MD. Prediabetes in Adolescents: Prevalence, Management and Diabetes Prevention Strategies. *Diabetes Metab Syndr Obes* 2021; **14**: 4609-4619 [PMID: 34858039 DOI: 10.2147/DMSO.S284401]
- 10 **Nwosu BU**. The Progression of Prediabetes to Type 2 Diabetes in Children and Adolescents in the United States: Current Challenges and Solutions. *Endocrines* 2022; **3**: 545-551 [DOI: 10.3390/endocrines3030045]
- 11 **ElSayed NA**, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA; on behalf of the American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. *Diabetes Care* 2023; **46**: S19-S40 [PMID: 36507649 DOI: 10.2337/dc23-S002]
- 12 **Lee EY**, Yoon KH. Epidemic obesity in children and adolescents: risk factors and prevention. *Front Med* 2018; **12**: 658-666 [PMID: 30280308 DOI: 10.1007/s11684-018-0640-1]
- 13 **The Lancet Diabetes Endocrinology**. Childhood obesity: a growing pandemic. *Lancet Diabetes Endocrinol* 2022; **10**: 1 [PMID: 34863372 DOI: 10.1016/S2213-8587(21)00314-4]
- 14 **Apperley LJ**, Blackburn J, Erlandson-Parry K, Gait L, Laing P, Senniappan S. Childhood obesity: A review of current and future management options. *Clin Endocrinol (Oxf)* 2022; **96**: 288-301 [PMID: 34750858 DOI: 10.1111/cen.14625]
- 15 **Aris IM**, Block JP. Childhood Obesity Interventions-Going Beyond the Individual. *JAMA Pediatr* 2022; **176**: e214388 [PMID: 34747988 DOI: 10.1001/jamapediatrics.2021.4388]
- 16 **Vazquez CE**, Cubbin C. Socioeconomic Status and Childhood Obesity: a Review of Literature from the Past Decade to Inform Intervention Research. *Curr Obes Rep* 2020; **9**: 562-570 [PMID: 32785878 DOI: 10.1007/s13679-020-00400-2]
- 17 **Van Lancker W**, Parolin Z. COVID-19, school closures, and child poverty: a social crisis in the making. *Lancet Public Health* 2020; **5**: e243-e244 [PMID: 32275858 DOI: 10.1016/S2468-2667(20)30084-0]
- 18 **Saliba K**, Cuschieri S. Amidst the COVID-19 pandemic childhood obesity is still an epidemic-spotlight on obesity's multifactorial determinants. *Health Sci Rev (Oxf)* 2021; **1**: 100006 [PMID: 34977915 DOI: 10.1016/j.hsr.2021.100006]
- 19 **Prospieri S**, Chiarelli F. COVID-19 and diabetes in children. *Ann Pediatr Endocrinol Metab* 2022; **27**: 157-168 [PMID: 36203266 DOI: 10.6065/apem.2244150.075]
- 20 **Hauerslev M**, Narang T, Gray N, Samuels TA, Bhutta ZA. Childhood obesity on the rise during COVID-19: A request for global leaders to change the trajectory. *Obesity (Silver Spring)* 2022; **30**: 288-291 [PMID: 34570430 DOI: 10.1002/oby.23307]
- 21 **Anderson LN**, Yoshida-Montezuma Y, Dewart N, Jalil E, Khattar J, De Rubeis V, Carsley S, Griffith LE, Mbuagbaw L. Obesity and weight change during the COVID-19 pandemic in children and adults: A systematic review and meta-analysis. *Obes Rev* 2023; **24**: e13550 [PMID: 36721999 DOI: 10.1111/obr.13550]
- 22 **Chang TH**, Chen YC, Chen WY, Chen CY, Hsu WY, Chou Y, Chang YH. Weight Gain Associated with COVID-19 Lockdown in Children and Adolescents: A Systematic Review and Meta-Analysis. *Nutrients* 2021; **13** [PMID: 34684669 DOI: 10.3390/nu13103668]
- 23 **Dietz WH**. The COVID-19 lockdown increased obesity disparities; will the increases in type 2 diabetes continue? *Obesity (Silver Spring)* 2023; **31**: 699-702 [PMID: 36447419 DOI: 10.1002/oby.23662]
- 24 **Eneli I**, Xu J, Pratt K. Change in weight category among youth early in the COVID-19 pandemic. *Clin Obes* 2022; **12**: e12522 [PMID: 35385212 DOI: 10.1111/cob.12522]
- 25 **Marcus C**, Danielsson P, Hagman E. Pediatric obesity-Long-term consequences and effect of weight loss. *J Intern Med* 2022; **292**: 870-891 [PMID: 35883220 DOI: 10.1111/joim.13547]
- 26 **Ng HY**. Acanthosis nigricans in obese adolescents: prevalence, impact, and management challenges. *Adolesc Health Med Ther* 2017; **8**: 1-10 [PMID: 28031729 DOI: 10.2147/AHMT.S103396]
- 27 **Ng HY**, Young JH, Huen KF, Chan LT. Acanthosis nigricans in obese Chinese children. *Hong Kong Med J* 2014; **20**: 290-296 [PMID: 24762331 DOI: 10.12809/hkmj134071]
- 28 **Gunaratne N**, Delewski D. Metabolic Consequences of Pediatric Obesity: A Review of Pathophysiology, Screening, and Treatment. *Pediatr Ann* 2023; **52**: e62-e67 [PMID: 36779885 DOI: 10.3928/19382359-20230102-06]
- 29 **Arsanian S**, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and Management of Youth-Onset Type 2 Diabetes: A Position Statement by the American Diabetes Association. *Diabetes Care* 2018; **41**: 2648-2668 [PMID: 30425094 DOI: 10.2337/dci18-0052]
- 30 **Magliano DJ**, Sacre JW, Harding JL, Gregg EW, Zimmet PZ, Shaw JE. Young-onset type 2 diabetes mellitus - implications for morbidity and mortality. *Nat Rev Endocrinol* 2020; **16**: 321-331 [PMID: 32203408 DOI: 10.1038/s41574-020-0334-z]
- 31 **Barrett T**, Jalaludin MY, Turan S, Hafez M, Shehadeh N; Novo Nordisk Pediatric Type 2 Diabetes Global Expert Panel. Rapid progression of

- type 2 diabetes and related complications in children and young people-A literature review. *Pediatr Diabetes* 2020; **21**: 158-172 [PMID: 31804738 DOI: 10.1111/pedi.12953]
- 32 Bjornstad P, Chao LC, Cree-Green M, Dart AB, King M, Looker HC, Magliano DJ, Nadeau KJ, Pinhas-Hamiel O, Shah AS, van Raalte DH, Pavkov ME, Nelson RG. Youth-onset type 2 diabetes mellitus: an urgent challenge. *Nat Rev Nephrol* 2023; **19**: 168-184 [PMID: 36316388 DOI: 10.1038/s41581-022-00645-1]
- 33 Song SH. Prediabetes in youth: an opportunity to make a difference. *Lancet Child Adolesc Health* 2018; **2**: 693-694 [PMID: 30236371 DOI: 10.1016/S2352-4642(18)30255-4]
- 34 Hosey CM, Halpin K, Yan Y. Considering metformin as a second-line treatment for children and adolescents with prediabetes. *J Pediatr Endocrinol Metab* 2022; **35**: 727-732 [PMID: 35503504 DOI: 10.1515/jpem-2021-0200]
- 35 TODAY Study Group, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, Tryggstad J, White NH, Zeitler P. Long-Term Complications in Youth-Onset Type 2 Diabetes. *N Engl J Med* 2021; **385**: 416-426 [PMID: 34320286 DOI: 10.1056/NEJMoa2100165]
- 36 Karavanaki K, Paschou SA, Tentolouris N, Karachaliou F, Soldatou A. Type 2 diabetes in children and adolescents: distinct characteristics and evidence-based management. *Endocrine* 2022; **78**: 280-295 [PMID: 36029440 DOI: 10.1007/s12020-022-03172-y]
- 37 Rett K, Gottwald-Hostalek U. Understanding prediabetes: definition, prevalence, burden and treatment options for an emerging disease. *Curr Med Res Opin* 2019; **35**: 1529-1534 [PMID: 30935247 DOI: 10.1080/03007995.2019.1601455]
- 38 Hostalek U. Global epidemiology of prediabetes - present and future perspectives. *Clin Diabetes Endocrinol* 2019; **5**: 5 [PMID: 31086677 DOI: 10.1186/s40842-019-0080-0]
- 39 Mittal M, Jethwani P, Naik D, Garg MK. Non-medicalization of medical science: Rationalization for future. *World J Methodol* 2022; **12**: 402-413 [PMID: 36186743 DOI: 10.5662/wjm.v12.i5.402]
- 40 Brodersen J, Schwartz LM, Heneghan C, O'Sullivan JW, Aronson JK, Woloshin S. Overdiagnosis: what it is and what it isn't. *BMJ Evid Based Med* 2018; **23**: 1-3 [PMID: 29367314 DOI: 10.1136/ebmed-2017-110886]
- 41 White F. Application of Disease Etiology and Natural History to Prevention in Primary Health Care: A Discourse. *Med Princ Pract* 2020; **29**: 501-513 [PMID: 32422632 DOI: 10.1159/000508718]
- 42 Kale MS, Korenstein D. Overdiagnosis in primary care: framing the problem and finding solutions. *BMJ* 2018; **362**: k2820 [PMID: 30108054 DOI: 10.1136/bmj.k2820]
- 43 Pedicelli S, Fintini D, Ravà L, Inzaghi E, Deodati A, Spreghini MR, Bizzarri C, Mariani M, Cianfarani S, Cappa M, Manco M. Prevalence of prediabetes in children and adolescents by class of obesity. *Pediatr Obes* 2022; **17**: e12900 [PMID: 35144324 DOI: 10.1111/ijpo.12900]
- 44 Law VYH, Young JHM, Ng HY, Chan LTW. Abnormal glucose tolerance in children: oral glucose tolerance test is fit-for-purpose. *Explor Med* 2023; 235-245 [DOI: 10.37349/emed.2023.00136]
- 45 Koutny F, Weghuber D, Bollow E, Greber-Platzer S, Hartmann K, Körner A, Reinehr T, Roehl M, Simic-Schleicher G, Wabitsch M, Widhalm K, Wiegand S, Holl RW. Prevalence of prediabetes and type 2 diabetes in children with obesity and increased transaminases in European German-speaking countries. Analysis of the APV initiative. *Pediatr Obes* 2020; **15**: e12601 [PMID: 31810110 DOI: 10.1111/ijpo.12601]
- 46 Echouffo-Tcheugui JB, Perreault L, Ji L, Dagogo-Jack S. Diagnosis and Management of Prediabetes: A Review. *JAMA* 2023; **329**: 1206-1216 [PMID: 37039787 DOI: 10.1001/jama.2023.4063]
- 47 Echouffo-Tcheugui JB, Selvin E. Prediabetes and What It Means: The Epidemiological Evidence. *Annu Rev Public Health* 2021; **42**: 59-77 [PMID: 33355476 DOI: 10.1146/annurev-publhealth-090419-102644]
- 48 Shah AS, Zeitler PS, Wong J, Pena AS, Wicklow B, Arslanian S, Chang N, Fu J, Dabadghao P, Pinhas-Hamiel O, Urakami T, Craig ME. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. *Pediatr Diabetes* 2022; **23**: 872-902 [PMID: 36161685 DOI: 10.1111/pedi.13409]
- 49 Harnois-Leblanc S, Van Hulst A, Ybarra M, Barnett TA, Mathieu MÈ, McGrath JJ, Tremblay A, Paradis G, Drapeau V, Sylvestre MP, Henderson M. Natural history and determinants of dysglycemia in Canadian children with parental obesity from ages 8-10 to 15-17 years: The QUALITY cohort. *Pediatr Diabetes* 2022; **23**: 274-285 [PMID: 35023257 DOI: 10.1111/pedi.13315]
- 50 Galderisi A, Giannini C, Weiss R, Kim G, Shabanova V, Santoro N, Pierpont B, Savoye M, Caprio S. Trajectories of changes in glucose tolerance in a multiethnic cohort of obese youths: an observational prospective analysis. *Lancet Child Adolesc Health* 2018; **2**: 726-735 [PMID: 30236381 DOI: 10.1016/S2352-4642(18)30235-9]
- 51 Jonas DE, Vander Schaaf EB, Riley S, Allison BA, Middleton JC, Baker C, Ali R, Voisin CE, LeBlanc ES. Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2022; **328**: 968-979 [PMID: 36098720 DOI: 10.1001/jama.2022.7957]
- 52 Peña A, Olson ML, Hooker E, Ayers SL, Castro FG, Patrick DL, Corral L, Lish E, Knowler WC, Shaibi GQ. Effects of a Diabetes Prevention Program on Type 2 Diabetes Risk Factors and Quality of Life Among Latino Youths With Prediabetes: A Randomized Clinical Trial. *JAMA Netw Open* 2022; **5**: e2231196 [PMID: 36094502 DOI: 10.1001/jamanetworkopen.2022.31196]
- 53 Vajravelu ME, Lee JM, Shah R, Shults J, Amaral S, Kelly A. Association between prediabetes diagnosis and body mass index trajectory of overweight and obese adolescents. *Pediatr Diabetes* 2020; **21**: 743-746 [PMID: 32314478 DOI: 10.1111/pedi.13028]
- 54 Hannon TS. Promoting Prevention, Identification, and Treatment of Prediabetes and Type 2 Diabetes in Youth. *Pediatrics* 2020; **146** [PMID: 32778540 DOI: 10.1542/peds.2020-010272]
- 55 Nicolucci A, Maffei C. The adolescent with obesity: what perspectives for treatment? *Ital J Pediatr* 2022; **48**: 9 [PMID: 35033162 DOI: 10.1186/s13052-022-01205-w]
- 56 Lawson C, Ahmed SN, Brady C, Shoemaker AH. A Clinic-based Approach to Diagnosis and Management of Prediabetes in High-risk Children and Adolescents. *J Endocr Soc* 2020; **4**: bvaa008 [PMID: 32215353 DOI: 10.1210/endo/bvaa008]
- 57 Iafusco D, Franceschi R, Maguolo A, Guercio Nuzio S, Crinò A, Delvecchio M, Iughetti L, Maffei C, Calcaterra V, Manco M. From Metabolic Syndrome to Type 2 Diabetes in Youth. *Children (Basel)* 2023; **10** [PMID: 36980074 DOI: 10.3390/children10030516]
- 58 US Preventive Services Task Force, Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Krist AH, Kubik M, Li L, Ogedegbe G, Owens DK, Pbert L, Silverstein M, Stevermer J, Tseng CW, Wong JB. Screening for Prediabetes and Type 2 Diabetes: US Preventive Services Task Force Recommendation Statement. *JAMA* 2021; **326**: 736-743 [PMID: 34427594 DOI: 10.1001/jama.2021.12531]
- 59 Schlesinger S, Neuenschwander M, Barbaresco J, Lang A, Maalmi H, Rathmann W, Roden M, Herder C. Prediabetes and risk of mortality, diabetes-related complications and comorbidities: umbrella review of meta-analyses of prospective studies. *Diabetologia* 2022; **65**: 275-285

- [PMID: 34718834 DOI: 10.1007/s00125-021-05592-3]
- 60 **Isganaitis E**, Laffel L. Recommendations for Screening Children and Adolescents for Prediabetes and Type 2 Diabetes. *JAMA* 2022; **328**: 933-934 [PMID: 36098736 DOI: 10.1001/jama.2022.13759]
 - 61 **US Preventive Services Task Force**, Mangione CM, Barry MJ, Nicholson WK, Cabana M, Chelmsow D, Coker TR, Davidson KW, Davis EM, Donahue KE, Jaén CR, Kubik M, Li L, Ogedegbe G, Pbert L, Ruiz JM, Stevermer J, Tseng CW, Wong JB. Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *JAMA* 2022; **328**: 963-967 [PMID: 36098719 DOI: 10.1001/jama.2022.14543]
 - 62 **Garonzi C**, Maguolo A, Maffei C. Pros and Cons of Current Diagnostic Tools for Risk-Based Screening of Prediabetes and Type 2 Diabetes in Children and Adolescents with Overweight or Obesity. *Horm Res Paediatr* 2023; **96**: 356-365 [PMID: 36509067 DOI: 10.1159/000528342]
 - 63 **Wallace AS**, Wang D, Shin JJ, Selvin E. Screening and Diagnosis of Prediabetes and Diabetes in US Children and Adolescents. *Pediatrics* 2020; **146** [PMID: 32778539 DOI: 10.1542/peds.2020-0265]
 - 64 Association AD. Type 2 Diabetes in Children and Adolescents. *Pediatrics* 2000; **105**: 671-680 [DOI: 10.1542/peds.105.3.671]
 - 65 **American Diabetes Association**. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018; **41**: S13-S27 [PMID: 29222373 DOI: 10.2337/dc18-S002]
 - 66 **Lee J**, Kim JH. Endocrine comorbidities of pediatric obesity. *Clin Exp Pediatr* 2021; **64**: 619-627 [PMID: 34445852 DOI: 10.3345/cep.2021.00213]
 - 67 **Savoie M**, Caprio S, Dziura J, Camp A, Germain G, Summers C, Li F, Shaw M, Nowicka P, Kursawe R, Depourcq F, Kim G, Tamborlane WV. Reversal of early abnormalities in glucose metabolism in obese youth: results of an intensive lifestyle randomized controlled trial. *Diabetes Care* 2014; **37**: 317-324 [PMID: 24062325 DOI: 10.2337/dc13-1571]
 - 68 **Zimmermann E**, Bjerregaard LG, Gamborg M, Vaag AA, Sørensen TIA, Baker JL. Childhood body mass index and development of type 2 diabetes throughout adult life-A large-scale danish cohort study. *Obesity (Silver Spring)* 2017; **25**: 965-971 [PMID: 28345789 DOI: 10.1002/oby.21820]
 - 69 **Saleh M**, Kim JY, March C, Gebara N, Arslanian S. Youth prediabetes and type 2 diabetes: Risk factors and prevalence of dysglycaemia. *Pediatr Obes* 2022; **17**: e12841 [PMID: 34382374 DOI: 10.1111/ijpo.12841]
 - 70 **American Diabetes Association Professional Practice Committee**. 14. Children and Adolescents: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; **45**: S208-S231 [PMID: 34964865 DOI: 10.2337/dc22-S014]
 - 71 **Ehehalt S**, Wiegand S, Körner A, Schweizer R, Liesenkötter KP, Partsch CJ, Blumenstock G, Spielau U, Denzer C, Ranke MB, Neu A, Binder G, Wabitsch M, Kiess W, Reinehr T. Diabetes screening in overweight and obese children and adolescents: choosing the right test. *Eur J Pediatr* 2017; **176**: 89-97 [PMID: 27888412 DOI: 10.1007/s00431-016-2807-6]
 - 72 **Brar PC**. Update on the current modalities used to screen high risk youth for prediabetes and/or type 2 diabetes mellitus. *Ann Pediatr Endocrinol Metab* 2019; **24**: 71-77 [PMID: 31261470 DOI: 10.6065/apem.2019.24.2.71]
 - 73 **Echouffo-Tcheugui JB**, Kengne AP, Ali MK. Issues in Defining the Burden of Prediabetes Globally. *Curr Diab Rep* 2018; **18**: 105 [PMID: 30229351 DOI: 10.1007/s11892-018-1089-y]
 - 74 **Davidson MB**. Historical review of the diagnosis of prediabetes/intermediate hyperglycemia: Case for the international criteria. *Diabetes Res Clin Pract* 2022; **185**: 109219 [PMID: 35134465 DOI: 10.1016/j.diabres.2022.109219]
 - 75 **American Diabetes Association Professional Practice Committee**. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; **45**: S17-S38 [PMID: 34964875 DOI: 10.2337/dc22-S002]
 - 76 **Hagman E**, Ek AE, Marcus C. Insulin function in obese children within the low and high ranges of impaired fasting glycemia. *Pediatr Diabetes* 2019; **20**: 160-165 [PMID: 30537059 DOI: 10.1111/pedi.12804]
 - 77 **Weiss R**, Santoro N, Giannini C, Galderisi A, Umamo GR, Caprio S. Prediabetes in youth - mechanisms and biomarkers. *Lancet Child Adolesc Health* 2017; **1**: 240-248 [PMID: 29075659 DOI: 10.1016/s2352-4642(17)30044-5]
 - 78 **Little RR**, Rohlfing J, Sacks DB. The National Glycohemoglobin Standardization Program: Over 20 Years of Improving Hemoglobin A(1c) Measurement. *Clin Chem* 2019; **65**: 839-848 [PMID: 30518660 DOI: 10.1373/clinchem.2018.296962]
 - 79 **Vajravelu ME**, Lee JM. Identifying Prediabetes and Type 2 Diabetes in Asymptomatic Youth: Should HbA1c Be Used as a Diagnostic Approach? *Curr Diab Rep* 2018; **18**: 43 [PMID: 29868987 DOI: 10.1007/s11892-018-1012-6]
 - 80 **Magge SN**, Silverstein J, Elder D, Nadeau K, Hannon TS. Evaluation and Treatment of Prediabetes in Youth. *J Pediatr* 2020; **219**: 11-22 [PMID: 32143933 DOI: 10.1016/j.jpeds.2019.12.061]
 - 81 **Nam HK**, Cho WK, Kim JH, Rhie YJ, Chung S, Lee KH, Suh BK. HbA1c Cutoff for Prediabetes and Diabetes Based on Oral Glucose Tolerance Test in Obese Children and Adolescents. *J Korean Med Sci* 2018; **33**: e93 [PMID: 29542302 DOI: 10.3346/jkms.2018.33.e93]
 - 82 **Di Bonito P**, Licenziati MR, Corica D, Wasniewska M, Di Sessa A, Miraglia Del Giudice E, Morandi A, Maffei C, Faienza MF, Mozzillo E, Calcaterra V, Franco F, Maltoni G, Valerio G. Which Is the Most Appropriate Cut-Off of HbA1c for Prediabetes Screening in Caucasian Youths with Overweight or Obesity? *Int J Environ Res Public Health* 2023; **20** [PMID: 36673682 DOI: 10.3390/ijerph20020928]
 - 83 **Khokhar A**, Naraparaju G, Friedman M, Perez-Colon S, Umpaichitra V, Chin VL. Comparison of A1C to Oral Glucose Tolerance Test for the Diagnosis of Prediabetes in Overweight and Obese Youth. *Clin Diabetes* 2017; **35**: 133-140 [PMID: 28761215 DOI: 10.2337/cd16-0037]
 - 84 **Batur T**, Akbay Hİ, ÇOkluk E, Esendemir A. Evaluation of the hemoglobin a1c test in detecting pediatric prediabetes. *Journal of Contemporary Medicine* 2023; **13**: 1-5 [DOI: 10.16899/jcm.1095786]
 - 85 **Kelsey MM**, Zeitler PS, Drews K, Chan CL. Normal Hemoglobin A1c Variability in Early Adolescence: Adult Criteria for Prediabetes Should Be Applied with Caution. *J Pediatr* 2020; **216**: 232-235 [PMID: 31405525 DOI: 10.1016/j.jpeds.2019.07.031]
 - 86 **Lim CYS**, Foo YW, Tok CLX, Lim YY, Loke KY, Lee YS, Ng NBH. Screening for metabolic complications of childhood and adolescent obesity: A scoping review of national and international guidelines. *Obes Rev* 2022; **23**: e13513 [PMID: 36286080 DOI: 10.1111/obr.13513]
 - 87 **Troisi RJ**, Cowie CC, Harris MI. Diurnal variation in fasting plasma glucose: implications for diagnosis of diabetes in patients examined in the afternoon. *JAMA* 2000; **284**: 3157-3159 [PMID: 11135780 DOI: 10.1001/jama.284.24.3157]
 - 88 **Libman IM**, Barinas-Mitchell E, Bartucci A, Robertson R, Arslanian S. Reproducibility of the oral glucose tolerance test in overweight children. *J Clin Endocrinol Metab* 2008; **93**: 4231-4237 [PMID: 18713820 DOI: 10.1210/jc.2008-0801]
 - 89 **Mcdonald GW**, Fisher GF, Burnham C. Reproducibility of the oral glucose tolerance test. *Diabetes* 1965; **14**: 473-480 [PMID: 14334838 DOI: 10.2337/diab.14.8.473]
 - 90 **Tura A**, Pacini G, Moro E, Vrbíková J, Bendlová B, Kautzky-Willer A. Sex- and age-related differences of metabolic parameters in impaired glucose metabolism and type 2 diabetes compared to normal glucose tolerance. *Diabetes Res Clin Pract* 2018; **146**: 67-75 [PMID: 30287229]

- DOI: [10.1016/j.diabres.2018.09.019](https://doi.org/10.1016/j.diabres.2018.09.019)]
- 91 **Di Bonito P**, Pacifico L, Chiesa C, Valerio G, Miraglia Del Giudice E, Maffei C, Morandi A, Invitti C, Licenziati MR, Loche S, Tornese G, Franco F, Manco M, Baroni MG; “CARDIometabolic risk factors in overweight and obese children in ITALY” (CARITALY) Study Group. Impaired fasting glucose and impaired glucose tolerance in children and adolescents with overweight/obesity. *J Endocrinol Invest* 2017; **40**: 409-416 [PMID: [27854028](https://pubmed.ncbi.nlm.nih.gov/27854028/) DOI: [10.1007/s40618-016-0576-8](https://doi.org/10.1007/s40618-016-0576-8)]
 - 92 **Di Bonito P**, Licenziati MR, Corica D, Wasniewska MG, Di Sessa A, Del Giudice EM, Morandi A, Maffei C, Faienza MF, Mozzillo E, Calcaterra V, Franco F, Maltoni G, Valerio G. Phenotypes of prediabetes and metabolic risk in Caucasian youths with overweight or obesity. *J Endocrinol Invest* 2022; **45**: 1719-1727 [PMID: [35579861](https://pubmed.ncbi.nlm.nih.gov/35579861/) DOI: [10.1007/s40618-022-01809-3](https://doi.org/10.1007/s40618-022-01809-3)]
 - 93 **Li Y**, Feng D, Esangbedo IC, Zhao Y, Han L, Zhu Y, Fu J, Li G, Wang D, Wang Y, Li M, Gao S, Willi SM. Insulin resistance, beta-cell function, adipokine profiles and cardiometabolic risk factors among Chinese youth with isolated impaired fasting glucose vs impaired glucose tolerance: the BCAMS study. *BMJ Open Diabetes Res Care* 2020; **8** [PMID: [32049638](https://pubmed.ncbi.nlm.nih.gov/32049638/) DOI: [10.1136/bmjdr-2019-000724](https://doi.org/10.1136/bmjdr-2019-000724)]
 - 94 **De Sanctis V**, Soliman A, Daar S, Tzoulis P, Di Maio S, Kattamis C. Oral glucose tolerance test: How to maximize its diagnostic value in children and adolescents. *Acta Biomed* 2022; **93**: e2022318 [PMID: [36300215](https://pubmed.ncbi.nlm.nih.gov/36300215/) DOI: [10.23750/abm.v93i5.13615](https://doi.org/10.23750/abm.v93i5.13615)]
 - 95 **Kasturi K**, Onuzuruike AU, Kunnam S, Shomaker LB, Yanovski JA, Chung ST. Two- vs one-hour glucose tolerance testing: Predicting prediabetes in adolescent girls with obesity. *Pediatr Diabetes* 2019; **20**: 154-159 [PMID: [30520201](https://pubmed.ncbi.nlm.nih.gov/30520201/) DOI: [10.1111/pedi.12803](https://doi.org/10.1111/pedi.12803)]
 - 96 **Di Bonito P**, Valerio G, Licenziati MR, Corica D, Wasniewska M, Di Sessa A, Miraglia Del Giudice E, Morandi A, Maffei C, Mozzillo E, Calcaterra V, Franco F, Maltoni G, Faienza MF. One-Hour Post-Load Plasma Glucose and Altered Glucometabolic Profile in Youths with Overweight or Obesity. *Int J Environ Res Public Health* 2023; **20** [PMID: [37297565](https://pubmed.ncbi.nlm.nih.gov/37297565/) DOI: [10.3390/ijerph20115961](https://doi.org/10.3390/ijerph20115961)]
 - 97 **van der Aa MP**, Fazeli Farsani S, Kromwijk LA, de Boer A, Knibbe CA, van der Vorst MM. How to screen obese children at risk for type 2 diabetes mellitus? *Clin Pediatr (Phila)* 2014; **53**: 337-342 [PMID: [24243989](https://pubmed.ncbi.nlm.nih.gov/24243989/) DOI: [10.1177/0009922813509480](https://doi.org/10.1177/0009922813509480)]
 - 98 **Poon SW**, Wong WH, Tsang AM, Poon GW, Tung JY. Who should return for an oral glucose tolerance test? A proposed clinical pathway based on retrospective analysis of 332 children. *J Pediatr Endocrinol Metab* 2021; **34**: 877-884 [PMID: [33866699](https://pubmed.ncbi.nlm.nih.gov/33866699/) DOI: [10.1515/jpem-2020-0689](https://doi.org/10.1515/jpem-2020-0689)]
 - 99 **Krhač M**, Lovrenčić MV. Update on biomarkers of glycemic control. *World J Diabetes* 2019; **10**: 1-15 [PMID: [30697366](https://pubmed.ncbi.nlm.nih.gov/30697366/) DOI: [10.4239/wjcd.v10.i1.1](https://doi.org/10.4239/wjcd.v10.i1.1)]
 - 100 **Klonoff DC**, Nguyen KT, Xu NY, Gutierrez A, Espinoza JC, Vidmar AP. Use of Continuous Glucose Monitors by People Without Diabetes: An Idea Whose Time Has Come? *J Diabetes Sci Technol* 2022. [PMID: [35856435](https://pubmed.ncbi.nlm.nih.gov/35856435/) DOI: [10.1177/19322968221110830](https://doi.org/10.1177/19322968221110830)]
 - 101 **Gottfried S**, Pontiggia L, Newberg A, Laynor G, Monti D. Continuous glucose monitoring metrics for earlier identification of pre-diabetes: protocol for a systematic review and meta-analysis. *BMJ Open* 2022; **12**: e061756 [PMID: [36008066](https://pubmed.ncbi.nlm.nih.gov/36008066/) DOI: [10.1136/bmjopen-2022-061756](https://doi.org/10.1136/bmjopen-2022-061756)]
 - 102 **Polidori N**, Mainieri F, Chiarelli F, Mohn A, Giannini C. Early Insulin Resistance, Type 2 Diabetes, and Treatment Options in Childhood. *Horm Res Paediatr* 2022; **95**: 149-166 [PMID: [34915489](https://pubmed.ncbi.nlm.nih.gov/34915489/) DOI: [10.1159/000521515](https://doi.org/10.1159/000521515)]
 - 103 **Hinchliffe N**, Capehorn MS, Bewick M, Feenie J. The Potential Role of Digital Health in Obesity Care. *Adv Ther* 2022; **39**: 4397-4412 [PMID: [35925469](https://pubmed.ncbi.nlm.nih.gov/35925469/) DOI: [10.1007/s12325-022-02265-4](https://doi.org/10.1007/s12325-022-02265-4)]
 - 104 **Stephens TN**, Joerin A, Rauws M, Werk LN. Feasibility of pediatric obesity and prediabetes treatment support through Tess, the AI behavioral coaching chatbot. *Transl Behav Med* 2019; **9**: 440-447 [PMID: [31094445](https://pubmed.ncbi.nlm.nih.gov/31094445/) DOI: [10.1093/tbm/ibz043](https://doi.org/10.1093/tbm/ibz043)]
 - 105 **Hostalek U**, Gwilt M, Hildemann S. Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. *Drugs* 2015; **75**: 1071-1094 [PMID: [26059289](https://pubmed.ncbi.nlm.nih.gov/26059289/) DOI: [10.1007/s40265-015-0416-8](https://doi.org/10.1007/s40265-015-0416-8)]
 - 106 **Bacha F**. FDA approval of GLP-1 receptor agonist (liraglutide) for use in children. *Lancet Child Adolesc Health* 2019; **3**: 595-597 [PMID: [31345736](https://pubmed.ncbi.nlm.nih.gov/31345736/) DOI: [10.1016/S2352-4642\(19\)30236-6](https://doi.org/10.1016/S2352-4642(19)30236-6)]
 - 107 **Chadda KR**, Cheng TS, Ong KK. GLP-1 agonists for obesity and type 2 diabetes in children: Systematic review and meta-analysis. *Obes Rev* 2021; **22**: e13177 [PMID: [33354917](https://pubmed.ncbi.nlm.nih.gov/33354917/) DOI: [10.1111/obr.13177](https://doi.org/10.1111/obr.13177)]
 - 108 **Nadeau KJ**, Anderson BJ, Berg EG, Chiang JL, Chou H, Copeland KC, Hannon TS, Huang TT, Lynch JL, Powell J, Sellers E, Tamborlane WV, Zeitler P. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. *Diabetes Care* 2016; **39**: 1635-1642 [PMID: [27486237](https://pubmed.ncbi.nlm.nih.gov/27486237/) DOI: [10.2337/dc16-1066](https://doi.org/10.2337/dc16-1066)]
 - 109 **Lascar N**, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. *Lancet Diabetes Endocrinol* 2018; **6**: 69-80 [PMID: [28847479](https://pubmed.ncbi.nlm.nih.gov/28847479/) DOI: [10.1016/S2213-8587\(17\)30186-9](https://doi.org/10.1016/S2213-8587(17)30186-9)]
 - 110 **Hampl SE**, Hassink SG, Skinner AC, Armstrong SC, Barlow SE, Bolling CF, Avila Edwards KC, Eneli I, Hamre R, Joseph MM, Lunsford D, Mendonca E, Michalsky MP, Mirza N, Ochoa ER, Sharifi M, Staiano AE, Weedn AE, Flinn SK, Lindros J, Okechukwu K. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics* 2023; **151** [PMID: [36622115](https://pubmed.ncbi.nlm.nih.gov/36622115/) DOI: [10.1542/peds.2022-060640](https://doi.org/10.1542/peds.2022-060640)]



Pre-autism: What a paediatrician should know about early diagnosis of autism

Mohammed Al-Beltagi

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Li Q, China

Received: July 10, 2023

Peer-review started: July 10, 2023

First decision: September 4, 2023

Revised: September 7, 2023

Accepted: September 25, 2023

Article in press: September 25, 2023

Published online: December 9, 2023



Mohammed Al-Beltagi, Department of Pediatric, Faculty of Medicine, Tanta University, Tanta 31511, Algharbia, Egypt

Mohammed Al-Beltagi, Department of Pediatric, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al Habib Medical Group, Manama 26671, Manama, Bahrain

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Academic Editor, Chairman, Consultant Physician-Scientist, Professor, Researcher, Department of Pediatric, Faculty of Medicine, Tanta University, Al Bahr Street, Tanta 31511, Algharbia, Egypt.

mbelrem@hotmail.com

Abstract

Autism, also known as an autism spectrum disorder, is a complex neurodevelopmental disorder usually diagnosed in the first three years of a child's life. A range of symptoms characterizes it and can be diagnosed at any age, including adolescence and adulthood. However, early diagnosis is crucial for effective management, prognosis, and care. Unfortunately, there are no established fetal, prenatal, or newborn screening programs for autism, making early detection difficult. This review aims to shed light on the early detection of autism prenatally, natally, and early in life, during a stage we call as "pre-autism" when typical symptoms are not yet apparent. Some fetal, neonatal, and infant biomarkers may predict an increased risk of autism in the coming baby. By developing a biomarker array, we can create an objective diagnostic tool to diagnose and rank the severity of autism for each patient. These biomarkers could be genetic, immunological, hormonal, metabolic, amino acids, acute phase reactants, neonatal brainstem function biophysical activity, behavioral profile, body measurements, or radiological markers. However, every biomarker has its accuracy and limitations. Several factors can make early detection of autism a real challenge. To improve early detection, we need to overcome various challenges, such as raising community awareness of early signs of autism, improving access to diagnostic tools, reducing the stigma attached to the diagnosis of autism, and addressing various culturally sensitive concepts related to the disorder.

Key Words: Autism; Pre-autism; Biomarkers; Autism spectrum disorder; Biophysical profile; Neurodevelopment; Antenatal; Neonatal

Core Tip: Pre-autism refers to an early stage of autism during which signs and symptoms may appear and indicate a potential risk of developing autism later in life. Early detection and intervention are crucial to improve outcomes for individuals with autism. Various physical, biochemical, hormonal, and imaging biomarkers are developed to assist prenatal and early-life diagnosis of autism. To improve the early detection of autism, we should try to overcome the various challenges that involve the diagnosis, such as enhancing community awareness, easing the diagnostic tools access, and removing and dealing with the autism-related stigma and culturally sensitive concepts.

Citation: Al-Beltagi M. Pre-autism: What a paediatrician should know about early diagnosis of autism. *World J Clin Pediatr* 2023; 12(5): 273-294

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/273.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.273>

INTRODUCTION

Autism is a word derived from the Greek word "autos," which means self, described in 1943 for the first time by Leo Kanner from Johns Hopkins University[1]. This word reflects the different perspectives by which the child sees the world. Autism, or autism spectrum disorder (ASD), is a complex neurodevelopmental disorder affecting specific brain developmental areas, impacting communication abilities, social interaction, and child behavior. It is typically diagnosed during the first three years of life with a spectrum of symptoms ranging from mild to severe and varies from child to child[2]. There is a wide variation of autism prevalence from one country to another and from one ethnicity to another, with an average prevalence of 0.1%. However, the prevalence could reach 1/64 in the United Kingdom and 1/36 in the United States. These differences could be related to the availability of diagnostic tools[3]. In other countries, *e.g.*, the Kingdom of Bahrain, the prevalence could be much lower with underestimation (0.1%), probably due to missed diagnosis of some cases and the absence of official recording due to the fear of stigma[1]. In addition, there are significant gender differences as boys are affected 4-5 times more than girls. Ethnicity also impacts the prevalence as it is more common in non-Hispanic white populations than in Hispanic and African American/black people, with vast differences in Asian/Pacific residents [4].

The exact pathogenesis of autism is still not precisely obvious. It is multifactorial mainly due to the interaction between genetic, environmental, advanced parental age, biological, psychological, and immunological factors[5]. About 80%-90% of the autism risk is heritable, which explains why autism runs in families[6]. With the enormous advances in genetic studies, we recently recognized various genetic mutations in the affected children, which can eventually provoke brain changes and inflammation during the early developmental phases[7]. Many genetic disorders are implicated in autism pathogenesis, from simple genetic mutation to complex numeric variations with large deletions, inversions, duplications, or chromosomal translocations[8]. These genetic mutations, such as Fragile X syndrome, may be inherited, *de novo* mutation, or due to accumulative changes over generations. These genetic factors raise the recurrence rate to between 2% and 8% in siblings of children with autism. Children with autism may have other chromosomal or genetic co-morbidities, such as Down syndrome, Fragile X syndrome, Duchenne muscular dystrophy, tuberous sclerosis complex, and neurofibromatosis type I[9]. However, the increased risk of recurrence does not take root only from the genetic factor but also from sharing the same environmental and epigenetic factors[10]. Various ecological factors could induce epigenetic changes through deoxyribonucleic acid (DNA) methylation, histone modifications, or microRNAs; all these can affect gene expression without modifying the primary underlying DNA sequence. These environmental factors include dietary modification, exposure to stressful conditions, environmental pollution, and toxin exposure. The increased awareness of autism, in addition to the interaction between genes and environment, are important causes for the rising autism prevalence[11].

Autism is classically diagnosed according to the basic criteria summarized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[12]. ASD is characterized by the impairment of at least two out of three main domains that describe the fundamental features and symptoms of autism: impaired social interaction and/or communication and restricted, repetitive, or stereotyped behavior, interests, and activities with the onset of these changes occurs during early development[13]. Impaired social interaction is manifested by difficulties in making friends, playing with others, or sharing their interests. Children with autism may struggle to make eye contact and understand social rules and their perspectives. Impaired social communication includes verbal and nonverbal communication difficulties, such as using and understanding facial expressions, gestures, body language, or voice tone. In addition, they have difficulty initiating and maintaining dialogues, understanding jokes or sarcasm, and using appropriate social clues[14]. Restricted and repetitive behaviors observed in children with autism appear as repetitive or stereotyped actions, such as hand flapping and persistent routines with a strong interest or obsession with a limited spectrum of topics or activities. They may also have abnormal sensory processing mechanisms with atypical responses to sensory stimuli. The child becomes hypersensitive to specific sensory stimuli, such as lights, sounds, tastes, or textures, or hyposensitive to other stimuli, such as pain or temperature changes[15]. It is crucial to note that the symptoms of these domains vary in severity and

presentation from one child to another, with different strengths and challenges. Some individuals may also have other comorbidities or challenges. Diagnosis of autism is complex and not an easy task. It requires a thorough evaluation by a competent healthcare professional and teamwork, such as a paediatrician, child psychiatrist, developmental and behavioral paediatrician, and clinical childhood psychologist[16].

Diagnosis of autism is usually achieved around the age of two to four years, depending on many factors, including the severity of autism, availability of healthcare access, parents' education level, and cultural and community factors[17]. Diagnosis of autism can be made at any age and could even be done for the first time during adolescence or adulthood. However, early diagnosis significantly impacts the child's management, prognosis, and welfare[18]. Early diagnosis allows early intervention, which helps children develop proper communication and social skills and enhances patient functioning and independence later in life. It also allows parents and caregivers to better understand the child's strengths and challenges. In addition, early diagnosis helps to improve the child and family's quality of life with a significant reduction in the long-term cost[19]. As the cost of autism may reach up to US\$3.2 million lifetime per capita, and early intervention may improve the prognosis and decrease the cost, we need to detect autism early. Directed actions could delay the autism progression, especially for language and cognitive abilities, and may help autism regression before it becomes irreversible. No well-established early fetal or newborn biomarker screening programs exist for autism. Therefore, this review will try to shed some light on the early detection of autism prenatally and in early life.

METHODS

To establish an evidence-based view of this aim, we accomplished a systematic literature review by searching the available electronic databases, including PubMed, PubMed Central, Cochrane Library, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Scopus, Library and Information Science Abstracts, and the National Library of Medicine catalog up until May 8, 2023, using the keywords: Autism, Pre-autism, Biomarkers, Autism spectrum Disorder, Biophysical Profile, Neurodevelopment, Antenatal, Neonatal. We included a total of full-text articles (175 articles), including research articles (102 articles), metanalysis (9 articles), systematic reviews (4 articles), reviews (58 articles), and consensus guidelines (2 articles). We included articles that were written in English and concerned with the effects of early diagnosis of autism. **Figure 1** shows the study flow chart. Reference lists were checked, and citation searches were performed on the included studies. We also reviewed the articles that are available as abstracts only. We excluded articles with a commercial background.

DISCUSSION

Pathophysiology of autism

Autism results from genetic and environmental developmental factors disrupting normal brain development and affecting many or all brain functions by activating pathological pathways. Despite the extensive efforts over the last few decades to elaborate the exact mechanism of autism, we are still in the first steps of a long way to be achieved, and its precise mechanism is still poorly understood. However, two critical domains are being tried to explain what could lead to the manifestations of autism. The first domain is the changes in the brain structure and pathophysiology usually observed in individuals with autism. The second domain is the neuropsychological and neurobiological links between the changes in the brain structure and the development of behavioral changes characteristic of autism[20,21]. Different theories tried to explain the occurrence of autism. One of them is related to the presence of excess neurons with significant changes in synaptic density and plasticity, which causes local overconnectivity in critical brain regions, which explains the high brain weight and volume and the large head circumference observed in children with autism, together with the enhanced expansion of the grey matter of cortical surface area in children with autism resulting in reduced maturation of the cortical white matter. However, these pathological changes' molecular and cellular mechanisms are not fully addressed, nor is it known whether the brain's overgrown causes the characteristic autism signs[22].

In addition, specific brain regions are affected in children with autism, such as the frontoparietal cortex, frontotemporal lobe, amygdala, basal ganglia, hippocampus, and anterior cingulate cortex[23]. For example, defects in social attention and social language processing are associated with abnormalities in Broca's area (inferior frontal gyrus), Wernicke's area (located in the posterior part of the upper temporal convolution of the left-brain hemisphere and concerned with speech comprehension), and superior temporal sulcus[24]. Impaired social behaviors are associated with abnormal functioning of the frontal lobe, parietal cortex, superior temporal cortex, and enlargement of the laterobasal amygdala[25]. Meanwhile, abnormalities in size, structure, and activity of the orbitofrontal cortex (which is involved in decision-making, social behavior, and emotion regulation) and caudate nucleus (which is involved in motor control, reward processing, and learning) are associated with increased risk of autism[26]. Accelerated cortical thinning was also observed in patients with autism aged 3-39 years after accelerated expansion in early childhood[27].

Neuronal migration is an essential process in fetal brain development, during which neurons migrate from their original place to their final destination. Disturbance of neuronal migration during early pregnancy alters neural connectivity and induces abnormal neural circuits, contributing to abnormal behavioral and impaired cognitive functions. Irregular neuronal migration with abnormal positioning and organization of neurons in the brain are implicated in developing a range of neurological conditions, including autism. Prenatal exposure to specific hazardous environmental hazards, such as environmental toxins, drugs (*e.g.*, thalidomide or valproic acid), and maternal infections, inflammation,

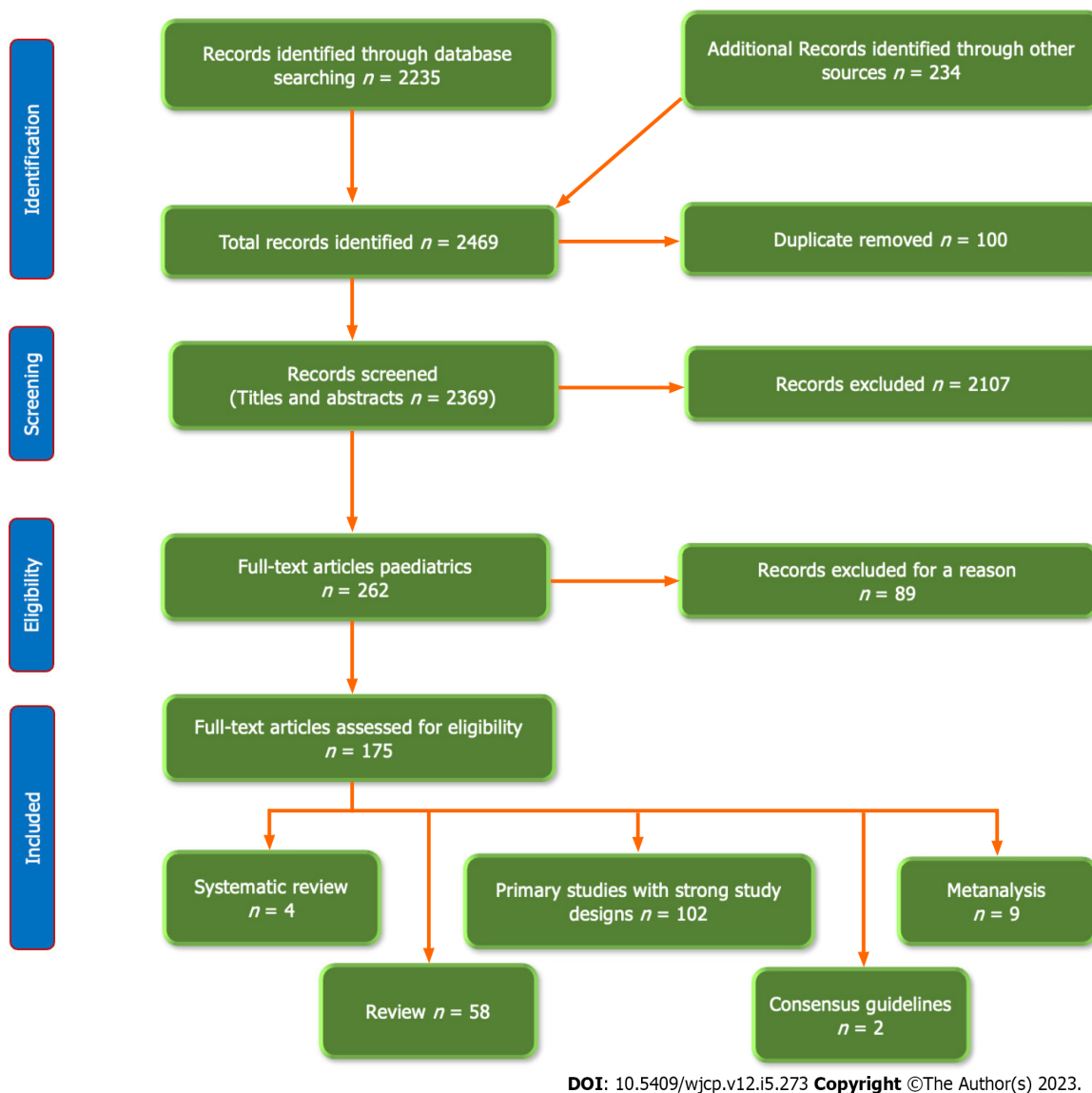


Figure 1 The flow chart of the included studies.

or immune dysfunction, can induce gene mutation (*e.g.*, gene CNTNAP2 which regulates neuronal migration and axon guidance or gene RELN, which regulates neuronal migration in the cerebral cortex, Lis1, DCX, and TUBA1A genes) and altering their expression, interrupting the normal neuronal migration, and raising the risk of autism[28,29]. Imaging studies showed that patients with autism have abnormal brain white matter organization, which could be related to neuronal migration disturbances during early development[30].

In addition to the structural and ultrastructural changes observed in patients with autism, there is growing evidence of altered brain connectivity and function due to imbalances in brain excitatory and inhibitory signaling. The excitatory neurons release the neurotransmitter glutamate, which promotes neuronal firing. In contrast, inhibitory neurons release the neurotransmitter Gamma-aminobutyric acid (GABA), suppressing neuronal activity[31]. An overall rise in neuronal excitation and reduced neuronal inhibition led to the social and communication deficits commonly observed in autism. This imbalance mostly results from decreased GABAergic inhibitory neurons' number or function, *e.g.*, reduced parvalbumin-positive interneurons, that naturally assist in controlling the excitatory neurons' activity. This imbalance could result from several factors, including genetic mutations, harmful environmental factors, and disturbed neural circuit development during early childhood[32]. This imbalance was proved by genetic analysis of the expression of the functional genes responsible for the inhibitory function and post-mortem and animal studies that demonstrated the reduction of the inhibitory neurons[33]. Treating this imbalance using medications that boost GABAergic signaling, such as certain antiepileptics, benzodiazepines, and GABAB receptor agonist STX209, has been proven effective in treating some autism symptoms, with variable degrees of success[34].

We can admit from the previously described pathophysiological mechanisms that autism results from genetic and environmental interaction with some predominance of the genetic factor. However, a growing list of exposures for mother and baby may sway the odds and affect the onset time of symptoms. There are three different pathways or trajectories for the development of autism, according to the timing of the insult that triggers the changes observed with autism. The first pathway is caused by in-utero insult/injury; obstetric complications at birth activate the second

pathway, while the third pathway is caused by environmental triggers of autism affecting infants 0-3 years of age[35]. In addition, we can classify autism according to the presence or absence and the number of minor physical defects into essential and complex autism. In essential autism, there is no evidence of an early embryological abnormality with no or very few minor physical defects. Conversely, in complex autism, the affected children have six or more minor physical defects. They are more likely to have genetic disorders, brain anatomical abnormalities, seizures, and a low intelligence quotient. They may also have peculiar facial features with a broader upper face, a shorter middle face comprising cheeks and a nose, wider eyes, a bigger mouth, and a philtrum. These facial features are better recognized using a 3-D camera with the help of artificial intelligence[36,37].

Pre-autism ("Preclinical")

We are using the term "pre-autism" for the first time to describe the early prodromal period that precedes the development of the full-blown and formal clinical picture of classic autism when the symptoms and signs of autism or ASD are not yet clearly evident. During the pre-autism phase, some risk factors, with few and/or non-classic signs, appear during the early developmental stage of the child's life that could indicate the increased potential risk of autism later in life. These early signs are often subtle, not yet fully developed, or may not be easily recognizable. The pre-autism phase typically happens during the neonatal period, infancy, or early childhood. It could be challenging to distinguish these early signs from typical developmental variations. It is central to admit that not all kids who display these early signs or risk factors will develop autism, and some children who develop autism may not show all these early signs. Therefore, a comprehensive evaluation by a trained professional is necessary to determine if a child has autism.

Presently, no newborn biomarker screening programs exist to detect autism. We should think about pre-autism in the presence of a positive family history of a patient with autism and/or other antenatal or post-natal risk factors. The more risk factors, the higher the risk of autism[38,39]. These risk factors are summarized in Table 1.

Preconception risk

Having a child with autism increases the risk of having another child with autism by 20-fold, especially in full-siblings compared to half-siblings and in the maternal half-siblings than paternal half-siblings. This supports the genetic and uterine environment effects in the pathogenesis of autism[40]. The risk further increases with a shorter time between the birth of a previous child with autism and the birth of the next sibling. The risk of autism recurrence reached 14.4% with an interbirth interval equal to or less than 18 mo, compared with 6.8% for an interval equal to or more than four years[41].

The birth order may also affect the risk of having autism. The first-born child might have a higher risk of having autism than later-born children. The increased risk in the firstborn child may be related to a higher exposure rate to pregnancy and delivery complications such as infections, stress, and inflammation. In contrast, the lower risk of the later-born children may be related to the social support and help provided by the first-born child to the later-born children[42]. On the other hand, Alvares *et al*[43] showed that intelligence scores and adaptive functioning decrease with increasing birth order. The later-born children are more prone to have an intellectual disability. However, they showed that first-born children without siblings have decreased cognitive functioning compared to those with siblings. This controversy may be related to other confounding factors, such as differences in the ethnicity of the studied group.

The age of the parents at the time of conception can predict the chance of having autism. Both the father and mother's age at the time of conception is independently associated with an increased risk of autism in the offspring. The risk will be higher if both parents are old[44]. Increased risk of autism with increasing paternal age may be due to increased risk of de novo mutations in their sperm or increased risk of having some features of autism phenotype that cause them to marry late[45]. Conversely, mothers over 35 have a 1.5 higher risk of having a child with autism than mothers between 25-29 years. Younger mother age gives more protection against autism. Higher maternal age is associated with a higher risk of chromosomal abnormalities and more exposure to environmental risk factors that affect DNA methylation in germ cells, with an increased risk of developmental consequences on the offspring[46]. The effect of higher maternal age is more evident in the male offspring, while higher paternal age is more evident in the female offspring[47].

Some data show that pre-conceptional maternal obesity might raise the risk of autism in the offspring. Wang *et al*[48] showed a linear dose-response relationship between pre-pregnancy maternal BMI and the risk of autism, with a relative risk of 1.16 for each 5 kg/m² increase in Mother BMI. Jo *et al*[49] showed that children born to mothers with severe obesity before pregnancy had a high risk for adverse developmental outcomes, including autism. Hinkle *et al*[50] also observed an increased incidence of learning and behavior disorders by kindergarten among children born to mothers with severe pre-pregnancy obesity. Pre-conceptional maternal obesity may alter the intrauterine milieu, increasing inflammation, affecting the function of insulin and other metabolic hormones, and affecting the developing fetal brain[51].

Antenatal Markers for the risks of autism

As mentioned before, no screening test can tell us that the baby will develop autism, as autism's aetiology and pathogenesis are not fully understood. However, some fetal and infant biomarkers may expect an increased risk of autism in the coming baby. These biomarkers could allow us to develop a biomarker array that, when properly developed and analyzed, could give us an objective diagnostic tool to diagnose and rank the severity of autism for each patient. These biomarkers could be genetic, immunological, hormonal, metabolic, amino acids, acute phase reactants, body measurements, or radiological markers[52] (Table 2).

Genetic profile

As our understanding of the genetic and environmental factors that contribute to the development of autism is improving, it may be feasible to develop more accurate techniques to predict the risk of autism based on examining

Table 1 Factors that increase the risk for autism

Risk	Details
Preconception risks	Presence of another child previously affected with autism Increased maternal and paternal age at birth (3.8% increase) Birth order: 61% increase in risk in firstborn Maternal Obesity or being overweight before pregnancy increases the risk of autism by 36%
Antenatal risk factors for autism[36]	Maternal asthma, allergies Preeclampsia Maternal bleeding (81% elevated risk) Maternal depression or emotional strain. It is believed that stress hormones can cross the placenta-blood barrier and affect the development of fetal brain Gestational diabetes (two-fold increased risk of autism) Hypothyroidism Phthalates (plasticizers) and pesticide exposure: <i>e.g.</i> , chlorpyrifos → sex-hormone pathways disruption → Autism. Folate deficiency Vitamin D deficiency Maternal Infections, <i>e.g.</i> , congenital rubella infection, increase the rate of autism to 1:13 Hospitalization due to antenatal infection increases the risk of autism by 30% Abnormal fetal growth could indicate disrupted fetal brain development. Being small or large for gestational age increases the risk of autism Prenatal Hormone Levels: Higher levels of prenatal testosterone may be related to an increased risk of autism
Postnatal risk factors for autism	Urbanization of birthplace Prematurity by more than 9 wks → higher odds of autism Birth injuries to the cerebellum increase the risk of autism by 3.8-fold Neonatal seizure
Potential risk factors for autism in neonates requiring NICU	Family history of neuropsychiatric disorders Maternal psychological distress during pregnancy Duration of stay ≥ 26 d in the NICU Tube feeding tube for ≥ 15 d Retinopathy of prematurity The need to use three or more antibiotics Co-sleeping until two years of age

NICU: Neonatal Intensive Care Unit.

genetic profiling. The presence of specific genetic markers in amniotic fluids or cord blood may indicate an increased risk of developing autism. Single-gene disorders such as Fragile X syndrome (FMR1 mutations), neurofibromatosis (NF1), tuberous sclerosis complex (TSC1 and TSC2 mutation), Dup15q syndrome, Rett syndrome (MeCP2 mutation), and deletions in the 16p11.2 region are present in about 3%–5% of patients with autism[53]. Other chromosomal and genetic disorders, such as Down syndrome (40% of them have autism or autism-like symptoms), Duchenne muscular dystrophy, and tuberous sclerosis complex, are associated with an increased risk of autism[9]. Large-scale genome-wide association studies have also identified numerous common genetic variants that are associated with an increased risk of autism. Among these mutations, mutations involving the SHANK3, NRXN1, CNTNAP2, and CHD8 genes increase the risk of autism[54,55]. 16p11.2 is a chromosomal region linked to autism and other neuropsychiatric conditions. The 16p11.2 genetic mutation with either deletion or duplication is associated with an increased risk of motor speech disorder, motor coordination difficulties, language disorder, and various psychiatric conditions, including autism. Detection of deletions or duplication in 16p11.2 in the cord blood might expect that the child may develop autism and other neuropsychiatric conditions[56]. However, the resulting severity varies significantly, and not all the patients with the mutation or deletion

Table 2 Antenatal markers for the risks of autism

Marker	Details
Genetic markers	<p>Single-gene disorders: Fragile X syndrome (FMR1 mutations), neurofibromatosis (NF1), tuberous sclerosis complex (TSC1 and TSC2 mutation), Dup15q syndrome, Rett syndrome (MeCP2 mutation), 16p11.2 region deletions, SHANK3, NRXN1, CNTNAP2, and CHD8 genes mutations</p> <p>Chromosomal Disorders: Down syndrome, aberrations on the long arm of Chromosome 15, and reciprocal chromosomal translocation between long arms of chromosomes 4 and 14</p> <p>Messenger RNA (mRNA) and microRNA (miRNA) expression abnormality</p> <p>Abnormal DNA methylation patterns</p>
Cytokines biomarkers	Abnormal profile of interleukin-6, tumor necrosis factor-alpha, interleukin-1 receptor antagonist, TNF- α , Serpin E1, vascular cell adhesion molecule 1, vascular endothelial growth factor D, Epidermal growth factor, Colony Stimulating Factor 1, and 2
Autoantibodies biomarkers	<p>The presence of circulating maternal autoantibodies, especially anti-brain autoantibodies, during pregnancy</p> <p>Maternal autoantibody response against Collapsin Response Mediator Protein 1 (CRMP1)</p> <p>Simultaneous reactivity against bands at 39 kDa and 73 kDa is associated with early-onset autism.</p>
Oxidative stress biomarkers	Maternal urinary levels of free 8-iso-prostaglandin F $_{2\alpha}$ (8-iso-PGF $_{2\alpha}$)
Hormonal biomarkers	<p>High prenatal testosterone levels</p> <p>Polycystic ovary syndrome</p> <p>Elevated levels of steroidogenic hormones (cortisol, androstenedione, testosterone, 17α-hydroxy-progesterone, and progesterone) in amniotic fluid</p> <p>Mid-pregnancy thyroid-stimulating hormone (inverse relationship)</p>
Maternal nutritional biomarkers	<p>Fetal levels of manganese and zinc</p> <p>Abnormal zinc-copper cycles (altered rhythmicity, shorter cycle duration, reduced regularity, and diminished complexity)</p> <p>Vitamin D deficiency</p> <p>Poor folic acid intake</p>
Biophysical markers	<p>Presence of multiple fetal abnormalities (especially cardiac, urinary, cranial, and brain anomalies)</p> <p>Presence of a narrower head and a relatively broader ocular distance</p> <p>Altered prenatal brain growth</p> <p>Abnormal Kurjak's antenatal neurodevelopmental scoring test in the last trimester</p>
Radiological profile	<p>Isolated ventriculomegaly</p> <p>Altered cortical development</p> <p>Enlarged insula lobe</p> <p>Increased amygdala volume and fast growth rate</p>

CHD8: Chromodomain helicase DNA binding protein 8; CNTNAP2: Contactin Associated Protein 2; Dup15q syndrome: Duplications of the portion of 15q11.2-13.1 chromosome; kDa: Kilodalton; MeCP2 mutation: Mutations of the methyl-CpG binding protein 2; NRXN1: Neurexin 1 RNA: Ribonucleic acid; SHANK3: SH3 and multiple ankyrin repeat domains 3; TNF- α : Tumor Necrosis Factor Alpha; TSC1: Tuberous sclerosis complex 1; TSC2: Tuberous sclerosis complex 2.

have the same clinical picture. Not all patients with these mutations will develop autism[57].

Another important genetic variation that could increase the risk of autism is the presence of single nucleotide polymorphisms (SNPs). The SHANK2 gene is an important gene for glutamate neurotransmission and synaptogenesis. A synergistic interaction between SNPs and the SHANK2 gene increases the risk for autism[58]. Other SNPs that affect the expression of genes that increase the risk of autism are MTHFR (Methylenetetrahydrofolate reductase has a significant role in folate metabolism.), RFC (genes encoding the reduced folate carrier), MTR (methionine synthase responsible for the regeneration of methionine from homocysteine and involved in the folate/homocysteine pathway), OXTR gene (a gene correlated with aggression, social dysfunction, and irritability), and CD38 gene (a gene linked to low CD38 expression and a lack of emotions)[59].

Not only structural gene changes can be used as a marker for risk autism, but also markers of gene expression, including messenger RNA (mRNA) and microRNA (miRNA) expression. mRNA is a single-stranded RNA molecule. It undergoes post-transcriptional modifications to carry the genetic information from nuclear DNA from the nucleus to

ribosomes in the cell cytoplasm to be used as a template for protein synthesis[60]. On the other hand, microRNA is a small, non-coding RNA molecule transcribed from DNA. It undergoes several processing steps before its incorporation into the RNA-induced silencing protein complex to guide this complex protein to its target mRNA through base pairing. Once base-paired with the targeted mRNA, it inhibits it by degradation or inhibiting its translation. A single miRNA can combine with several hundred targeted sites in the 3' untranslated regions of mRNAs, thus controlling the expression of many genes. There are about 5104 miRNA variants have been identified till now[61]. Studies have suggested the role of miRNAs in the development of autism. Wong *et al*[62] identified variants in five brain-expressed miRNAs, which target 326 genes, and 3' UTR miRNA target regions of 152 genes potentially involved in neurodevelopmental disorders, including autism. miRNA could post-transcriptionally regulate autism-related risk genes and affect various molecular pathways related to autism and associated disorders. In addition, Noroozi *et al*[63] identified five modules linked with neurexins and neuroligins, cell adhesion molecules, glutamatergic synapse, L1CAM interactions, MECP2 and circadian clock pathways, NOTCH, and neurotransmitter release cycle. Functional analysis of these genes helps to determine critical pathways related to neurological disorders and the pathogenesis of autism.

Methylation is a process of adding a methyl group to a DNA molecule to affect gene expression. Changes in the methylation patterns of certain genes could influence the development of autism. Patients with autism are in their DNA methylation patterns in specific genes from typically developing children. DNA methylation Epimutations can be developed throughout life. Reprogramming of the global DNA methylation is a dynamic process that occurs during the embryonic and the early postnatal period that parallels the peak time of synaptogenesis[64]. Abnormal methylation of specific genes could result in an increased risk of autism. Garcia-Ortiz *et al*[65] detected higher Neural Cell Adhesion Molecule and Nerve Growth Factor methylation levels in children with autism. Testing abnormal methylation patterns in biological specimens obtained from the parents could help to predict the possibility that the child may be born with autism. Global DNA hypomethylation was observed in mothers of children with autism. In addition, specific methylation patterns were observed in sperms obtained from fathers of children with autism[66,67]. Despite being a promising antenatal marker of autism, methylation has a complex nature and interaction with other environmental factors such as vitamin intake and prenatal tobacco exposure[68].

Cytokines profile

Cytokines are specific proteins that have an essential function in the immune system and could affect brain development and function. Specific cytokines, such as interleukin-6 and tumor necrosis factor-alpha, could play a role in brain development as they may initiate neuroinflammation, contributing to autism development. Therefore, the irregular profile of these cytokines, especially interleukin-6 in the fetus, might be related to the increased risk of autism during childhood[69]. Another study by Abdallah *et al*[70] showed increased levels of TNF-alpha in the amniotic fluid in mothers of children with autism than in mothers of children with typical development. In addition, Che *et al*[71] showed that the maternal mid-gestational and neonatal cord blood immune markers are strongly associated with increased risk of autism in the offspring, including but not limited to interleukin-1 receptor antagonist, TNF-alpha, Serpin E1, vascular cell adhesion molecule 1, vascular endothelial growth factor D, Epidermal growth factor, Colony Stimulating Factor 1, and 2. Maternal mid-gestational findings were outstanding, with remarkably great effect sizes in girls. However, Brynne *et al*[72] found no strong evidence of the association of maternal immune markers during early pregnancy with autism. Therefore, it is critical to endorse that the relationship between abnormal intrauterine cytokine profiles and the risk of autism is not fully understood and needs more research. We should consider other genetic and environmental factors that can impact the development of autism.

In addition to the previous markers, Ji *et al*[73] found in their prospective study that cord biomarkers of fetal acetaminophen exposure, such as 3-[N-acetyl-L-cystein-S-yl]-acetaminophen, acetaminophen glucuronide, or unchanged acetaminophen were associated with a significantly high risk of developing attention deficit hyperactivity disorder and autism during childhood in a dose-response fashion. Acetaminophen can cross the placental barrier and remain in the infant's blood circulation for a long time[74]. However, no specific time window was confirmed during which the developing brain is most sensitive to acetaminophen exposure. At the same time, we could not ensure whether the effects are due to the direct acetaminophen exposure or the cause of its use, *e.g.*, maternal fever during pregnancy, which increases the risk of autism. Even the observed dose-response effects can be related to the severity of the cause of its use and not to acetaminophen itself. However, we need more animal studies to confirm acetaminophen's direct brain toxic effects.

Maternal plasma or fetal blood anti-fetal brain autoantibodies profile

Many studies correlated the presence of circulating maternal autoantibodies, especially anti-brain autoantibodies during pregnancy, to the occurrence of neonatal neuronal dysfunction. These autoantibodies can cross the placental blood barrier and access the developing fetal brain and inducing the development of autism[75-77]. Dalton *et al*[77] performed a very interesting experiment. They injected 0.5-1 mL of sera obtained from mothers of children with autism and mothers of typically developed children into pregnant mice daily. They found that the offspring of mice injected with sera from mothers of children with autism developed altered motor coordination and exploration and had cerebellar changes in magnetic resonance spectroscopy in the mouse offspring, compared with offspring of mice injected with sera from mothers of typically developed children. Fox-Edmiston *et al*[78] recognized maternal autoantibodies against seven neurodevelopmental proteins associated with developing maternal autoantibody-related (MAR) autism in the offspring. Ramirez-Celis *et al*[79] found that maternal autoantibody response against Collapsin Response Mediator Protein 1 is associated with a significant increase in the chance that the child has autism, indicating the potential use of these autoantibodies as potential biomarkers of autism risk in up to 18% of autism cases termed as MAR autism.

The mechanism and the triggers for developing these autoantibodies are not clear. These autoantibodies against the fetal brain can be identified in the mother's blood and can be used as a marker for autism risk[80]. Croen *et al*[81] showed that maternal mid-gestation autoantibody against human fetal brain protein (especially reactivity to a band at 39 kDa) is associated with the risk of developing autism. In addition, simultaneous reactivity against bands at 39 kDa and 73 kDa is associated with early-onset autism. However, identifying these anti-fetal brain autoantibodies has two critical implications: diagnostic and potential therapeutic benefits. Preventing the development of these maternal autoantibodies can prevent the irreversible damage that could happen to the developing fetal brain. More searches are needed to elucidate the trigger for these autoantibodies, prevent their generation, and develop different therapeutic modalities to remove these antibodies, such as *in vivo* autoantibody competition or *ex vivo* autoantibody removal.

Oxidative stress biomarkers

Oxidative stress may have a role in the pathogenesis of autism. Oxidative stress means excessive production of reactive oxygen species beyond the detoxification ability of cells, leading to damage of the cellular components such as lipids (peroxidation), proteins (*e.g.*, post-translational changes), DNA, and toxic build-up by these reactive radicals, causing cellular dysfunction and damage[82]. Many studies have figured out the relationship between intrauterine oxidative stress markers and the increased risk of developing autism. For example, Rommel *et al*[83] found that maternal urinary levels of free 8-iso-prostaglandin F_{2α} (8-iso-PGF_{2α}) and its metabolites (markers of oxidative stress) were significantly increased in mothers of children who developed autism than in mothers of typically developing children. Maternal immune activation (MIA) during pregnancy is another example of the effects of oxidative stress and one of the common environmental risk factors for developing autism. MIA induces an unusual immune reaction in the pregnant woman, causing further inflammation and increasing oxidative stress in the placenta, crossing it to affect the fetal brain, causing activation and accumulation of microglia, dysregulating neurodevelopmental and autism-associated genes, inducing neurodevelopmental impairments in the developing fetal brain, and afterward triggering behavioral problems in the offspring[84-86].

In addition, oxidative stress is one of the possible mechanisms by which gestational diabetes and some antenatal infections increase the risk of autism. Lanté *et al*[87] experimentally prevented the harmful neurodevelopmental damage induced by bacterial endotoxin lipopolysaccharide with strong oxidant stress effects by using the antioxidant N-acetylcysteine, confirming the effect of oxidative stress on the pathogenesis of autism. However, Carey *et al*[88] found weak or no association between oxidative stress markers (glutathione, glutathione disulfide, 8-oxo-deoxyguanine, and nitrotyrosine) in late pregnancy and the risk of autism in the offspring. This discrepancy between their results and previous studies can be explained by the differences in the markers used and the time points they investigated the mothers (late trimester). We should also consider that association is not equal to causation. Therefore, we need more research to confirm the role of oxidative stress, choose the proper marker, and also the proper timing for the test to give more reliable results.

Hormonal profile

Antenatal exposure to steroid hormones can directly impact fetal gene transcription and expression during vulnerable stages of embryonic development. High prenatal testosterone levels can predict an elevated prevalence of behavioral and cognitive traits that are usually associated with autism in both typically developing males and females from early to late childhood, even if they did not develop frank autism with long-lasting effects on brain structures and organization and emotional reward processing in late childhood[89,90]. Therefore, female offspring (but not male) of mothers with hyperandrogenism, such as in polycystic ovary syndrome, have an increased prevalence of autism features than girls born to mothers without hyperandrogenism[91]. The effect is higher when polycystic ovary is combined with maternal obesity due to more hyperandrogenism[92]. Baron-Cohen *et al*[93] showed that. Elevated levels of steroidogenic hormones (cortisol, androstenedione, testosterone, 17 α -hydroxy-progesterone, and progesterone) in amniotic fluid samples are associated with an increased risk of autism due to their effects on early fetal brain development. The difference in sex steroid hormone exposure can explain why autism affects males more than females and can be used as an early biological risk factor marker. Steroid hormones have a substantial impact on the biological sexual differentiation of autism. Perinatal testicular androgen surge is responsible for brain sexual differentiation as prenatal sex hormones affect microglial activation during early neurodevelopment and consequently affect many neurodevelopmental disorders [94]. An exciting study by Yau *et al*[95] showed an inverse association between autism and mid-pregnancy thyroid-stimulating hormone levels in maternal serum samples, indicating the critical role of thyroid hormones for in-utero normal brain development. Therefore, the in-utero hormonal environment could increase or alleviate the risk of autism, explaining the male dominance and female protection of autism[96].

Maternal nutritional profile

Metals are essential to neurodevelopment. Essential elements deficiency during specific critical developmental windows could increase autism risk and severity, indicating a state of systemic elemental dysregulation in autism. Arora found that fetal levels of manganese and zinc were reduced in infants who developed autism than their monozygotic or dizygotic twin discordant for autism[97]. In addition, Curtin *et al*[98] studied zinc-copper cycles in a Sweden nationwide study of twins using unique tooth-matrix biomarkers that directly measure fetal elemental uptake. They found an altered fetal and postnatal zinc-copper rhythmicity in autism with shorter cycle duration, reduced regularity, and diminished complexity than in those who did not develop autism. This altered pattern of zinc-copper cycles had a sensitivity between 85% and 100% and a specificity between 90% and 100% for the diagnosis of autism. Some studies showed that maternal vitamin D deficiency in the first or second trimester is associated with an increased risk of autism[99,100]. However, a more recent

study by Madley-Dowd found no significant association or causation of maternal vitamin D deficiency during pregnancy with an increased risk of autism in the offspring[101]. These contradictory results of studies may need more research to confirm or rule out the effects of vitamin D deficiency on the increased risk of autism. Folic acid is an essential nutrient for cell division and rapid tissue growth during fetal development, affecting all the tissues, including the brain[102]. In the same way as vitamin D, gestational folic acid has a complex relationship with autism development. There are some contradictory results about the effects of folic acid deficiency during pregnancy and the risk of the development of autism. It is suggested that poor folic acid intake during pregnancy may raise the risk of neurodevelopmental disorders, including autism[103]. Steenweg-de Graaff *et al*[104] found no association of maternal folic acid concentration at 13 wk of gestation with the risk of autism in the offspring. However, they found that maternal antenatal supplementation with folic acid is associated with fewer child autistic traits. On the other hand, Egorova *et al*[105] found weak evidence that high maternal serum folate during early pregnancy may increase the risk of autism in offspring. This contradiction of the result may be explained by the differences between the reduced (folinic acid or methyl-tetrahydrofolate) and the synthetic oxidized forms of folic acid. The oxidized form inhibits folate metabolism, while reduced forms do not[106]. Because of the conflicting results of different studies, we need to do more research at different gestational periods and with reduced forms of folic acid supplementation.

Biophysical profile

Fetal ultrasound is an outstanding tool for studying abnormal fetal development. It is commonly used to follow up on fetal growth and detect early fetal anomalies throughout pregnancy. Multiple fetal abnormalities (especially cardiac, urinary, cranial, and brain anomalies) are significantly more prevalent in patients with autism, especially in severe cases [107]. Fetuses with autism have a narrower head and a relatively broader ocular distance than typically developed fetuses. The more anomalies present, the more severe the autism is. The association between fetal anomalies and autism may be due to underlying genetic and/or environmental factors that cause autism and congenital disabilities, or the birth presence of abnormalities may predispose a child to develop autism[108]. The presence of these multi-anomalies may also indicate the abnormal multiorgan embryonic development in patients with autism and suggest the importance of using fetal ultrasonography as a biomarker for autism. Regev *et al*[109] observed that female patients with autism have significantly more ultrasonography-detected fetal anomalies and a higher prevalence of multiple abnormalities than male patients with autism.

During antenatal life, the brain goes through complex and coordinated differentiation and growth processes, which are critical for typical brain structure and function development. Abnormalities in these processes can cause brain structure and function changes and increase the risk of neurodevelopmental disorders[110]. Altered brain growth is often observed in individuals with autism, specifically during the first year of life. Several studies have recognized numerous abnormalities in different brain regions and structures in individuals with autism, particularly the cortex, amygdala, and cerebellum[22]. Blanken *et al*[111] also reported this abnormal brain growth, who prospectively examined the altered fetal brain growth trajectories by examining prenatal head growth in babies who further developed autism. They compared them with typically developed children and related this finding to the severity of autism symptoms. They studied 3,820 children from two population groups: The Netherlands and Australia; 60 children developed autism. They used latent growth curve models to examine the relationship between fetal head circumference measured by fetal ultrasound at three different time points (at first, second, and third trimesters) and autistic features measured in postnatal life using the Social Responsiveness Scale or the Autism-Spectrum Quotient. They found a weak association between lower initial prenatal head circumference and increasing autistic traits in the Dutch cohort but not in the Australian cohort, nor when the two cohorts were analyzed together. These mixed findings suggest that we need more research on this point. Altered prenatal brain growth seems to be a significant risk factor for autism. Although the exact mechanisms underlying this association are still not fully realized, studies suggest that neural circuit development and connectivity changes may have a role[112].

Fetal ultrasound can provide useful information about fetal motor activity, heart rate variability, and other behavioral markers. Many studies have suggested that there may be some differences in fetal neurodevelopmental behavior between children who later have typical development and those who develop autism[113]. Fetal ultrasound is also used to assess fetal neurodevelopmental behavior, which could predict the neuronal outcome of the baby. Hata *et al*[114] used antenatal four-dimensional ultrasound to assess fetal neurodevelopment using Kurjak's antenatal neurodevelopmental scoring test between 28 and 38 wk of gestation. A low score between 0 and 5 is abnormal and denotes a strong possibility of postnatal developmental disabilities, including autism. Conversely, a score between 6 and 9 is borderline, and a score between 10 and 16 is considered normal. They suggested that the KANET assessment may be a helpful diagnostic tool to predict postnatal developmental disabilities. However, many confounding factors could affect the fetus's behavior, such as maternal stress or medication use and other environmental factors that could affect the fetus and consequently affect the scoring. These factors make it challenging to determine whether fetal behavior differences accurately indicate the increased risk of autism.

Radiological profile

Antenatal magnetic resonance imaging (MRI) brain is a diagnostic method that can be used to assess the fetal brain during pregnancy and might be applied as a potential tool to identify the risk of autism in infants. Recently, there has been a growing interest in the relationship between fetal MRI brain and the risk of having autism in childhood[115]. However, studies brought mixed results. Kyriakopoulou *et al.* investigated the presence of autism in twenty-four children [20 males/4 females] with isolated ventriculomegaly and altered cortical development by fetal MRI brain, compared with ten controls. Children with ventriculomegaly were more liable to have difficulties in sustained attention, working memory, and sensation-seeking behaviors and were more likely to have autistic features[116]. In addition, a group of scientists from Harvard University and Boston Children's Hospital, United States, examined MRI

scans of thirty-nine fetuses with an average gestational age of 25 wk. They noted two enlarged brain areas in fetuses who developed autism in infancy and childhood. Babies who developed autism had an enlarged insula lobe (seen as early as 25 wk). Insula is linked to sensory stimuli processing, socialization, and decision-making processes. It appeared more prominent than the typically developed fetuses. They also showed increased amygdala volume. The amygdala is also responsible, among other brain areas, for emotional processing and interpretation of the facial expressions of others[117]. This observed hypertrophism was previously discovered a few years ago in school-age children with autism[118].

On the other hand, a study from the University of North Carolina, United States, showed that the amygdala was normal in babies who developed autism up to 6 mo of age, then began to enlarge between 6 and 12 mo before the appearance of the clinical manifestations of autism, and continue to grow to 12-24 mo, the age at which the first clinical manifestations of autism including interpersonal difficulties usually appear. There is a positive correlation between the Amygdala growth rate and the severity of autism. The faster the growth rate, the worse the autism manifestations of the condition[119]. We should consider the safety of fetal MRI as it may induce maternal stress, high acoustic noise, and induction of preterm labor. However, the benefits of fetal MRI mostly outweigh the risks, mainly when experienced radiographer technicians perform the procedure. Table 2 summarises the various antenatal markers of autism.

Neonatal and early infancy markers for the risks of autism

Early identification of autism allows the timely launching of targeted therapies, which can help optimize different cognitive functions impaired in autism. Different studies tried to identify autism early in newborns and early infancy, depending on different physical, behavioral, biochemical, and imaging markers (Table 3).

Neonatal physical and behavioural profile of autism

Even though clinicians are identifying autism earlier than before, some children still have a delayed diagnosis till the age of six years. Differences in screening tools and diagnostic abilities in various clinical settings can affect the timing of autism diagnosis. A neonatal physical and behavioral profile of autism refers to the physical and behavioral characteristics identified in infants who later develop autism. However, we should emphasize that there is no one standard set of features that could predict the development of autism. Some patterns have emerged and are associated with an increased risk of autism[120].

Many studies focused on studying the motor and behavioral response changes that could be observed during the first year of life and their relation to later diagnosis of autism. Physically, neonates with future diagnoses of autism may have large or abnormal head sizes at birth and throughout early childhood, which may reflect early brain overgrowth in children with autism[121]. However, in their meta-analysis, Crucitti *et al*[122] showed age and sex differences in the head circumference of neonates and infants who developed autism. They found that girls with autism aged 12-17 mo had smaller head sizes, while boys were more likely to have significant head size differences at birth and between 60 and 100 mo, being small between 6 and 11 mo and large between 12 and 17 mo. They also found that average head size was not atypical finding in autism. Moreover, girls were more likely to have significant head size differences between 36 and 59 mo and were less likely at birth.

They may also have hypertelorism (Increased intra-ocular distance), anteriorly rotated ears, long nose back, abnormal mouth shape, and facial asymmetries[123]. Gorczyca *et al*[124] found a statistically non-significant connection between the degree of dysmorphia and the presence of some physical disorders in first-degree relatives. In addition, some studies reported that infants who develop autism later in childhood tend to have longer birth body lengths than typically developed infants[125]. This finding may be related to genetic or environmental effects on fetal growth and development.

Some studies have reported that infants who later develop autism may show subtle changes in the neonatal period before the onset of more overt symptoms. Therefore, it could be challenging to be recognized. They may have abnormalities in motor development during the first year of life. For example, by the age of one month, they may have arm tone deficits and asymmetric visual tracking. They may also have hypotonia, hyperreflexia, poor movement quality, head lag, delayed or missing major motor development, and delayed milestones, such as sitting or crawling, or prefer using one hand over the other[126,127]. Children with autism have lower heart rate variability, as shown by Lory *et al*[128], who found significantly lower tonic heart rate variability in children with autism than in children with typical development. Reducing noradrenergic activity could enhance and improve different aspects of network processing and thus improve cognitive abilities, such as verbal problem-solving, in children with autism[129]. Moreover, the presence of reduced heart rate variability could predict the response to propranolol therapy in improving cognitive functions in children with autism[130]. In addition, Nyström *et al*[131] found that the presence of enhanced pupillary light reflex during infancy is associated with a greater risk of developing autism in toddlerhood, which may indicate the important role of sensory atypicality in the pathogenesis of autism. They also are more liable for sleep disturbances and gastrointestinal symptoms, such as constipation, diarrhea, or gastroesophageal reflux, in the neonatal period than typically developing infants[132, 133].

As abnormal motor behaviors are a very characteristic feature of autism, movement analysis during early infancy may be a valuable tool for the early diagnosis of autism. However, autism-associated movement disorders vary from child to child, with disturbances in some or all of the development milestones, including lying, righting, sitting, crawling, and walking[134]. Disturbances of movement could be identified obviously at the age of 4-6 mo and occasionally even at birth, using the Eshkol-Wachman Movement Analysis System using still-frame videodisc analysis. Movement disturbances represent an intrinsic part of autism that could present at birth. It can be used to diagnose the presence of autism even during the first few months of life[135].

Infants later diagnosed with autism may demonstrate early deficits in social behavior, specifically in joint attention, eye contact, orienting to names, facial expressions, social smiles, attention, and tolerance of social touch. They may exhibit atypical sensory processing, with hypersensitivity or hyposensitivity to touch, sounds, or visual stimuli, representing

Table 3 Neonatal and early infancy markers for the risks of autism

Marker	Details
Physical markers	<p>Large or abnormal head sizes at birth and throughout early childhood</p> <p>Smaller head sizes in girls</p> <p>Long body lengths at birth</p> <p>Hypertelorism, anteriorly rotated ears, long back of the nose, abnormal shape of the mouth, and facial asymmetries</p> <p>Abnormal motor development during the first year of life <i>e.g.</i>, hypotonia, hyperreflexia, poor movement quality, head lag, delayed or missing major motor development, and delayed milestones, such as sitting or crawling, or prefer using one hand over the other</p> <p>Asymmetric visual tracking</p> <p>Reduced heart rate variability</p> <p>Enhanced pupillary light reflex during infancy</p> <p>More liable for sleep disturbances and gastrointestinal symptoms, such as constipation, diarrhea, or gastroesophageal reflux</p>
Social & behavioural markers	<p>Deficits in social behavior, specifically in joint attention, eye contact, orienting to names, facial expressions, social smiles, attention, and tolerance of social touch</p> <p>Atypical sensory processing, with hypersensitivity or hyposensitivity to touch, sounds, or visual stimuli</p> <p>Dislike being touched and cuddled</p> <p>Lie in the bassinet constantly and cry when being held up</p> <p>Avoid eye contact or have difficulty following a person's gaze when directing the infant's attention to something</p> <p>Reduced visual attention to social stimulation</p> <p>Impaired orienting to novel stimuli at the age of two months</p> <p>Reduced interest in social interaction or decreased responsiveness to social cues</p> <p>Lie on one of the extremes of being very low or very high needs</p>
Immunological profile	<p>Neonatal cord blood anti-brain antibodies, especially against both 39kDa and 73kDa proteins</p> <p>Abnormalities in the concentrations of total IgG and IgG 4</p> <p>Presence of anti-dopamine D2L receptors and anti-tubulin autoantibodies and the ratio of the anti-dopamine D2L to D1 receptor antibodies</p> <p>Folate receptor-alpha autoantibodies</p> <p>High immunoglobulin A in the stool</p>
Inflammatory profile	<p>High neonatal C-reactive protein levels</p> <p>Decreased levels of α-2-macroglobulin, ferritin, and serum amyloid P</p> <p>High IL-1B, IL-4, IL-6, IL-8, interferon-gamma, eotaxin, and monocyte chemotactic protein-1 levels</p> <p>Low transforming growth factor-β1 levels</p>
Biochemical & metabolic profile	<p>Low blood levels of Brain-derived neurotrophic factor</p> <p>Neonatal hyperbilirubinemia</p>
Hormonal profile	<p>Reduced neonatal CSF or plasma vasopressin concentration</p> <p>Low plasma or salivary oxytocin levels</p> <p>Reduced oxytocin receptor number</p>
Brainstem function	<p>Abnormal neonatal auditory brainstem responses</p>

CSF: Cerebrospinal fluid; IgG: Immunoglobulin G; IL: Interleukin; kDa: Kilodalton.

manifestations of atypical sensory processing. They dislike being touched or cuddled, constantly lie in the bassinet, and cry when held up. Infants who later develop autism may also show differences in eye gaze compared to typically developing infants. They may avoid eye contact or have difficulty following a person's gaze when directing the infant's attention to something[136-138]. They also do not look at the face and try to avoid eye contact even during nursing, which may appear too early by the age of two weeks. They may have reduced visual attention to social stimulation and impaired orienting to novel stimuli at the age of two months[139]. They may also show differences in social respons-

iveness, such as reduced interest in social interaction or decreased responsiveness to social cues. They also lie on one of the extremes of having very low or very high needs, *e.g.*, needing to be held constantly or avoiding touching. They also may lack proper response to sounds after rolling out hearing problems[140,141]. These early signs could be hard to detect and are not always apparent in all infants who will develop autism. Still, they may be crucial and helpful for early autism identification and intervention.

Prematurity is a significant risk factor for autism. Wong *et al*[142] showed that premature babies below 30 wk of gestation had more significant social-communication problems and autistic behavior in early childhood than seen in full-term babies as assessed by the Quantitative Checklist for Autism in Toddlers (Q-CHAT). Less attention maturation observed in preterm babies can negatively impact how long they can stay actively interested in social interaction. Eye gaze is an indisputable means of communication. Preterm babies are different from full term in many behavioral aspects. They typically avert their gaze more often and for longer periods in early social interactions than full-term infants due to less optimal attention maturation in preterm children[143]. Therefore, preterm babies who demonstrated gaze aversion and endpoint nystagmus had better language scores on the Bayley-III. On the other hand, Pineda *et al*[144] found that preterm babies with absent gaze aversion and absent endpoint nystagmus during the neonatal period showed positive screening for autism using Modified Checklist for Autism in Toddlers (M-CHAT) at the age of two years.

In neonates, a fascinating Japanese study by Tokunaga *et al*[145] prospectively demonstrated the relationship between behavioral features during the neonatal period and social behavior and sensory disorders at 18 mo to early detect and intervene in children with autism. They studied apparently healthy 105 full-term neonates for the behavioral features using the Neonatal Behavioral Assessment Scale (NBAS) between 2 and 7 d after birth. Then, they were re-assessed at 18 mo of age using the Japanese version of M-CHAT (M-CHAT-JV) and the Infant/Toddler Sensory Profile (ITSP). They found that 15.2% of the infants were M-CHAT-JV-positive, with significant differences between the M-CHAT-JV-positive and M-CHAT-JV-negative groups in two of the NBAS clusters: motor and orientation. They also found a significant negative correlation between the NBAS orientation cluster and the "low registration" and "auditory processing" sections in the ITSP. In addition, they found a negative correlation between the NBAS motor cluster and the "sensation avoiding" and "tactile processing" sections in ITSP. Logistic regression analysis also showed a significant association between the NBAS orientation cluster and ITSP low registration with the M-CHAT-JV at 18 mo. Their results suggested a significant relationship between the NBAS orientation cluster in full-term neonates and the social behavior and sensory features at 18 mo[145]. These findings imply the need to develop therapeutic methods that can be applied from the first few months of life to manage autism.

Neonatal immunological profile of autism

As previously mentioned, prenatal and/or postnatal exposure to anti-brain antibodies plays an important pathoplastic role in autism as they enhance autism severity by damaging cognitive processes and adaptive functioning, boosting motor stereotypies, altering the sleep/wake cycle, and delaying or halting neurodevelopment, primarily verbal and non-verbal language. Some mothers of children with autism (about 7%) had antibodies to 39kDa and 73kDa proteins during gestation. Detection of antibodies against both 39kDa and 73kDa proteins during mid-gestation predicts early and severe autism in the offspring[81]. Anti-brain antibodies can be used as biomarkers predicting autism severity and clinical features and possibly providing new avenues for preventive and therapeutic strategies, including predicting the response to treatment. A systematic review and meta-analysis by Rossignol *et al*[146] showed abnormalities in the total IgG and IgG 4 subclass concentrations related to social impairments and aberrant behavior. They also studied the immunomodulatory effects of intravenous immunoglobulins in children with autism. Using intravenous immunoglobulins showed clinical improvements in irritability, hyperactivity, cognition, attention, communication, social interaction, eye contact, speech, response to commands, echolalia, drowsiness, and decreased activity. In some cases, the early use of intravenous immunoglobulins led to the complete resolution of autism symptoms. The presence of anti-dopamine D2L receptors and anti-tubulin autoantibodies and the ratio of the anti-dopamine D2L to D1 receptor antibodies can predict the treatment response to intravenous immunoglobulin. These antibodies can serve as a marker to predict patients who may respond better to intravenous immunoglobulin therapy[147].

Another interesting finding is the high prevalence of folate receptor-alpha autoantibodies in children with autism (71%) compared to children with typical development or children with developmental disabilities but not with their siblings[148]. These antibodies induce cerebral folate deficiency and consequently induce autism symptoms. Consequently, the presence of folate receptor-alpha autoantibodies in infancy may help to predict the risk of autism as well as the response to leucovorin (folinic acid) treatment[149]. Another crucial immunological marker of autism in infants and children is immunoglobulin A (Ig A) in the stool. Ig A is the main immunoglobulin secreted by the gastrointestinal immune cells. Zhou *et al*[150] found higher stool Ig A levels in children with autism than in typically developed children, suggesting the presence of gut immune abnormalities in patients with autism and can explain the gene-environmental interaction in the pathogenesis of autism. It also suggests the possible use of stool Ig A as a possible marker of autism.

Neonatal and infancy inflammatory profile of autism

As previously mentioned, the immune activation and signaling pathways can impact the child's neurodevelopment and may contribute to the pathogenesis of autism. However, this effect varies considerably with the genetic background and many perinatal environmental factors[151]. High neonatal C-reactive protein levels are consistently associated with an increased risk of autism compared to the controls. On the other hand, decreased levels of α -2-macroglobulin, ferritin, and serum amyloid P are associated with increased autism risk in the matched sibling comparison. The changes observed in these acute-phase reactant proteins are indications of maternal immune activation, which in turn increases the risk of autism[152]. In addition, a meta-analysis by Masi *et al*[153] showed that elevated levels of IL-1 β , IL-6, IL-8, interferon-

gamma, eotaxin, and monocyte chemotactic protein-1, and lower levels of transforming growth factor- β 1 in children who have autism than healthy control. Another study by Krakowiak *et al*[154] showed that high neonatal levels of IL-1 β are associated with an increased risk of mild to moderate autism. Furthermore, high neonatal levels of IL-4 are independently associated with an increased risk of severe autism. However, there is no single cytokine abnormality can be used as a marker of increased risk of autism. We need more extensive prospective studies to investigate the abnormal cytokine profiles that could be strongly associated with autism at different stages of development.

Neonatal and infancy biochemical and metabolic profile of autism

Brain-derived neurotrophic factor (BDNF) is essential for neuronal survival and growth. It serves as a neurotransmitter modulator and contributes to neuronal plasticity, which is critical for learning and memory[155]. A Meta-analysis by Liu *et al*[156] found that the blood levels of BDNF were lower in neonates who later developed autism than in children with typical neurodevelopment. However, contradictory results with previous studies warrant more studies to facilitate a more robust conclusion[157]. There is substantial evidence for the possible association between neonatal hyperbilirubinemia and the later risk of developing autism. The risk increases in the presence of prematurity, severe jaundice, insufficient milk intake, phototherapy, and dark-skinned babies due to a heightened risk of missed diagnosis, delayed care access, and poorer settings[158,159].

Neonatal and infancy hormonal profile

Besides the antenatal effects of sex and steroid hormones on brain development and the risk of autism, other hormones could also play a role. Vasopressin, a social neuropeptide arginine, is found to be significantly lower in the cerebrospinal fluid (CSF) of children with autism than in healthy controls. Oztan *et al*[160] studied CSF samples from 913 febrile infants between 0-3 mo as a part of their medical care. They stored the collected samples at -70°C. Eleven children out of 913 developed manifestations of autism. They compared the vasopressin concentration in the CSF samples obtained from these eleven children with 22 children with typical neurodevelopment (Ratio 1:2). They found a significant reduction of vasopressin concentration in the neonatal CSF samples from children who developed autism compared to those with typical development, with the highest accuracy when patients who had comorbid attention-deficit/hyperactivity disorder with autism were removed from the analysis. These findings suggest the beneficial use of CSF vasopressin levels as an early marker for autism in neonates with a high risk of developing autism and in behaviourally symptomatic infants. In addition, Zhang *et al*[161] found lower plasma levels of vasopressin in mothers of children with autism than in mothers of typically developed children. They also found that children with autism with higher vasopressin levels are less likely to have repetitive behavior. They also found that children with higher plasma oxytocin levels have less verbal communication impairment[161]. Moreover, Pichugina *et al*[162] found lower salivary oxytocin levels in children with autism and intellectual disabilities than in children with Intellectual disabilities without autism. They also found a direct negative correlation between salivary oxytocin levels and the severity of autism. Another study by Gottlieb *et al*[163] showed that the severity of autism is inversely proportional to the normalized number of oxytocin receptors, indicating the significant role of the oxytocin receptor number in the severity of autism. It also suggests the potential use of vasopressin and promising therapeutic tool to improve social cognition in children with autism[164].

Neonatal brainstem function

Only the lower parts of the nervous system (the brain stem and spinal cord) are very well developed by birth. In contrast, the higher regions (the limbic system and cerebral cortex) are still relatively primitive. Therefore, the lower brain mainly controls a newborn's behavior. Therefore, kicking, grasping, rooting, crying, sleeping, and feeding are mainly functions of the brain stem and spinal cord[165]. The brainstem has a revolutionary role in developing humans' social development. Therefore, the integrity of brainstem sensory information transmission during the final weeks of gestation and the early neonatal period may support the development of social engagement[166].

Cohen *et al*[167] evaluated the contribution of initially abnormal neonatal auditory brainstem responses (ABRs) and 4-month arousal-modulated attention visual preference to later autism behaviors in neonatal intensive care unit graduates. They compared NICU graduates with normal ABRs ($n = 28$) to those with initially abnormal ABRs ($n = 46$) that later resolved. At four months post-term age, visual preference (measured after feeding) for a random check pattern flashing at 1, 3, or 8 Hz and gestational age served as additional predictors. Outcome measures were Pervasive Developmental Disorder Behavior Inventory (PDDBI) scores at 3.4 years and developmental quotients (DQ) obtained around the same age with the Griffiths Mental Development Scales (GMDS). They found that the preferences for higher stimulation rates at four months were highly correlated with PDDBI scores and the GMDS Hearing and Speech DQ, but only in those with initially abnormal ABRs. The effects were most potent for a PDDBI social competence measure most associated with a diagnosis of autism. For those with abnormal ABRs, increases in preference for higher stimulation rates as infants were linked to nonlinear increases in the severity of autism at three years and an autism diagnosis. Therefore, abnormal ABRs were associated with later reports of repetitive and ritualistic behaviors irrespective of a 4-mo preference for stimulation. The common occurrence of initially abnormal neonatal ABRs and preference for more stimulation at four months, both indices of early brainstem dysfunction, may be a marker for the development of autism in this cohort[167].

Challenges to early detection of autism

Several reasons make early detection of autism a real challenge. Lack of parental, family, caregivers, or even healthcare providers' awareness about the disorder is one of the main challenges that enface early detection of autism. Despite rising awareness of autism, many people are not familiar with the symptoms and signs of autism, resulting in delayed diagnosis and treatment. Another critical challenge is the variability in symptoms[136]. Autism is a complex and common

neurodevelopmental disorder that affects children differently, with various symptoms and severity levels. Symptoms may also vary depending on the child's age, gender, and cultural background. This observation is particularly evident in young infants and children under 24 mo of age who may not yet display many characteristic symptoms[168]. In addition, the lack of specific biological markers or diagnostic tests for a definitive diagnosis of autism is another real challenge (Table 4).

Furthermore, the diagnostic criteria for autism are changing over time, and experts continuously debate about what establishes a diagnosis of autism. Diagnosis is typically based on behavioral observations and evaluations, and the screening tools are not always accurate. These diagnostic tools are very subjective and vary between clinicians. All these together can result in false positives or negatives, leading to overdiagnosis, underdiagnosis, misdiagnosis, or delayed diagnosis[169]. Moreover, autism frequently occurs with many neurological, psychological, and physical co-morbidities and overlaps with many other conditions, such as attention deficit hyperactivity disorder, intellectual disability, and language disorders, making it hard to differentiate between them[170].

Differences in cultural and linguistic backgrounds harden the abilities of healthcare providers to recognize early signs of autism, remarkably in minority or immigrant populations with significant cultural and linguistic barriers. Healthcare providers may not be familiar with cultural customs, norms, and practices that can impact the presentation of symptoms [171]. Even with the increased awareness about autism, many families still suffer from the stigma and fear surrounding autism, making it difficult for parents and caregivers to ask for help for their children. This stigma may prevent early diagnosis and intervention, significantly impacting children's development, well-being, and long-term outcomes of children with autism[172]. In addition to all these obstacles, limited funding may prevent the early detection and treatment of children with autism. Early detection and intervention for autism require resources and funding, which may be limited in some areas or for some families[173].

In addition, screening tools, such as the Modified Checklist for Autism in Toddlers (M-CHAT), which are used to identify children who may be at risk for autism, are not always readily available, and many pediatricians and healthcare providers may not be familiar with them, particularly in rural or low-income areas. These limited financial and expert resources can make it challenging to obtain a timely diagnosis of autism, resulting in delayed treatment and poorer outcomes for children with autism[174]. Handling these challenges requires raising awareness, improving access to diagnostic tools, dealing with culturally sensitive concepts, and defining straightforward approaches to screening and diagnosis. Early recognition and management are critical for improving outcomes for children with autism. It is crucial to continue addressing these challenges to enhance the quality of life of children with autism and their families[175].

Limitations of the study

As autism is a multi-dimensional disorder, various techniques and approaches have been used to develop different biomarkers to diagnose autism. However, only some biomarkers underwent validation studies. In addition, many other potential diagnostic biomarkers underwent just preliminary investigation and still need further optimization. Moreover, many of the included studies were based on questionnaires depending on the parents or the caregiver's memories and subjective judgment, therefore carrying the risk of memory effects bias such as rosy retrospection, egocentric bias, and cross-race effect, and consequently affecting the accuracy of the results. In addition to the memory bias, many studies used typically developing non-sibling children as controls and did not include typically developed siblings or children with developmental delays without autism. These two types of controls are clinically ideal and relevant as a comparison population as they share many risk factors with the children who developed autism and consequently improve the biomarkers' sensitivity, specificity, and predictive values. One more limitation of the suggested biomarkers is the stage of measurement. Many of the suggested biomarkers were measured after the child was diagnosed with autism, therefore missing the early detection phase and may not be accurate or sensitive enough if used early.

CONCLUSION

Autism is a complex neurodevelopmental disorder, typically diagnosed during the first three years. Of life with a spectrum of symptoms ranging from mild to severe and varies from one child to another. Pre-autism refers to the early stage of autism and the signs and symptoms that appear during the developmental stages of a child that may indicate a potential risk for developing autism later in life. Early detection and intervention are crucial for improving outcomes for individuals with autism. Various physical, biochemical, hormonal, and imaging biomarkers are developed to assist in prenatal and early-life diagnosis of autism. However, every biomarker has its accuracy and limitations. To improve early detection of autism, we should try to overcome the various challenges that enface the diagnosis, such as improving the community awareness of early signs of autism, easing the access to diagnostic tools, trying to remove the stigma attached to the diagnosis of autism, and dealing with the different culturally sensitive concepts related to it. In addition, the scientific community must work hard to replicate studies with more different targeted populations, perform more randomized controlled studies with larger numbers of participants, and define straightforward and accessible gold standard screening and diagnostic approaches to detect autism early among newly developing young infants and children. We also should consider that autism is a heterogeneous spectrum with different presentations, symptomatology, and severity. Therefore, we may need to develop a group of biomarkers and diagnostic tools that could fit the various conditions we may face, aiming to provide optimized and individualized types of treatment. Therefore, we can say that we have just started our first step in screening autism. However, the journey is too long to achieve the aim.

Table 4 Challenges to early detection of autism

Challenges	Details
Cultural & educational	Lack of adequate awareness Cultural and linguistic barriers Stigma and fear
Disease-related	Continuous variability in symptoms and signs Diagnosis is largely subjective Frequent co-morbidities and overlapping with other disorders Lack of specific biological markers and diagnostic criteria and tests
Resources-related	Limited funding, access to screening, and healthcare facilities

ACKNOWLEDGEMENTS

We thank the anonymous referees and editors for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M collected the data, wrote, and revised the manuscript; The guidelines of the PRISMA 2009 were adopted while writing the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Egypt

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536.

Corresponding Author's Membership in Professional Societies: Faculty of Medicine, Tanta University, Egypt; University Medical Center, King Abdulla Medical City. Arabian Gulf University.

S-Editor: Liu JH

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- 1 **Park HR**, Lee JM, Moon HE, Lee DS, Kim BN, Kim J, Kim DG, Paek SH. A Short Review on the Current Understanding of Autism Spectrum Disorders. *Exp Neurobiol* 2016; **25**: 1-13 [PMID: 26924928 DOI: 10.5607/en.2016.25.1.1]
- 2 **Al-Biltagi M**, Saeed NK, Qaraghuli S. Gastrointestinal disorders in children with autism: Could artificial intelligence help? *Artif Intell Gastroenterol* 2022; **3**: 1-12 [DOI: 10.35712/aig.v3.i1.1]
- 3 **Baird G**, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, Charman T. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet* 2006; **368**: 210-215 [PMID: 16844490 DOI: 10.1016/S0140-6736(06)69041-7]
- 4 **Becerra TA**, von Ehrenstein OS, Heck JE, Olsen J, Arah OA, Jeste SS, Rodriguez M, Ritz B. Autism spectrum disorders and race, ethnicity, and nativity: a population-based study. *Pediatrics* 2014; **134**: e63-e71 [PMID: 24958588 DOI: 10.1542/peds.2013-3928]
- 5 **Bahmani M**, Sarrafchi A, Shirzad H, Rafieian-Kopaei M. Autism: Pathophysiology and Promising Herbal Remedies. *Curr Pharm Des* 2016; **22**: 277-285 [PMID: 26561063 DOI: 10.2174/1381612822666151112151529]
- 6 **Sandin S**, Lichtenstein P, Kuja-Halkola R, Hultman C, Larsson H, Reichenberg A. The Heritability of Autism Spectrum Disorder. *JAMA* 2017; **318**: 1182-1184 [PMID: 28973605 DOI: 10.1001/jama.2017.12141]
- 7 **Famitafreshi H**, Karimian M. Overview of the Recent Advances in Pathophysiology and Treatment for Autism. *CNS Neurol Disord Drug Targets* 2018; **17**: 590-594 [PMID: 29984672 DOI: 10.2174/1871527317666180706141654]
- 8 **Al-Beltagi M**, Saeed NK, Elbeltagi R, Bediwy AS, Aftab SAS, Alhawamdeh R. Viruses and autism: A Bi-mutual cause and effect. *World J Virol* 2023; **12**: 172-192 [PMID: 37396705 DOI: 10.5501/wjv.v12.i3.172]
- 9 **Al-Beltagi M**. Autism medical comorbidities. *World J Clin Pediatr* 2021; **10**: 15-28 [PMID: 33972922 DOI: 10.5409/wjcp.v10.i3.15]

- 10 Müller RA. The study of autism as a distributed disorder. *Ment Retard Dev Disabil Res Rev* 2007; **13**: 85-95 [PMID: 17326118 DOI: 10.1002/mrdd.20141]
- 11 Oztenekcioglu B, Mavis M, Osum M, Kalkan R. Genetic and Epigenetic Alterations in Autism Spectrum Disorder. *Glob Med Genet* 2021; **8**: 144-148 [PMID: 34877571 DOI: 10.1055/s-0041-1735540]
- 12 Rosen NE, Lord C, Volkmar FR. The Diagnosis of Autism: From Kanner to DSM-III to DSM-5 and Beyond. *J Autism Dev Disord* 2021; **51**: 4253-4270 [PMID: 33624215 DOI: 10.1007/s10803-021-04904-1]
- 13 Faras H, Al Ateeqi N, Tidmarsh L. Autism spectrum disorders. *Ann Saudi Med* 2010; **30**: 295-300 [PMID: 20622347 DOI: 10.4103/0256-4947.65261]
- 14 Frye RE. Social Skills Deficits in Autism Spectrum Disorder: Potential Biological Origins and Progress in Developing Therapeutic Agents. *CNS Drugs* 2018; **32**: 713-734 [PMID: 30105528 DOI: 10.1007/s40263-018-0556-y]
- 15 Ravizza SM, Solomon M, Ivry RB, Carter CS. Restricted and repetitive behaviors in autism spectrum disorders: the relationship of attention and motor deficits. *Dev Psychopathol* 2013; **25**: 773-784 [PMID: 23880391 DOI: 10.1017/S0954579413000163]
- 16 Hus Y, Segal O. Challenges Surrounding the Diagnosis of Autism in Children. *Neuropsychiatr Dis Treat* 2021; **17**: 3509-3529 [PMID: 34898983 DOI: 10.2147/NDT.S282569]
- 17 Mandell DS, Novak MM, Zubritsky CD. Factors associated with age of diagnosis among children with autism spectrum disorders. *Pediatrics* 2005; **116**: 1480-1486 [PMID: 16322174 DOI: 10.1542/peds.2005-0185]
- 18 Hyman SL, Levy SE, Myers SM; Council on children with disabilities, section on developmental and behavioral pediatrics. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics* 2020; **145** [PMID: 31843864 DOI: 10.1542/peds.2019-3447]
- 19 Elder JH, Kreider CM, Brasher SN, Ansell M. Clinical impact of early diagnosis of autism on the prognosis and parent-child relationships. *Psychol Res Behav Manag* 2017; **10**: 283-292 [PMID: 28883746 DOI: 10.2147/PRBM.S117499]
- 20 Penn HE. Neurobiological correlates of autism: a review of recent research. *Child Neuropsychol* 2006; **12**: 57-79 [PMID: 16484102 DOI: 10.1080/09297040500253546]
- 21 Hashem S, Nisar S, Bhat AA, Yadav SK, Azeem MW, Bagga P, Fakhro K, Reddy R, Frenneaux MP, Haris M. Genetics of structural and functional brain changes in autism spectrum disorder. *Transl Psychiatry* 2020; **10**: 229 [PMID: 32661244 DOI: 10.1038/s41398-020-00921-3]
- 22 Ha S, Sohn IJ, Kim N, Sim HJ, Cheon KA. Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan. *Exp Neurol* 2015; **24**: 273-284 [PMID: 26713076 DOI: 10.5607/en.2015.24.4.273]
- 23 Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. *Trends Neurosci* 2008; **31**: 137-145 [PMID: 18258309 DOI: 10.1016/j.tins.2007.12.005]
- 24 Redcay E. The superior temporal sulcus performs a common function for social and speech perception: implications for the emergence of autism. *Neurosci Biobehav Rev* 2008; **32**: 123-142 [PMID: 17706781 DOI: 10.1016/j.neubiorev.2007.06.004]
- 25 Kim JE, Lyoo IK, Estes AM, Renshaw PF, Shaw DW, Friedman SD, Kim DJ, Yoon SJ, Hwang J, Dager SR. Laterobasal amygdalar enlargement in 6- to 7-year-old children with autism spectrum disorder. *Arch Gen Psychiatry* 2010; **67**: 1187-1197 [PMID: 21041620 DOI: 10.1001/archgenpsychiatry.2010.148]
- 26 Adorjan I, Ahmed B, Feher V, Torso M, Krug K, Esiri M, Chance SA, Szele FG. Calretinin interneuron density in the caudate nucleus is lower in autism spectrum disorder. *Brain* 2017; **140**: 2028-2040 [PMID: 29177493 DOI: 10.1093/brain/awx131]
- 27 Zielinski BA, Prigge MB, Nielsen JA, Froehlich AL, Abildskov TJ, Anderson JS, Fletcher PT, Zygmunt KM, Travers BG, Lange N, Alexander AL, Bigler ED, Lainhart JE. Longitudinal changes in cortical thickness in autism and typical development. *Brain* 2014; **137**: 1799-1812 [PMID: 24755274 DOI: 10.1093/brain/awu083]
- 28 Pan YH, Wu N, Yuan XB. Toward a Better Understanding of Neuronal Migration Deficits in Autism Spectrum Disorders. *Front Cell Dev Biol* 2019; **7**: 205 [PMID: 31620440 DOI: 10.3389/fcell.2019.00205]
- 29 Hwang HM, Ku RY, Hashimoto-Torii K. Prenatal Environment That Affects Neuronal Migration. *Front Cell Dev Biol* 2019; **7**: 138 [PMID: 31380373 DOI: 10.3389/fcell.2019.00138]
- 30 Godel M, Andrews DS, Amaral DG, Ozonoff S, Young GS, Lee JK, Wu Nordahl C, Schaer M. Altered Gray-White Matter Boundary Contrast in Toddlers at Risk for Autism Relates to Later Diagnosis of Autism Spectrum Disorder. *Front Neurosci* 2021; **15**: 669194 [PMID: 34220428 DOI: 10.3389/fnins.2021.669194]
- 31 Zikopoulos B, Barbas H. Altered neural connectivity in excitatory and inhibitory cortical circuits in autism. *Front Hum Neurosci* 2013; **7**: 609 [PMID: 24098278 DOI: 10.3389/fnhum.2013.00609]
- 32 Eltokhi A, Santuy A, Merchan-Perez A, Sprengel R. Glutamatergic Dysfunction and Synaptic Ultrastructural Alterations in Schizophrenia and Autism Spectrum Disorder: Evidence from Human and Rodent Studies. *Int J Mol Sci* 2020; **22** [PMID: 33374598 DOI: 10.3390/ijms22010059]
- 33 Montanari M, Martella G, Bonsi P, Meringolo M. Autism Spectrum Disorder: Focus on Glutamatergic Neurotransmission. *Int J Mol Sci* 2022; **23** [PMID: 35409220 DOI: 10.3390/ijms23073861]
- 34 Jiang S, Xiao L, Sun Y, He M, Gao C, Zhu C, Chang H, Ding J, Li W, Wang Y, Sun T, Wang F. The GABAB receptor agonist STX209 reverses the autismlike behaviour in an animal model of autism induced by prenatal exposure to valproic acid. *Mol Med Rep* 2022; **25** [PMID: 35244195 DOI: 10.3892/mmr.2022.12670]
- 35 Barbeau WE. Neonatal and regressive forms of autism: Diseases with similar symptoms but a different etiology. *Med Hypotheses* 2017; **109**: 46-52 [PMID: 29150292 DOI: 10.1016/j.mehy.2017.09.015]
- 36 Angkustsiri K, Krakowiak P, Moghaddam B, Wardinsky T, Gardner J, Kalamkarian N, Hertz-Picciotto I, Hansen RL. Minor physical anomalies in children with autism spectrum disorders. *Autism* 2011; **15**: 746-760 [PMID: 21610186 DOI: 10.1177/1362361310397620]
- 37 Rabia A, Mahmood S, Maqbool S. Prevalence of minor physical anomalies in children with autism spectrum disorder reporting to a tertiary care hospital Lahore-Pakistan. *Pak J Med Sci* 2022; **38**: 1918-1923 [PMID: 36246712 DOI: 10.12669/pjms.38.7.6639]
- 38 Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. *Br J Psychiatry* 2009; **195**: 7-14 [PMID: 19567888 DOI: 10.1192/bjp.bp.108.051672]
- 39 Matos MB, Bara TS, Felden ÉPG, Cordeiro ML. Potential Risk Factors for Autism in Children Requiring Neonatal Intensive Care Unit. *Neuropediatrics* 2021; **52**: 284-293 [PMID: 33853162 DOI: 10.1055/s-0041-1726401]
- 40 Hoffmann TJ, Windham GC, Anderson M, Croen LA, Grether JK, Risch N. Evidence of reproductive stoppage in families with autism spectrum disorder: a large, population-based cohort study. *JAMA Psychiatry* 2014; **71**: 943-951 [PMID: 24942798 DOI: 10.1001/jamapsychiatry.2014.420]
- 41 Risch N, Hoffmann TJ, Anderson M, Croen LA, Grether JK, Windham GC. Familial recurrence of autism spectrum disorder: evaluating

- genetic and environmental contributions. *Am J Psychiatry* 2014; **171**: 1206-1213 [PMID: 24969362 DOI: 10.1176/appi.ajp.2014.13101359]
- 42 **Andoy Galvan JA**, Ramalingam PN, Patil SS, Bin Shobri MAS, Chinna K, Sahir MS, Chidambaram K. Mode of delivery, order of birth, parental age gap and autism spectrum disorder among Malaysian children: A case-control study. *Heliyon* 2020; **6**: e05068 [PMID: 33083595 DOI: 10.1016/j.heliyon.2020.e05068]
 - 43 **Alvares GA**, Licari MK, Stevenson PG, Bebbington K, Cooper MN, Glasson EJ, Tan DW, Uljarević M, Varcin KJ, Wray J, Whitehouse AJO. Investigating associations between birth order and autism diagnostic phenotypes. *J Child Psychol Psychiatry* 2021; **62**: 961-970 [PMID: 33164221 DOI: 10.1111/jcpp.13349]
 - 44 **Sandin S**, Schendel D, Magnusson P, Hultman C, Surén P, Susser E, Grønberg T, Gissler M, Gunnes N, Gross R, Henning M, Bresnahan M, Sourander A, Hornig M, Carter K, Francis R, Parner E, Leonard H, Rosanoff M, Stoltenberg C, Reichenberg A. Autism risk associated with parental age and with increasing difference in age between the parents. *Mol Psychiatry* 2016; **21**: 693-700 [PMID: 26055426 DOI: 10.1038/mp.2015.70]
 - 45 **Hultman CM**, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. *Mol Psychiatry* 2011; **16**: 1203-1212 [PMID: 21116277 DOI: 10.1038/mp.2010.121]
 - 46 **Sandin S**, Hultman CM, Klevzon A, Gross R, MacCabe JH, Reichenberg A. Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2012; **51**: 477-486.e1 [PMID: 22525954 DOI: 10.1016/j.jaac.2012.02.018]
 - 47 **Croen LA**, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. *Arch Pediatr Adolesc Med* 2007; **161**: 334-340 [PMID: 17404129 DOI: 10.1001/archpedi.161.4.334]
 - 48 **Wang Y**, Tang S, Xu S, Weng S, Liu Z. Maternal Body Mass Index and Risk of Autism Spectrum Disorders in Offspring: A Meta-analysis. *Sci Rep* 2016; **6**: 34248 [PMID: 27687989 DOI: 10.1038/srep34248]
 - 49 **Jo H**, Schieve LA, Sharma AJ, Hinkle SN, Li R, Lind JN. Maternal prepregnancy body mass index and child psychosocial development at 6 years of age. *Pediatrics* 2015; **135**: e1198-e1209 [PMID: 25917989 DOI: 10.1542/peds.2014-3058]
 - 50 **Hinkle SN**, Sharma AJ, Kim SY, Schieve LA. Maternal prepregnancy weight status and associations with children's development and disabilities at kindergarten. *Int J Obes (Lond)* 2013; **37**: 1344-1351 [PMID: 23860335 DOI: 10.1038/ijo.2013.128]
 - 51 **Neri C**, Edlow AG. Effects of Maternal Obesity on Fetal Programming: Molecular Approaches. *Cold Spring Harb Perspect Med* 2015; **6**: a026591 [PMID: 26337113 DOI: 10.1101/cshperspect.a026591]
 - 52 **Ratajczak HV**. Theoretical aspects of autism: biomarkers--a review. *J Immunotoxicol* 2011; **8**: 80-94 [PMID: 21299356 DOI: 10.3109/1547691X.2010.538749]
 - 53 **Thapar A**, Rutter M. Genetic Advances in Autism. *J Autism Dev Disord* 2021; **51**: 4321-4332 [PMID: 32940822 DOI: 10.1007/s10803-020-04685-z]
 - 54 **Nisar S**, Hashem S, Bhat AA, Syed N, Yadav S, Azeem MW, Uddin S, Bagga P, Reddy R, Haris M. Association of genes with phenotype in autism spectrum disorder. *Aging (Albany NY)* 2019; **11**: 10742-10770 [PMID: 31744938 DOI: 10.18632/aging.102473]
 - 55 **Weiss LA**, Arking DE; Gene Discovery Project of Johns Hopkins & the Autism Consortium, Daly MJ, Chakravarti A. A genome-wide linkage and association scan reveals novel loci for autism. *Nature* 2009; **461**: 802-808 [PMID: 19812673 DOI: 10.1038/nature08490]
 - 56 **Connacher R**, Williams M, Prem S, Yeung PL, Matteson P, Mehta M, Markov A, Peng C, Zhou X, McDermott CR, Pang ZP, Flax J, Brzustowicz L, Lu CW, Millonig JH, DiCicco-Bloom E. Autism NPCs from both idiopathic and CNV 16p11.2 deletion patients exhibit dysregulation of proliferation and mitogenic responses. *Stem Cell Reports* 2022; **17**: 1786 [PMID: 35830838 DOI: 10.1016/j.stemcr.2022.06.007]
 - 57 **Rein B**, Yan Z. 16p11.2 Copy Number Variations and Neurodevelopmental Disorders. *Trends Neurosci* 2020; **43**: 886-901 [PMID: 32993859 DOI: 10.1016/j.tins.2020.09.001]
 - 58 **Qiu S**, Li Y, Bai Y, Shi J, Cui H, Gu Y, Ren Y, Zhao Q, Zhang K, Lu M, Wang Y, Zhong W, Zhu X, Liu Y, Cheng Y, Qiao Y. SHANK1 polymorphisms and SNP-SNP interactions among SHANK family: A possible cue for recognition to autism spectrum disorder in infant age. *Autism Res* 2019; **12**: 375-383 [PMID: 30629339 DOI: 10.1002/aur.2065]
 - 59 **Jensen AR**, Lane AL, Werner BA, McLees SE, Fletcher TS, Frye RE. Modern Biomarkers for Autism Spectrum Disorder: Future Directions. *Mol Diagn Ther* 2022; **26**: 483-495 [PMID: 35759118 DOI: 10.1007/s40291-022-00600-7]
 - 60 **O'Brien J**, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front Endocrinol (Lausanne)* 2018; **9**: 402 [PMID: 30123182 DOI: 10.3389/fendo.2018.00402]
 - 61 **Ha M**, Kim VN. Regulation of microRNA biogenesis. *Nat Rev Mol Cell Biol* 2014; **15**: 509-524 [PMID: 25027649 DOI: 10.1038/nrm3838]
 - 62 **Wong A**, Zhou A, Cao X, Mahaganapathy V, Azaro M, Gwin C, Wilson S, Buyske S, Bartlett CW, Flax JF, Brzustowicz LM, Xing J. MicroRNA and MicroRNA-Target Variants Associated with Autism Spectrum Disorder and Related Disorders. *Genes (Basel)* 2022; **13** [PMID: 35893067 DOI: 10.3390/genes13081329]
 - 63 **Noroozi R**, Dinger ME, Fatehi R, Taheri M, Ghafouri-Fard S. Identification of miRNA-mRNA Network in Autism Spectrum Disorder Using a Bioinformatics Method. *J Mol Neurosci* 2021; **71**: 761-766 [PMID: 32875540 DOI: 10.1007/s12031-020-01695-5]
 - 64 **Tremblay MW**, Jiang YH. DNA Methylation and Susceptibility to Autism Spectrum Disorder. *Annu Rev Med* 2019; **70**: 151-166 [PMID: 30691368 DOI: 10.1146/annurev-med-120417-091431]
 - 65 **García-Ortiz MV**, de la Torre-Aguilar MJ, Morales-Ruiz T, Gómez-Fernández A, Flores-Rojas K, Gil-Campos M, Martín-Borreguero P, Ariza RR, Roldán-Arjona T, Pérez-Navero JL. Analysis of Global and Local DNA Methylation Patterns in Blood Samples of Patients With Autism Spectrum Disorder. *Front Pediatr* 2021; **9**: 685310 [PMID: 34676183 DOI: 10.3389/fped.2021.685310]
 - 66 **James SJ**, Melnyk S, Jernigan S, Pavlov O, Trusty T, Lehman S, Seidel L, Gaylor DW, Cleves MA. A functional polymorphism in the reduced folate carrier gene and DNA hypomethylation in mothers of children with autism. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 1209-1220 [PMID: 20468076 DOI: 10.1002/ajmg.b.31094]
 - 67 **Garrido N**, Cruz F, Egea RR, Simon C, Sadler-Rigglesman I, Beck D, Nilsson E, Ben Maamar M, Skinner MK. Sperm DNA methylation epimutation biomarker for paternal offspring autism susceptibility. *Clin Epigenetics* 2021; **13**: 6 [PMID: 33413568 DOI: 10.1186/s13148-020-00995-2]
 - 68 **Hannon E**, Schendel D, Ladd-Acosta C, Grove J; iPSYCH-Broad ASD Group, Hansen CS, Andrews SV, Hougaard DM, Bresnahan M, Mors O, Hollegaard MV, Bækvad-Hansen M, Hornig M, Mortensen PB, Børghlum AD, Werge T, Pedersen MG, Nordentoft M, Buxbaum J, Daniele Fallin M, Bybjerg-Grauholm J, Reichenberg A, Mill J. Elevated polygenic burden for autism is associated with differential DNA methylation at birth. *Genome Med* 2018; **10**: 19 [PMID: 29587883 DOI: 10.1186/s13073-018-0527-4]

- 69 **Parker-Athill EC**, Tan J. Maternal immune activation and autism spectrum disorder: interleukin-6 signaling as a key mechanistic pathway. *Neurosignals* 2010; **18**: 113-128 [PMID: [20924155](#) DOI: [10.1159/000319828](#)]
- 70 **Abdallah MW**, Larsen N, Grove J, Nørgaard-Pedersen B, Thorsen P, Mortensen EL, Hougaard DM. Amniotic fluid inflammatory cytokines: potential markers of immunologic dysfunction in autism spectrum disorders. *World J Biol Psychiatry* 2013; **14**: 528-538 [PMID: [22175527](#) DOI: [10.3109/15622975.2011.639803](#)]
- 71 **Che X**, Hornig M, Bresnahan M, Stoltenberg C, Magnus P, Surén P, Mjaaland S, Reichborn-Kjennerud T, Susser E, Lipkin WI. Maternal mid-gestational and child cord blood immune signatures are strongly associated with offspring risk of ASD. *Mol Psychiatry* 2022; **27**: 1527-1541 [PMID: [34987169](#) DOI: [10.1038/s41380-021-01415-4](#)]
- 72 **Brynge M**, Gardner RM, Sjöqvist H, Lee BK, Dalman C, Karlsson H. Maternal Levels of Cytokines in Early Pregnancy and Risk of Autism Spectrum Disorders in Offspring. *Front Public Health* 2022; **10**: 917563 [PMID: [35712277](#) DOI: [10.3389/fpubh.2022.917563](#)]
- 73 **Ji Y**, Azuine RE, Zhang Y, Hou W, Hong X, Wang G, Riley A, Pearson C, Zuckerman B, Wang X. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. *JAMA Psychiatry* 2020; **77**: 180-189 [PMID: [31664451](#) DOI: [10.1001/jamapsychiatry.2019.3259](#)]
- 74 **Philippot G**, Gordh T, Fredriksson A, Viberg H. Adult neurobehavioral alterations in male and female mice following developmental exposure to paracetamol (acetaminophen): characterization of a critical period. *J Appl Toxicol* 2017; **37**: 1174-1181 [PMID: [28448685](#) DOI: [10.1002/jat.3473](#)]
- 75 **Braunschweig D**, Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. Autism: maternally derived antibodies specific for fetal brain proteins. *Neurotoxicology* 2008; **29**: 226-231 [PMID: [18078998](#) DOI: [10.1016/j.neuro.2007.10.010](#)]
- 76 **Braunschweig D**, Duncanson P, Boyce R, Hansen R, Ashwood P, Pessah IN, Hertz-Picciotto I, Van de Water J. Behavioral correlates of maternal antibody status among children with autism. *J Autism Dev Disord* 2012; **42**: 1435-1445 [PMID: [22012245](#) DOI: [10.1007/s10803-011-1378-7](#)]
- 77 **Dalton P**, Deacon R, Blamire A, Pike M, McKinlay I, Stein J, Styles P, Vincent A. Maternal neuronal antibodies associated with autism and a language disorder. *Ann Neurol* 2003; **53**: 533-537 [PMID: [12666123](#) DOI: [10.1002/ana.10557](#)]
- 78 **Fox-Edmiston E**, Van de Water J. Maternal Anti-Fetal Brain IgG Autoantibodies and Autism Spectrum Disorder: Current Knowledge and its Implications for Potential Therapeutics. *CNS Drugs* 2015; **29**: 715-724 [PMID: [26369920](#) DOI: [10.1007/s40263-015-0279-2](#)]
- 79 **Ramirez-Celis A**, Becker M, Nuño M, Schauer J, Aghaeepour N, Van de Water J. Risk assessment analysis for maternal autoantibody-related autism (MAR-ASD): a subtype of autism. *Mol Psychiatry* 2021; **26**: 1551-1560 [PMID: [33483694](#) DOI: [10.1038/s41380-020-00998-8](#)]
- 80 **Singer HS**, Morris CM, Gause CD, Gillin PK, Crawford S, Zimmerman AW. Antibodies against fetal brain in sera of mothers with autistic children. *J Neuroimmunol* 2008; **194**: 165-172 [PMID: [18093664](#) DOI: [10.1016/j.jneuroim.2007.11.004](#)]
- 81 **Croen LA**, Braunschweig D, Haapanen L, Yoshida CK, Fireman B, Grether JK, Kharrazi M, Hansen RL, Ashwood P, Van de Water J. Maternal mid-pregnancy autoantibodies to fetal brain protein: the early markers for autism study. *Biol Psychiatry* 2008; **64**: 583-588 [PMID: [18571628](#) DOI: [10.1016/j.biopsych.2008.05.006](#)]
- 82 **Liu X**, Lin J, Zhang H, Khan NU, Zhang J, Tang X, Cao X, Shen L. Oxidative Stress in Autism Spectrum Disorder-Current Progress of Mechanisms and Biomarkers. *Front Psychiatry* 2022; **13**: 813304 [PMID: [35299821](#) DOI: [10.3389/fpsy.2022.813304](#)]
- 83 **Rommel AS**, Milne GL, Barrett ES, Bush NR, Nguyen R, Sathyanarayana S, Swan SH, Ferguson KK. Associations between urinary biomarkers of oxidative stress in the third trimester of pregnancy and behavioral outcomes in the child at 4 years of age. *Brain Behav Immun* 2020; **90**: 272-278 [PMID: [32905853](#) DOI: [10.1016/j.bbi.2020.08.029](#)]
- 84 **Usui N**, Kobayashi H, Shimada S. Neuroinflammation and Oxidative Stress in the Pathogenesis of Autism Spectrum Disorder. *Int J Mol Sci* 2023; **24** [PMID: [36982559](#) DOI: [10.3390/ijms24065487](#)]
- 85 **Lombardo MV**, Moon HM, Su J, Palmer TD, Courchesne E, Pramparo T. Maternal immune activation dysregulation of the fetal brain transcriptome and relevance to the pathophysiology of autism spectrum disorder. *Mol Psychiatry* 2018; **23**: 1001-1013 [PMID: [28322282](#) DOI: [10.1038/mp.2017.15](#)]
- 86 **Mueller FS**, Scarborough J, Schallbetter SM, Richetto J, Kim E, Couch A, Yee Y, Lerch JP, Vernon AC, Weber-Stadlbauer U, Meyer U. Behavioral, neuroanatomical, and molecular correlates of resilience and susceptibility to maternal immune activation. *Mol Psychiatry* 2021; **26**: 396-410 [PMID: [33230204](#) DOI: [10.1038/s41380-020-00952-8](#)]
- 87 **Lanté F**, Meunier J, Guiramand J, Maurice T, Cavalier M, de Jesus Ferreira MC, Aimar R, Cohen-Solal C, Vignes M, Barbanel G. Neurodevelopmental damage after prenatal infection: role of oxidative stress in the fetal brain. *Free Radic Biol Med* 2007; **42**: 1231-1245 [PMID: [17382204](#) DOI: [10.1016/j.freeradbiomed.2007.01.027](#)]
- 88 **Carey ME**, Rando J, Melnyk S, James SJ, Snyder N, Salafia C, Croen LA, Fallin MD, Hertz-Picciotto I, Volk H, Newschaffer C, Lyall K. Examining associations between prenatal biomarkers of oxidative stress and ASD-related outcomes using quantile regression. *J Autism Dev Disord* 2023; **53**: 2975-2985 [PMID: [35678944](#) DOI: [10.1007/s10803-022-05625-9](#)]
- 89 **Auyeung B**, Lombardo MV, Baron-Cohen S. Prenatal and postnatal hormone effects on the human brain and cognition. *Pflugers Arch* 2013; **465**: 557-571 [PMID: [23588379](#) DOI: [10.1007/s00424-013-1268-2](#)]
- 90 **Lombardo MV**, Ashwin E, Auyeung B, Chakrabarti B, Lai MC, Taylor K, Hackett G, Bullmore ET, Baron-Cohen S. Fetal programming effects of testosterone on the reward system and behavioral approach tendencies in humans. *Biol Psychiatry* 2012; **72**: 839-847 [PMID: [22763187](#) DOI: [10.1016/j.biopsych.2012.05.027](#)]
- 91 **Palomba S**, Marotta R, Di Cello A, Russo T, Falbo A, Orio F, Tolino A, Zullo F, Esposito R, La Sala GB. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case-control study. *Clin Endocrinol (Oxf)* 2012; **77**: 898-904 [PMID: [22612600](#) DOI: [10.1111/j.1365-2265.2012.04443.x](#)]
- 92 **Kosidou K**, Dalman C, Widman L, Arver S, Lee BK, Magnusson C, Gardner RM. Maternal polycystic ovary syndrome and the risk of autism spectrum disorders in the offspring: a population-based nationwide study in Sweden. *Mol Psychiatry* 2016; **21**: 1441-1448 [PMID: [26643539](#) DOI: [10.1038/mp.2015.183](#)]
- 93 **Baron-Cohen S**, Auyeung B, Nørgaard-Pedersen B, Hougaard DM, Abdallah MW, Melgaard L, Cohen AS, Chakrabarti B, Ruta L, Lombardo MV. Elevated fetal steroidogenic activity in autism. *Mol Psychiatry* 2015; **20**: 369-376 [PMID: [24888361](#) DOI: [10.1038/mp.2014.48](#)]
- 94 **Lenz KM**, Nugent BM, Haliyur R, McCarthy MM. Microglia are essential to masculinization of brain and behavior. *J Neurosci* 2013; **33**: 2761-2772 [PMID: [23407936](#) DOI: [10.1523/JNEUROSCI.1268-12.2013](#)]
- 95 **Yau VM**, Lutsky M, Yoshida CK, Lasley B, Kharrazi M, Windham G, Gee N, Croen LA. Prenatal and neonatal thyroid stimulating hormone levels and autism spectrum disorders. *J Autism Dev Disord* 2015; **45**: 719-730 [PMID: [25178989](#) DOI: [10.1007/s10803-014-2227-2](#)]

- 96 **Lai MC**, Lombardo MV, Auyeung B, Chakrabarti B, Baron-Cohen S. Sex/gender differences and autism: setting the scene for future research. *J Am Acad Child Adolesc Psychiatry* 2015; **54**: 11-24 [PMID: [25524786](#) DOI: [10.1016/j.jaac.2014.10.003](#)]
- 97 **Arora M**, Reichenberg A, Willfors C, Austin C, Gennings C, Berggren S, Lichtenstein P, Anckarsäter H, Tammimies K, Bölte S. Fetal and postnatal metal dysregulation in autism. *Nat Commun* 2017; **8**: 15493 [PMID: [28569757](#) DOI: [10.1038/ncomms15493](#)]
- 98 **Curtin P**, Austin C, Curtin A, Gennings C, Arora M; (for the Emergent Dynamical Systems Group), Tammimies K, Willfors C, Berggren S, Siper P, Rai D, Meyerling K, Kolevzon A, Mollon J, David AS, Lewis G, Zammit S, Heilbrun L, Palmer RF, Wright RO, Bölte S, Reichenberg A. Dynamical features in fetal and postnatal zinc-copper metabolic cycles predict the emergence of autism spectrum disorder. *Sci Adv* 2018; **4**: eaat1293 [PMID: [29854952](#) DOI: [10.1126/sciadv.aat1293](#)]
- 99 **Chen J**, Xin K, Wei J, Zhang K, Xiao H. Lower maternal serum 25(OH) D in first trimester associated with higher autism risk in Chinese offspring. *J Psychosom Res* 2016; **89**: 98-101 [PMID: [27663117](#) DOI: [10.1016/j.jpsychores.2016.08.013](#)]
- 100 **Magnusson C**, Lundberg M, Lee BK, Rai D, Karlsson H, Gardner R, Kosidou K, Arver S, Dalman C. Maternal vitamin D deficiency and the risk of autism spectrum disorders: population-based study. *BJPsych Open* 2016; **2**: 170-172 [PMID: [27703770](#) DOI: [10.1192/bjpo.bp.116.002675](#)]
- 101 **Madley-Dowd P**, Dardani C, Wootton RE, Dack K, Palmer T, Thurston R, Havdahl A, Golding J, Lawlor D, Rai D. Maternal vitamin D during pregnancy and offspring autism and autism-associated traits: a prospective cohort study. *Mol Autism* 2022; **13**: 44 [PMID: [36371219](#) DOI: [10.1186/s13229-022-00523-4](#)]
- 102 **Hoxha B**, Hoxha M, Domi E, Gervasoni J, Persichilli S, Malaj V, Zappacosta B. Folic Acid and Autism: A Systematic Review of the Current State of Knowledge. *Cells* 2021; **10** [PMID: [34440744](#) DOI: [10.3390/cells10081976](#)]
- 103 **Iglesias Vázquez L**, Canals J, Arijia V. Review and meta-analysis found that prenatal folic acid was associated with a 58% reduction in autism but had no effect on mental and motor development. *Acta Paediatr* 2019; **108**: 600-610 [PMID: [30466185](#) DOI: [10.1111/apa.14657](#)]
- 104 **Steenweg-de Graaff J**, Ghassabian A, Jaddoe VW, Tiemeier H, Roza SJ. Folate concentrations during pregnancy and autistic traits in the offspring. The Generation R Study. *Eur J Public Health* 2015; **25**: 431-433 [PMID: [25085472](#) DOI: [10.1093/eurpub/cku126](#)]
- 105 **Egorova O**, Myte R, Schneede J, Hägglöf B, Bölte S, Domellöf E, Ivars A'roch B, Elgh F, Ueland PM, Silfverdal SA. Maternal blood folate status during early pregnancy and occurrence of autism spectrum disorder in offspring: a study of 62 serum biomarkers. *Mol Autism* 2020; **11**: 7 [PMID: [32131900](#) DOI: [10.1186/s13229-020-0315-z](#)]
- 106 **Menezo Y**, Elder K, Clement A, Clement P. Folic Acid, Folinic Acid, 5 Methyl TetraHydroFolate Supplementation for Mutations That Affect Epigenesis through the Folate and One-Carbon Cycles. *Biomolecules* 2022; **12** [PMID: [35204698](#) DOI: [10.3390/biom12020197](#)]
- 107 **Ozgen HM**, Hop JW, Hox JJ, Beemer FA, van Engeland H. Minor physical anomalies in autism: a meta-analysis. *Mol Psychiatry* 2010; **15**: 300-307 [PMID: [18626481](#) DOI: [10.1038/mp.2008.75](#)]
- 108 **Dawson S**, Glasson EJ, Dixon G, Bower C. Birth defects in children with autism spectrum disorders: a population-based, nested case-control study. *Am J Epidemiol* 2009; **169**: 1296-1303 [PMID: [19372213](#) DOI: [10.1093/aje/kwp059](#)]
- 109 **Regev O**, Hadar A, Meiri G, Flusser H, Michaelovski A, Dinstein I, Hershkovitz R, Menashe I. Association between ultrasonography foetal anomalies and autism spectrum disorder. *Brain* 2022; **145**: 4519-4530 [PMID: [35037687](#) DOI: [10.1093/brain/awac008](#)]
- 110 **Vasung L**, Abaci Turk E, Ferradal SL, Sutin J, Stout JN, Ahtam B, Lin PY, Grant PE. Exploring early human brain development with structural and physiological neuroimaging. *Neuroimage* 2019; **187**: 226-254 [PMID: [30041061](#) DOI: [10.1016/j.neuroimage.2018.07.041](#)]
- 111 **Blanken LME**, Dass A, Alvares G, van der Ende J, Schoemaker NK, El Marroun H, Hickey M, Pennell C, White S, Maybery MT, Dissanayake C, Jaddoe VW, Verhulst FC, Tiemeier H, McIntosh W, White T, Whitehouse A. A prospective study of fetal head growth, autistic traits and autism spectrum disorder. *Autism Res* 2018; **11**: 602-612 [PMID: [29356450](#) DOI: [10.1002/aur.1921](#)]
- 112 **DiCicco-Bloom E**, Lord C, Zwaigenbaum L, Courchesne E, Dager SR, Schmitz C, Schultz RT, Crawley J, Young LJ. The developmental neurobiology of autism spectrum disorder. *J Neurosci* 2006; **26**: 6897-6906 [PMID: [16807320](#) DOI: [10.1523/JNEUROSCI.1712-06.2006](#)]
- 113 **Shen MD**, Piven J. Brain and behavior development in autism from birth through infancy. *Dialogues Clin Neurosci* 2017; **19**: 325-333 [PMID: [29398928](#) DOI: [10.31887/DCNS.2017.19.4/mshen](#)]
- 114 **Hata T**, Kanenishi K, Mori N, AboEllail MAM, Hanaoka U, Koyano K, Kato I, Kusaka T. Prediction of postnatal developmental disabilities using the antenatal fetal neurodevelopmental test: KANET assessment. *J Perinat Med* 2018; **47**: 77-81 [PMID: [30098288](#) DOI: [10.1515/jpm-2018-0169](#)]
- 115 **Levman J**, Takahashi E. Multivariate analyses applied to fetal, neonatal and pediatric MRI of neurodevelopmental disorders. *Neuroimage Clin* 2015; **9**: 532-544 [PMID: [26640765](#) DOI: [10.1016/j.nicl.2015.09.017](#)]
- 116 **Kyriakopoulou V**, Davidson A, Chew A, Gupta N, Arichi T, Nosarti C, Rutherford MA. Characterisation of ASD traits among a cohort of children with isolated fetal ventriculomegaly. *Nat Commun* 2023; **14**: 1550 [PMID: [36941265](#) DOI: [10.1038/s41467-023-37242-0](#)]
- 117 **Ortug A**, Guo Y, Feldman HA, Ou Y, Dieuveuil H, Baumer NT, Faja SK, Takahashi E. "Human Fetal Brain Magnetic Resonance Imaging (MRI) Tells Future Emergence of Autism Spectrum Disorders." *The FASEB Journal*, 2022, vol. 36, [DOI: [10.1096/fasebj.2022.36.S1.R2353](#)]
- 118 **De Asis-Cruz J**, Andescavage N, Limperopoulos C. Adverse Prenatal Exposures and Fetal Brain Development: Insights From Advanced Fetal Magnetic Resonance Imaging. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2022; **7**: 480-490 [PMID: [34848383](#) DOI: [10.1016/j.bpsc.2021.11.009](#)]
- 119 **Shen MD**, Swanson MR, Wolff JJ, Elison JT, Girault JB, Kim SH, Smith RG, Graves MM, Weisenfeld LAH, Flake L, MacIntyre L, Gross JL, Burrows CA, Fonov VS, Collins DL, Evans AC, Gerig G, McKinstry RC, Pandey J, St John T, Zwaigenbaum L, Estes AM, Dager SR, Schultz RT, Styner MA, Botteron KN, Hazlett HC, Piven J; IBIS Network. Subcortical Brain Development in Autism and Fragile X Syndrome: Evidence for Dynamic, Age- and Disorder-Specific Trajectories in Infancy. *Am J Psychiatry* 2022; **179**: 562-572 [PMID: [35331012](#) DOI: [10.1176/appi.ajp.21090896](#)]
- 120 **Guthrie W**, Swineford LB, Nottke C, Wetherby AM. Early diagnosis of autism spectrum disorder: stability and change in clinical diagnosis and symptom presentation. *J Child Psychol Psychiatry* 2013; **54**: 582-590 [PMID: [23078094](#) DOI: [10.1111/jcpp.12008](#)]
- 121 **Girault JB**, Piven J. The Neurodevelopment of Autism from Infancy Through Toddlerhood. *Neuroimaging Clin N Am* 2020; **30**: 97-114 [PMID: [31759576](#) DOI: [10.1016/j.nic.2019.09.009](#)]
- 122 **Crucitti J**, Hyde C, Enticott PG, Stokes MA. Head circumference trends in autism between 0 and 100 months. *Autism* 2020; **24**: 1726-1739 [PMID: [32476434](#) DOI: [10.1177/1362361320921037](#)]
- 123 **Tan DW**, Gilani SZ, Boutrus M, Alvares GA, Whitehouse AJO, Mian A, Suter D, Maybery MT. Facial asymmetry in parents of children on the autism spectrum. *Autism Res* 2021; **14**: 2260-2269 [PMID: [34529361](#) DOI: [10.1002/aur.2612](#)]
- 124 **Gorczyca P**, Kapinos-Gorczyca A, Ziora K, Oświećimska J. Photoanthropometric study of dysmorphic features of the face in children with autism and asperger syndrome. *Iran J Psychiatry* 2012; **7**: 41-46 [PMID: [23056117](#)]

- 125 **Surén P**, Stoltenberg C, Bresnahan M, Hirtz D, Lie KK, Lipkin WI, Magnus P, Reichborn-Kjennerud T, Schjølberg S, Susser E, Oyen AS, Li L, Hornig M. Early growth patterns in children with autism. *Epidemiology* 2013; **24**: 660-670 [PMID: [23867813](#) DOI: [10.1097/EDE.0b013e31829e1d45](#)]
- 126 **Posar A**, Visconti P. Early Motor Signs in Autism Spectrum Disorder. *Children (Basel)* 2022; **9** [PMID: [35205014](#) DOI: [10.3390/children9020294](#)]
- 127 **Mohd Nordin A**, Ismail J, Kamal Nor N. Motor Development in Children With Autism Spectrum Disorder. *Front Pediatr* 2021; **9**: 598276 [PMID: [34604128](#) DOI: [10.3389/fped.2021.598276](#)]
- 128 **Lory C**, Kadlaskar G, McNally Keehn R, Francis AL, Keehn B. Brief Report: Reduced Heart Rate Variability in Children with Autism Spectrum Disorder. *J Autism Dev Disord* 2020; **50**: 4183-4190 [PMID: [32219633](#) DOI: [10.1007/s10803-020-04458-8](#)]
- 129 **Beversdorf DQ**, Carpenter AL, Miller RF, Cios JS, Hillier A. Effect of propranolol on verbal problem solving in autism spectrum disorder. *Neurocase* 2008; **14**: 378-383 [PMID: [18766980](#) DOI: [10.1080/13554790802368661](#)]
- 130 **Zamzow RM**, Ferguson BJ, Ragsdale AS, Lewis ML, Beversdorf DQ. Effects of acute beta-adrenergic antagonism on verbal problem solving in autism spectrum disorder and exploration of treatment response markers. *J Clin Exp Neuropsychol* 2017; **39**: 596-606 [PMID: [27841098](#) DOI: [10.1080/13803395.2016.1252724](#)]
- 131 **Nyström P**, Gliga T, Nilsson Jobs E, Gredebäck G, Charman T, Johnson MH, Bölte S, Falck-Ytter T. Enhanced pupillary light reflex in infancy is associated with autism diagnosis in toddlerhood. *Nat Commun* 2018; **9**: 1678 [PMID: [29735992](#) DOI: [10.1038/s41467-018-03985-4](#)]
- 132 **Wasilewska J**, Klukowski M. Gastrointestinal symptoms and autism spectrum disorder: links and risks - a possible new overlap syndrome. *Pediatric Health Med Ther* 2015; **6**: 153-166 [PMID: [29388597](#) DOI: [10.2147/PHMT.S85717](#)]
- 133 **Buie T**, Campbell DB, Fuchs GJ 3rd, Furuta GT, Levy J, Vandewater J, Whitaker AH, Atkins D, Bauman ML, Beaudet AL, Carr EG, Gershon MD, Hyman SL, Jirapinyo P, Jyonouchi H, Kooros K, Kushak R, Levitt P, Levy SE, Lewis JD, Murray KF, Natowicz MR, Sabra A, Wershil BK, Weston SC, Zeltzer L, Winter H. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics* 2010; **125** Suppl 1: S1-18 [PMID: [20048083](#) DOI: [10.1542/peds.2009-1878C](#)]
- 134 **Le Menn-Tripi C**, Vachaud A, Defas N, Malvy J, Roux S, Bonnet-Brilhaut F. [Sensory-psychomotor evaluation in Autism: A new tool for functional diagnosis]. *Encephale* 2019; **45**: 312-319 [PMID: [30922517](#) DOI: [10.1016/j.encep.2018.12.003](#)]
- 135 **Teitelbaum P**, Teitelbaum O, Nye J, Fryman J, Maurer RG. Movement analysis in infancy may be useful for early diagnosis of autism. *Proc Natl Acad Sci U S A* 1998; **95**: 13982-13987 [PMID: [9811912](#) DOI: [10.1073/pnas.95.23.13982](#)]
- 136 **Towle PO**, Patrick PA. Autism Spectrum Disorder Screening Instruments for Very Young Children: A Systematic Review. *Autism Res Treat* 2016; **2016**: 4624829 [PMID: [28116159](#) DOI: [10.1155/2016/4624829](#)]
- 137 **Magrelli S**, Jermann P, Noris B, Ansermet F, Hentsch F, Nadel J, Billard A. Social orienting of children with autism to facial expressions and speech: a study with a wearable eye-tracker in naturalistic settings. *Front Psychol* 2013; **4**: 840 [PMID: [24312064](#) DOI: [10.3389/fpsyg.2013.00840](#)]
- 138 **Zwaigenbaum L**, Bauman ML, Fein D, Pierce K, Buie T, Davis PA, Newschaffer C, Robins DL, Wetherby A, Choueiri R, Kasari C, Stone WL, Yirmiya N, Estes A, Hansen RL, McPartland JC, Natowicz MR, Carter A, Granpeesheh D, Mailloux Z, Smith Roley S, Wagner S. Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research. *Pediatrics* 2015; **136** Suppl 1: S41-S59 [PMID: [26430169](#) DOI: [10.1542/peds.2014-3667D](#)]
- 139 **Simpson EA**, Maylott SE, Mitsven SG, Zeng G, Jakobsen KV. Face detection in 2- to 6-month-old infants is influenced by gaze direction and species. *Dev Sci* 2020; **23**: e12902 [PMID: [31505079](#) DOI: [10.1111/desc.12902](#)]
- 140 **Jones W**, Klin A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. *Nature* 2013; **504**: 427-431 [PMID: [24196715](#) DOI: [10.1038/nature12715](#)]
- 141 **Elsabbagh M**, Mercure E, Hudry K, Chandler S, Pasco G, Charman T, Pickles A, Baron-Cohen S, Bolton P, Johnson MH; BASIS Team. Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. *Curr Biol* 2012; **22**: 338-342 [PMID: [22285033](#) DOI: [10.1016/j.cub.2011.12.056](#)]
- 142 **Wong HS**, Huertas-Ceballos A, Cowan FM, Modi N; Medicines for Neonates Investigator Group. Evaluation of early childhood social-communication difficulties in children born preterm using the Quantitative Checklist for Autism in Toddlers. *J Pediatr* 2014; **164**: 26-33.e1 [PMID: [23972644](#) DOI: [10.1016/j.jpeds.2013.07.013](#)]
- 143 **De Schuymer L**, De Groote I, Desoete A, Roeyers H. Gaze aversion during social interaction in preterm infants: a function of attention skills? *Infant Behav Dev* 2012; **35**: 129-139 [PMID: [21893348](#) DOI: [10.1016/j.infbeh.2011.08.002](#)]
- 144 **Pineda R**, Melchior K, Oberle S, Inder T, Rogers C. Assessment of Autism Symptoms During the Neonatal Period: Is There Early Evidence of Autism Risk? *Am J Occup Ther* 2015; **69**: 6904220010p1-690422001011 [PMID: [26114457](#) DOI: [10.5014/ajot.2015.015925](#)]
- 145 **Tokunaga A**, Akiyama T, Miyamura T, Honda S, Nakane H, Iwanaga R, Tanaka G. Neonatal behavior and social behavior and sensory issues in 18-month toddlers. *Pediatr Int* 2019; **61**: 1202-1209 [PMID: [31655009](#) DOI: [10.1111/ped.14033](#)]
- 146 **Rossignol DA**, Frye RE. A Systematic Review and Meta-Analysis of Immunoglobulin G Abnormalities and the Therapeutic Use of Intravenous Immunoglobulins (IVIG) in Autism Spectrum Disorder. *J Pers Med* 2021; **11** [PMID: [34070826](#) DOI: [10.3390/jpm11060488](#)]
- 147 **Connery K**, Tippet M, Delhey LM, Rose S, Slattery JC, Kahler SG, Hahn J, Kruger U, Cunningham MW, Shimasaki C, Frye RE. Intravenous immunoglobulin for the treatment of autoimmune encephalopathy in children with autism. *Transl Psychiatry* 2018; **8**: 148 [PMID: [30097568](#) DOI: [10.1038/s41398-018-0214-7](#)]
- 148 **Rossignol DA**, Frye RE. Cerebral Folate Deficiency, Folate Receptor Alpha Autoantibodies and Leucovorin (Folinic Acid) Treatment in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis. *J Pers Med* 2021; **11** [PMID: [34834493](#) DOI: [10.3390/jpm11111141](#)]
- 149 **Frye RE**, Lane A, Worner A, Werner BA, McCarty PJ, Scheck AC, Collins HL, Adelman SJ, Quadros EV, Rossignol DA. The Soluble Folate Receptor in Autism Spectrum Disorder: Relation to Autism Severity and Leucovorin Treatment. *J Pers Med* 2022; **12** [PMID: [36556254](#) DOI: [10.3390/jpm12122033](#)]
- 150 **Zhou J**, He F, Yang F, Yang Z, Xie Y, Zhou S, Liang J, Xu R, Wang Y, Guo H, Zhou W, Wang M. Increased stool immunoglobulin A level in children with autism spectrum disorders. *Res Dev Disabil* 2018; **82**: 90-94 [PMID: [29102384](#) DOI: [10.1016/j.ridd.2017.10.009](#)]
- 151 **Ravaccia D**, Ghafourian T. Critical Role of the Maternal Immune System in the Pathogenesis of Autism Spectrum Disorder. *Biomedicines* 2020; **8** [PMID: [33271759](#) DOI: [10.3390/biomedicines8120557](#)]
- 152 **Gardner RM**, Lee BK, Brynne M, Sjöqvist H, Dalman C, Karlsson H. Neonatal Levels of Acute Phase Proteins and Risk of Autism Spectrum Disorder. *Biol Psychiatry* 2021; **89**: 463-475 [PMID: [33187600](#) DOI: [10.1016/j.biopsych.2020.09.005](#)]
- 153 **Masi A**, Quintana DS, Glozier N, Lloyd AR, Hickie IB, Guastella AJ. Cytokine aberrations in autism spectrum disorder: a systematic review and meta-analysis. *Mol Psychiatry* 2015; **20**: 440-446 [PMID: [24934179](#) DOI: [10.1038/mp.2014.59](#)]

- 154 **Krakowiak P**, Goines PE, Tancredi DJ, Ashwood P, Hansen RL, Hertz-Picciotto I, Van de Water J. Neonatal Cytokine Profiles Associated With Autism Spectrum Disorder. *Biol Psychiatry* 2017; **81**: 442-451 [PMID: [26392128](#) DOI: [10.1016/j.biopsych.2015.08.007](#)]
- 155 **Bathina S**, Das UN. Brain-derived neurotrophic factor and its clinical implications. *Arch Med Sci* 2015; **11**: 1164-1178 [PMID: [26788077](#) DOI: [10.5114/aoms.2015.56342](#)]
- 156 **Liu YK**, Gao H, Jin SB, Tu WJ, Chen YJ. Association of neonatal blood levels of brain-derived neurotrophic factor with development of autism spectrum disorder: a systematic review and meta-analysis. *World J Pediatr* 2021; **17**: 164-170 [PMID: [33650030](#) DOI: [10.1007/s12519-021-00415-2](#)]
- 157 **Croen LA**, Goines P, Braunschweig D, Yolken R, Yoshida CK, Grether JK, Fireman B, Kharrazi M, Hansen RL, Van de Water J. Brain-derived neurotrophic factor and autism: maternal and infant peripheral blood levels in the Early Markers for Autism (EMA) Study. *Autism Res* 2008; **1**: 130-137 [PMID: [19119429](#) DOI: [10.1002/aur.14](#)]
- 158 **Amin SB**, Smith T, Wang H. Is neonatal jaundice associated with Autism Spectrum Disorders: a systematic review. *J Autism Dev Disord* 2011; **41**: 1455-1463 [PMID: [22009628](#) DOI: [10.1007/s10803-010-1169-6](#)]
- 159 **Wilde VK**. Neonatal Jaundice and Autism: Precautionary Principle Invocation Overdue. *Cureus* 2022; **14**: e22512 [PMID: [35228983](#) DOI: [10.7759/cureus.22512](#)]
- 160 **Oztan O**, Garner JP, Constantino JN, Parker KJ. Neonatal CSF vasopressin concentration predicts later medical record diagnoses of autism spectrum disorder. *Proc Natl Acad Sci U S A* 2020; **117**: 10609-10613 [PMID: [32341146](#) DOI: [10.1073/pnas.1919050117](#)]
- 161 **Zhang HF**, Dai YC, Wu J, Jia MX, Zhang JS, Shou XJ, Han SP, Zhang R, Han JS. Plasma Oxytocin and Arginine-Vasopressin Levels in Children with Autism Spectrum Disorder in China: Associations with Symptoms. *Neurosci Bull* 2016; **32**: 423-432 [PMID: [27342432](#) DOI: [10.1007/s12264-016-0046-5](#)]
- 162 **Pichugina YA**, Maksimova IV, Berezovskaya MA, Afanaseva NA, Pichugin AB, Dmitrenko DV, Timechko EE, Salmina AB, Lopatina OL. Salivary oxytocin in autistic patients and in patients with intellectual disability. *Front Psychiatry* 2022; **13**: 969674 [PMID: [36506430](#) DOI: [10.3389/fpsy.2022.969674](#)]
- 163 **Gottlieb MM**. Mathematical Models for Possible Roles of Oxytocin and Oxytocin Receptors in Autism. *Comput Math Methods Med* 2019; **2019**: 7308197 [PMID: [31827587](#) DOI: [10.1155/2019/7308197](#)]
- 164 **Carson DS**, Garner JP, Hyde SA, Libove RA, Berquist SW, Hornbeak KB, Jackson LP, Sumiyoshi RD, Howerton CL, Hannah SL, Partap S, Phillips JM, Hardan AY, Parker KJ. Arginine Vasopressin Is a Blood-Based Biomarker of Social Functioning in Children with Autism. *PLoS One* 2015; **10**: e0132224 [PMID: [26200852](#) DOI: [10.1371/journal.pone.0132224](#)]
- 165 **Tierney AL**, Nelson CA 3rd. Brain Development and the Role of Experience in the Early Years. *Zero Three* 2009; **30**: 9-13 [PMID: [23894221](#)]
- 166 **Geva R**, Sopher K, Kurtzman L, Galili G, Feldman R, Kuint J. Neonatal brainstem dysfunction risks infant social engagement. *Soc Cogn Affect Neurosci* 2013; **8**: 158-164 [PMID: [22146141](#) DOI: [10.1093/scan/nsr082](#)]
- 167 **Cohen IL**, Gardner JM, Karmel BZ, Phan HT, Kittler P, Gomez TR, Gonzalez MG, Lennon EM, Parab S, Barone A. Neonatal brainstem function and 4-month arousal-modulated attention are jointly associated with autism. *Autism Res* 2013; **6**: 11-22 [PMID: [23165989](#) DOI: [10.1002/aur.1259](#)]
- 168 **Ozonoff S**, Young GS, Landa RJ, Brian J, Bryson S, Charman T, Chawarska K, Macari SL, Messinger D, Stone WL, Zwaigenbaum L, Iosif AM. Diagnostic stability in young children at risk for autism spectrum disorder: a baby siblings research consortium study. *J Child Psychol Psychiatry* 2015; **56**: 988-998 [PMID: [25921776](#) DOI: [10.1111/jcpp.12421](#)]
- 169 **Ozonoff S**, Iosif AM, Young GS, Hepburn S, Thompson M, Colombi C, Cook IC, Werner E, Goldring S, Baguio F, Rogers SJ. Onset patterns in autism: correspondence between home video and parent report. *J Am Acad Child Adolesc Psychiatry* 2011; **50**: 796-806.e1 [PMID: [21784299](#) DOI: [10.1016/j.jaac.2011.03.012](#)]
- 170 **Leitner Y**. The co-occurrence of autism and attention deficit hyperactivity disorder in children - what do we know? *Front Hum Neurosci* 2014; **8**: 268 [PMID: [24808851](#) DOI: [10.3389/fnhum.2014.00268](#)]
- 171 **St Amant HG**, Schrager SM, Peña-Ricardo C, Williams ME, Vanderbilt DL. Language Barriers Impact Access to Services for Children with Autism Spectrum Disorders. *J Autism Dev Disord* 2018; **48**: 333-340 [PMID: [28988384](#) DOI: [10.1007/s10803-017-3330-y](#)]
- 172 **Lockwood Estrin G**, Bhavnani S, Arora R, Gulati S, Divan G. Caregiver Perceptions of Autism and Neurodevelopmental Disabilities in New Delhi, India. *Int J Environ Res Public Health* 2023; **20** [PMID: [37047907](#) DOI: [10.3390/ijerph20075291](#)]
- 173 **Zwaigenbaum L**, Bauman ML, Choueiri R, Fein D, Kasari C, Pierce K, Stone WL, Yirmiya N, Estes A, Hansen RL, McPartland JC, Natowicz MR, Buie T, Carter A, Davis PA, Granpeesheh D, Mailloux Z, Newschaffer C, Robins D, Smith Roley S, Wagner S, Wetherby A. Early Identification and Interventions for Autism Spectrum Disorder: Executive Summary. *Pediatrics* 2015; **136** Suppl 1: S1-S9 [PMID: [26430167](#) DOI: [10.1542/peds.2014-3667B](#)]
- 174 **Dai YG**, Porto KS, Skapek M, Barton ML, Dumont-Mathieu T, Fein DA, Robins DL. Comparison of the Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F) Positive Predictive Value by Race. *J Autism Dev Disord* 2021; **51**: 855-867 [PMID: [32125566](#) DOI: [10.1007/s10803-020-04428-0](#)]
- 175 **de Leeuw A**, Happé F, Hoekstra RA. A Conceptual Framework for Understanding the Cultural and Contextual Factors on Autism Across the Globe. *Autism Res* 2020; **13**: 1029-1050 [PMID: [32083402](#) DOI: [10.1002/aur.2276](#)]



Renal calcification in children with renal tubular acidosis: What a paediatrician should know

Mohammed Al-Beltagi, Nermin Kamal Saeed, Adel Salah Bediwy, Reem Elbeltagi, Samir Hasan, Mohamed Basony Hamza

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Cabezu AS, Spain

Received: July 29, 2023

Peer-review started: July 29, 2023

First decision: September 14, 2023

Revised: September 15, 2023

Accepted: October 16, 2023

Article in press: October 16, 2023

Published online: December 9, 2023



Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31511, Algharbia, Egypt

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Dr. Sulaiman Al Habib Medical Group, Manama, Bahrain, Manama 26671, Manama, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 12, Manama, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Irish Royal College of Surgeon, Bahrain, Busaiteen 15503, Muharraq, Bahrain

Adel Salah Bediwy, Department of Pulmonology, Faculty of Medicine, Tanta University, Tanta 31527, Algharbia, Egypt

Adel Salah Bediwy, Department of Chest Disease, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al Habib Medical Group, Manama, Manama 26671, Manama, Bahrain

Reem Elbeltagi, Department of Medicine, The Royal College of Surgeons in Ireland - Bahrain, Busaiteen 15503, Muharraq, Bahrain

Samir Hasan, Department of Pediatrics, Faculty of Medicine, Tanta University Hospital, Tanta 31511, Algharbia, Egypt

Mohamed Basony Hamza, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31511, Algharbia, Egypt

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Academic Editor, Chairman, Consultant Physician-Scientist, Professor, Researcher, Department of Pediatrics, Faculty of Medicine, Tanta University, Al Bahr Street, Tanta 31527, Algharbia, Egypt.

mbelrem@hotmail.com

Abstract

Renal tubular acidosis (RTA) can lead to renal calcification in children, which can cause various complications and impair renal function. This review provides pediatricians with a comprehensive understanding of the relationship between RTA and renal calcification, highlighting essential aspects for clinical manage-

ment. The article analyzed relevant studies to explore the prevalence, risk factors, underlying mechanisms, and clinical implications of renal calcification in children with RTA. Results show that distal RTA (type 1) is particularly associated with nephrocalcinosis, which presents a higher risk of renal calcification. However, there are limitations to the existing literature, including a small number of studies, heterogeneity in methodologies, and potential publication bias. Longitudinal data and control groups are also lacking, which limits our understanding of long-term outcomes and optimal management strategies for children with RTA and renal calcification. Pediatricians play a crucial role in the early diagnosis and management of RTA to mitigate the risk of renal calcification and associated complications. In addition, alkaline therapy remains a cornerstone in the treatment of RTA, aimed at correcting the acid-base imbalance and reducing the formation of kidney stones. Therefore, early diagnosis and appropriate therapeutic interventions are paramount in preventing and managing renal calcification to preserve renal function and improve long-term outcomes for affected children. Further research with larger sample sizes and rigorous methodologies is needed to optimize the clinical approach to renal calcification in the context of RTA in the pediatric population.

Key Words: Renal tubular acidosis; Nephrocalcinosis; Renal calcification; Hypercalciuria; Kidney stones; Metabolic acidosis; Children

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Children with renal tubular acidosis (RTA) may develop renal calcification, leading to complications and negatively affecting kidney function. This comprehensive review aims to provide pediatricians with a better understanding of the connection between RTA and renal calcification, emphasizing key aspects of clinical management. Relevant studies were analyzed to examine the prevalence, risk factors, underlying mechanisms, and clinical implications of renal calcification in children with RTA. Nephrocalcinosis in type 1 RTA is mainly associated with a higher risk of renal calcification. Further research with larger sample sizes and rigorous methodologies is necessary to improve our understanding of RTA-related renal calcification.

Citation: Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R, Hasan S, Hamza MB. Renal calcification in children with renal tubular acidosis: What a paediatrician should know. *World J Clin Pediatr* 2023; 12(5): 295-309

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/295.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.295>

INTRODUCTION

Renal tubular acidosis (RTA) is a group of inherited or acquired disorders. It is characterized by impaired renal tubules' ability to reabsorb bicarbonate or excrete hydrogen ions. This results in an inability to maintain acid-base balance in the body[1]. Different types of RTA are based on the specific defect in renal tubular function. Distal RTA (dRTA), also known as type 1 RTA, is the most common form of RTA. It is characterized by impaired hydrogen ion secretion in the distal renal tubules, causing reduced kidney ability to acidify urine, with acid buildup in the blood inducing metabolic acidosis. It is often associated with and can lead to the formation of calcium phosphate kidney stones[2]. Proximal RTA (type 2 RTA) is characterized by defective bicarbonate reabsorption in the proximal renal tubules, resulting in increased urinary bicarbonate loss and metabolic acidosis. Unlike type 1 RTA, type 2 RTA is associated with urinary phosphate wasting, resulting in hypophosphatemia[3]. Combined proximal and distal RTA (type 3 RTA) is a rare form of RTA that involves defects in both proximal and distal tubular acidification mechanisms with combined features of type 1 and type 2 RTA. Type 4 RTA (RTA 4), also known as RTA due to hyporeninemic hypoaldosteronism, is characterized by impaired renal acidification due to hypoaldosteronism or aldosterone resistance, resulting in reduced secretion of hydrogen ions and impaired potassium excretion[4,5].

The cause of RTA varies depending on the specific type. RTA can be inherited and caused by genetic mutations affecting the transport proteins responsible for renal tubular acidification[6]. Other causes include autoimmune diseases (such as systemic lupus erythematosus), medications (such as certain diuretics), chronic kidney disease, or urinary tract obstruction[7]. Symptoms can range from mild to severe, depending on the underlying cause and extent of acid-base imbalance. Symptoms include fatigue, weakness, poor growth or weight gain (in children), increased urinary frequency, and bone abnormalities due to metabolic acidosis[8].

RTA can cause various complications in multiple organ systems, depending on the type and severity of acid-base imbalance. The primary complication of RTA is metabolic acidosis, which occurs due to the kidneys' inability to excrete hydrogen ions or reabsorb bicarbonate effectively[1]. This can cause issues such as impaired growth and development, muscle wasting, bone demineralization (osteoporosis), and an increased risk of kidney stone formation. RTA can also disrupt electrolyte balance, leading to abnormalities like hypokalemia or hyperkalemia[9]. Hypokalemia can result in muscle weakness, fatigue, and cardiac arrhythmias, while hyperkalemia can be life-threatening and cause cardiac

abnormalities. Chronic metabolic acidosis in children with RTA can impact growth and development and lead to developmental delays. Long-standing metabolic acidosis can also affect bone health, leading to osteoporosis or rickets in children due to compensatory mechanisms like increased bone resorption to buffer the acidosis[10,11].

In some cases of RTA, the increased excretion of calcium in the urine can cause calcium deposits in the kidneys and nephrocalcinosis. This can lead to kidney function impairment and the development of chronic kidney disease[12]. RTA can also increase the risk of kidney stone formation due to urinary abnormalities, such as increased calcium, phosphate, and oxalate excretion. If left untreated, RTA can cause chronic kidney disease and renal damage. Children with RTA and recurrent kidney stone formation or nephrocalcinosis are at higher risk for renal complications[13]. This review provides an overview of renal calcification in children with RTA, including its pathophysiology, clinical presentation, diagnostic evaluation, and management strategies. By enhancing our understanding of this complex condition, clinicians can improve early detection, implement appropriate interventions, and optimize long-term outcomes for children affected by renal calcification associated with RTA.

METHODS

We conducted a systematic literature review to gain an evidence-based understanding of our goal. This review involved searching various electronic databases like PubMed, PubMed Central, Cochrane Library, Embase, Web of Science, CINAHL, Scopus, LISA, and NLM catalog up until July 28, 2023. We used specific keywords like Renal Tubular acidosis, Nephrocalcinosis, Renal Calcification, Hypercalciuria, Kidney Stones, Metabolic Acidosis, and Children. Our review included 111 full-text articles comprising 70 reviews, 20 research articles, 16 case reports, four consensus guidelines, one systematic review, one editorial, and one more systematic review. We only included English-language articles discussing the effects of RTA on the risk of renal calcification. Figure 1 illustrates the study's flow chart. We also checked reference lists and conducted citation searches on the included studies. We excluded articles with commercial backgrounds and reviewed those available as abstracts only.

DISCUSSION

Role of the kidneys in acid-base homeostasis

The kidneys play a crucial role in maintaining the body's acid-base balance through various mechanisms such as acid secretion and excretion, bicarbonate reabsorption and generation, ammonia regulation, and response to pH changes. One of its primary functions is to excrete excess acid by releasing hydrogen ions (H^+) into the urine. This process is essential in preventing the buildup of acid in the blood, which can result in a condition known as acidosis[14].

Bicarbonate plays a crucial role in neutralizing excess acids in the blood. The majority (85%-90%) of filtered bicarbonate is reabsorbed in the proximal tubules of the kidneys[15]. This reabsorption occurs through the secretion of protons (H^+) *via* sodium hydrogen exchangers and proton pumps (H^+ -ATPase). In the lumen, hydrogen ions combine with HCO_3^- to form carbonic acid, which quickly dissociates into water and carbon dioxide. This reaction is catalyzed by the enzyme carbonic anhydrase. The generated carbon dioxide diffuses freely into the proximal tubule cell and reacts with water to form carbonic acid, catalyzed by carbonic anhydrase (CA II). The bicarbonate ions resulting from the dissociated carbonic acid exit through the basolateral membrane *via* the sodium bicarbonate exchanger[16,17].

In the kidneys' distal tubules are specialized cells known as alpha-intercalated cells that secrete hydrogen ions into the urine. At the same time, beta-intercalated cells generate new bicarbonate ions to maintain a balance between acid and base by replenishing bicarbonate in the blood. Principal cells reabsorb sodium and water while secreting K^+ to fine-tune the acid, base excretion, and urine output[18]. The bicarbonate (HCO_3^-) generated is transported to the blood in exchange for chloride (Cl^-) through the basolateral Cl^-/HCO_3^- exchanger. Additionally, the kidneys can produce ammonia (NH_3), which can combine with hydrogen ions to form ammonium (NH_4^+). Ammonium is then excreted into the urine, further contributing to acid excretion and acid-base balance[19].

The kidneys can respond to changes in blood pH by adjusting their acid-base handling mechanisms. When blood pH is too acidic, the kidneys can increase the excretion of hydrogen ions and generate more bicarbonate to restore balance. Conversely, when blood pH is too basic (alkaline), the kidneys can reduce bicarbonate reabsorption and retain more hydrogen ions, promoting acid excretion and balancing pH[16]. This intricate control of acid-base balance is essential for proper cellular function, enzyme activity, and overall physiological processes throughout the body. Any disruption in these mechanisms can lead to acid-base imbalances, such as metabolic acidosis or alkalosis, which can have significant health implications if not appropriately managed[20].

Role of the kidneys in calcium homeostasis and prevention of urolithiasis

The kidneys play a vital role in maintaining calcium homeostasis by regulating the reabsorption and excretion of calcium in response to changes in blood calcium levels and hormonal signals[21]. This fine-tuned control of calcium levels is essential for various physiological functions and for maintaining healthy bones and tissues throughout the body. Disruptions in the kidneys' ability to regulate calcium homeostasis can lead to disorders such as hypercalcemia (elevated blood calcium levels) or hypocalcemia (low blood calcium levels), which can significantly affect various organ systems and overall health. Proper kidney function is crucial for maintaining optimal calcium balance and overall calcium homeostasis in the body. Calcium homeostasis is the process of maintaining optimal calcium levels in the bloodstream

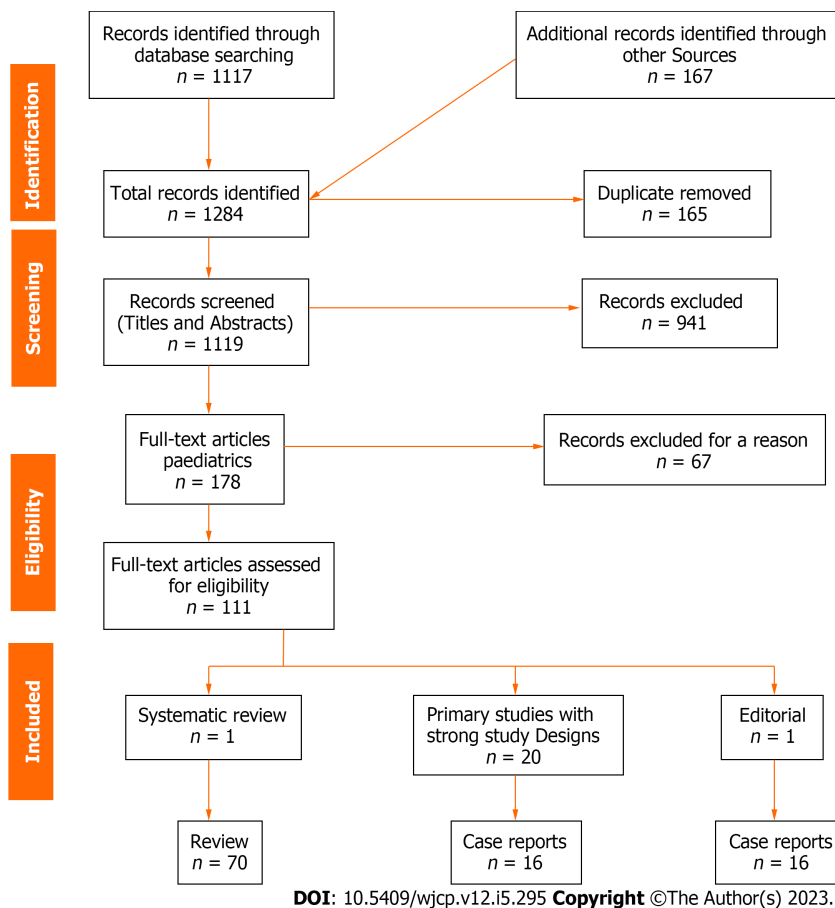


Figure 1 Flow chart of included studies.

[22]. The kidneys play a crucial role in this process by reabsorbing filtered calcium, producing parathyroid hormone, metabolizing vitamin D, and excreting excess calcium. Disruptions in kidney function can lead to disorders like hypercalcemia or hypocalcemia, affecting overall health. Proper kidney function is essential for maintaining optimal calcium balance and overall calcium homeostasis in the body[23].

The kidneys play a vital role in maintaining acid-base homeostasis, which influences the solubility of minerals in the urine. Imbalances in acid-base levels can promote the formation of specific types of stones, such as uric acid stones. The kidneys are also involved in regulating calcium levels in the bloodstream. Proper calcium balance helps prevent the formation of calcium-containing stones, such as calcium oxalate stones[24]. The urinary stones, also known as uroliths, can block the urinary system and cause urolithiasis. The kidneys play a crucial role in preventing the formation of these stones. They filter waste products and excess substances from the bloodstream to form urine and regulate the amount of water reabsorbed in the renal tubules to maintain an appropriate urine concentration. Dilute urine reduces the risk of supersaturation of minerals in the urine, making it less likely for crystals to form and lead to stone formation[25].

The kidneys filter various substances from the blood, including crystal precursors like calcium, oxalate, and uric acid. Adequate fluid intake and maintaining proper urine pH are essential in preventing the accumulation of crystal precursors [26]. The kidneys produce and excrete substances like citrate, magnesium, and glycosaminoglycans that inhibit the formation and growth of crystals in the urine. These substances prevent the aggregation of crystal precursors and promote their dissolution, reducing the risk of stone formation[27]. Citrate inhibits the formation of calcium oxalate stones, a common type of kidney stone. Citrate chelates calcium ions in urine, interfering with the growth of crystals and enhancing the solubility of calcium oxalate, making it less likely for crystals to form and cause stones[28]. Proper citrate levels can be maintained through adequate fluid intake, diet, and necessary supplementation.

Efficient kidney function ensures the timely clearance of waste products and excess minerals from the urinary system. Proper acid-base balance prevents specific kidney stones like uric acid[29]. The kidneys regulate calcium levels in the bloodstream, which helps prevent the formation of calcium-containing stones like calcium oxalate stones. The kidneys play a vital role in maintaining acid-base homeostasis, which influences the solubility of minerals in the urine. Imbalances in acid-base levels can promote the formation of specific types of stones[30].

Etiology and pathogenesis of RTA

RTA refers to a group of kidney disorders that impair acid-base regulation. This results in the kidneys being unable to excrete acid or maintain the body's pH balance properly. There are various types of RTA, each with its own etiology and pathogenesis (Table 1).

Table 1 Comparison of different renal tubular acidosis types based on their etiology, pathogenesis, and key features.

Type of RTA	Type 1 RTA	Type 2 RTA	Type 3 RTA	Type 4 RTA
Prevalence	The most common type of RTA (1-2/100.000)	Less common than type 1 RTA (0.5/100.000)	Very rare	Slightly less common than type 1 RTA (1/100.000)
Location of defect	Distal nephron	Proximal nephron	Variable	Collecting duct
Etiology	Primary	Sporadic or hereditary (mutation of CA-IV, NHE-3, NBC-1)	Mutation in CA-II	PHA-1, PHA-2 (Gordon's syndrome)
	Secondary	Autoimmune: Sjogren's; Nephrotoxins: Tetracycline, topiramate, valproate, acetazolamide; Metabolic: Wilson's disease, cystinosis, Lowe's syndrome, galactosemia, chronic hypocalcemia; Hereditary fructose intolerance, tyrosinemia; Miscellaneous: Multiple myeloma, amyloidosis	Type 1 RTA with secondary proximal tubule dysfunction, type 2 RTA with secondary distal tubule dysfunction	Aldosterone deficiency or aldosterone resistance: Hypoaldosteronism, ACEIs, ARBs; Hyporeninemic hypoaldosteronism: Diabetes, sickle cell disease; Tubulointerstitial disease (eGFR: 20-50 ml/min); Drugs: Potassium sparing diuretics, NSAIDs, trimethoprim, pentamidine, cyclosporine, tacrolimus
Pathogenesis	Impaired hydrogen ion secretion & reduced bicarbonate reabsorption in the distal tubules	Impaired bicarbonate reabsorption in the proximal tubules	Impaired distal acidification and reduced bicarbonate reabsorption	Impaired hydrogen ion secretion and decreased potassium excretion due to reduced aldosterone activity
Degree of acidosis	Severe	Mild to moderate	Mild	Mild to moderate
Key features	Acidemia, hypobicarbonatemia, inability to acidify urine properly, and loss of bicarbonate ions in urine. Hypokalemia is common	Metabolic acidosis, loss of bicarbonate ions in urine, hypobicarbonatemia, electrolyte imbalances (e.g., hypokalemia, hypophosphatemia)	Metabolic acidosis, hypobicarbonatemia, variable features depending on the underlying systemic disease or medication	Metabolic acidosis, hyperkalemia, associated with hypoaldosteronism or resistance to aldosterone, potential electrolyte imbalances (e.g., hyponatremia, mild hyperchloremic acidosis)
Risk of renal calcification	High	Lower than type 1 RTA	Very low (variable)	Unknown

AE1: Anion exchanger 1; CA: Carbonic anhydrase; NHE-3: Sodium-hydrogen exchanger 3; NBC-1: Sodium-bicarbonate cotransporter 1; PHA: Pseudohypoaldosteronism; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; PBC: Primary biliary cirrhosis; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; RTA: Renal tubular acidosis.

Usually, 80% of the bicarbonate ions filtered by the glomerulus are reabsorbed from the urine back into the blood in the proximal tubules of the kidneys, and the remainder are reabsorbed in the distal nephron[31]. An autosomal recessive genetic defect in the *SLC4A1* gene causes RTA type 1. This gene encodes the anion exchanger protein AE1, which transports bicarbonate ions out of the alpha-intercalated cells in the distal tubules of the kidneys[32]. The genetic defect impairs the function of the AE1 protein, which reduces the distal tubules' ability to secrete hydrogen ions into the urine and reabsorb bicarbonate ions from the urine. The defective AE1 protein reduces the transport of hydrogen ions into the urine, leading to acid buildup in the blood and acidemia. In type 1 RTA, the defective AE1 protein also impairs the reabsorption of bicarbonate ions, resulting in a loss of bicarbonate in the urine. This leads to decreased bicarbonate concentration in the blood, which causes metabolic acidosis and various RTA symptoms[33].

Another genetic defect in the *ATP6V1B1* gene, which encodes for a subunit of the proton pump in the alpha-intercalated cells of the distal tubules, can cause type 1 RTA[34]. This type of RTA can also be associated with other systemic genetic diseases, such as Ehler-Danlos syndrome, Marfan syndrome, congenital urinary tract obstruction, or sickle cell disease[35]. It may also occur secondary to chronic kidney diseases such as chronic hypercalcemia, familial hypercalciuria, medullary sponge kidney, chronic interstitial nephritis, chronic pyelonephritis, obstructive uropathy, and renal transplant rejection. Systemic disorders can also induce type 1 RTA, such as glue sniffing and hypergammaglobulinemic states[36,37]. The inherited form of type 1 RTA is mainly diagnosed in early life or young adulthood, while the acquired secondary form can be seen at any age but commonly in adulthood. The incomplete form of type 1 RTA has an incompletely understood pathogenesis. Patients with this disorder have a constantly elevated urinary pH and hypocit-raturia, as in the complete form. However, they can maintain adequate acid excretion to keep the plasma bicarbonate levels within the normal range. Meanwhile, these patients suffer from nephrolithiasis due to hypercalciuria and hypocit-raturia. Therefore, an incomplete form of type 1 RTA should be considered in every calcium stone former[37].

Type 2 RTA is often caused by underlying conditions or medications affecting the function of the proximal tubules in the kidneys. However, genetic disorders like Dent disease can also lead to type 2 RTA[3]. Fanconi syndrome, which impairs reabsorption in the proximal tubules, can be inherited or acquired. It can occur due to conditions such as multiple myeloma, Wilson's disease, or certain medications (e.g., ifosfamide or outdated tetracyclines)[38]. The pathogenesis of type 2 RTA involves impaired bicarbonate reabsorption in the proximal tubules, leading to a decreased net reabsorption of bicarbonate from the glomerular filtrate and contributing to metabolic acidosis. The critical pathogenic mechanism is dysfunction in the transporters or enzymes needed for bicarbonate reabsorption in the proximal tubules from the

glomerular filtrate back into the blood[39]. This dysfunction reduces bicarbonate reabsorption with bicarbonate loss in the urine instead of reabsorbing, leading to decreased blood bicarbonate levels and subsequent metabolic acidosis, which can cause various symptoms of RTA[40].

Type 3 RTA is a complex condition often caused by underlying systemic diseases or certain medications. Systemic diseases, such as autoimmune diseases (*e.g.*, systemic lupus erythematosus and Sjögren's syndrome), primary biliary cirrhosis, sickle cell disease, Marble bone disease (due to congenital carbonic anhydrase deficiency type II), and some metabolic disorders, can lead to dysfunction or renal tubular damage, impairing acid-base regulation[41,42]. Medications such as carbonic anhydrase inhibitors and some chemotherapeutic agents can cause type 3 RTA[43]. The pathogenesis of type 3 RTA is not fully understood and may vary depending on the underlying systemic disease or medication. However, the main pathogenic mechanisms include a combination of impaired distal acidification and reduced bicarbonate reabsorption. Similar to type 1 RTA, type 3 RTA may involve impaired hydrogen ion secretion in the distal tubules, resulting in reduced distal acidification of the urine. The mechanisms underlying diseases or medications that disrupt this acidification process may vary. Type 3 RTA can also involve impaired bicarbonate reabsorption, which leads to metabolic acidosis with decreased blood pH and bicarbonate levels[44,45]. The combination of impaired distal acidification and reduced bicarbonate reabsorption contributes to metabolic acidosis, with decreased blood pH and bicarbonate levels. The severity and clinical manifestations of type 3 RTA can vary depending on the underlying systemic disease or medication involved[46].

Type 4 RTA is primarily caused by conditions that affect the production or action of the hormone aldosterone. The main etiological factors include hypoaldosteronism or aldosterone resistance[47]. Aldosterone plays a crucial role in maintaining electrolyte balance and acid-base regulation. In aldosterone deficiency or dysfunction, there is impaired renal acidification, as aldosterone promotes the distal tubules of the kidneys to secrete hydrogen ions into the urine, reducing the ability to acidify the urine[48]. Hypoaldosteronism can be caused by adrenal gland disorders such as Addison's disease, congenital adrenal hyperplasia, or adrenal gland destruction, resulting in a deficiency in the production or release of aldosterone[49]. In aldosterone resistance, the kidneys fail to respond adequately to the action of aldosterone. This resistance can result from conditions like certain medications (*e.g.*, spironolactone, eplerenone), kidney diseases, or genetic disorders affecting the mineralocorticoid receptor[50]. As aldosterone also regulates potassium levels in the body by enhancing its excretion in the urine, the reduced aldosterone activity in type 4 RTA leads to impaired potassium secretion, resulting in hyperkalemia. Patients with type 4 RTA can present with muscle weakness, arrhythmia, or even cardiac arrest due to hyperkalemia[9,51].

Renal calcification in RTA

Calcification of the kidneys occurs when calcium deposits accumulate in the kidneys, leading to various issues such as kidney stones, nephrocalcinosis, and chronic kidney disease[52]. Nephrocalcinosis happens when calcium salts accumulate in the renal tubules and interstitium of the kidneys. Kidney stones, on the other hand, form due to the presence of solid masses or calculi made of hard calcium deposits in the renal pelvis, calyces, or ureters[53]. Nephrocalcinosis can occur at three levels. Molecular or chemical levels are usually observed in patients with evident hypercalcemia and can be treated by correction of hypercalcemia. Microscopic nephrocalcinosis occurs when the mineral deposits of renal tissue can be seen by light microscopy, and it is often a precursor to the macroscopic type. The macroscopic type can be identified by different imaging methods[54]. Renal calcification can be a complication of RTA, and its severity is influenced by the level of acidosis, hypercalciuria, and other risk factors such as dehydration and a high protein diet, which increase the risk of nephrocalcinosis in RTA. Nephrocalcinosis occurs more frequently in type 1 RTA, less frequently in type 4 RTA and 2 RTA, and rarely in type 3 RTA[4]. About 20% of patients with nephrocalcinosis have either inherited or acquired type 1 RTA. Therefore, when a patient presents with kidney stones and nephrocalcinosis, it is essential to consider a diagnosis of type 1 RTA, as the prevalence of either complete or incomplete type 1 RTA in nephrolithiasis is about 7% and 14%, respectively[55].

Renal calcification in RTA can arise from various factors, including low urinary citrate, high urinary calcium, and metabolic acidosis. Chronic metabolic acidosis stimulates bone resorption, releasing calcium into the bloodstream and potentially depositing it in the kidneys[56]. The severity of metabolic acidosis directly affects the prevalence of renal calcification. Type 1 RTA (classical RTA) exhibits an H^+ excretion defect in the distal nephron, leading to urinary alkalization and calcium phosphate precipitation, eventually forming stones[57]. Additionally, patients with RTA have kidneys that cannot synthesize enough citrate, which helps prevent calcium deposition in the kidneys. Citrate is filtered into the urine but is partly reabsorbed in the proximal tubule, where its absorption depends on pH and systemic and intracellular factors[58]. Acidosis increases citrate reabsorption and its intracellular metabolism, resulting in low urinary citrate levels that increase the risk of renal calcification. Low citrate levels, combined with increased bone resorption, elevate urinary calcium levels, further increasing the risk of renal calcification. Other factors such as hyperparathyroidism, increased dietary calcium intake, and certain medications can also contribute to serum calcium levels, potentially increasing the risk of renal calcification[59].

Factors that increase the risk of renal calcification

It has been previously mentioned that the type and severity of RTA can increase the risk and magnitude of acidosis. Other conditions that a child with RTA may experience can also increase the risk of renal calcification. One of the most common risk factors for renal calcification is hypercalciuria. Hypercalciuria may be primary, such as idiopathic hypercalciuria, or secondary due to hyperparathyroidism, hypervitaminosis D, bone resorption caused by immobilization, or long-term use of medications like furosemide, corticosteroids, or adrenocorticotrophic hormone[54,60,61].

Hyperoxaluria is another critical factor that can induce urinary crystallization. Most oxalates come from an endogenous source, as nutrition only provides about 10% of urinary oxalates. Primary hyperoxaluria type 1 is a rare, autosomal recessive disease of the glyoxylate metabolism due to weak or absent activity of hepatic-specific peroxisomal alanine-glyoxylate aminotransferase[62]. Primary hyperoxaluria type II is even rarer and is caused by defects in D-glycerate dehydrogenase and hydroxy pyruvate reductase[63]. Primary hyperoxaluria type III is due to a recently discovered mutation in the *HOGA1* gene on chromosome 10, which encodes for a mitochondrial 4-hydroxy-2-oxoglutarate aldolase[64]. Secondary enteric hyperoxaluria occurs due to increased intestinal oxalate absorption caused by intestinal surgery, necrotizing enterocolitis, inflammatory bowel disease, celiac disease, cystic fibrosis, abetalipoproteinemia, and ethylene glycol intoxication[65]. Hypocitraturia is another risk factor in the pathogenesis of nephrocalcinosis, commonly seen in the complete type of RTA, especially with severe metabolic acidosis. However, it can also be observed in patients with malabsorption syndromes, hypokalaemia, and persistent mild or latent metabolic acidosis. Hypocitraturia is common in certain parts of the world, such as Turkey. Preterm infants are also more likely to have hypocitraturia[66,67]. Certain medications may also increase the risk of nephrolithiasis. Poorly soluble drugs can act as a nidus for stone formation. Other medications have lithogenic effects, such as vitamin D supplementation and loop diuretics, while some drugs, such as carbonic anhydrase inhibitors, can induce hypercalciuria[68,69].

Clinical presentation and diagnosis of renal calcification in RTA

The diagnosis and clinical manifestations of renal calcification in RTA depend on the specific type of RTA. Renal calcifications can appear as kidney stones or nephrolithiasis, which is caused by the buildup of calcium and other minerals in the renal tubules. To diagnose renal calcification in RTA, doctors use a combination of clinical evaluation, laboratory tests, and imaging studies. Kidney stones can cause symptoms such as nausea, vomiting, severe flank pain, haematuria, polyuria, polydipsia, and recurrent urinary tract infections[24]. Other symptoms of RTA vary depending on the type. For instance, acidotic breathing, salt cravings, and electrolyte imbalances such as hypokalaemia can lead to weakness, muscle cramps, and cardiac arrhythmias[70]. In the long term, metabolic acidosis associated with RTA can hinder a child's growth and development, causing failure to thrive, poor mineralization of bones, resistant rickets, and bone pain in some instances. Therefore, physicians need to measure infants and young children's length/height and weight and calculate their body mass index every 3 mo and every 6 mo for older children until they reach their final height. Chronic and progressive nephrocalcinosis may lead to chronic renal failure and its typical manifestations[71]. Other systemic symptoms depend on the underlying cause of RTA. For example, autosomal recessive forms of type 1 RTA are associated with hearing loss. In addition, Fanconi syndrome, a potential cause of type 2 RTA, may cause symptoms such as hypokalaemia, bicarbonate wasting, polyuria, low-molecular-weight proteinuria, glycosuria, generalized aminoaciduria, and phosphaturia, leading to hypophosphatemia[72,73].

Various laboratory tests can help determine the electrolyte levels, kidney function, and acid-base balance of a person with RTA and nephrocalcinosis. Urine tests help measure the pH and citrate levels of urine, which can provide information about the presence of kidney stones, crystals, and other abnormalities[74]. A safe and simple acid load test is performed to confirm the diagnosis of RTA and determine its type. This test assesses the ability of the kidneys to excrete and remove a predetermined acid load. The patient is given a known amount of ammonium chloride, which acidifies the blood for 3 d. Then, the patient's urine pH is monitored over time to test the kidneys' ability to excrete acid in the urine. In persons with normal kidney function, the urine pH will decrease to less than 5.3 after administering ammonium chloride. However, in patients with RTA, the urine pH may not decrease due to the kidneys' inability to excrete acid properly[75]. The test helps differentiate between different types of RTA. For instance, in type 2 RTA, the urine pH will decrease after administering ammonium chloride, but the fractional bicarbonate excretion will be elevated. In type 1 RTA, the urine pH will not decrease, and the fractional bicarbonate excretion will be normal or reduced[76]. The results of the acid load test in different types of RTA are summarized in Table 2. In some cases, genetic testing may be done to identify underlying genetic causes of RTA. Prenatal genetic testing can also be performed in high-risk families with a known case of hereditary RTA[77]. Table 3 compares clinical and laboratory data between type 1 and type 2 RTA. Table 4 shows some of the genetic disorders that may cause different types of RTA.

In addition, laboratory investigations are necessary for serial follow-up of already diagnosed patients. For example, in patients with hereditary type 1 RTA, fasting venous blood gas analysis, blood urea, serum creatinine, potassium, sodium, chloride, phosphate, calcium, alkaline phosphatase, and albumin are needed every 3-4 mo in infants and young children and every 6 mo for older children and adults[7]. Annual urinalysis, urine creatinine, sodium, potassium, calcium, and citrate are also required. The analysis frequency may be increased in individual cases. Annual audiometry is necessary for cases with type 1 RTA due to the high risk of hearing impairment[78].

When diagnosing renal calcification in patients with RTA, imaging studies can help detect kidney stones or calcifications within the kidneys. The type of imaging used depends on availability, patient characteristics, and the suspected extent of calcification (Table 5). X-rays commonly detect kidney stones, which appear as dense, white shadows in the kidneys and urinary tract. Ultrasound is a non-invasive technique that is useful in creating images of the kidneys and surrounding structures to detect kidney stones. Ultrasound can be done annually to evaluate nephrocalcinosis, urolithiasis, and cysts in asymptomatic individuals[79]. Computed tomography (CT) scans provide detailed cross-sectional images of the kidneys, allowing for a more precise evaluation of renal calcifications and any associated complications. Non-contrast CT is to be done first; then, contrast study may sometimes be helpful to clarify complex or confusing cases. However, contrast can obscure calcific densities. Therefore, contrast scans are usually indicated during the follow-up evaluation of patients with kidney stones[80]. Magnetic resonance imaging (MRI) is used in cases where CT scans are contraindicated or not preferred, such as in patients with allergies to contrast agents used in CT scans. MRI can also provide detailed images of the kidneys, but it may not be as readily available as other imaging modalities[81]. Imaging studies, especially ultrasound and CT scans, are crucial for diagnosing and managing renal calcification in patients with

Table 2 Acid load test in different types of renal tubular acidosis

Type of RTA	Urine pH	Fractional bicarbonate excretion
Type 1 RTA	Does not decrease	Normal or decreased
Type 2 RTA	Decreases	Increased
Type 3 RTA	Variable	Variable
Type 4 RTA	Does not decrease	Decreased

RTA: Renal tubular acidosis.

Table 3 Comparison of clinical and laboratory data between type 1 and type 2 renal tubular acidosis

Feature	Type 1 RTA	Type 2 RTA
Prevalence	More common than type 2 RTA	Less common than type 1 RTA
Cause	Usually isolated, inherited, autosomal recessive forms are associated with hearing loss	Usually secondary to a systemic disease, most often metabolic disease, <i>e.g.</i> , Fanconi syndrome
Clinical features	Nephrocalcinosis	Often present
	Polyuria (increased urine output)	Occasionally present
	Polydipsia (increased thirst)	Common
	Dehydration	Common
	Bone abnormalities	Less common
	Failure to thrive (children)	Variable
	Rickets/osteomalacia (children)	Uncommon
	Metabolic acidosis	Uncommon
Laboratory Finding	Serum HCO ₃ ⁻ (bicarbonate)	Severe acidosis; is easily corrected with bicarbonate supplementation
	Serum potassium	Usually milder but difficult to correct; requires high doses of bicarbonate supplementation
	Urine pH	Decreased
	Fractional excretion of bicarbonate	Low
	Urine-blood PCO ₂	> 5.5
	Phosphaturia and hypophosphatemia	< 5%
	Tubular defects – low-molecular-weight proteinuria, aminoaciduria, glycosuria	> 15%
	Hypercalciuria	> 20 mmHg
		Present (variable)
		Present (variable)
		Occasionally present

RTA: Renal tubular acidosis.

RTA. They allow clinicians to visualize the extent and nature of the calcifications, determine appropriate treatment strategies, and monitor treatment response over time[82]. However, it is essential to remember that the choice of imaging modality should be based on the specific clinical scenario, and imaging findings should be integrated with other clinical information to arrive at a comprehensive diagnosis and treatment plan. Early diagnosis and treatment of renal calcification in RTA can help prevent serious complications[1].

Management of nephrocalcinosis

Managing nephrocalcinosis in RTA involves identifying the root cause and addressing the complications associated with the condition. The treatment method utilized depends on the type of RTA and the severity of nephrocalcinosis. The primary objectives of management are to correct the acidosis, reduce urinary calcium excretion, and prevent further calcification. For type 1 RTA, the primary management goal is to decrease urinary calcium excretion. Oral alkaline therapy, such as oral sodium bicarbonate or citrate, is utilized to correct metabolic acidosis. The average dosage is 1.9 mEq/kg/d and is adjusted based on the blood and urine pH. Young patients typically require higher doses due to their high growth rate[83]. Patients with type 1 RTA caused by vacuolar H⁺-ATPase variants may require higher doses of alkali

Table 4 Genetic causes of different types of renal tubular acidosis

Gene involved	Inheritance	Location of gene	RTA type caused	Affected protein	Main clinical feature
<i>SLC4A1</i> gene	AD AR	17q21-q22	Type 1 RTA	AE1	Type 1 RTA, hereditary spherocytosis
<i>CA2</i> gene	AR	8q21.2	Type 1 RTA, type 3 RTA	CA II	Osteopetrosis, brain calcification, RTA
<i>ATP6V1B1</i> <i>ATP6V0A4</i>	AR	2q13 7q33-q34	Type 1 RTA	H ⁺ -ATPase	Sensorineural deafness
<i>SLC4A2</i> gene	AR	7q36.1	Type 2 RTA	AE2	PBC
<i>SLC4A4</i> gene	AR	4q13.3	Type 2 RTA	(NBC)	Ocular abnormalities
<i>SLC2A2</i> gene	AR	3q26.2	Type 2 RTA	GLUT2	Fanconi-Bickel syndrome, NIDDM
<i>CLCN5</i> gene	X-linked recessive	Xp11.23	Type 2 RTA	H ⁺ /Cl ⁻ exchanger	Dent disease type 1, HHR
<i>OCRL1</i> gene	X-linked recessive	Xq26.1	Type 2 RTA	OCRL enzyme	Dent disease, type 2, LOCRS
<i>NR3C2 (MR)</i> gene	AD	4p	Type 4 RTA	MLR NRC	PHA1, hyperkalemia, salt wasting & hypotension
<i>SCNN1A</i> , <i>SCNN1B</i> , and <i>SCNN1G</i> genes	AR	<i>SCNN1A</i> (12p3). <i>SCNN1B</i> , & <i>SCNN1G</i> located in (16p12-p13)	Type 4 RTA	ENaC	Liddle syndrome, sodium loss from the kidneys and other organs, including the sweat glands, salivary glands, and colon

AD: Autosomal dominant; AE1: Anion exchanger 1 protein; AE2: Anion exchanger 2 protein; AR: Autosomal recessive; CA II: Carbonic anhydrase II; ENaC: Epithelial sodium channels located on the luminal membrane of the collecting tubule; GLUT2: Glucose transporter 2; HHR: Hereditary hypophosphatemic rickets; OCRL: Lowe oculocerebrorenal syndrome; MLR NRC: The mineralocorticoid receptor (or MR, MLR, MCR), also known as the aldosterone receptor or nuclear receptor subfamily 3, MR: Mineralocorticoid receptor, group C; NBC: Sodium bicarbonate cotransporter, which regulates bicarbonate secretion, absorption, and intracellular pH. NIDDM: Noninsulin-dependent diabetes mellitus, PBC: Primary biliary cirrhosis; PHA1: Primary pseudohypoaldosteronism type 1; RTA: Renal tubular acidosis.

Table 5 Comparison of different imaging modalities in nephrocalcinosis due to RTA

Modality	Advantages	Limitations
X-ray	Readily available; Cost-effective; Quick initial assessment; Suitable for detecting large, dense stones	Limited sensitivity for smaller or radiolucent stones; No detailed anatomical information
Ultrasound	Can be used to assess kidney size, shape, and echogenicity; Non-invasive; Real-time imaging; Widely available; Initial assessment of kidney stones and medullary cyst	Reduced sensitivity for smaller or deeply located calcifications; Limited anatomical details
CT	Excellent spatial resolution; Detailed cross-sectional images; Highly sensitive for detecting kidney stones and calcifications; Assesses impact on kidney function and urinary tract	Involves exposure to ionizing radiation; Contrast agents may be contraindicated in some patients; Not suitable for all patients due to contrast use
MRI	No ionizing radiation; Detailed images of the extent of calcification and surrounding soft tissue damage; Multiplanar imaging capability; Can provide information on tissue characteristics and perfusion	It may not be as readily available as other modalities; Limited sensitivity for detecting small or faint calcifications

CT: Computed tomography; MRI: Magnetic resonance imaging.

than those with heterozygous *SLC4A1* gene mutations[84]. A sustained-release granular form of potassium citrate and bicarbonate can be used in a 1:2 ratio to maintain normal serum bicarbonate levels[85]. This action improves urinary citrate, reduces the rate of nephrolithiasis, and ensures adequate growth in children[2]. Potassium citrate and additional potassium chloride are supplied as needed to correct hypokalemia. Thiazide diuretics, particularly hydrochlorothiazide, have been used to treat renal hypercalciuria and reduce the risk of nephrolithiasis[86]. The calcium/creatinine ratio can detect hypercalciuria and hypocitraturia, which may indicate inadequate correction of acidosis. In some cases, surgery may be necessary to remove kidney stones. Screening for sensorineural hearing loss during childhood is essential, and any issues should be monitored and treated accordingly[87].

When managing type 2 RTA, the primary goals are treating the root cause, correcting acidosis, promoting growth, and preventing bone deformities. These goals are typically achieved through oral bicarbonate supplements to compensate for urinary bicarbonate losses, with high doses of alkalis (10-15 mEq/kg/d)[88]. Depending on the severity, additional

measures may be necessary to address potassium and electrolyte imbalances. Potassium is administered at a dose of 1-5 mEq/kg/d, phosphate at a dose of 20-40 mg/kg/d, sodium at a dose of 3-5 mEq/kg/d, and magnesium at a dose of 25-50 mg/kg/d. Children with type 2 RTA usually require higher doses of bicarbonate therapy than those with type 1 RTA to maintain bicarbonate levels around the kidney threshold. In some cases, a potassium-sparing diuretic may be prescribed[3]. Vitamin D is vital in promoting calcium absorption and bone health. In type 1 RTA, the kidneys struggle to activate vitamin D, so active vitamin D supplementation in the form of calcitriol 20-40 ng/kg/day, combined with regular monitoring of urinary calcium levels and annual renal ultrasounds, is necessary to prevent nephrocalcinosis and osteoporosis[89]. Vitamin D supplementation may be unnecessary for type 2 RTA, as vitamin D activation is unaffected. However, vitamin D deficiency can induce type 2 RTA[90]. Nutritional intake should be monitored by specialized nutritionists, as children with RTA often have compromised nutritional status due to poor nutrient intake, polyuria, polydipsia, and increased sodium and nutrient loss. It is recommended to consume calorie-dense foods rich in potassium and phosphorus, along with sufficient fluids. Patients with RTA should consume less acidic foods, such as animal meat, and more alkaline-based foods, such as vegetables and fruits[1].

The treatment for type 3 RTA involves using alkaline therapy and addressing any specific underlying causes. In type 4 RTA, management requires controlling the underlying reason for the mineralocorticoid disorder. This may involve treating conditions like hyperaldosteronism or evaluating medication use[91]. Daily intake of 0.1 mg of fludrocortisone can effectively manage hyperaldosteronism-associated hyperkalemia. However, this is not generally recommended due to the high risk of hypertension, edema, and heart failure. Patients with hyperkalemia can effectively manage their condition by limiting their dietary potassium intake to 40 to 60 mEq daily and using diuretics such as loop or thiazide when necessary[92].

Nephrocalcinosis management in RTA should be tailored to each patient's specific condition, medical history, and the underlying cause of RTA. Since it is a progressive condition, it is crucial to start strategies to prevent, diagnose, and treat RTA-associated nephrocalcinosis early[93]. These early strategies and interventions can help control nephrocalcinosis and prevent it from producing severe complications. Encouraging adequate fluid intake can help dilute the urine, prevent the concentration and crystallization of calcium and other minerals in the urine, and reduce the risk of calcium deposition in the kidneys[24]. It is crucial to keep urinary calcium levels below $< 0.1 \text{ mmol} (< 4 \text{ mg})/\text{kg}$ and oxalate $< 0.5 \text{ mmol} (< 45 \text{ mg})/1.73 \text{ m}^2$ within 24 h of urine collection. Additionally, it is vital to keep urinary citrate levels above $1.9 \text{ mmol} (365 \text{ mg})/1.73 \text{ m}^2$ in males and $1.6 \text{ mmol} (310 \text{ mg})/1.73 \text{ m}^2$ in females within 24 h of urine collection[94].

Dietary adjustments should be made based on the type of RTA to prevent and treat nephrocalcinosis. Limiting calcium and oxalate intake is recommended to reduce the formation of kidney stones[95]. A low-sodium diet can also help decrease urinary calcium excretion, but sodium salts like sodium bicarbonate and citrate may increase calcium excretion and worsen stone disease[96]. Therefore, potassium bicarbonate or potassium citrate may be better alternatives, especially for patients with active calcium stone disease. In type 1 RTA, minimizing urinary potassium loss and correcting hypokalemia can alleviate or even reverse nephrocalcinosis, lowering the rate of calcium kidney stones and potentially correcting osteoporosis[97]. Reducing acidic and oxalate-rich foods like spinach, rhubarb, and beets can also be beneficial, but it is essential to consult a healthcare professional to avoid nutrient deficiencies[98]. Regular exercise and maintaining a healthy weight are also crucial in improving kidney function and reducing the risk of kidney stones. Lastly, avoiding passive smoking is essential in preventing nephrocalcinosis in children with RTA, as smoking can harm the kidneys[99].

Reviewing the medication chart, specifically for type 1 RTA, is important. Medications that can worsen nephrocalcinosis, such as carbonic anhydrase inhibitors, should be assessed and adjusted if needed[100]. Conversely, certain medications may help manage nephrocalcinosis depending on its severity and cause. For instance, thiazide diuretics can minimize calcium excretion in the urine, which could benefit specific cases of nephrocalcinosis[101]. Potassium-sparing diuretics, like amiloride, may help maintain blood potassium levels, especially when taking thiazide diuretics[102]. Pain management may be necessary for those experiencing kidney stone-related pain. Non-steroidal anti-inflammatory drugs or opioids are standard options for pain relief[103].

Regular monitoring of kidney function, electrolyte levels, and urinary calcium excretion is crucial for detecting any complications early, evaluating the effectiveness of the treatment, and identifying any progression of nephrocalcinosis [104]. Nephrocalcinosis can increase the likelihood of developing kidney stones, so preventive measures like dietary adjustments, increased fluid intake, and medication (such as potassium citrate) may be advised[66]. Genetic counselling can help provide information about inheritance patterns, assess the risk to family members, and guide family planning decisions for hereditary forms of RTA[105].

Prognosis of renal calcification in patients with RTA

The outlook for renal calcification in patients with RTA can differ depending on factors such as the type of RTA, underlying cause, extent of calcification, and treatment effectiveness. The type of RTA can impact the prognosis and management of renal calcification. For instance, type 1 RTA is usually linked with nephrocalcinosis and kidney stones[1]. Early detection of renal calcification and proper RTA management are crucial for a better prognosis. Treating the underlying acid-base imbalance, alkaline therapy, and controlling calcium excretion can help slow down the progression of nephrocalcinosis and prevent further kidney damage[106]. Nephrocalcinosis increases the risk of kidney stone formation, leading to recurrent kidney stone episodes and potential complications if not managed effectively. Preventive measures such as dietary adjustments, fluid intake, and medication can help reduce the risk of stone formation[107]. The extent of nephrocalcinosis and its impact on kidney function are vital in determining the prognosis. Extensive nephrocalcinosis can sometimes lead to chronic kidney disease and its associated complications. Identifying and treating the underlying cause of RTA and nephrocalcinosis are crucial[108]. For example, in type 1 RTA, potassium citrate or bicarbonate supplementation can help correct the acidosis and prevent stone formation. In type 2 RTA (proximal RTA), treatment may involve addressing the underlying cause, such as a genetic disorder or specific medications. Other medical

conditions or comorbidities can also impact the prognosis of nephrocalcinosis in RTA patients[109]. Managing these conditions alongside RTA and nephrocalcinosis is essential for overall health and outcomes. Regular monitoring and follow-up with healthcare providers are necessary for patients with RTA and renal calcification. Periodic evaluation of kidney function, imaging studies (*e.g.*, ultrasound and CT scans), and urine analysis can help assess the progression of the condition and guide treatment adjustments if needed[110]. The prognosis can vary significantly among individuals due to individual variability. It is important to recognize that early and comprehensive medical management is essential to optimize outcomes. Regular follow-up with healthcare providers, adherence to treatment plans, and lifestyle modifications can help improve the long-term prognosis for patients with nephrocalcinosis and RTA[111].

Limitations of the study

Several potential limitations could impact the reliability and generalizability of the study findings. There might be a limited number of studies and data available on renal calcification in children with RTA due to the relative rarity of this condition. This can reduce the included studies' sample size and statistical power, making it challenging to draw robust conclusions. In addition, the studies included in the review have differences in methodologies, patient populations, and definitions of renal calcification. This heterogeneity can make it challenging to compare and synthesize the results. We should also consider that RTA is not a single condition but rather a group of disorders with different underlying causes and manifestations. We should consider the variability in RTA types, their treatment approaches, and their potential impact on renal calcification. There is also a lack of longitudinal data and control groups in some studies, which limits our ability to fully understand the progression and impact of renal calcification on children with RTA. Furthermore, many studies included in the review may have been conducted in specific populations, which can limit the generalizability of the findings to other populations. Another significant limitation of the study is that we included studies published in English, which could result in the omission of important studies and potentially bias the results.

CONCLUSION

Our comprehensive review of the current literature underscores the significance of renal calcification as a critical concern for children with RTA. Our analysis reveals that renal calcification is a prevalent issue among children with RTA, with varying degrees of risk associated with different RTA types. Notably, type 1 RTA is frequently linked to nephrocalcinosis, emphasizing the importance of early detection and tailored management strategies for affected patients. While we acknowledge the limitations within the reviewed studies, such as the small number of available studies, methodological heterogeneity, and potential publication bias, they collectively emphasize the critical role of timely diagnosis and appropriate RTA management in reducing the risk of renal calcification and its associated complications. In particular, alkaline therapy remains a cornerstone treatment, effectively addressing the acid-base imbalance and minimizing the formation of kidney stones. To advance our understanding and guide clinical practice further, it is evident that future research efforts should focus on larger sample sizes, longitudinal data, and more rigorous methodologies. These endeavors will undoubtedly contribute to a more nuanced comprehension of the intricate relationship between RTA and renal calcification. By doing so, we can better inform treatment and prevention strategies, ultimately enhancing the long-term outcomes and quality of life for children affected by this condition.

ACKNOWLEDGEMENTS

We thank the anonymous referees and editors for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M developed the idea, collected the data, and wrote and revised the manuscript; Saeed NK, Bediwy AS, Hasan S, and Hamza MB collected the data and revised the manuscript from the laboratory aspect; Elbeltagi R collected the data, wrote the method section, and revised the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Egypt

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207; Adel Salah Bediwy 0000-0002-0281-0010; Reem Elbeltagi 0000-0001-9969-5970; Samir Hasan 0000-0002-0759-7394.

S-Editor: Liu JH

L-Editor: Wang TQ

P-Editor: Cai YX

REFERENCES

- 1 **Palmer BF**, Kelepouris E, Clegg DJ. Renal Tubular Acidosis and Management Strategies: A Narrative Review. *Adv Ther* 2021; **38**: 949-968 [PMID: 33367987 DOI: 10.1007/s12325-020-01587-5]
- 2 **Giglio S**, Montini G, Trepiccione F, Gambaro G, Emma F. Distal renal tubular acidosis: a systematic approach from diagnosis to treatment. *J Nephrol* 2021; **34**: 2073-2083 [PMID: 33770395 DOI: 10.1007/s40620-021-01032-y]
- 3 **Haque SK**, Ariceta G, Batlle D. Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. *Nephrol Dial Transplant* 2012; **27**: 4273-4287 [PMID: 23235953 DOI: 10.1093/ndt/gfs493]
- 4 **Boro H**, Khatiwada S, Alam S, Kubihal S, Dogra V, Mannar V, Khadgawat R. Renal Tubular Acidosis Manifesting as Severe Metabolic Bone Disease. *touchREV Endocrinol* 2021; **17**: 59-67 [PMID: 35118447 DOI: 10.17925/EE.2021.17.1.59]
- 5 **Bello CHPT**, Duarte JS, Vasconcelos C. Diabetes mellitus and hyperkalemic renal tubular acidosis: case reports and literature review. *J Bras Nefrol* 2017; **39**: 481-485 [PMID: 29319780 DOI: 10.5935/0101-2800.20170086]
- 6 **Gómez-Conde S**, García-Castaño A, Aguirre M, Herrero M, Gondra L, Castaño L, Madariaga L. Hereditary distal renal tubular acidosis: Genotypic correlation, evolution to long term, and new therapeutic perspectives. *Nefrologia (Engl Ed)* 2021; **41**: 383-390 [PMID: 36165107 DOI: 10.1016/j.nefro.2021.09.004]
- 7 **Yaxley J**, Pirrone C. Review of the Diagnostic Evaluation of Renal Tubular Acidosis. *Ochsner J* 2016; **16**: 525-530 [PMID: 27999512]
- 8 **Soares SBM**, de Menezes Silva LAW, de Carvalho Mrad FC, Simões E Silva AC. Distal renal tubular acidosis: genetic causes and management. *World J Pediatr* 2019; **15**: 422-431 [PMID: 31079338 DOI: 10.1007/s12519-019-00260-4]
- 9 **Menegussi J**, Tatagiba LS, Vianna JGP, Seguro AC, Luchi WM. A physiology-based approach to a patient with hyperkalemic renal tubular acidosis. *J Bras Nefrol* 2018; **40**: 410-417 [PMID: 30048563 DOI: 10.1590/2175-8239-JBN-3821]
- 10 **Gasser JA**, Hulter HN, Imboden P, Krapf R. Effect of chronic metabolic acidosis on bone density and bone architecture in vivo in rats. *Am J Physiol Renal Physiol* 2014; **306**: F517-F524 [PMID: 24352505 DOI: 10.1152/ajprenal.00494.2013]
- 11 **Oduwole AO**, Giwa OS, Arogundade RA. Relationship between rickets and incomplete distal renal tubular acidosis in children. *Ital J Pediatr* 2010; **36**: 54 [PMID: 20699008 DOI: 10.1186/1824-7288-36-54]
- 12 **Oliveira B**, Kleta R, Bockenbauer D, Walsh SB. Genetic, pathophysiological, and clinical aspects of nephrocalcinosis. *Am J Physiol Renal Physiol* 2016; **311**: F1243-F1252 [PMID: 27605580 DOI: 10.1152/ajprenal.00211.2016]
- 13 **Alhasan KA**, Shalaby MA, Albanna AS, Temsah MH, Alhayek Z, Abdalla MS, Alotaibi NG, Kalakattawi NM, Zaher ZF, Kari JA. Comparison of Renal Stones and Nephrocalcinosis in Children: Findings From Two Tertiary Centers in Saudi Arabia. *Front Pediatr* 2021; **9**: 736308 [PMID: 35111701 DOI: 10.3389/fped.2021.736308]
- 14 **Trepiccione F**, Prosperi F, de la Motte LR, Hübner CA, Chambrey R, Eladari D, Capasso G. New Findings on the Pathogenesis of Distal Renal Tubular Acidosis. *Kidney Dis (Basel)* 2017; **3**: 98-105 [PMID: 29344504 DOI: 10.1159/000478781]
- 15 **Seifter JL**. Integration of acid-base and electrolyte disorders. *N Engl J Med* 2014; **371**: 1821-1831 [PMID: 25372090 DOI: 10.1056/NEJMra1215672]
- 16 **Hamm LL**, Nakhoul N, Hering-Smith KS. Acid-Base Homeostasis. *Clin J Am Soc Nephrol* 2015; **10**: 2232-2242 [PMID: 26597304 DOI: 10.2215/CJN.07400715]
- 17 **Curthoys NP**, Moe OW. Proximal tubule function and response to acidosis. *Clin J Am Soc Nephrol* 2014; **9**: 1627-1638 [PMID: 23908456 DOI: 10.2215/CJN.10391012]
- 18 **Balzer MS**, Rohacs T, Susztak K. How Many Cell Types Are in the Kidney and What Do They Do? *Annu Rev Physiol* 2022; **84**: 507-531 [PMID: 34843404 DOI: 10.1146/annurev-physiol-052521-121841]
- 19 **Weiner ID**, Verlander JW. Renal ammonia metabolism and transport. *Compr Physiol* 2013; **3**: 201-220 [PMID: 23720285 DOI: 10.1002/cphy.c120010]
- 20 **Phetrittikun R**, Suvirat K, Horsiritham K, Ingviya T, Chaichulee S. Prediction of Acid-Base and Potassium Imbalances in Intensive Care Patients Using Machine Learning Techniques. *Diagnostics (Basel)* 2023; **13** [PMID: 36980479 DOI: 10.3390/diagnostics13061171]
- 21 **Jeon US**. Kidney and calcium homeostasis. *Electrolyte Blood Press* 2008; **6**: 68-76 [PMID: 24459525 DOI: 10.5049/EBP.2008.6.2.68]
- 22 **Moe SM**. Calcium Homeostasis in Health and in Kidney Disease. *Compr Physiol* 2016; **6**: 1781-1800 [PMID: 27783859 DOI: 10.1002/cphy.c150052]
- 23 **Hanna RM**, Ahdoot RS, Kalantar-Zadeh K, Ghobry L, Kurtz I. Calcium Transport in the Kidney and Disease Processes. *Front Endocrinol (Lausanne)* 2021; **12**: 762130 [PMID: 35299844 DOI: 10.3389/fendo.2021.762130]
- 24 **Alelign T**, Petros B. Kidney Stone Disease: An Update on Current Concepts. *Adv Urol* 2018; **2018**: 3068365 [PMID: 29515627 DOI: 10.1155/2018/3068365]
- 25 **Game KN**, Jamnadas E, Sulaiman SK, Pietropaolo A, Aboumarzouk O, Somani BK. The role of fluid intake in the prevention of kidney stone disease: A systematic review over the last two decades. *Turk J Urol* 2020; **46**: S92-S103 [PMID: 32525478 DOI: 10.5152/tud.2020.20155]
- 26 **Wagner CA**, Mohebbi N. Urinary pH and stone formation. *J Nephrol* 2010; **23** Suppl 16: S165-S169 [PMID: 21170875]
- 27 **Ratkalkar VN**, Kleinman JG. Mechanisms of Stone Formation. *Clin Rev Bone Miner Metab* 2011; **9**: 187-197 [PMID: 22229020 DOI: 10.1007/s12018-011-9104-8]
- 28 **Caudarella R**, Vescini F. Urinary citrate and renal stone disease: the preventive role of alkali citrate treatment. *Arch Ital Urol Androl* 2009; **81**: 182-187 [PMID: 19911682]
- 29 **Ngo TC**, Assimios DG. Uric Acid nephrolithiasis: recent progress and future directions. *Rev Urol* 2007; **9**: 17-27 [PMID: 17396168]
- 30 **Stepanova N**. Oxalate Homeostasis in Non-Stone-Forming Chronic Kidney Disease: A Review of Key Findings and Perspectives. *Biomedicines* 2023; **11** [PMID: 37371749 DOI: 10.3390/biomedicines11061654]
- 31 **Weiner ID**, Verlander JW. Emerging Features of Ammonia Metabolism and Transport in Acid-Base Balance. *Semin Nephrol* 2019; **39**: 394-

- 405 [PMID: 31300094 DOI: 10.1016/j.semnephrol.2019.04.008]
- 32 **Park E**, Phaymany V, Yi ES, Phangmanixay S, Cheong HI, Choi Y. Primary Autosomal Recessive Distal Renal Tubular Acidosis Caused by a Common Homozygous SLC4A1 Mutation in Two Lao Families. *J Korean Med Sci* 2018; **33**: e95 [PMID: 29573245 DOI: 10.3346/jkms.2018.33.e95]
 - 33 **Mumtaz R**, Trepiccione F, Hennings JC, Huebner AK, Serbin B, Picard N, Ullah AKMS, Păunescu TG, Capen DE, Lashhab RM, Mouro-Chanteloup I, Alper SL, Wagner CA, Cordat E, Brown D, Eladari D, Hübner CA. Intercalated Cell Depletion and Vacuolar H(+)-ATPase Mistargeting in an Ae1 R607H Knockin Model. *J Am Soc Nephrol* 2017; **28**: 1507-1520 [PMID: 27932475 DOI: 10.1681/ASN.2016020169]
 - 34 **Escobar LI**, Simian C, Treard C, Hayek D, Salvador C, Guerra N, Matos M, Medeiros M, Enciso S, Camargo MD, Vargas-Poussou R. Mutations in ATP6V1B1 and ATP6V0A4 genes cause recessive distal renal tubular acidosis in Mexican families. *Mol Genet Genomic Med* 2016; **4**: 303-311 [PMID: 27247958 DOI: 10.1002/mgg3.205]
 - 35 **Herrnstadt GR**, Holzer MT, Steinmetz OM, Kötter I, Melderis S. [Renal manifestations in connective tissue diseases]. *Z Rheumatol* 2022; **81**: 829-844 [PMID: 36348023 DOI: 10.1007/s00393-022-01281-7]
 - 36 **Both T**, Zietse R, Hoorn EJ, van Hagen PM, Dalm VA, van Laar JA, van Daele PL. Everything you need to know about distal renal tubular acidosis in autoimmune disease. *Rheumatol Int* 2014; **34**: 1037-1045 [PMID: 24682397 DOI: 10.1007/s00296-014-2993-3]
 - 37 **Kumagai I**, Matsuo S, Kato T. A case of incomplete renal tubular acidosis (type 1) associated with medullary sponge kidney followed by nephrocalcinosis. *J Urol* 1980; **123**: 250-252 [PMID: 7354533 DOI: 10.1016/s0022-5347(17)55884-x]
 - 38 **Foreman JW**. Fanconi Syndrome. *Pediatr Clin North Am* 2019; **66**: 159-167 [PMID: 30454741 DOI: 10.1016/j.pcl.2018.09.002]
 - 39 **Kashoor I**, Batlle D. Proximal renal tubular acidosis with and without Fanconi syndrome. *Kidney Res Clin Pract* 2019; **38**: 267-281 [PMID: 31474092 DOI: 10.23876/j.krcp.19.056]
 - 40 **Berend K**. Review of the Diagnostic Evaluation of Normal Anion Gap Metabolic Acidosis. *Kidney Dis (Basel)* 2017; **3**: 149-159 [PMID: 29344509 DOI: 10.1159/000479279]
 - 41 **Goswami RP**, Mondal S, Karmakar PS, Ghosh A. Type 3 renal tubular acidosis. *Indian J Nephrol* 2012; **22**: 466-468 [PMID: 23439805 DOI: 10.4103/0971-4065.106058]
 - 42 **Stark Z**, Savarirayan R. Osteopetrosis. *Orphanet J Rare Dis* 2009; **4**: 5 [PMID: 19232111 DOI: 10.1186/1750-1172-4-5]
 - 43 **Sacré A**, Jouret F, Manicourt D, Devuyt O. Topiramate induces type 3 renal tubular acidosis by inhibiting renal carbonic anhydrase. *Nephrol Dial Transplant* 2006; **21**: 2995-2996 [PMID: 16735391 DOI: 10.1093/ndt/gfi251]
 - 44 **Kumagai N**, Kondoh T, Matsumoto Y, Ikezumi Y. Transient Type 3 Renal Tubular Acidosis during Cyclic Vomiting Syndrome. *Tohoku J Exp Med* 2022; **257**: 73-76 [PMID: 35354692 DOI: 10.1620/tjem.2022.J015]
 - 45 **Alexander RT**, Bitzan M. Renal Tubular Acidosis. *Pediatr Clin North Am* 2019; **66**: 135-157 [PMID: 30454739 DOI: 10.1016/j.pcl.2018.08.011]
 - 46 **Hoorn EJ**, Zietse R. Combined renal tubular acidosis and diabetes insipidus in hematological disease. *Nat Clin Pract Nephrol* 2007; **3**: 171-175 [PMID: 17322929 DOI: 10.1038/ncpneph0424]
 - 47 **Batlle D**, Arruda J. Hyperkalemic Forms of Renal Tubular Acidosis: Clinical and Pathophysiological Aspects. *Adv Chronic Kidney Dis* 2018; **25**: 321-333 [PMID: 30139459 DOI: 10.1053/j.ackd.2018.05.004]
 - 48 **Wagner CA**. Effect of mineralocorticoids on acid-base balance. *Nephron Physiol* 2014; **128**: 26-34 [PMID: 25377117 DOI: 10.1159/000368266]
 - 49 **Krysiak R**, Kedzia A, Krupej-Kedzierska J, Okopień B. [Hypoaldosteronism]. *Przegl Lek* 2013; **70**: 69-75 [PMID: 23879007]
 - 50 **Zennaro MC**, Hubert EL, Fernandes-Rosa FL. Aldosterone resistance: structural and functional considerations and new perspectives. *Mol Cell Endocrinol* 2012; **350**: 206-215 [PMID: 21664233 DOI: 10.1016/j.mce.2011.04.023]
 - 51 **Montford JR**, Linas S. How Dangerous Is Hyperkalemia? *J Am Soc Nephrol* 2017; **28**: 3155-3165 [PMID: 28778861 DOI: 10.1681/ASN.2016121344]
 - 52 **Le JD**, Eisner BH, Tseng TY, Chi T, Stoller ML. Laterality of nephrocalcinosis in kidney stone formers with severe hypocitraturia. *BJU Int* 2011; **107**: 106-110 [PMID: 20590541 DOI: 10.1111/j.1464-410X.2010.09492.x]
 - 53 **Dickson FJ**, Sayer JA. Nephrocalcinosis: A Review of Monogenic Causes and Insights They Provide into This Heterogeneous Condition. *Int J Mol Sci* 2020; **21** [PMID: 31935940 DOI: 10.3390/ijms21010369]
 - 54 **Shavit L**, Jaeger P, Unwin RJ. What is nephrocalcinosis? *Kidney Int* 2015; **88**: 35-43 [PMID: 25807034 DOI: 10.1038/ki.2015.76]
 - 55 **Magni G**, Unwin RJ, Moochhala SH. Renal tubular acidosis (RTA) and kidney stones: Diagnosis and management. *Arch Esp Urol* 2021; **74**: 123-128 [PMID: 33459628]
 - 56 **Alexander RT**, Cordat E, Chambrey R, Dimke H, Eladari D. Acidosis and Urinary Calcium Excretion: Insights from Genetic Disorders. *J Am Soc Nephrol* 2016; **27**: 3511-3520 [PMID: 27468975 DOI: 10.1681/ASN.2016030305]
 - 57 **Santos F**, Ordóñez FA, Claramunt-Taberner D, Gil-Peña H. Clinical and laboratory approaches in the diagnosis of renal tubular acidosis. *Pediatr Nephrol* 2015; **30**: 2099-2107 [PMID: 25823989 DOI: 10.1007/s00467-015-3083-9]
 - 58 **Goraya N**, Simoni J, Sager LN, Madias NE, Wesson DE. Urine citrate excretion as a marker of acid retention in patients with chronic kidney disease without overt metabolic acidosis. *Kidney Int* 2019; **95**: 1190-1196 [PMID: 30846270 DOI: 10.1016/j.kint.2018.11.033]
 - 59 **Hill Gallant KM**, Spiegel DM. Calcium Balance in Chronic Kidney Disease. *Curr Osteoporos Rep* 2017; **15**: 214-221 [PMID: 28474258 DOI: 10.1007/s11914-017-0368-x]
 - 60 **Gambara G**, Vezzoli G, Casari G, Rampoldi L, D'Angelo A, Borghi L. Genetics of hypercalciuria and calcium nephrolithiasis: from the rare monogenic to the common polygenic forms. *Am J Kidney Dis* 2004; **44**: 963-986 [PMID: 15558518 DOI: 10.1053/j.ajkd.2004.06.030]
 - 61 **Wan M**, Patel J, Rait G, Shroff R. Hypervitaminosis D and nephrocalcinosis: too much of a good thing? *Pediatr Nephrol* 2022; **37**: 2225-2229 [PMID: 35352192 DOI: 10.1007/s00467-022-05513-5]
 - 62 **Hoppe B**, Beck BB, Milliner DS. The primary hyperoxalurias. *Kidney Int* 2009; **75**: 1264-1271 [PMID: 19225556 DOI: 10.1038/ki.2009.32]
 - 63 **Garrelfs SF**, Rumsby G, Peters-Sengers H, Erger F, Groothoff JW, Beck BB, Oosterveld MJS, Pelle A, Neuhaus T, Adams B, Cochat P, Salido E, Lipkin GW, Hoppe B, Hulton SA; OxalEurope Consortium. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. *Kidney Int* 2019; **96**: 1389-1399 [PMID: 31685312 DOI: 10.1016/j.kint.2019.08.018]
 - 64 **Monico CG**, Rossetti S, Belostotsky R, Cogal AG, Herges RM, Seide BM, Olson JB, Bergstrahl EJ, Williams HJ, Haley WE, Frishberg Y, Milliner DS. Primary hyperoxaluria type III gene HOGA1 (formerly DHAPSL) as a possible risk factor for idiopathic calcium oxalate urolithiasis. *Clin J Am Soc Nephrol* 2011; **6**: 2289-2295 [PMID: 21896830 DOI: 10.2215/CJN.02760311]
 - 65 **Hoppe B**, von Unruh GE, Blank G, Rietschel E, Sidhu H, Laube N, Hesse A. Absorptive hyperoxaluria leads to an increased risk for

- urolithiasis or nephrocalcinosis in cystic fibrosis. *Am J Kidney Dis* 2005; **46**: 440-445 [DOI: [10.1053/j.ajkd.2005.06.003](https://doi.org/10.1053/j.ajkd.2005.06.003)]
- 66 **Peerapen P**, Thongboonkerd V. Kidney Stone Prevention. *Adv Nutr* 2023; **14**: 555-569 [PMID: [36906146](https://pubmed.ncbi.nlm.nih.gov/36906146/) DOI: [10.1016/j.advnut.2023.03.002](https://doi.org/10.1016/j.advnut.2023.03.002)]
 - 67 **Rimer JD**, Sakhae K, Maalouf NM. Citrate therapy for calcium phosphate stones. *Curr Opin Nephrol Hypertens* 2019; **28**: 130-139 [PMID: [30531474](https://pubmed.ncbi.nlm.nih.gov/30531474/) DOI: [10.1097/MNH.0000000000000474](https://doi.org/10.1097/MNH.0000000000000474)]
 - 68 **Habbig S**, Beck BB, Hoppe B. Nephrocalcinosis and urolithiasis in children. *Kidney Int* 2011; **80**: 1278-1291 [PMID: [21956187](https://pubmed.ncbi.nlm.nih.gov/21956187/) DOI: [10.1038/ki.2011.336](https://doi.org/10.1038/ki.2011.336)]
 - 69 **Bartges JW**, Callens AJ. Urolithiasis. *Vet Clin North Am Small Anim Pract* 2015; **45**: 747-768 [PMID: [26002797](https://pubmed.ncbi.nlm.nih.gov/26002797/) DOI: [10.1016/j.cvsm.2015.03.001](https://doi.org/10.1016/j.cvsm.2015.03.001)]
 - 70 **Alexander RT**, Law L, Gil-Peña H, Greenbaum LA, Santos F. Hereditary Distal Renal Tubular Acidosis. 2019 Oct 10. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993– [PMID: [31600044](https://pubmed.ncbi.nlm.nih.gov/31600044/)]
 - 71 **Kurtz I**. Renal Tubular Acidosis: H(+)/Base and Ammonia Transport Abnormalities and Clinical Syndromes. *Adv Chronic Kidney Dis* 2018; **25**: 334-350 [PMID: [30139460](https://pubmed.ncbi.nlm.nih.gov/30139460/) DOI: [10.1053/j.ackd.2018.05.005](https://doi.org/10.1053/j.ackd.2018.05.005)]
 - 72 **Enerbäck S**, Nilsson D, Edwards N, Heglind M, Alkanderi S, Ashton E, Deeb A, Kokash FEB, Bakhsh ARA, Van't Hoff W, Walsh SB, D'Arco F, Daryadel A, Bourgeois S, Wagner CA, Kleta R, Bockenhauer D, Sayer JA. Acidosis and Deafness in Patients with Recessive Mutations in FOXI1. *J Am Soc Nephrol* 2018; **29**: 1041-1048 [PMID: [29242249](https://pubmed.ncbi.nlm.nih.gov/29242249/) DOI: [10.1681/ASN.2017080840](https://doi.org/10.1681/ASN.2017080840)]
 - 73 **Finer G**, Landau D. Clinical Approach to Proximal Renal Tubular Acidosis in Children. *Adv Chronic Kidney Dis* 2018; **25**: 351-357 [DOI: [10.1053/j.ackd.2018.05.006](https://doi.org/10.1053/j.ackd.2018.05.006)]
 - 74 **Williams JC Jr**, Gambaro G, Rodgers A, Asplin J, Bonny O, Costa-Bauzá A, Ferraro PM, Fogazzi G, Fuster DG, Goldfarb DS, Grases F, Heilberg IP, Kok D, Letavernier E, Lippi G, Marangella M, Nouvenne A, Petrarulo M, Siener R, Tiselius HG, Traxer O, Trinchieri A, Croppi E, Robertson WG. Urine and stone analysis for the investigation of the renal stone former: a consensus conference. *Urolithiasis* 2021; **49**: 1-16 [PMID: [33048172](https://pubmed.ncbi.nlm.nih.gov/33048172/) DOI: [10.1007/s00240-020-01217-3](https://doi.org/10.1007/s00240-020-01217-3)]
 - 75 **Singh PP**, Pendse AK, Ahmed A, Ramavaram DV, Rajpurohit SK. A study of recurrent stone formers with special reference to renal tubular acidosis. *Urol Res* 1995; **23**: 201-203 [PMID: [7483148](https://pubmed.ncbi.nlm.nih.gov/7483148/) DOI: [10.1007/BF00389574](https://doi.org/10.1007/BF00389574)]
 - 76 **Guerra-Hernández NE**, Ordaz-López KV, Escobar-Pérez L, Gómez-Tenorio C, García-Nieto VM. Distal Renal Tubular Acidosis Screening by Urinary Acidification Testing in Mexican Children. *Rev Invest Clin* 2015; **67**: 191-198 [PMID: [26202743](https://pubmed.ncbi.nlm.nih.gov/26202743/)]
 - 77 **Heras Benito M**, Garcia-Gonzalez MA, Valdenebro Recio M, Molina Ordás Á, Callejas Martínez R, Rodríguez Gómez MA, Calle García L, Sousa Silva L, Fernández-Reyes Luis MJ. The need for genetic study to diagnose some cases of distal renal tubular acidosis. *Nefrología* 2016; **36**: 552-555 [PMID: [27493007](https://pubmed.ncbi.nlm.nih.gov/27493007/) DOI: [10.1016/j.nefro.2016.06.008](https://doi.org/10.1016/j.nefro.2016.06.008)]
 - 78 **Trepiccione F**, Walsh SB, Ariceta G, Boyer O, Emma F, Camilla R, Ferraro PM, Haffner D, Konrad M, Levchenko E, Lopez-Garcia SC, Santos F, Stabouli S, Szczepanska M, Tasic V, Topaloglu R, Vargas-Poussou R, Wlodkowski T, Bockenhauer D. Distal renal tubular acidosis: ERKNet/ESPN clinical practice points. *Nephrol Dial Transplant* 2021; **36**: 1585-1596 [PMID: [33914889](https://pubmed.ncbi.nlm.nih.gov/33914889/) DOI: [10.1093/ndt/gfab171](https://doi.org/10.1093/ndt/gfab171)]
 - 79 **Brisbane W**, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. *Nat Rev Urol* 2016; **13**: 654-662 [PMID: [27578040](https://pubmed.ncbi.nlm.nih.gov/27578040/) DOI: [10.1038/nrurol.2016.154](https://doi.org/10.1038/nrurol.2016.154)]
 - 80 **Tasian GE**, Copelovitch L. Evaluation and medical management of kidney stones in children. *J Urol* 2014; **192**: 1329-1336 [PMID: [24960469](https://pubmed.ncbi.nlm.nih.gov/24960469/) DOI: [10.1016/j.juro.2014.04.108](https://doi.org/10.1016/j.juro.2014.04.108)]
 - 81 **Nikken JJ**, Krestin GP. MRI of the kidney-state of the art. *Eur Radiol* 2007; **17**: 2780-2793 [PMID: [17646992](https://pubmed.ncbi.nlm.nih.gov/17646992/) DOI: [10.1007/s00330-007-0701-3](https://doi.org/10.1007/s00330-007-0701-3)]
 - 82 **Dhar M**, Denstedt JD. Imaging in diagnosis, treatment, and follow-up of stone patients. *Adv Chronic Kidney Dis* 2009; **16**: 39-47 [PMID: [19095204](https://pubmed.ncbi.nlm.nih.gov/19095204/) DOI: [10.1053/j.ackd.2008.10.005](https://doi.org/10.1053/j.ackd.2008.10.005)]
 - 83 **Lopez-Garcia SC**, Emma F, Walsh SB, Fila M, Hooman N, Zaniew M, Bertholet-Thomas A, Colussi G, Burgmaier K, Levchenko E, Sharma J, Singhal J, Soliman NA, Ariceta G, Basu B, Murer L, Tasic V, Tsygin A, Decramer S, Gil-Peña H, Koster-Kamphuis L, La Scola C, Gellermann J, Konrad M, Lilien C, Francisco T, Tramma D, Trnka P, Yüksel S, Caruso MR, Chromek M, Ekinci Z, Gambaro G, Kari JA, König J, Taroni F, Thumfart J, Trepiccione F, Winding L, Wühl E, Ağbaş A, Belkevich A, Vargas-Poussou R, Blanchard A, Conti G, Boyer O, Dursun I, Pınarbaşı AS, Melek E, Miglinas M, Novo R, Mallett A, Milosevic D, Szczepanska M, Wente S, Cheong HI, Sinha R, Gucev Z, Dufek S, Iancu D; European dRTA Consortium, Kleta R, Schaefer F, Bockenhauer D. Treatment and long-term outcome in primary distal renal tubular acidosis. *Nephrol Dial Transplant* 2019; **34**: 981-991 [PMID: [30773598](https://pubmed.ncbi.nlm.nih.gov/30773598/) DOI: [10.1093/ndt/gfy409](https://doi.org/10.1093/ndt/gfy409)]
 - 84 **Besouw MTP**, Bienias M, Walsh P, Kleta R, Van't Hoff WG, Ashton E, Jenkins L, Bockenhauer D. Clinical and molecular aspects of distal renal tubular acidosis in children. *Pediatr Nephrol* 2017; **32**: 987-996 [PMID: [28188436](https://pubmed.ncbi.nlm.nih.gov/28188436/) DOI: [10.1007/s00467-016-3573-4](https://doi.org/10.1007/s00467-016-3573-4)]
 - 85 **Bertholet-Thomas A**, Guittet C, Manso-Silván MA, Castang A, Baudouin V, Cailliez M, Di Maio M, Gillion-Boyer O, Golubovic E, Harambat J, Klein A, Knebelmann B, Nobili F, Novo R, Podracka L, Roussey-Kesler G, Stylianou C, Granier LA. Efficacy and safety of an innovative prolonged-release combination drug in patients with distal renal tubular acidosis: an open-label comparative trial versus standard of care treatments. *Pediatr Nephrol* 2021; **36**: 83-91 [PMID: [32712761](https://pubmed.ncbi.nlm.nih.gov/32712761/) DOI: [10.1007/s00467-020-04693-2](https://doi.org/10.1007/s00467-020-04693-2)]
 - 86 **Lucaccioni L**, Coccolini E, Dozza A, Cantatore SL, Berardi A, Predieri B, Iughetti L. Severe metabolic alkalosis due to diuretic treatment in a patient with distal renal tubular acidosis: a rare association. *Acta Biomed* 2019; **90**: 348-352 [PMID: [31125018](https://pubmed.ncbi.nlm.nih.gov/31125018/) DOI: [10.23750/abm.v90i2.6886](https://doi.org/10.23750/abm.v90i2.6886)]
 - 87 **Akın Y**, Uçar M, Yücel S. Current medical treatment in pediatric urolithiasis. *Turk J Urol* 2013; **39**: 253-263 [PMID: [26328120](https://pubmed.ncbi.nlm.nih.gov/26328120/) DOI: [10.5152/tud.2013.063](https://doi.org/10.5152/tud.2013.063)]
 - 88 **Bagga A**, Sinha A. Renal Tubular Acidosis. *Indian J Pediatr* 2020; **87**: 733-744 [PMID: [32591997](https://pubmed.ncbi.nlm.nih.gov/32591997/) DOI: [10.1007/s12098-020-03318-8](https://doi.org/10.1007/s12098-020-03318-8)]
 - 89 **Haffner D**, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, Wicart P, Bockenhauer D, Santos F, Levchenko E, Harvengt P, Kirchhoff M, Di Rocco F, Chaussain C, Brandi ML, Savendahl L, Briot K, Kamenicky P, Rejnmark L, Linglart A. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol* 2019; **15**: 435-455 [PMID: [31068690](https://pubmed.ncbi.nlm.nih.gov/31068690/) DOI: [10.1038/s41581-019-0152-5](https://doi.org/10.1038/s41581-019-0152-5)]
 - 90 **Ali Y**, Parekh A, Baig M, Ali T, Rafiq T. Renal tubular acidosis type II associated with vitamin D deficiency presenting as chronic weakness. *Ther Adv Endocrinol Metab* 2014; **5**: 86-89 [PMID: [25343024](https://pubmed.ncbi.nlm.nih.gov/25343024/) DOI: [10.1177/2042018814547359](https://doi.org/10.1177/2042018814547359)]
 - 91 **Galbiati F**. Type IV RTA in Chronic Adrenal Insufficiency and Concomitant Lisinopril Treatment. *Case Rep Endocrinol* 2020; **2020**: 8897112 [PMID: [33133704](https://pubmed.ncbi.nlm.nih.gov/33133704/) DOI: [10.1155/2020/8897112](https://doi.org/10.1155/2020/8897112)]
 - 92 **Dobbins SJH**, Petrie JR, Lean MEJ, McKay GA. Fludrocortisone therapy for persistent hyperkalaemia. *Diabet Med* 2017; **34**: 1005-1008 [PMID: [28375568](https://pubmed.ncbi.nlm.nih.gov/28375568/) DOI: [10.1111/dme.13359](https://doi.org/10.1111/dme.13359)]

- 93 **Cho SG**, Yi JH, Han SW, Kim HJ. Electrolyte imbalances and nephrocalcinosis in acute phosphate poisoning on chronic type 1 renal tubular acidosis due to Sjögren's syndrome. *J Korean Med Sci* 2013; **28**: 336-339 [PMID: [23400265](#) DOI: [10.3346/jkms.2013.28.2.336](#)]
- 94 **Hoppe B**, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. *Pediatr Nephrol* 2010; **25**: 403-413 [PMID: [19104842](#) DOI: [10.1007/s00467-008-1073-x](#)]
- 95 **Han H**, Segal AM, Seifter JL, Dwyer JT. Nutritional Management of Kidney Stones (Nephrolithiasis). *Clin Nutr Res* 2015; **4**: 137-152 [PMID: [26251832](#) DOI: [10.7762/cnr.2015.4.3.137](#)]
- 96 **Ticinesi A**, Nouvenne A, Maalouf NM, Borghi L, Meschi T. Salt and nephrolithiasis. *Nephrol Dial Transplant* 2016; **31**: 39-45 [PMID: [25031016](#) DOI: [10.1093/ndt/gfu243](#)]
- 97 **Preminger GM**, Sakhae K, Skurla C, Pak CY. Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. *J Urol* 1985; **134**: 20-23 [PMID: [4009822](#) DOI: [10.1016/s0022-5347\(17\)46963-1](#)]
- 98 **Nouvenne A**, Meschi T, Guerra A, Allegri F, Prati B, Borghi L. Dietary treatment of nephrolithiasis. *Clin Cases Miner Bone Metab* 2008; **5**: 135-141 [PMID: [22460996](#)]
- 99 **Mao W**, Zhang L, Sun S, Wu J, Zou X, Zhang G, Chen M. Physical Activity Reduces the Effect of High Body Mass Index on Kidney Stones in Diabetes Participants From the 2007-2018 NHANES Cycles: A Cross-Sectional Study. *Front Public Health* 2022; **10**: 936552 [PMID: [35844866](#) DOI: [10.3389/fpubh.2022.936552](#)]
- 100 **Kitterer D**, Schwab M, Alscher MD, Braun N, Latus J. Drug-induced acid-base disorders. *Pediatr Nephrol* 2015; **30**: 1407-1423 [PMID: [25370778](#) DOI: [10.1007/s00467-014-2958-5](#)]
- 101 **Weigert A**, Hoppe B. Nephrolithiasis and Nephrocalcinosis in Childhood-Risk Factor-Related Current and Future Treatment Options. *Front Pediatr* 2018; **6**: 98 [PMID: [29707529](#) DOI: [10.3389/fped.2018.00098](#)]
- 102 **Roush GC**, Kaur R, Ernst ME. Diuretics: a review and update. *J Cardiovasc Pharmacol Ther* 2014; **19**: 5-13 [PMID: [24243991](#) DOI: [10.1177/1074248413497257](#)]
- 103 **Holdgate A**, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *BMJ* 2004; **328**: 1401 [PMID: [15178585](#) DOI: [10.1136/bmj.38119.581991.55](#)]
- 104 **García-Maset R**, Bover J, Segura de la Morena J, Goicoechea Diezhandino M, Cebollada Del Hoyo J, Escalada San Martin J, Fácila Rubio L, Gamarra Ortiz J, García-Donaire JA, García-Matarín L, Gràcia Garcia S, Isabel Gutiérrez Pérez M, Hernández Moreno J, Mazón Ramos P, Montañés Bermudez R, Muñoz Torres M, de Pablos-Velasco P, Pérez-Maraver M, Suárez Fernández C, Tranche Iparraguirre S, Luis Górriz J. Information and consensus document for the detection and management of chronic kidney disease. *Nefrologia (Engl Ed)* 2022; **42**: 233-264 [PMID: [36210616](#) DOI: [10.1016/j.nefro.2022.07.003](#)]
- 105 **Kumar P**. Genetic counselling in family planning. *Antiseptic* 1968; **65**: 831-834 [PMID: [12254320](#)]
- 106 **Imenez Silva PH**, Mohebbi N. Kidney metabolism and acid-base control: back to the basics. *Pflugers Arch* 2022; **474**: 919-934 [PMID: [35513635](#) DOI: [10.1007/s00424-022-02696-6](#)]
- 107 **Fontenelle LF**, Sarti TD. Kidney Stones: Treatment and Prevention. *Am Fam Physician* 2019; **99**: 490-496 [PMID: [30990297](#)]
- 108 **Pournasiri Z**, Madani A, Ghaemi A, Adl Z, Salehpour S. Long-Term Effect of Nephrocalcinosis on Renal Function and Body Growth Index in Children: A Retrospective Single Center Study. *Iran J Pediatr* 2018; **28**: e22029 [DOI: [10.5812/ijp.22029](#)]
- 109 **Ilzkovitz M**, Kayembe EE, Geers C, Pozdzik A. Kidney Stones, Proteinuria and Renal Tubular Metabolic Acidosis: What Is the Link? *Healthcare (Basel)* 2022; **10** [PMID: [35627973](#) DOI: [10.3390/healthcare10050836](#)]
- 110 **Ang AJS**, Sharma AA, Sharma A. Nephrolithiasis: Approach to Diagnosis and Management. *Indian J Pediatr* 2020; **87**: 716-725 [PMID: [32794099](#) DOI: [10.1007/s12098-020-03424-7](#)]
- 111 **Watanabe T**. Improving outcomes for patients with distal renal tubular acidosis: recent advances and challenges ahead. *Pediatric Health Med Ther* 2018; **9**: 181-190 [PMID: [30588151](#) DOI: [10.2147/PHMT.S174459](#)]



Case Control Study

Brain metabolic profile assessed by magnetic resonance spectroscopy in children with Down syndrome: Relation to intelligence quotient

Nesreen Safwat El Feil, Heba S Elmahdy, Rasha Ahmed Elmahdy, Ahmed Abd-Elbasset Aboelezz, Heba S Dawoud, Mohammed Al-Beltagi

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Kaufman AS, United States

Received: July 17, 2023

Peer-review started: July 17, 2023

First decision: August 31, 2023

Revised: September 18, 2023

Accepted: September 28, 2023

Article in press: September 28, 2023

Published online: December 9, 2023



Nesreen Safwat El Feil, Heba S Elmahdy, Ahmed Abd-Elbasset Aboelezz, Heba S Dawoud, Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31527, Al Gharbia, Egypt

Rasha Ahmed Elmahdy, Department of Radiology, University Medical Center, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Manama, Bahrain

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Manama, Bahrain

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Manama, Bahrain

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Academic Editor, Chairman, Consultant Physician-Scientist, Professor, Researcher, Department of Pediatrics, Faculty of Medicine, Tanta University, Al bahr street, Tanta 31527, Al Gharbia, Egypt.
mbelrem@hotmail.com

Abstract

BACKGROUND

Down syndrome (DS) is one of the most common causes of intellectual disability. Children with DS have varying intelligence quotient (IQ) that can predict their learning abilities.

AIM

To assess the brain metabolic profiles of children with DS and compare them to standard controls, using magnetic resonance spectroscopy (MRS) and correlating the results with IQ.

METHODS

This case-control study included 40 children with DS aged 6-15 years and 40 age and sex-matched healthy children as controls. MRS was used to evaluate ratios of choline/creatine (Cho/Cr), N-acetyl aspartic acid/creatine (NAA/Cr), and myoinositol/creatine (MI/Cr) (in the frontal, temporal, and occipital lobes and basal ganglia and compared to controls and correlated with IQ.

RESULTS

Children with DS showed significant reductions in NAA/Cr and MI/Cr and a non-significant reduction in Cho/Cr in frontal lobes compared to controls. Additionally, we observed significant decreases in NAA/Cr, MI/Cr, and Cho/Cr in the temporal and occipital lobes and basal ganglia in children with DS compared to controls. Furthermore, there was a significant correlation between IQ and metabolic ratios in the brains of children with DS.

CONCLUSION

Brain metabolic profile could be a good predictor of IQ in children with DS.

Key Words: Children; Down syndrome; Magnetic resonance spectroscopy; Metabolic profile; Intelligence quotient

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This study compared the brain metabolic profiles of children with Down syndrome (DS) using magnetic resonance spectroscopy to healthy controls. The results showed significant reductions in specific metabolic ratios (N-acetyl aspartic acid/creatinine and myoinositol/creatinine) in the frontal lobes of children with DS compared to controls, as well as decreases in these ratios in the temporal and occipital lobes and basal ganglia. The study also found a significant correlation between intelligence quotient (IQ) and metabolic ratios in children with DS. These findings suggest that brain metabolic profiling could be a valuable predictor of IQ in children with DS.

Citation: El Feil NS, Elmahdy HS, Elmahdy RA, Aboelezz AAE, Dawoud HS, Al-Beltagi M. Brain metabolic profile assessed by magnetic resonance spectroscopy in children with Down syndrome: Relation to intelligence quotient. *World J Clin Pediatr* 2023; 12(5): 310-318

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/310.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.310>

INTRODUCTION

Down syndrome (DS) is the most prevalent chromosomal disorder in humans and one of the leading causes of intellectual disability. It arises from the presence of an additional chromosome 21[1]. Children with DS exhibit various physical dysmorphic features affecting nearly every part of their bodies[2]. DS is a systemic disorder that impacts all body systems, particularly the central nervous system. Individuals with DS experience cognitive impairment and a range of conditions related to speech, language, and motor functions. They also face an elevated risk of early-onset dementia and Alzheimer's disease (AD)[3]. Two hypotheses have been proposed to elucidate the pathogenesis of DS: Developmental instability resulting from chromosomal imbalance loss and the gene-dosage effect[4]. According to the gene-dosage effect hypothesis, the genes located on chromosome 21 are overexpressed in the cells and tissues of DS patients, contributing to various phenotypic abnormalities[5].

Magnetic resonance (MR) spectroscopy (MRS) is an analytical technique used to quantify metabolites. Unlike conventional MR imaging (MRI), MRS provides physiological and chemical information rather than anatomical details[6]. Proton MRS (1 H-MRS) is widely employed to characterize brain neurochemical changes associated with health and disease. N-acetyl aspartic acid (NAA) is a derivative of aspartic acid primarily synthesized and stored in neurons. Therefore, it is a marker for neuronal density and viability[7]. As a neuronal marker, the concentration of NAA decreases in conditions such as extensive brain lesions, dementia, hypoxia, or multiple sclerosis, where neuronal destruction occurs[8]. Total creatine (Cr) reflects the amount of phosphocreatine and Cr present in neurons and glial cells. It appears as a prominent peak at 3.0 ppm in MR spectra, with an additional peak for Cr possibly visible at 3.94 ppm[9]. Cr remains relatively constant in the brain's energetic cellular metabolism and is often used as a reference metabolite for *in vivo* MRS. For instance, it is frequently employed in the calculation of metabolite ratios such as choline (Cho)/Cr, NAA/Cr, and myoinositol (MI)/Cr[10].

Cho serves as an indicator of cellular proliferation and cell membrane integrity. Increased choline levels reflect heightened synthesis and degradation of cell membranes[11]. MI functions as a marker primarily synthesized in glial cells. Elevated MI levels are often observed in cerebral diseases associated with significant gliosis[12]. Metabolic abnormalities, specifically elevated MI levels, have been observed throughout development in mouse models of DS and the brains of children and adults with DS. However, there is a scarcity of studies investigating brain metabolism during early childhood[13].

The intelligence quotient (IQ) is critical in assessing the neurological and cognitive development of children with DS. It may also reflect their physical and somatic growth, as documented by Kłosowska *et al*[14]. Therefore, establishing a connection between the brain's metabolic profiles and IQ in children with DS could provide insights into the underlying reasons for this relationship and aid in developing strategies to improve their IQ. Limited research has been conducted on elucidating metabolic changes in the developing brains of children with DS. Hence, this study aims to evaluate the brain's metabolic profile using MRS in children with DS, comparing it with normal controls and examining the correlation

between this metabolic profile and IQ.

MATERIALS AND METHODS

This case-control study was conducted between April 2019 and April 2021, involving a patient group of 60 children with DS. Out of these, 40 children completed the study. We also included a control group of 40 healthy children, matched in age and sex. The age range of the participating children was between 6 and 15 years. We recruited the children from the Outpatient Clinic of the Genetics Unit, Pediatric Department, at Tanta University in Egypt. The diagnosis of DS was based on clinical findings and confirmed through karyotyping. A comprehensive medical history was obtained, including demographic data, prenatal, natal, postnatal, family, and developmental history. Thorough clinical and psychiatric evaluations were performed as well. All patients underwent thyroid function tests, echocardiography, and glycated hemoglobin (HbA1c) measurements. We utilized the Stanford-Binet Intelligence Scales, Fifth Edition, to assess the IQ of the study groups. Cases with diseases that could potentially influence the results or pose risks during the MRS procedure were excluded. Exclusion criteria encompassed complex congenital heart disease, congenital neurological abnormalities, a history of perinatal asphyxia, suspected metabolic disease, epilepsy, attention deficit hyperactivity disorder, autistic spectrum disorders, and conditions that precluded MRI scans, such as the presence of metal devices like pacemakers, defibrillators, orthodontic braces, implants, or severe claustrophobia. Patients with known endocrine disorders like hypothyroidism or diabetes mellitus were excluded from the study. Ethical approval for this research was obtained from the Faculty of Medicine Ethics Committee, Tanta University. Written informed consent was acquired from the legal guardians of both patients and controls before the imaging procedure. The study adhered to the principles of the Declaration of Helsinki and good clinical practice. No adverse physiological effects resulting from the main magnetic field are known. Furthermore, no unexpected risks emerged during the research.

MRS study

The MRS studies were conducted at the Radiology Department of Tanta University in Egypt. A 1.5 Tesla system (Signa; GE Medical Systems, Milwaukee, WI, United States) with a quadrature head coil was used for all MRI and 1H-MRS procedures. Before the examination, the children were sedated using chloral hydrate at 25-100 mg/kg (maximum 2 g).

Initially, a conventional MRI scan was performed, followed by placing the voxel at various positions. Water suppression and the point-resolved spectroscopy methods were then employed, with a Time to Echo of 135 msec and a Repetition Time of 1500 msec. The NAA, Cho, MI, and Cr spectra were analyzed, and ratios for Cho/Cr, NAA/Cr, and MI/Cr were calculated in the frontal, temporal, occipital lobes, and basal ganglia. These ratios were compared between the patients and controls. NAA serves as an indicator of neuronal integrity, with its peak occurring at 2.02 ppm. Cho reflects cell turnover, with its highest point at 3.22 ppm. Cr is involved in cellular metabolism and peaks at three ppm. Normally, no lipid or lactate peak is observed in the brain; even if present, they overlap at 1.33 ppm[15].

Oxygen saturation, heart rate, and temperature were continuously monitored during the scan, and a skilled pediatrician was present for all examinations. The total examination time for each child did not exceed one hour. The child lay supine with their head positioned in the head coil, which was surrounded by a lunar pillow to minimize the sound from the magnetic field. Subsequently, the patient and coil were moved into the magnetic bore.

Statistical analysis

The study's power level was estimated using The Power and Precision V3 program (<http://www.Power-Analysis.com>, Englewood, New Jersey). The collected data were organized, tabulated, and subjected to statistical analysis using the SPSS version 19. For parametric variables, the mean and standard deviation were calculated. A comparison of mean values between the cases and controls was conducted using an unpaired Student's *t*-test, assuming equal variance in the two populations. Nonparametric variables were analyzed by calculating the number and percentage. The chi-square test was employed to compare different observations of categorical variables. Pearson's correlation coefficient was utilized to examine the association between two variables. A *P* value less than 0.01 was considered statistically significant after applying the Bonferroni correction of multiple comparisons to avoid any spurious significance and to mitigate the risk of Type I errors associated with multiple comparisons.

RESULTS

Table 1 illustrates the study's demographics. Sixty children with DS were initially recruited for the study, but 20 were excluded due to missed follow-up, inability to participate, or refusal to do an MRI. Ultimately, the study included 40 children with DS and 40 healthy children who completed the study. There were no significant differences in age, sex, and mean IQ between the excluded and included children with DS. **Table 1** presents the demographic data of the included children. The patient group had an age range of 6-15 years, with a mean of 10.85 ± 2.7 , while the control group ranged from 5-17 years, with a mean of 10.70 ± 2.6 . Among the children with DS, 28 were males, and 12 were females, resulting in a male-to-female ratio of 1.4:1. The control group consisted of 24 males and 16 females, with a male-to-female ratio of 1.5:1. There were no significant differences in age and sex between the two groups. All included children with DS had the non-disjunction type of DS. The IQ was significantly lower in children with DS (68.45 ± 6.11) compared to the controls (96.73 ± 2.68), with a *P* value < 0.001.

Table 1 Demographic data and intelligence quotient of children with Down syndrome and their controls

	DS (n = 40)	Controls (n = 40)	P value
Age (yr, mean $\pm$ SD)	10.85 $\pm$ 2.72	10.70 $\pm$ 2.64	0.87
Sex, n (%)			0.24
Male	28 (70%)	26 (65%)	
Female	12 (30%)	14 (35%)	
IQ (mean $\pm$ SD)	68.45 $\pm$ 6.11	96.73 $\pm$ 2.68	0.001 ¹

¹P < 0.01 is significant.

DS: Down syndrome; IQ: Intelligence quotient.

Table 2 presents the metabolic profile of the studied groups. It revealed a significant reduction in NAA/Cr and MI/Cr ratios (P value < 0.001) and a non-significant reduction in the Cho/Cr ratio in the frontal lobe of children with DS compared to the controls. Furthermore, children with DS exhibited non-significant reductions in NAA/Cr (P < 0.05), Cho/Cr, and MI/Cr ratios in the temporal and occipital lobes compared to the control group. The occipital lobe showed the highest significant reduction in MI/Cr ratio (P value < 0.001). In addition, the basal ganglia exhibited the most substantial reduction in NAA/Cr, Cho/Cr, and MI/Cr ratios in children with DS compared to the control group.

Figures 1-3 display the correlation between IQ and various metabolic ratios. There was a statistically significant positive correlation between IQ and NAA/Cr ratio in the frontal lobe and Cho/Cr ratio in the temporal lobe among children with DS. Conversely, a statistically significant negative correlation existed between IQ and Cho/Cr ratio in the occipital lobe among children with DS, as shown in Table 3. The IQ was primarily influenced by NAA/Cr in the frontal lobe, Cho/Cr in the temporal lobe, and Cho/Cr in the occipital lobe in order of significance. Regression analysis for frontal NAA/Cr and IQ demonstrated a P value of < 0.001. However, the multivariate analysis presented in Table 4 showed that frontal NAA/Cr and temporal Cho/Cr had the most significant correlation with IQ.

DISCUSSION

The current study demonstrated a significant reduction in IQ among children with DS (55-75) compared to normal children. This is consistent with previous research, including Rachidi and Lopes's[3] study, which indicated that cognitive impairment is consistently observed in all individuals with DS. Most children and adults with DS exhibit mild to moderate intellectual disability, with an average IQ score of around 50 and individual values ranging from 30 to 70. Approximately 10% of individuals with DS fall within the low average borderline range of intellectual disability, while a minority have severe intellectual disability. The exact mechanisms underlying brain development in DS remain poorly understood. Still, multiple volumetric MRI studies have been conducted to gain further insights into the brain characteristics of individuals with DS. Several neuroimaging studies have reported reductions in total brain volume, as demonstrated by Beacher *et al*[16] in 2010, who observed volume reductions in the cerebrum, cerebellum, hippocampus, brain stem, and frontal lobes.

Our study calculated ratios for Cho/Cr, NAA/Cr, and MI/Cr in the frontal, temporal, occipital lobes, and basal ganglia, comparing the patient and control groups. We found a significant reduction in NAA/Cr and MI/Cr ratios in the frontal lobe, with a non-significant reduction in Cho/Cr among children with DS compared to the control group. This finding aligns with the study by Smigielska-Kuzia and Sobaniec[15], who investigated 34 children (14 with DS and 20 healthy children) and reported decreased Glx/Cr, NAA/Cr, Cho/Cr, and MI/Cr in patients with DS, with the first two markers showing a statistically significant difference. Lamar *et al*[17] also found a reduction in the absolute concentration of NAA in the frontal, temporal, and occipital lobes in patients with DS and AD. However, Shonk *et al*[18] detected elevated MI in adult patients with DS and AD compared to DS patients without AD. This difference could be attributed to our study's age range (6-15 years), as AD development may be associated with aging in DS.

Additionally, we observed a significant reduction in NAA/Cr, Cho/Cr, and MI/Cr ratios in the temporal lobe of children with DS compared to the control group. This finding agrees with Smigielska-Kuzia *et al*[19] in 2010, who conducted a study on 40 children (20 with DS and 20 healthy children) and reported a statistically significant decrease in NAA/Cr, Cho/Cr, MI/Cr, and GABA/Cr.

Furthermore, a significant reduction in NAA/Cr, Cho/Cr, and MI/Cr ratios in the basal ganglia was observed in children with DS relative to the control group. This finding is consistent with a previous report by Fruen and Lester[20] in 1990, which described an increased MI/Cr ratio in adults with DS. The increased MI levels in brain tissue may be attributed to an extra *SLC5A3* gene in trisomic 21 cells, responsible for inositol transporter synthesis. These co-transporters regulate MI concentration in DS cortical cells. The results of the Fruen and Lester's[20] study and our study suggest that individuals with DS, whether demented or not, exhibit altered neuron-glia metabolism (reduced NAA and increased MI). Lin *et al*[21] found that this metabolic shift was more pronounced in DS individuals with dementia compared to those without dementia.

Table 2 Brain metabolite ratios of children with down syndrome and controls

Brain metabolite ratios (mean $\pm$ SD)	DS (n = 40)	Controls (n = 40)	P value
Frontal lobe			
NAA/Cr	1.19 $\pm$ 0.44	1.788 $\pm$ 0.273	0.001 ¹
Cho/Cr	1.03 $\pm$ 0.40	1.08 $\pm$ 0.187	0.473
MI/Cr	0.56 $\pm$ 0.21	1.50 $\pm$ 0.47	0.001 ¹
Temporal lobe			
NAA/Cr	1.26 $\pm$ 1.19	1.75 $\pm$ 0.21	0.011
Cho/Cr	0.71 $\pm$ 0.30	1.07 $\pm$ 0.16	0.001 ¹
MI/Cr	0.41 $\pm$ 0.19	1.40 $\pm$ 0.56	0.001 ¹
Basal ganglia			
NAA/Cr	1.21 $\pm$ 0.55	1.78 $\pm$ 0.19	0.001 ¹
Cho/Cr	0.68 $\pm$ 0.33	1.06 $\pm$ 0.17	0.001 ¹
MI/Cr	0.35 $\pm$ 0.17	1.50 $\pm$ 0.54	0.001 ¹
Occipital lobe			
NAA/Cr	1.72 $\pm$ 0.49	1.92 $\pm$ 0.34	0.033
Cho/Cr	0.83 $\pm$ 0.35	0.99 $\pm$ 0.14	0.011
MI/Cr	0.44 $\pm$ 0.17	1.48 $\pm$ 0.54	0.001 ¹

¹P < 0.01 is significant.

Cho: Choline; Cr: Creatine; DS: Down syndrome; MI: Myoinositol; Naa: N-acetyl aspartate.

Table 3 Correlation between intelligence quotient and the brain metabolite ratios in children with down syndrome

Correlations with IQ	r	P value
F NAA/Cr	0.533	< 0.001 ¹
F Cho/Cr	-0.210	0.193
F MI/Cr	-0.259	0.107
T NAA/Cr	0.215	0.182
T Cho/Cr	0.330	0.037
T MI/Cr	-0.018	0.913
BG NAA/Cr	0.100	0.541
BG Cho/Cr	0.105	0.518
BG MI/Cr	0.008	0.961
O NAA/Cr	0.091	0.578
O Cho/Cr	-0.346	0.029
O MI/Cr	0.215	0.184

¹P < 0.01 is significant.

BG: Basal ganglia; Cho: Choline; Cr: Creatine; DS: Down syndrome; F: Frontal; IQ: Intelligence quotient; MI: Myoinositol; NAA: N-acetyl aspartate; O: Occipital; T: Temporal.

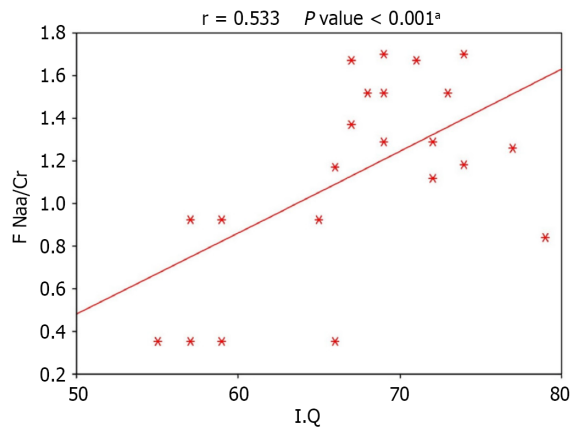
In the occipital lobe, we found a significant reduction in NAA/Cr, Cho/Cr, and MI/Cr ratios among children with DS compared to the control group. This is consistent with a case-control study by Shonk and Ross[22] in 1995, which included 23 young DS patients without dementia, revealing elevated MI levels. They also reported one patient with DS and dementia who exhibited high MI but decreased NAA in the occipital cortex and parietal white matter. The decreased NAA findings align with our study, although our results differ from theirs regarding MI. This discrepancy could be attributed to age differences. NAA indicates brain maturation, dendritic and synaptic development, and oligodendroglial

Table 4 Multivariate analysis of the brain metabolite ratios that significantly affect intelligence quotient in children with down syndrome

	Unstandardized coefficients		Standardized coefficients	t value	P value
	B	SE	Beta		
F NAA/Cr	10.123	2.260	0.726	4.480	< 0.001 ¹
T Cho/Cr	10.950	3.347	0.541	3.272	0.002 ¹
O Cho/Cr	5.695	3.391	0.324	1.679	0.102

¹P < 0.01 is significant.

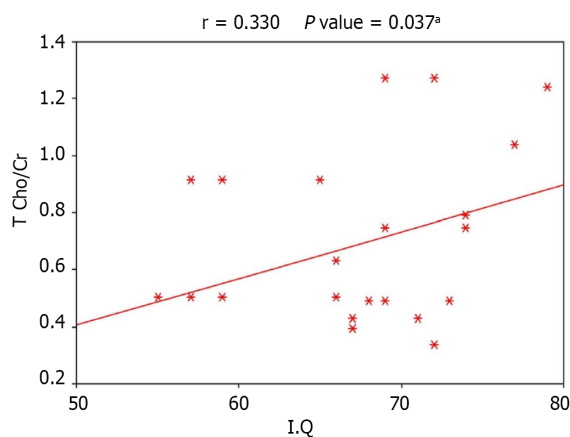
Dependent variable: IQ; Cho: Choline; Cr: Creatine; F: Frontal; IQ: Intelligence quotient; NAA: N-acetyl aspartate; O: Occipital; T: Temporal.



DOI: 10.5409/wjcp.v12.i5.310 Copyright ©The Author(s) 2023.

Figure 1 Correlation between intelligence quotient and N-acetyl aspartate/creatine ratio in the frontal lobe of the Down syndrome group.

IQ: Intelligence quotient; NAA/Cr ratio: N-acetyl aspartate/creatine ratio.



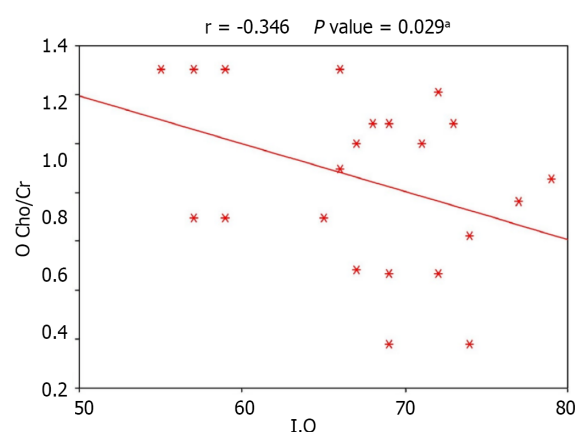
DOI: 10.5409/wjcp.v12.i5.310 Copyright ©The Author(s) 2023.

Figure 2 Correlation between intelligence quotient and choline/creatine ratio in the temporal lobe of the Down syndrome group. Cho/Cr:

Choline/creatine; IQ: Intelligence quotient.

proliferation and differentiation (Kato *et al*[23], 1997). Previous studies in adults with DS have reported lower NAA ratios compared to healthy controls[18,21]. The observed decrease in NAA/Cr ratios in different brain regions among children with DS in our study suggests reduced brain maturation in these individuals.

Our research demonstrated that frontal NAA/Cr had the most significant correlation with IQ, followed by T Cho/Cr, while O Cho/Cr had the least effect. To the best of our knowledge, only one previous study utilized MRS to evaluate brain metabolites in children with DS. Due to the scarcity of studies in the literature, we could not find extensive data for comparison.



DOI: 10.5409/wjcp.v12.i5.310 Copyright ©The Author(s) 2023.

Figure 3 Correlation between intelligence quotient and choline/creatine ratio in the occipital lobe of the Down syndrome group. Cho/Cr: Choline/Creatine ratio, DS: Down Syndrome, IQ: Intelligence quotient.

Limitation of the study

The study is subject to certain limitations, including a relatively small sample size and being conducted at a single center. Our study is mainly exploratory and should be followed by confirmatory studies to validate the observed associations. It would also be valuable to examine the correlation between the metabolic profile and the patient's medical conditions, parents' educational levels, and developmental milestones. Assessing any changes in the metabolic profile resulting from occupational and behavioral therapy could provide insights into improving IQ and promoting self-independence in children with DS. It is recommended to conduct future studies with larger sample sizes to better understand the DS brain's intricacies. Moreover, longitudinal studies involving adolescents and adults with DS, both with and without dementia, would be beneficial in monitoring metabolite changes and their impact on the mental health of patients with DS, particularly those who develop early-onset dementia. In addition, we would like to emphasize that the correlation of IQ to metabolic ratios in the brain does not imply causality. Correlations only establish relationships. We also acknowledge that our study design did not include a separate group of low-functioning children without DS for direct comparison. We will consider this point in the coming research. Adding such a group would have provided a valuable reference point for evaluating whether the observed differences in brain metabolic profiles and their correlation with IQ are specific to DS or could apply to low-functioning children in general.

CONCLUSION

The brain's metabolic profile in children with DS exhibits differences compared to typically developing children. Additionally, specific brain areas show positive and negative correlations between IQ and specific metabolic ratios. Thus, the brain's metabolic profile could serve as a predictor of IQ in children with DS.

ARTICLE HIGHLIGHTS

Research background

Down syndrome (DS) is the most prevalent chromosomal disorder in humans and one of the leading causes of intellectual disability. Magnetic resonance (MR) spectroscopy (MRS) is an analytical technique used to quantify metabolites. Proton MRS (1 H-MRS) is widely employed to characterize brain neurochemical changes associated with health and disease. N-acetyl aspartic acid (NAA) is a derivative of aspartic acid primarily synthesized and stored in neurons. Therefore, it is a marker for neuronal density and viability.

Research motivation

Establishing a connection between the brain's metabolic profiles and intelligence quotient (IQ) in children with DS could provide insights into the underlying reasons for this relationship and aid in developing strategies to improve their IQ.

Research objectives

We aimed to evaluate the brain's metabolic profile using MRS in children with DS, comparing it with that of normal controls and examining the correlation between this metabolic profile and IQ.

Research methods

The study was a case-control study that included sixty children with DS and forty healthy controls. IQ was assessed using Stanford-Binet Intelligence Scales, Fifth Edition. A conventional MR imaging scan followed by point-resolved spectroscopy was performed for all the participants.

Research results

Children with DS showed significant reductions in NAA/creatine (Cr) and myoinositol (MI)/Cr and a non-significant reduction in choline (Cho)/Cr in frontal lobes compared to controls. Additionally, we observed significant decreases in NAA/Cr, MI/Cr, and Cho/Cr in the temporal and occipital lobes and basal ganglia in children with DS compared to controls. Furthermore, there was a significant correlation between IQ and metabolic ratios in the brains of children with DS.

Research conclusions

Brain metabolic profile could be a good predictor of IQ in children with DS.

Research perspectives

To generalize our results, the authors must include a larger sample size and perform a multicentre study. We also need to include another group with low IQ for different reasons to investigate the unique features of brain metabolic profiles in children with DS.

ACKNOWLEDGEMENTS

We thank the parents and children who participated in this study. We also thank the editors and the reviewers for their efforts to improve the quality of the study.

FOOTNOTES

Author contributions: Dawoud HS provided the research idea and initiated the study design; El-Feil SE and El Mahdy HS collected the patients and their information; Aboelezz AA was responsible for statistical analysis; Elshafey RA was responsible for the technical part of the study; Also, Elshafey RA oversaw imaging and data analysis; Al-Biltagi M analyzed the data and revised the manuscript. All the authors revised and agreed on the final version of the manuscript.

Institutional review board statement: We performed the study according to the latest version of Helsinki's Declaration. The Institutional Ethical and Research Review Board of Faculty of Medicine, Tanta University, approved the study.

Informed consent statement: All parents, guardians, or next of kin signed informed consent for the minors to participate in this study.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

Data sharing statement: Data are available upon reasonable request.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Egypt

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536.

S-Editor: Lin C

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- 1 Karmiloff-Smith A, Al-Janabi T, D'Souza H, Groet J, Massand E, Mok K, Startin C, Fisher E, Hardy J, Nizetic D, Tybulewicz V, Strydom A. The importance of understanding individual differences in Down syndrome. *F1000Res* 2016; 5 [PMID: 27019699 DOI: 10.12688/f1000research.7506.1]

- 2 **Stoll C**, Dott B, Alembik Y, Roth MP. Associated congenital anomalies among cases with Down syndrome. *Eur J Med Genet* 2015; **58**: 674-680 [PMID: 26578241 DOI: 10.1016/j.ejmg.2015.11.003]
- 3 **Rachidi M**, Lopes C. Mental retardation in Down syndrome: from gene dosage imbalance to molecular and cellular mechanisms. *Neurosci Res* 2007; **59**: 349-369 [PMID: 17897742 DOI: 10.1016/j.neures.2007.08.007]
- 4 **Reeves RH**, Baxter LL, Richtsmeier JT. Too much of a good thing: mechanisms of gene action in Down syndrome. *Trends Genet* 2001; **17**: 83-88 [PMID: 11173117 DOI: 10.1016/s0168-9525(00)02172-7]
- 5 **Cheon MS**, Bajo M, Kim SH, Claudio JO, Stewart AK, Patterson D, Kruger WD, Kondoh H, Lubec G. Protein levels of genes encoded on chromosome 21 in fetal Down syndrome brain: challenging the gene dosage effect hypothesis (Part II). *Amino Acids* 2003; **24**: 119-125 [PMID: 12624743 DOI: 10.1007/s00726-002-0337-1]
- 6 **Bertholdo D**, Watcharakorn A, Castillo M. Brain proton magnetic resonance spectroscopy: introduction and overview. *Neuroimaging Clin N Am* 2013; **23**: 359-380 [PMID: 23928194 DOI: 10.1016/j.nic.2012.10.002]
- 7 **Smith JK**, Castillo M, Kwock L. MR spectroscopy of brain tumors. *Magn Reson Imaging Clin N Am* 2003; **11**: 415-429, v [PMID: 14768727 DOI: 10.1016/s1064-9689(03)00061-8]
- 8 **Gupta RK**, Jobanputra KJ, Yadav A. MR spectroscopy in brain infections. *Neuroimaging Clin N Am* 2013; **23**: 475-498 [PMID: 23928201 DOI: 10.1016/j.nic.2013.03.004]
- 9 **Bulik M**, Jancalek R, Vanicek J, Skoch A, Mechl M. Potential of MR spectroscopy for assessment of glioma grading. *Clin Neurol Neurosurg* 2013; **115**: 146-153 [PMID: 23237636 DOI: 10.1016/j.clineuro.2012.11.002]
- 10 **Nelson SJ**. Multivoxel magnetic resonance spectroscopy of brain tumors. *Mol Cancer Ther* 2003; **2**: 497-507 [PMID: 12748312]
- 11 **Brandão LA**, Castillo M. Adult Brain Tumors: Clinical Applications of Magnetic Resonance Spectroscopy. *Magn Reson Imaging Clin N Am* 2016; **24**: 781-809 [PMID: 27742117 DOI: 10.1016/j.mric.2016.07.005]
- 12 **Patke PA**, Baburamani AA, Kyriakopoulou V, Davidson A, Avini E, Dimitrova R, Allsop J, Hughes E, Kangas J, McAlonan G, Rutherford MA. Early alterations in cortical and cerebellar regional brain growth in Down Syndrome: An *in vivo* fetal and neonatal MRI assessment. *Neuroimage Clin* 2020; **25**: 102139 [PMID: 31887718 DOI: 10.1016/j.nicl.2019.102139]
- 13 **Alam MS**, Sajjad Z, Hafeez S, Akhter W. Magnetic resonance spectroscopy in focal brain lesions. *J Pak Med Assoc* 2011; **61**: 540-543 [PMID: 22204206]
- 14 **Kłosowska A**, Kuchta A, Ćwiklińska A, Sałaga-Zaleska K, Jankowski M, Kłosowski P, Mański A, Zwiefka M, Anikiej-Wiczenbach P, Wierzbica J. Relationship between growth and intelligence quotient in children with Down syndrome. *Transl Pediatr* 2022; **11**: 505-513 [PMID: 35558976 DOI: 10.21037/tp-21-424]
- 15 **Śmigielska-Kuzia J**, Sobaniec W. Brain metabolic profile obtained by proton magnetic resonance spectroscopy HMRS in children with Down syndrome. *Adv Med Sci* 2007; **52** Suppl 1: 183-187 [PMID: 18229661]
- 16 **Beacher F**, Daly E, Simmons A, Prasher V, Morris R, Robinson C, Lovestone S, Murphy K, Murphy DG. Brain anatomy and ageing in non-demented adults with Down's syndrome: an *in vivo* MRI study. *Psychol Med* 2010; **40**: 611-619 [PMID: 19671216 DOI: 10.1017/S0033291709990985]
- 17 **Lamar M**, Foy CML, Beacher F, Daly E, Poppe M, Archer N, Prasher V, Murphy KC, Morris RG, Simmons A, Lovestone S, Murphy DGM. Down syndrome with and without dementia: an *in vivo* proton Magnetic Resonance Spectroscopy study with implications for Alzheimer's disease. *Neuroimage* 2011; **57**: 63-68 [PMID: 21504795 DOI: 10.1016/j.neuroimage.2011.03.073]
- 18 **Shonk TK**, Moats RA, Gifford P, Michaelis T, Mandigo JC, Izumi J, Ross BD. Probable Alzheimer disease: diagnosis with proton MR spectroscopy. *Radiology* 1995; **195**: 65-72 [PMID: 7892497 DOI: 10.1148/radiology.195.1.7892497]
- 19 **Śmigielska-Kuzia J**, Boćkowski L, Sobaniec W, Kułak W, Sendrowski K. Amino acid metabolic processes in the temporal lobes assessed by proton magnetic resonance spectroscopy (1H MRS) in children with Down syndrome. *Pharmacol Rep* 2010; **62**: 1070-1077 [PMID: 21273664 DOI: 10.1016/s1734-1140(10)70369-8]
- 20 **Fruen BR**, Lester BR. Down's syndrome fibroblasts exhibit enhanced inositol uptake. *Biochem J* 1990; **270**: 119-123 [PMID: 2144418 DOI: 10.1042/bj2700119]
- 21 **Lin AL**, Powell D, Caban-Holt A, Jicha G, Robertson W, Gold BT, Davis R, Abner E, Wilcock DM, Schmitt FA, Head E. (1)H-MRS metabolites in adults with Down syndrome: Effects of dementia. *Neuroimage Clin* 2016; **11**: 728-735 [PMID: 27330972 DOI: 10.1016/j.nicl.2016.06.001]
- 22 **Shonk T**, Ross BD. Role of increased cerebral myo-inositol in the dementia of Down syndrome. *Magn Reson Med* 1995; **33**: 858-861 [PMID: 7651126 DOI: 10.1002/mrm.1910330619]
- 23 **Kato T**, Nishina M, Matsushita K, Hori E, Mito T, Takashima S. Neuronal maturation and N-acetyl-L-aspartic acid development in human fetal and child brains. *Brain Dev* 1997; **19**: 131-133 [PMID: 9105660 DOI: 10.1016/s0387-7604(96)00496-2]



Retrospective Study

Clinical factors predicting rotavirus diarrhea in children: A cross-sectional study from two hospitals

Michelle Indrawan, Jason Chendana, Tan Gabriella Heidina Handoko, Melanie Widjaja, Gilbert Sterling Octavius

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dauyey K, Kazakhstan; Viswanathan VK, United States

Received: July 19, 2023

Peer-review started: July 19, 2023

First decision: August 31, 2023

Revised: September 7, 2023

Accepted: September 25, 2023

Article in press: September 25, 2023

Published online: December 9, 2023



Michelle Indrawan, Jason Chendana, Tan Gabriella Heidina Handoko, Melanie Widjaja, Gilbert Sterling Octavius, Department of Pediatric, Universitas Pelita Harapan, Banten 15811, Indonesia

Corresponding author: Gilbert Sterling Octavius, MD, MM, Doctor, Researcher, Department of Pediatric, Universitas Pelita Harapan, Jl. Jend. Sudirman No. 20 Bencong, Kec. Klp. Dua, Kabupaten Tangerang, Banten 15811, Indonesia. sterlinggilbert613@hotmail.com

Abstract

BACKGROUND

Rotavirus is still a significant contributing morbidity and mortality in pediatric patients.

AIM

To look at clinical signs and symptoms and laboratory findings that can predict rotavirus gastroenteritis compared to non-rotavirus gastroenteritis.

METHODS

This was a cross-sectional study with medical records obtained from December 2015 to December 2019. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea. The receiver operating curve and Hosmer-Lemeshow test would be used to assess the final prediction findings' calibration (goodness of fit) and discrimination performance.

RESULTS

This study included 267 participants with 187 (70%) rotavirus-diarrhea cases. The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old). Multivariate analysis shows that wet season ($OR_{adj} = 2.5$; 95%CI: 1.3-4.8, $P_{adj} = 0.006$), length of stay (LOS) ≥ 3 days ($OR_{adj} = 5.1$; 95%CI: 1.4-4.8, $P_{adj} = 0.015$), presence of abdominal pain ($OR_{adj} = 3.0$; 95%CI: 1.3-6.8, $P_{adj} = 0.007$), severe dehydration ($OR_{adj} = 2.9$; 95%CI: 1.1-7.9, $P_{adj} = 0.034$), abnormal white blood cell counts ($OR_{adj} = 2.8$; 95%CI: 1.3-6.0, $P_{adj} = 0.006$), abnormal random blood glucose ($OR_{adj} = 2.3$; 95%CI: 1.2-4.4, $P_{adj} = 0.018$) and presence of fecal leukocytes ($OR_{adj} = 4.1$, 95%CI: 1.7-9.5, $P_{adj} = 0.001$) are predictors of rotavirus diarrhea. The area under the curve for this model

is 0.819 (95%CI: 0.746-0.878, *P* value < 0.001), which shows that this model has good discrimination.

CONCLUSION

Wet season, LOS ≥ 3 d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose, and presence of fecal leukocytes predict rotavirus diarrhea.

Key Words: Rotavirus; Pediatric; Gastroenteritis; Diarrhea; Indonesia

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. This cross-sectional study involving 267 children found that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, *P*_{adj} = 0.006), length of stay ≥ 3 d (OR_{adj} = 5.1; 95%CI: 1.4-4.8, *P*_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, *P*_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, *P*_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, *P*_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, *P*_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, *P*_{adj} = 0.001) are predictors of rotavirus diarrhea.

Citation: Indrawan M, Chendana J, Handoko TGH, Widjaja M, Octavius GS. Clinical factors predicting rotavirus diarrhea in children: A cross-sectional study from two hospitals. *World J Clin Pediatr* 2023; 12(5): 319-330

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/319.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.319>

INTRODUCTION

Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. Surveillance data from 2008-2018 showed that 40.78% of all diarrheal diseases in children in Southeast Asia were attributable to rotavirus infection[1]. The fecal-oral transmission from person-to-person contact or ingestion of fecally contaminated food and water commonly leads to a rapid spread among communities, especially in developing countries[2].

When diagnosing gastroenteritis, it is necessary to analyse fecal specimens using widely available assays because rotavirus-caused gastroenteritis cannot be clinically distinguished from that caused by other enteric pathogens[3]. However, because the findings do not change clinical management, which primarily depends on effective rehydration therapy, rotavirus is not routinely tested for in patients with gastroenteritis[4]. Despite its worldwide prevalence, detecting rotavirus in stool samples is still a logistical and financial challenge in developing countries[5].

Considering the disease burden, it is essential to know reliable clinical signs and symptoms and other non-confirmatory laboratory tests that clinicians can use to guide their treatment. Hence, this study aims to look at clinical signs and symptoms and laboratory findings that can predict rotavirus gastroenteritis compared to non-rotavirus gastroenteritis.

MATERIALS AND METHODS

This study was cross-sectional, with medical records obtained from December 2015 to December 2019 from Siloam General Hospital and Siloam Hospital Lippo Village (SHLV). Patients covered by Indonesia's national health insurance can receive care at Siloam General Hospital, a teaching hospital. SHLV, on the other hand, primarily consists of patients who are self-paying or have private insurance. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea, defined as the passing of ≥ 3 watery or loose stools each day [6]. Children who have previously experienced significant immunosuppression due to prolonged steroid usage or illnesses like the human immunodeficiency virus or primary immunodeficiency were excluded from this study. Another exclusion criterion was the presence of concurrent infections such as urinary tract infections or pneumonia. The sample size calculation used the following formula:

$$N = \frac{z^2(pq)}{e^2} \quad (1)$$

Where *N* is the sample size, *z* denotes the standard error, which was 1.96, *p* was the estimated prevalence in the population, *q* was 100-*p*, and *e* was the acceptable sample error set at 6% in this study. The prevalence of pediatric rotavirus diarrhea in Indonesia is 37.5% to 53.5%[7]. Hence, the minimum sample size required was 265 children.

We collected demographic data such as age, gender, and nutritional status. Clinical signs such as temperature upon arrival, vital signs, clinical manifestations (abdominal pain, respiratory symptoms, dehydration status according to World Health Organization (WHO)[6], duration and frequency of symptoms (diarrhea, vomiting, fever), length of stay (LOS),

treatment given during hospitalisation [intravenous (IV) rehydration and any antibiotics], rotavirus vaccination status, as well as the seasons during which the children contracted diarrhea. The need for IV rehydration represented severe dehydration in this study. Meteorology Climatology and Geophysics Council's data in 2017 were used to determine the seasons where October – February was the rainy season, and the rest was the dry season in Tangerang[8]. We adhered to WHO 2006 growth chart for children below five years, while the Centers for Disease Control and Prevention 2000 growth charts were used for children aged 5-18 years old to classify nutritional status[9]. We did not collect any data on zinc used for diarrhea as all children were given zinc for diarrhea as per standard protocol in our hospitals. Lastly, we collected laboratory findings such as complete blood count, serum electrolytes, random blood glucose, erythrocyte sedimentation rate (ESR), and urinary ketone for dehydration markers and fecal leukocytes[10]. We present laboratory values dichotomously (normal *vs* abnormal values) for multivariate analysis and in numerical forms for descriptive purposes. The reference range will be based on our population study's mean or median age group.

The neutrophil-lymphocyte ratio (NLR) is obtained by dividing the total band and segmented neutrophil by the lymphocyte. In contrast, the monocyte-lymphocyte ratio is obtained by dividing the monocyte by the lymphocyte. Absolute neutrophil count is calculated with the formula as follows: $(\text{Total WBC} \times \% [\text{PMNs} + \text{bands}]) \div 100$.

While the absolute lymphocyte count is calculated with the formula: $\text{WBC count} \times 1000 \times \% \text{ lymphocyte}$. (NLR were obtained by dividing the total neutrophils by lymphocyte counts, and the same methodology was applied to obtain lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR)[11]. One or two ccs of peripheral venous blood samples were collected by antecubital venipuncture into vacutainer tubes (Becton Dickinson, Rutherford, NJ, United States) containing tri potassium ethylenediaminetetraacetic acid. The complete blood count was done within one to two hours after the blood samples were drawn, and the analysis was performed using the Advia 2120i automated analyser (Siemens Healthcare Diagnostics, Deerfield, IL, United States). Erythrocyte sedimentation rate levels were measured by TEST 1 (Alifax, Padova, Italy). The rotavirus analysis was done using immunochromatography (Alcore One-Step Rotavirust Test). Those who tested positive would be categorised as having rotavirus diarrhea, and those who tested negative would be categorised as having non-rotavirus diarrhea. Strict quality control procedures were adopted. All of the independent variables were chosen based on previous studies[7,12,13].

The data was processed using IBM SPSS 26.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, United States). After a normality test, data with a normal distribution will be presented as mean and standard deviation. If not, the median and range will be applied. The Mann-Whitney-U test is used when the distribution of numerical data is non-normal, while the T-test is used when the distribution of numerical data is normal. Chi-square was used for bivariate analysis, and variables with p-values less than 0.25 would be used in multivariate logistic regression analysis. The receiver operating curve (ROC) and Hosmer-Lemeshow test would be used to assess the final prediction findings' calibration (goodness of fit) and discrimination performance. The area under the curve (AUC) is equal to 0.5 when the ROC curve represents chance, and it is equal to 1.0 when the ROC curve represents accuracy. A good calibration would be indicated by a *P* value > 0.05. The sensitivity and specificity of the various predictor variables in identifying non-severe and severe pneumonia were then calculated using the area under the curve. We also analysed casewise diagnostics to identify any outliers.

This study protocol was approved by the Committee on Ethics at the University of Pelita Harapan, Tangerang, Indonesia, with Code Ethic No. 430/FK-UPH/Ext./V/2019. The ethical board exempted informed consent due to the retrospective nature of our study. Identities were removed entirely, and data were analysed anonymously.

RESULTS

Descriptive characteristics

This study included 267 participants with 187 (70%) rotavirus-diarrhea cases (Table 1). The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old), with the majority belonging to the 0-11 mo old category (34.5%). Most patients had good nutritional status in the non-rotavirus group (51.3%) and rotavirus group (53.5%). Most rotavirus cases occurred during the dry season (77.1%), while non-rotavirus cases occurred mainly in the wet seasons (37.8%) with an odds ratio (OR) of 0.49 [95% confidence interval (CI) 0.29-0.93, *P* value 0.01]. The majority of patients had a length of stay of ≥ 3 d in both groups (95% in the non-rotavirus group and 83.4% in the rotavirus group) (OR 0.27; 95%CI: 0.1-0.78, *P* value 0.02). Only one patient was put in the intensive care unit, belonging to the non-rotavirus group. In both groups, most patients are not vaccinated for rotavirus (86.3% in non-rotavirus diarrhea *vs* 94.7% in rotavirus diarrhea) with an OR of 0.35 (95%CI: 0.14-0.97, *P* value 0.04) (Table 1).

Clinical manifestations

The clinical manifestations vary between the two groups. Most patients presented with mild-moderate dehydration (67.4%) in rotavirus diarrhea, while most in the non-rotavirus group presented with no dehydration (43.8%). Fever mostly lasts less than three days for rotavirus diarrhea (55.1%), while fever lasts mostly ≥ 3 d in the non-rotavirus group (56.3%). The last difference in clinical manifestation between the two groups is in diarrhea duration, where in rotavirus diarrhea it lasts 2-4 d (51.3%) while it mostly lasts > 4 d (57.5%) in the non-diarrhea group. Meanwhile, in both groups, most patients suffer from more than five diarrhea episodes per day, 0-3 vomiting episodes, abdominal pain, and respiratory symptoms (Figure 1).

Table 1 Characteristics of the study population

Characteristics	Frequency		OR (95%CI)	P value
	Non-rotavirus	Rotavirus		
Gender				
Male	50 (29.1)	122 (70.9)	0.89 (0.52-1.53)	0.77
Female	30 (31.6)	65 (68.4)		
Age (mo)				
0-11	21	71	Ref	Ref
12-23	24	60	0.74 (0.38-1.46)	0.38
24-59	17	44	0.77 (0.37-1.61)	0.48
≥ 60	18	12	0.19 (0.08-0.47)	< 0.001
Nutritional status				
Severely underweight	10	34	1.39 (0.63-3.08)	0.4
Underweight	14	32	0.94 (0.45-1.94)	0.86
Normoweight	41	100	Ref	Ref
Overweight	7	6	0.35 (0.11-1.11)	0.08
Obese	8	15	0.77 (0.30-1.95)	0.58
Season				
Dry	32 (22.9)	108 (77.1)	0.49 (0.29-0.83)	0.01
Wet	48 (37.8)	79 (62.2)		
Hospitalisation				
In-patient	79 (29.7)	187 (70.3)	N/A	0.30
Intensive Care Unit	1 (100)	0 (0)		
Length of stay (d)				
< 3	4 (11.4)	31 (88.6)	0.27 (0.10-0.78)	0.02
≥ 3	76 (32.8)	156 (67.2)		
Clinical manifestations				
Diarrhea duration (d)				
< 2	2 (22.2)	7 (77.8)	Ref	Ref
2-4	32 (25)	96 (75)	0.86 (0.17-4.34)	1
> 4	46 (35.4)	84 (64.6)	0.52 (0.10-2.62)	0.72
Diarrhea frequency (d)				
< 3	4 (66.7)	2 (33.3)	Ref	Ref
3-4	32 (30.2)	74 (69.8)	4.63 (0.81-26.54)	0.08
> 5	44 (28.4)	111 (71.6)	5.05 (0.90-28.54)	0.07
Vomiting frequency (d)				
0-3	50 (36)	89 (64)	Ref	Ref
4-5	9 (20)	36 (80)	2.25 (1.00-5.04)	0.07
> 5	21 (25.3)	62 (74.7)	1.66 (0.91-3.04)	0.13
Fever duration (d)				
< 3	35 (25.4)	103 (74.6)	0.63 (0.38-1.01)	0.12
≥3	45 (34.9)	84 (65.1)		
Abdominal pain				

Negative	56 (25)	168 (75)	0.26 (0.14-0.52)	< 0.01
Positive	24 (55.8)	19 (44.2)		
Respiratory symptoms				
Negative	59 (28.8)	146 (71.2)	0.79 (0.43-1.45)	0.54
Positive	21 (33.9)	41 (66.1)		
Dehydration				
No dehydration	35 (46.7)	40 (53.3)	Ref	Ref
Mild-moderate	33 (20.8)	126 (79.2)	3.34 (1.85-6.10)	< 0.01
Severe	12 (36.4)	21 (63.6)	1.53 (0.66-3.55)	0.43
Treatment				
Antibiotic				
Negative	3 (1.7)	176 (98.3)	0.002 (0.001-0.01)	< 0.01
Positive	77 (87.5)	11 (12.5)		
IV rehydration				
Negative	19 (32.2)	40 (67.8)	1.15 (0.61-2.13)	0.80
Positive	61 (29.3)	147 (70.7)		
Rotavirus vaccination				
Negative	69 (28)	177 (72)	0.35 (0.14-0.97)	0.04
Positive	11 (52.4)	10 (47.6)		
Laboratory examinations				
Hemoglobin				
Normal	52 (28.1)	133 (71.9)	0.75 (0.43-1.32)	0.40
Abnormal	28 (34.1)	54 (65.9)		
White blood cell count				
Normal	50 (24.6)	153 (75.4)	0.37 (0.21-0.67)	< 0.01
Abnormal	30 (46.9)	34 (53.1)		
Basophils				
Normal	63 (31.5)	137 (68.5)	1.35 (0.72-2.53)	0.43
Abnormal	17 (25.4)	50 (74.6)		
Eosinophils				
Normal	23 (26.1)	65 (73.9)	0.76 (0.43-1.34)	0.42
Abnormal	57 (31.8)	122 (68.2)		
Band neutrophils				
Normal	66 (30.7)	149 (69.3)	1.20 (0.61-2.37)	0.72
Abnormal	14 (26.9)	38 (73.1)		
Segment neutrophils				
Normal	9 (18.8)	39 (81.3)	0.48 (0.22-1.05)	0.09
Abnormal	71 (32.4)	148 (67.6)		
Total neutrophils				
Normal	10 (20.4)	39 (79.6)	0.54 (0.26-1.15)	0.15
Abnormal	70 (32.1)	148 (67.9)		
Lymphocytes				
Normal	13 (26)	37 (74)	0.79 (0.40-1.58)	0.61

Abnormal	67 (30.9)	150 (69.1)		
Monocytes				
Normal	44 (32.1)	93 (67.9)	1.24 (0.73-2.10)	0.51
Abnormal	36 (27.7)	94 (72.3)		
Absolute lymphocytes count				
Normal	28 (23.5)	91 (76.5)	0.57 (0.33-0.98)	0.05
Abnormal	52 (35.1)	96 (64.9)		
Absolute neutrophils count				
Normal	40 (23.8)	128 (76.2)	0.46 (0.30-0.79)	0.007
Abnormal	40 (40.4)	59 (59.6)		
Neutrophils-to-lymphocyte ratio				
Normal	33 (29.5)	4 (57.1)	0.96 (0.57-1.63)	0.99
Abnormal	77 (29.6)	183 (70.4)		
Lymphocyte-to-monocyte ratio				
Normal	3 (42.9)	4 (57.1)	1.79 (0.40-8.15)	0.74
Abnormal	77 (29.6)	183 (70.4)		
Platelet-to-lymphocyte ratio				
Normal	6 (22.2)	21 (77.8)	0.64 (0.25-1.64)	0.47
Abnormal	74 (31)	165 (69)		
Erythrocyte sedimentation rate				
Normal	37 (31.1)	82 (68.9)	1.1 (0.65-1.86)	0.82
Abnormal	43 (29.1)	105 (70.9)		
Random blood glucose				
Normal	45 (24.6)	138 (75.4)	0.46 (0.26-0.80)	0.007
Abnormal	35 (41.7)	49 (58.3)		
Sodium				
Normal	42 (27.5)	111 (72.5)	0.76 (0.45-1.28)	0.37
Abnormal	38 (33.3)	76 (66.7)		
Potassium				
Normal	33 (29.5)	79 (70.5)	0.96 (0.56-1.63)	0.99
Abnormal	47 (30.3)	108 (69.7)		
Chloride				
Normal	42 (29.6)	100 (70.4)	0.96 (0.57-1.63)	0.99
Abnormal	38 (30.4)	87 (69.6)		
Urine and fecal tests				
Urinary ketone				
Negative	74 (29.8)	174 (70.2)	0.92 (0.34-2.52)	1.00
Positive	6 (31.6)	13 (68.4)		
Fecal leukocytes				
Negative	58 (25.9)	166 (74.1)	0.33 (0.17-0.65)	0.002
Positive	22 (51.2)	21 (48.8)		

N/A: Not applicable.

Treatment

98.3% of patients that are rotavirus positive did not receive antibiotics. In comparison, almost all (96.3%) patients who suffer from non-rotavirus diarrhea receive antibiotics with an OR of 0.002 (95%CI: 0.001-0.01, P value < 0.01). In both groups, most patients receive IV rehydration with no significant statistical difference (OR 1.15; 95%CI: 0.61-2.13, P value 0.08).

Laboratory parameters

Most laboratory parameters are within normal range except for decreased LMR and PLR in both groups, while ESR is slightly elevated. The potassium level is also slightly below the normal reference range, with a median of 4 mmol/L in both groups. Most urinary ketones are negative in both groups (92.5% in the non-rotavirus *vs* 93% in the rotavirus group). There is a significant difference in fecal leukocyte findings between both groups with an OR of 0.33 (95%CI: 0.17-0.65, P value 0.002) (Tables 1 and 2).

Multivariate logistic regression

Multivariate logistic regression analysis adjusted for variables with a p -value of < 0.25 is shown in Table 3. Multivariate analysis shows that wet season ($OR_{adj} = 2.5$; 95%CI: 1.3-4.8, $P_{adj} = 0.006$), LOS ≥ 3 d ($OR_{adj} = 5.1$; 95%CI: 1.4-4.8, $P_{adj} = 0.015$), presence of abdominal pain ($OR_{adj} = 3.0$; 95%CI: 1.3-6.8, $P_{adj} = 0.007$), severe dehydration ($OR_{adj} = 2.9$; 95%CI: 1.1-7.9, $P_{adj} = 0.034$), abnormal white blood cell counts ($OR_{adj} = 2.8$; 95%CI: 1.3-6.0, $P_{adj} = 0.006$), abnormal random blood glucose ($OR_{adj} = 2.3$; 95%CI: 1.2-4.4, $P_{adj} = 0.018$) and presence of fecal leukocytes ($OR_{adj} = 4.1$, 95%CI: 1.7-9.5, $P_{adj} = 0.001$) are predictors of rotavirus diarrhea. The Hosmer-Lemeshow test shows this model is a good fit with a p -value of 0.361. The AUC for this model is 0.819 (95%CI: = 0.746-0.878, P value < 0.001), which shows that this model has good discrimination (Figure 1).

DISCUSSION

Comparison with other studies

Rotavirus was shown to be the leading cause of morbidity and mortality in children, especially five years old and below [13]. Symptoms tend to be most severe in children between 3-24 mo old. However, in approximately 25% of rotavirus cases, severe disease occurs after two years of age. Serologic evidence of rotavirus infection can be virtually observed in all children aged 4-5 [12]. Our results showed that our samples have a median age of 1.3 years old. In multivariate analysis, the wet season showed a significant association with rotavirus infection. A previous study showed that in the tropics, rotavirus infection tends to occur all year round compared to the seasonal pattern of infection in countries with temperate climates. However, factors other than temperature, such as rainfall and humidity, play a significant role in rotavirus incidence in the tropics. Due to the waterborne nature of rotavirus transmission, the outbreak pattern might be altered by precipitation levels [14]. In low-income areas, stagnant water sources and poor access to uncontaminated water and sanitation were hypothesised to pose a higher risk for rotavirus infection [15]. Study showed that monsoon season was significantly correlated with dehydrating rotavirus diarrhea among children aged 0-59 mo in South Asia [16]. Previous meta-analyses have also concluded that every 1°C increase in temperature is associated with a 4%-10% decrease in rotavirus infection incidence in the tropics. However, for every one-centimetre increase in mean monthly rainfall and 1% increase in relative humidity (22%), rotavirus incidence decreased by 1% and 3%, respectively. Based on the evidence, it was previously concluded that rotavirus incidence in the tropics was the highest during colder and drier times of the year [17].

Gastroenteritis is generally more severe in the rotavirus group than in the non-rotavirus sample. Length of stay was shown to be prolonged in children age below two years old with rotavirus gastroenteritis. Prolonged LOS, especially in pediatric patients, promote work absenteeism in 70% of parents and could negatively impact the quality of life [18]. Prolonged LOS ≥ 3 d is significantly associated with rotavirus gastroenteritis in this study.

Rotavirus has a broad spectrum of symptoms after 1 to 3 d of incubation, varying from subclinical illness to severe dehydration, shock and death. Rotavirus infection has a similar but more severe clinical manifestation than other gastrointestinal infections. Diagnosis of rotavirus gastroenteritis is commonly clinical based on the presence of vomiting and low-grade fever, followed by watery, non-bloody diarrhea. Moderate fever (temperature < 39°C) is found in approximately one-third of infected patients. Fever and vomiting frequently cease within 1 to 3 d. This finding explains our findings that prolonged fever and vomiting are not significantly associated with rotavirus gastroenteritis. Other physical findings such as abdominal cramping, fatigue and signs of dehydration might also occur during the 5 to 7 d disease course. Diagnosis can be further established by the absence of atypical features such as high-grade fever, which is more commonly present in bacterial gastroenteritis, projectile vomiting, bilious vomiting, blood or mucus in stool, persistent diarrhea for more than seven days, focal abdominal pain, absent bowel sound, and history of antibiotic use [4,19,20]. Presence of abdominal pain and severe dehydration was associated with rotavirus infection in this study. These findings correlate with findings from the previous study that rotavirus-positive subjects were more likely to present with severe dehydration and tend to require intravenous rehydration therapy than rotavirus-negative subjects [16]. However, the role of abdominal pain as a predictor of rotavirus infection is still controversial. Abdominal pain is hypothesised to be limited in rotavirus infection due to low inflammatory response demonstrated by minimal elevation of C-reactive protein or calprotectin levels as clinical markers of inflammation. Rotavirus replication appears to be limited exclusively in the villous epithelium of small intestines, and the diarrhea was considered malabsorptive secondary to enterocyte destruction. Despite non-specific symptomatology, severe abdominal pain and tenesmus tend to indicate large intestines

Table 2 Descriptive values of the laboratory findings

Variable	Reference range	Non rotavirus	Rotavirus
Hemoglobin (g/dL)	10.5-14.0	13.49 (± 16.0)	13.0 (± 11.3)
White blood cell count (10 ⁹ L)	6.0-17.5	14.54 (4.21-42.07)	11.72 (2.86-38.6)
Basophils (%)	0-0.75	0 (0-1)	0 (0-1)
Eosinophils (%)	1-3	0 (0-5)	0 (0-5)
Band neutrophils (%)	3-5	3 (2-12)	3 (1-8)
Segment neutrophils (%)	54-62	62 (20-90)	51 (15-92)
Total neutrophils (%)	58-66	65 (23-93)	54 (18-95)
Lymphocytes (%)	25-33	27 (3-69)	37 (3-75)
Monocytes (%)	3-7	7 (3-13)	7 (1-15)
Absolute lymphocyte count	4000-10500	3354.6 (290.1-15356)	4232.8 (459-24532.2)
Absolute neutrophils count	1500-8500	8662 (1768.7-32814.6)	6100 (972.4-27898)
Neutrophil-to-lymphocyte ratio	Male: 1.48-6.37; Female: 1.22-5.59	2.5 (0-31)	2 (0-32)
Lymphocyte-to-monocyte ratio	Male: 11.12-26.82; Female: 16.08-28.18	4.29 (0.38-16.50)	5.29 (0.50-54)
Platelet-to-lymphocyte ratio	Male: 132.07-178.53; Female: 132.46-181.90	96.7 (20.5-722)	98 (15.89-969)
Thrombocyte count (μ/mm ³)	150000-350000	350000 (109800-1099000)	381000 (115000-1094000)
Erythrocyte sedimentation rate (mm/hour)	0-10	12 (2-215)	14 (1-68)
Random blood glucose (mg/dL)	60-100	94.5 (48-238)	85 (15-160)
Sodium (mmol/L)	134-143	136 (113-154)	135 (124-165)
Potassium (mmol/L)	4.1-5.3	4 (1.6-5.9)	4 (1.4-7.1)
Chloride (mmol/L)	98-106	100 (34.5-134)	101 (9.7-141)

Table 3 Results from multivariate logistic regression analysis for rotavirus diarrhea

Values	OR _{adj} (95%CI)	P value _{adj}
Wet season	2.5 (1.3-4.8)	0.006
Length of stay ≥ 3 d	5.1 (1.4-4.8)	0.015
Fever lasts ≥ 3 d	1.9 (0.97-3.5)	0.06
Abdominal pain	3.0 (1.3-6.8)	0.007
Mild-moderate dehydration	1.2 (0.4-3.5)	0.75
Severe dehydration	2.9 (1.1-7.9)	0.034
Abnormal white blood cell counts	2.8 (1.3-6.0)	0.006
Abnormal absolute neutrophil counts	1.9 (0.9-3.8)	0.072
Abnormal random blood glucose	2.3 (1.2-4.4)	0.018
Presence of fecal leukocytes	4.1 (1.7-9.5)	0.001

CI: Confidence intervals; OR: Odds ratio, OR_{adj}: Adjusted odds ratio.

involvement[21,22]. Previous studies demonstrated that abdominal pain is particularly frequent in rotavirus-positive subjects or co-infection with rotavirus subjects. However, no significant association has been found in statistical analyses [23]. Ambiguous interpretation of abdominal pain by parents of young children during history taking could lead to a bias in pain assessment. This finding might explain the contradictory result regarding abdominal pain in this study.

Rotavirus diarrhea and laboratory values

In this study, rotavirus-positive patients demonstrated abnormal white blood cell counts and abnormal random blood glucose. However, previous studies showed no significant difference in white blood cell count between the rotavirus-

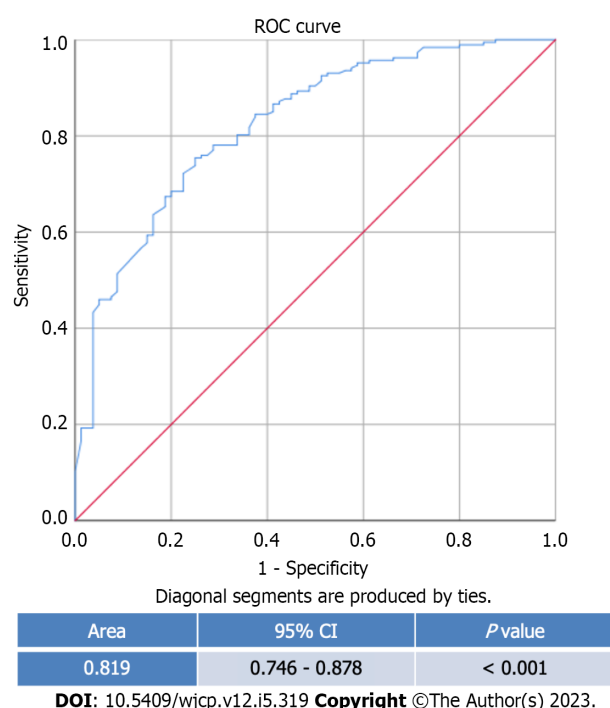


Figure 1 The receiver operating curve curve analysis.

positive and rotavirus-negative groups. These studies did not mainly compare rotavirus and the specific etiologic agent of gastroenteritis[24-26]. The wide causative range of non-rotavirus gastroenteritis might explain the different findings. Other more significant variables to be compared with rotavirus are indicators of metabolic acidosis secondary to fluid loss. A previous study showed that rotavirus-positive subjects had lower blood pH, higher base deficit, and lower bicarbonate[25]. Complete blood count examination appears to have minimal value in predicting rotavirus infection.

Rotavirus diarrhea and respiratory symptoms

Several reports have stated that respiratory symptoms might also occur during the rotavirus infection course. However, the mechanism that explains this finding is still controversial. Coincidental infection with respiratory viruses during rotavirus endemic season might manifest as respiratory symptoms. Previous studies have indicated that rotavirus might infect extra-intestinal organs during viremia, but there has not been sufficient evidence to prove its replication ability outside the intestine. Rotavirus antigens or RNA were detected in the spleen, heart, kidneys, testes, bladder, liver, cells or secretions from the respiratory tract, and endothelial cells[20,27]. Our result showed that respiratory symptoms do not predict rotavirus infection in children. Stool analyses in rotavirus-positive subjects are common without blood or white blood cells[20]. This result correlates with our findings that faecal leukocytes are a predictor of rotavirus infection. The presence of fecal leukocytes in rotavirus infection may indicate inflammatory processes in the intestines[28]. No other hematologic findings were significantly correlated with rotavirus infection in this study.

Limitation

This study has its limitations. Our research is a cross-sectional study to start with. As a result, we could not account for some factors that might affect the severity of rotavirus diarrhea, such as birth weight, source of water, and house-crowding status. Second, the study's focus on just two institutions raises the possibility that this study may not be generalisable to other centres. However, given the nature of the two different hospitals, we were able to include kids from a range of racial and ethnic backgrounds, assuring that both high- and low-income parents were represented in this study. Some variables have insufficient strength for analysis due to missing or unanalysed laboratory data. Third, we could not account for any temporal changes occurring in the four years of the study period. Any seasonality, changes in guidelines and diagnosis of rotavirus diarrhea, as well as immunization update may have altered the results of the study. Lastly, we did not analyse the antigenic properties of the rotavirus due to limited equipment and funding.

CONCLUSION

In this study, wet season, LOS ≥ 3 d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose and presence of fecal leukocytes predict rotavirus diarrhea. Since these parameters have good discrimination, these findings should alert clinicians to the presence of rotavirus diarrhea. Clinicians may use these parameters to further alert them to the possibility of rotavirus diarrhea in children and order tests more prudently as well as prescribing appropriate therapy.

ARTICLE HIGHLIGHTS

Research background

Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. Surveillance data from 2008-2018 showed that 40.78% of all diarrheal diseases in children in Southeast Asia were attributable to rotavirus infection.

Research motivation

Rotavirus diarrhea is still a leading cause of mortality among Indonesian children. However, since antigen detection is not affordable amongst many families, other cheap clinical proxies for rotavirus diarrhea must be determined.

Research objectives

This study aims to determine clinical and laboratory values that may serve as an indicator to raise clinicians' awareness about rotavirus diarrhea.

Research methods

This study was cross-sectional, with medical records obtained from December 2015 to December 2019 from Siloam General Hospital and Siloam Hospital Lippo Village. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea, defined as the passing of ≥ 3 watery or loose stools each day. We collected demographic data such as age, gender, and nutritional status. Clinical signs such as temperature upon arrival, vital signs, clinical manifestations (abdominal pain, respiratory symptoms, dehydration status according to World Health Organization), duration and frequency of symptoms (diarrhea, vomiting, fever), length of stay (LOS), treatment given during hospitalisation [intravenous (IV) rehydration and any antibiotics], rotavirus vaccination status, as well as the seasons during which the children contracted diarrhea.

Research results

This study included 267 participants with 187 (70%) rotavirus-diarrhea cases. The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old). Multivariate analysis shows that wet season ($OR_{adj} = 2.5$; 95%CI: 1.3-4.8, $P_{adj} = 0.006$), $LOS \geq 3$ d ($OR_{adj} = 5.1$; 95%CI: 1.4-4.8, $P_{adj} = 0.015$), presence of abdominal pain ($OR_{adj} = 3.0$; 95%CI: 1.3-6.8, $P_{adj} = 0.007$), severe dehydration ($OR_{adj} = 2.9$; 95%CI: 1.1-7.9, $P_{adj} = 0.034$), abnormal white blood cell counts ($OR_{adj} = 2.8$; 95%CI: 1.3-6.0, $P_{adj} = 0.006$), abnormal random blood glucose ($OR_{adj} = 2.3$; 95%CI: 1.2-4.4, $P_{adj} = 0.018$) and presence of fecal leukocytes ($OR_{adj} = 4.1$, 95%CI: 1.7-9.5, $P_{adj} = 0.001$) are predictors of rotavirus diarrhea. The area under the curve for this model is 0.819 (95%CI: = 0.746-0.878, P value < 0.001), which shows that this model has good discrimination.

Research conclusions

In this study, wet season, $LOS \geq 3$ d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose and presence of fecal leukocytes predict rotavirus diarrhea. Since these parameters have good discrimination, these findings should alert clinicians to the presence of rotavirus diarrhea. Clinicians may use these parameters to further alert them to the possibility of rotavirus diarrhea in children and order tests more prudently as well as prescribing appropriate therapy.

Research perspectives

More bigger and confirmatory studies are needed to confirm our findings.

FOOTNOTES

Author contributions: Octavius GS and Widjaja M designed the research study; Indrawan M, Chendana J, Handoko TGH, and Octavius GS performed the research; Indrawan M and Chendana J gathered and analyzed the data; Indrawan M, Chendana J, Octavius GS, and Handoko TGH wrote the draft; All authors have read, edited and approved the final manuscript.

Institutional review board statement: This study protocol was approved by the Committee on Ethics at the University of Pelita Harapan, Tangerang, Indonesia, with Code Ethic No. 430/FK-UPH/Ext./V/2019.

Informed consent statement: The ethical board exempted informed consent due to the retrospective nature of our study. Identities were removed entirely, and data were analysed anonymously.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: Data is available upon reasonable request.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to

distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Indonesia

ORCID number: Michelle Indrawan 0000-0002-2198-1472; Jason Chendana 0009-0003-4939-7627; Gilbert Sterling Octavius 0000-0002-6439-6265.

S-Editor: Liu JH

L-Editor: A

P-Editor: Zhang XD

REFERENCES

- Du Y, Chen C, Zhang X, Yan D, Jiang D, Liu X, Yang M, Ding C, Lan L, Hecht R, Zhu C, Yang S. Global burden and trends of rotavirus infection-associated deaths from 1990 to 2019: an observational trend study. *Virol J* 2022; **19**: 166 [PMID: 36266651 DOI: 10.1186/s12985-022-01898-9]
- Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, Jha P, Campbell H, Walker CF, Cibulskis R, Eisele T, Liu L, Mathers C; Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010; **375**: 1969-1987 [PMID: 20466419 DOI: 10.1016/S0140-6736(10)60549-1]
- Zuccotti G, Meneghin F, Dilillo D, Romanò L, Bottone R, Mantegazza C, Giacchino R, Besana R, Ricciardi G, Sterpa A, Altamura N, Andreotti M, Montrasio G, Macchi L, Pavan A, Paladini S, Zanetti A, Radaelli G. Epidemiological and clinical features of rotavirus among children younger than 5 years of age hospitalized with acute gastroenteritis in Northern Italy. *BMC Infect Dis* 2010; **10**: 218 [PMID: 20649961 DOI: 10.1186/1471-2334-10-218]
- Parashar UD, Nelson EA, Kang G. Diagnosis, management, and prevention of rotavirus gastroenteritis in children. *BMJ* 2013; **347**: f7204 [PMID: 24379214 DOI: 10.1136/bmj.f7204]
- Justino MCA, Campos EA, Mascarenhas JDP, Soares LS, Guerra SFS, Furlaneto IP, Pavão MJC Jr, Maciel TS, Farias FP, Bezerra OM, Vinente CBG, Barros RJS, Linhares AC. Rotavirus antigenemia as a common event among children hospitalised for severe, acute gastroenteritis in Belém, northern Brazil. *BMC Pediatr* 2019; **19**: 193 [PMID: 31189470 DOI: 10.1186/s12887-019-1535-2]
- World Health Organization. The Treatment of diarrhoea: a manual for physicians and other senior health workers. 5th April, 2023. Available from: <https://apps.who.int/iris/bitstream/handle/10665/43209/9241593180.pdf?sequence=1>
- Prasetyo D, Ermaya YS, Sabaroedin IM, Widhiastuti D, Bachtar NS, Kartasmita CB. Genotype Profiles of Rotavirus Strains in Children under 5-year-old Outpatients with Diarrhea in Bandung, West Java, Indonesia. *J Glob Infect Dis* 2022; **14**: 142-146 [PMID: 36636306 DOI: 10.4103/jgid.jgid_101_22]
- Badan Meteorologi K, dan Geofisika. Prakiraan Musim Hujan 2016/2017 Di Indonesia. 5th April, 2023. Available from: <https://www.bmkg.go.id/iklim/prakiraan-musim.bmkg?p=prakiraan-musim-hujan-20162017-di-indonesia&tag=prakiraan-musim&lang=ID>
- Sjarif DR, Nasar SS, Devaera Y, Tanjung CF. Asuhan Nutrisi Pediatrik (Pediatric Nutrition Care). 1st ed. Unit Kerja Koordinasi Nutrisi dan Penyakit Metabolik Ikatan Dokter Anak Indonesia; 2011
- Steiner MJ, Nager AL, Wang VJ. Urine specific gravity and other urinary indices: inaccurate tests for dehydration. *Pediatr Emerg Care* 2007; **23**: 298-303 [PMID: 17505271 DOI: 10.1097/01.pcc.0000270162.76453.f8]
- Moosmann J, Krusemark A, Dittrich S, Ammer T, Rauh M, Woelfle J, Metzler M, Zierk J. Age- and sex-specific pediatric reference intervals for neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio. *Int J Lab Hematol* 2022; **44**: 296-301 [PMID: 34816610 DOI: 10.1111/ijlh.13768]
- Tate JE, Burton AH, Boschi-Pinto C, Parashar UD; World Health Organization–Coordinated Global Rotavirus Surveillance Network. Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000-2013. *Clin Infect Dis* 2016; **62** Suppl 2: S96-S105 [PMID: 27059362 DOI: 10.1093/cid/civ1013]
- Hallowell BD, Chavers T, Parashar U, Tate JE. Global Estimates of Rotavirus Hospitalizations Among Children Below 5 Years in 2019 and Current and Projected Impacts of Rotavirus Vaccination. *J Pediatric Infect Dis Soc* 2022; **11**: 149-158 [PMID: 34904636 DOI: 10.1093/jpids/piab114]
- Kraay ANM, Brouwer AF, Lin N, Collender PA, Remais JV, Eisenberg JNS. Modeling environmentally mediated rotavirus transmission: The role of temperature and hydrologic factors. *Proc Natl Acad Sci USA* 2018; **115**: E2782-E2790 [PMID: 29496960 DOI: 10.1073/pnas.1719579115]
- Ghoshal V, Das RR, Nayak MK, Singh S, Das P, Mohakud NK. Climatic Parameters and Rotavirus Diarrhea Among Hospitalized Children: A Study of Eastern India. *Front Pediatr* 2020; **8**: 573448 [PMID: 33194902 DOI: 10.3389/fped.2020.573448]
- Yeasmin S, Hasan SMT, Chisti MJ, Khan MA, Faruque ASG, Ahmed T. Factors associated with dehydrating rotavirus diarrhea in children under five in Bangladesh: An urban-rural comparison. *PLoS One* 2022; **17**: e0273862 [PMID: 36018895 DOI: 10.1371/journal.pone.0273862]
- Levy K, Hubbard AE, Eisenberg JN. Seasonality of rotavirus disease in the tropics: a systematic review and meta-analysis. *Int J Epidemiol* 2009; **38**: 1487-1496 [PMID: 19056806 DOI: 10.1093/ije/dyn260]
- Albano F, Bruzzese E, Bella A, Cascio A, Titone L, Arista S, Izzi G, Virdis R, Pecco P, Principi N, Fontana M, Guarino A. Rotavirus and not age determines gastroenteritis severity in children: a hospital-based study. *Eur J Pediatr* 2007; **166**: 241-247 [PMID: 16941130 DOI: 10.1007/s00431-006-0237-6]
- Bernstein DI. Rotavirus overview. *Pediatr Infect Dis J* 2009; **28**: S50-S53 [PMID: 19252423 DOI: 10.1097/INF.0b013e3181967bee]
- Crawford SE, Ramani S, Tate JE, Parashar UD, Svensson L, Hagbom M, Franco MA, Greenberg HB, O'Ryan M, Kang G, Desselberger U, Estes MK. Rotavirus infection. *Nat Rev Dis Primers* 2017; **3**: 17083 [PMID: 29119972 DOI: 10.1038/nrdp.2017.83]
- Greenberg HB, Estes MK. Rotaviruses: from pathogenesis to vaccination. *Gastroenterology* 2009; **136**: 1939-1951 [PMID: 19457420 DOI: 10.1053/j.gastro.2009.02.076]
- Graves NS. Acute gastroenteritis. *Prim Care* 2013; **40**: 727-741 [PMID: 23958366 DOI: 10.1016/j.pop.2013.05.006]

- 23 **Borade A**, Bais AS, Bapat V, Dhongade R. Characteristics of rotavirus gastroenteritis in hospitalized children in Pune. *Indian J Med Sci* 2010; **64**: 210-218 [PMID: [22842320](#) DOI: [10.4103/0019-5359.98942](#)]
- 24 **Greenberg DE**, Wilimas JA, Buckingham SC. Hematologic findings in children with rotavirus-positive and -negative diarrhea. *Pediatr Hematol Oncol* 2003; **20**: 453-456 [PMID: [14631619](#)]
- 25 **Karampatsas K**, Osborne L, Seah ML, Tong CYW, Prendergast AJ. Clinical characteristics and complications of rotavirus gastroenteritis in children in east London: A retrospective case-control study. *PLoS One* 2018; **13**: e0194009 [PMID: [29565992](#) DOI: [10.1371/journal.pone.0194009](#)]
- 26 **Zaraket R**, Salami A, Bahmad M, El Roz A, Khalaf B, Ghssein G, Bahmad HF. Prevalence, risk factors, and clinical characteristics of rotavirus and adenovirus among Lebanese hospitalized children with acute gastroenteritis. *Heliyon* 2020; **6**: e04248 [PMID: [32613122](#) DOI: [10.1016/j.heliyon.2020.e04248](#)]
- 27 **Candy DC**. Rotavirus infection: a systemic illness? *PLoS Med* 2007; **4**: e117 [PMID: [17439293](#) DOI: [10.1371/journal.pmed.0040117](#)]
- 28 **Chen CC**, Chang CJ, Lin TY, Lai MW, Chao HC, Kong MS. Usefulness of fecal lactoferrin in predicting and monitoring the clinical severity of infectious diarrhea. *World J Gastroenterol* 2011; **17**: 4218-4224 [PMID: [22072854](#) DOI: [10.3748/wjg.v17.i37.4218](#)]

Migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion: A systematic literature review and meta-analysis

Rajendra Kumar Ghritlaharey

Specialty type: Neurosciences

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Rajderkar DA, United States

Received: June 25, 2023

Peer-review started: June 25, 2023

First decision: August 17, 2023

Revised: September 4, 2023

Accepted: October 30, 2023

Article in press: October 30, 2023

Published online: December 9, 2023



Rajendra Kumar Ghritlaharey, Department of Paediatric Surgery, Gandhi Medical College and Associated, Kamla Nehru and Hamidia Hospitals, Bhopal 462001, Madhya Pradesh, India

Corresponding author: Rajendra Kumar Ghritlaharey, MBBS, MS, MCh, Professor, Department of Paediatric Surgery, Gandhi Medical College and Associated, Kamla Nehru and Hamidia Hospitals, Royal Market, Bhopal 462001, Madhya Pradesh, India.

drrajendrak1@rediffmail.com

Abstract

BACKGROUND

Intra-gastric migration of the distal ventriculoperitoneal shunt (VPS) catheter clinically presenting with or without trans-oral extrusion is one of the rare complications of VPS catheter insertion.

AIM

To identify the demographics, clinical presentation, clinical findings, and results of surgical therapy offered for the treatment of intra-gastric migration of the distal VPS catheter, clinically presented with or without trans-oral extrusion.

METHODS

An online search was performed for the extraction/retrieval of the published/available literature pertaining to the above-mentioned VPS complication. Manuscripts were searched from PubMed, PMC (PubMed Central), ResearchGate, and Google Scholar databases using various terminology relating to the VPS complications. The first case of migration of a VPS catheter into the stomach was reported in the year 1980, and the data were retrieved from 1980 to December 2022. Cases were categorized into two groups; Group A: Cases who had migration of the distal VPS catheter into the stomach and clinically presented with trans-oral extrusion of the same, and Group B: Cases who had migration of the distal VPS catheter into the stomach, but presented without trans-oral extrusion.

RESULTS

A total of $n = 46$ cases ($n = 27$; 58.69% male, and $n = 19$; 41.3% females) were recruited for the systematic review. Group A included $n = 32$, and Group B $n = 14$ cases. Congenital hydrocephalus was the indication for the primary VPS insertion for approximately half of the ($n = 22$) cases. Approximately sixty percent ($n = 27$) of them were children ≤ 5 years of age at the time of the diagnosis of the

complication mentioned above. In seventy-two percent ($n = 33$) cases, this complication was detected within 24 mo after the VPS insertion/last shunt revision. Clinical diagnosis was evident for the entire group A cases. Various diagnostic modalities were used to confirm the diagnosis for Group B cases. Various surgical procedures were offered for the management of the complication in $n = 43$ cases of both Groups. In two instances, intra-gastric migration of the distal VPS catheter was detected during the autopsy. This review documented four deaths.

CONCLUSION

Intra-gastric migration of the peritoneal end of a VPS catheter is one of the rare complications of VPS catheter implantation done for the treatment of hydrocephalus across all age groups. It was more frequently reported in children, although also reported in adults and older people. A very high degree of clinical suspicion is required for the diagnosis of a case of an intra-gastric migration of the distal VPS catheter clinically presenting without trans-oral extrusion.

Key Words: Complication; Extrusion; Hydrocephalus; Migration; Protrusion; Stomach; Shunt revision; Ventriculoperitoneal shunt; Ventriculoperitoneal shunt complications

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This systematic review included $n = 46$ cases of intra-gastric migration of the peritoneal end of a ventriculoperitoneal shunt (VPS) catheter. Thirty-two cases clinically presented with the peroral extrusion of the distal VPS catheter. The remaining $n = 14$ cases clinically presented with other symptoms but without peroral extrusion of the distal VPS catheter. Sixty percent were children ≤ 5 years of age at the time of diagnosis of VPS complication mentioned above. In more than two-thirds of cases, the VPS complication was evident within 24 mo after the primary VPS insertion/last VPS revision. The demographics, indications for the primary/initial VPS insertion, age distribution at the time of VPS insertion and diagnosis of the VPS complication, the interval, and the surgical procedures carried out by the various authors for the above-described VPS complication are described in the manuscript.

Citation: Ghritlaharey RK. Migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion: A systematic literature review and meta-analysis. *World J Clin Pediatr* 2023; 12(5): 331-349

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/331.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.331>

INTRODUCTION

The treatment of hydrocephalus has evolved over centuries, but progress has occurred during the past few decades[1,2]. The ventriculoperitoneal shunt insertion is the commonly performed surgical procedure for treating hydrocephalus caused by various etiologies and is performed across all age groups[3-7]. Various complications occur in approximately one-fifth to four-fifths of the cases following the VPS insertion, and many of them require shunt revisions[5-9]. VPS revisions are needed more during the first 12 mo following the initial VPS placement[5,6,8]. VPS complications and shunt revisions are more frequently documented and required in children than adults[5,8]. Perforation of the hollow viscus viz gastrointestinal tract, urinary bladder, and uterus (female genital tract) by the peritoneal end of a VPS catheter is known, and it may occur with or without extrusion of the distal VPS catheter through the natural orifices[10-14]. Perforation of the large bowel by the peritoneal end of a VPS catheter and protrusion/extrusion of the same *via* the anal canal is commonly reported[10,11]. Migration of the distal VPS catheter into the stomach is a rare clinical entity[14]. The preferred reporting items for systematic reviews and metaanalyses (PRISMA) guidelines are followed for reporting this manuscript [15,16]. This manuscript is a systematic literature review of the $n = 46$ cases published (1980 to December 2022) on the management of the intra-gastric migration of the distal VPS catheter clinically presented with or without trans-oral extrusion[17-62]. Thirty-two cases had intra-gastric migration of the distal VPS catheter and clinically presented with trans-oral extrusion of the same[17-48]. Remaining $n = 14$ cases had intra-gastric migration of the distal VPS catheter but clinically presented without trans-oral extrusion of the distal VPS catheter[49-62].

MATERIALS AND METHODS

PubMed, PMC, ResearchGate, and Google Scholar databases were searched for retrieval of the published/available literature pertaining to the migration of the distal VPS catheter into the stomach with or without trans-oral extrusion. Various terminology relating to VPS complications were utilized during the online search. Some of the keywords employed during the online search were “trans-oral extrusion of distal VPS catheter”, “per-oral/oral extrusion of distal VPS catheter”, “intra-gastric migration of distal VPS catheter”, “protrusion/extrusion of VPS catheter”, “bowel

perforation by distal VPS catheter”, and “rare complication of VPS catheter”. The maiden case of migration of a VPS catheter into the stomach was reported by Nishijima *et al*[49] in 1980, and related literature/manuscripts were retrieved from 1980 to December 2022, and those were preferably available in the English language. Four cases ($n = 2$ duodenal and $n = 2$ jejunal) of bowel perforation (not gastric perforation) by the distal VPS catheter, clinically presented with trans-oral extrusion were also included in the present review. Cases/case reports retrieved during online search with incomplete details were excluded from the review. Cases are categorized into two groups, Groups A and Group B. Group A: Cases who had migration of the distal VPS catheter into the stomach and clinically presented with trans-oral extrusion of the same, and Group B: Cases who had migration of the distal VPS catheter into the stomach but clinically presented without trans-oral extrusion. The “Preferred Reporting Items for Systematic Reviews and MetaAnalyses” (PRISMA) guidelines are followed for reporting this systematic review. The selection of articles for systematic review was done by assessing the titles, abstracts, and full texts of the manuscripts. Literature selection and extraction of the desired information from the manuscripts were independently carried out by the author alone, as this is a single-author manuscript. The desired information retrieved from the published literature/case reports were the patient’s age, sex, indication for the VPS insertion, interval from VPS insertion to the diagnosis of the complication, clinical characteristics, diagnostic modalities used, surgical procedures offered/performed, postoperative complications, and the outcome of surgical therapy. This manuscript is a systematic review of the published cases, and institutional ethical committee approval is not required.

RESULTS

A total of $n = 46$ cases of intra-gastric migration of the peritoneal end of a VPS catheter clinically presented with or without peroral extrusion were included for the systematic review and retrieved from the $n = 46$ manuscripts. The process of database search, screening, and selection of the manuscripts for the present systematic review is presented in a PRISMA flow diagram in Figure 1. Group A included $n = 32$ cases and details are provided in Table 1. Group B included $n = 14$ cases and details are provided in Table 2. The causes of hydrocephalus and indications for the primary VPS insertion for the entire case are detailed in Figure 2. Congenital hydrocephalus was the indication for the primary VPS insertion for approximately half of the ($n = 22$) cases. Figure 3 detailed the distribution of the age of the entire cases at the time of primary VPS insertion. The initial VPS catheter placement was done during infancy in two-thirds ($n = 22$) of Group A cases. The initial VPS catheter placement was done during infancy only in one-fourth ($n = 4$) of Group B cases. Figure 4 details the distribution of the age of the entire cases at the time of diagnosis of the above-mentioned VPS complication. Approximately sixty percent ($n = 27$) of them were children ≤ 5 years of age at the time of diagnosis of the complication mentioned above. Figure 5 details the interval from the primary/initial VPS insertion/last VPS revision to the diagnosis of the VPS complication mentioned above. In seventy-two percent ($n = 33$) cases, this complication was detected within 24 mo after the VPS insertion/last shunt revision.

The chief complaint and clinical finding for Group A cases was the trans-oral extrusion of the distal VPS catheter (Figure 6). In most cases, it was associated with a bout of vomiting of short duration. Mild abdominal pain/discomfort relating to the upper gastrointestinal (GI) tract was also documented in some cases. Clinical presentation in Group B cases was vague and not specific to the distal VPS catheter complication. Group B cases mostly had symptoms relating to the central nervous system (CNS) or upper GI tract. Clinical diagnosis was evident in the entire Group A cases due to the clinical finding of the presence of trans-oral extrusion/protrusion of the distal VPS catheter. Various diagnostic modalities (radiological and endoscopic) were used to confirm the diagnosis in Group B cases. Different surgical procedures were offered for the management of the above-mentioned VPS complication and are detailed in Figure 7. Removal of the entire VPS catheter/removal of part of the peritoneal /peritoneal catheter with or without external ventricular drainage (EVD) was preferred by the authors. In $n = 2$ Group B cases, an intra-gastric migration of the distal VPS catheter was detected during the autopsy. For one Group B case, the surgical therapy was not carried out, as his VPS catheter was not causing any problems. Percutaneous surgical removal of the entire or the distal VPS catheter with or without an EVD was a procedure of choice and was opted for $n = 27$ ($n = 24$ Group A and $n = 3$ Group B) cases. For the management of VPS complications mentioned above, formal laparotomy was carried out only in $n = 11$ ($n = 7$ Group A and $n = 4$ Group B) cases. The site of bowel perforation caused by the distal VPS catheter is detailed in (Figure 8A). In eighty-five percent of cases, the site of bowel perforation was the stomach. The site of bowel perforation was repaired only in $n = 11$ cases and is detailed in (Figure 8B). The review revealed $n = 4$ (8.69%) deaths, two from each group.

DISCUSSION

Perforation of the gastrointestinal tract, urinary bladder, and uterus by the distal VPS catheter is a known complication of the VPS placement carried out for the treatment of hydrocephalus, and most of them clinically present with the extrusion of the peritoneal part of a VPS catheter through the natural orifices[10-14]. Perforation of the large bowel by the peritoneal end of a VPS catheter and extrusion of the same *via* the anal canal is most common and is reported to occur in 0.1% to 2.5% of the cases[10,11]. Migration of the distal VPS catheter into the stomach is a rare clinical entity, and two-thirds of them presented with the trans-oral extrusion of the distal part of peritoneal catheter[17-62].

Summary of evidence

A total of $n = 46$ manuscripts including $n = 46$ cases of the above-mentioned VPS complication were reviewed for

Table 1 Demographics, clinical features, and outcome of the surgical procedures performed for the migration of the distal ventriculoperitoneal shunt catheter into the stomach with trans-oral extrusion (*n* = 32)

Ref.	Indication for VPS insertion	Age VPS insertion sex	Age trans-oral extrusion	Interval (mo)	VPS (R)	History GI Surg	Shunt tract infection	Peritonitis meningitis	CSF infection	Operative procedures executed	Site repaired (Yes/No)	Complication	Outcome
Griffith <i>et al</i> [17], 1987	Hydrocephalus (Post infective)	9.6 yr Female	9.9 yr	3	Yes	Yes	No	No	No	Part of distal VPS catheter cut by child, proximal VPS catheter as EVD, delayed ventriculo-atrial shunt done	Stomach (No)	Yes	Death
Danismend <i>et al</i> [18], 1988	Hydrocephalus (Congenital?)	8 mo Female	18 mo	10	No	No	No	No	No	Removal of distal VPS catheter and Immediate ventriculo-atrial shunt done	Stomach (Yes)	Nil	R
Park <i>et al</i> [19], 2000	Hydrocephalus (Post-haemorrhagic)	12 mo female	5 yr	48	No	No	Yes	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed re-VPS/VPS (R) done	Stomach (No)	Nil	R
Jiménez Moya <i>et al</i> [20], 2001	Hydrocephalus (Brain tumor)	9.11 yr female	11.2 yr	2	Yes	Yes	No	No	No	Removal of entire VPS catheter, Delayed re-VPS insertion done	Stomach (NA)	Nil	R
Kothari <i>et al</i> [21], 2006	Hydrocephalus (Congenital)	1 mo male	18 mo	17	No	No	No	No	Yes	Removal of entire VPS catheter, Delayed re-VPS insertion done	Stomach? (No)	Nil	R
Odebode <i>et al</i> [22], 2007	Hydrocephalus (Congenital?)	9 mo female	15 mo	6	No	No	Yes	No	No	Removal of entire VPS catheter, Delayed re-VPS insertion done	Jejunum (Yes)	Nil	R
Berhouma <i>et al</i> [23], 2008	Hydrocephalus with NTD (Congenital)	9 mo male	2 yr	15	No	No	No	No	Yes	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD	NA (No)	Yes	Death
Murali <i>et al</i> [24], 2008	Hydrocephalus (Congenital)	6 mo male	6 yr	66	No	No	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Removal of cranial catheter failed	Stomach (No)	Nil	R
Sridhar <i>et al</i> [25], 2009	Hydrocephalus (Post infective)	2 mo female	8 mo	6	No	No	No	No	No	Removal of entire VPS catheter (re-VPS catheter insertion not required)	Stomach? (No)	Nil	R
Sinnadurai <i>et al</i> [26], 2009	Hydrocephalus (Cyst)	12 yr female	27 yr	2 wk	Yes	No	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed VPS (R) done	Stomach (No)	Nil	R
Low <i>et al</i> [27], 2010	Hydrocephalus (Post infective)	6 mo male	12 mo	6	No	Yes	No	No	No	Removal of entire VPS catheter, Insertion of EVD, Delayed re-VPS insertion done	Stomach (No)	Nil	R
Dua <i>et al</i> [28], 2011	Hydrocephalus with NTD (Congenital)	20 d male	8 mo	7	No	No	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed re-VPS insertion done	Stomach (No)	Nil	R
Agarwal <i>et al</i> [29], 2011	Hydrocephalus (Congenital)	4 mo male	12 mo	8	No	No	No	No	No	Removal of entire VPS catheter, Delayed re-VPS insertion done	NA (No)	Nil	R
Gupta <i>et al</i>	Hydrocephalus	6 mo male	4 yr	42	No	No	No	No	No	Removal of entire VPS catheter (re-VPS	Stomach (No)	Nil	R

[30], 2012	(Congenital)										insertion not required)			
Kundal <i>et al</i> [31], 2012	Hydrocephalus (Post infective)	6 yr male	7 yr	12	No	No	No	No	No	Removal of entire VPS catheter, Delayed re-VPS insertion done	NA (No)	Nil	R	
Yilmaz <i>et al</i> [32], 2013	Hydrocephalus (Pseudotumor)	37 yr female	47 yr	120	No	Yes	No	No	No	Removal of entire VPS catheter (re-VPS insertion not required)	Stomach (Yes)	Nil	R	
Gupta <i>et al</i> [33], 2014	Hydrocephalus (Congenital)	12 mo male	11 yr	7	Yes	No	No	No	No	Removal of entire VPS catheter (Previous VPS functioning well)	Stomach (No)	Nil	R	
Mandhan <i>et al</i> [34], 2015	Hydrocephalus with NTD (Congenital)	Infant female	11 yr	53	No	Yes	No	No	No	Removal of entire VPS catheter (re-VPS insertion not done/required?)	Stomach (No)	Nil	R	
Thiong'o <i>et al</i> [35], 2015	Hydrocephalus (Congenital)	10 d female	3 mo	2	No	No	No	No	No	Removal of entire VPS catheter, Insertion of EVD, Delayed re-VPS insertion done	Stomach? (No)	Nil	R	
Sohal <i>et al</i> [36], 2015	Hydrocephalus (Congenital?)	NA male	11 mo	10 d	Yes	Yes	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed ventriculo-atrial shunt done	Stomach (No)	Nil	R	
Ghritlaharey <i>et al</i> [37], 2015	Hydrocephalus (Post infective/Congenital)	12 mo female	24 mo	9	Yes	No	No	No	No	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed VPS (R) done	Stomach? (No)	Yes	R	
Shah <i>et al</i> [38], 2016	Hydrocephalus (Congenital)	12 mo male	4 yr	12	Yes	No	No	No	No	Removal of entire VPS catheter (re-VPS insertion not required)	Stomach (No)	Nil	R	
Sharma <i>et al</i> [39], 2017	Hydrocephalus (Congenital)	Neonate male	8 mo	7	No	No	No	No	No	Removal and re-positioning of distal VPS catheter into the peritoneal cavity	Stomach (No)	Nil	R	
Al Fauzi A <i>et al</i> [40], 2017	Hydrocephalus (Brain tumor)	4 yr male	5 yr	12	No	No	No	No	No	Removal of entire VPS catheter (re-VPS insertion not required)	Stomach (No)	Nil	R	
Reyes <i>et al</i> [41], 2017	Hydrocephalus (Post-haemorrhagic)	2 mo male	16 mo	8	Yes	No	No	No	No	Removal of entire VPS catheter, Immediate re-VPS insertion done	Stomach (No)	Nil	R	
Badri <i>et al</i> [42], 2018	Hydrocephalus (Congenital)	4 yr male	4 yr	1	No	No	No	No	No	Removal of distal VPS catheter, Immediate VPS (R) done	Duodenum (Yes)	Nil	R	
Romuald <i>et al</i> [43], 2018	Hydrocephalus (Congenital)	24 mo male	34 mo	10	No	No	No	No	Yes	Removal of entire VPS catheter, Insertion of EVD, Delayed re-VPS insertion done	Duodenum (Yes)	Nil	R	
Ezzat <i>et al</i> [44], 2018	Hydrocephalus (Congenital)	2 mo male	22 mo	20	No	No	No	No	No	Removal of entire VPS catheter, Cranial catheter as EVD? Delayed re-VPS insertion done	Stomach? (No)	Nil	R	
Bemora <i>et al</i> [45], 2019	Hydrocephalus (Post infective)	7 mo female	16 mo	9	No	No	No	No	NA	Removal of entire VPS catheter, Immediate re-VPS insertion done	Stomach (No?)	Nil	R	
Feeney <i>et al</i> [46], 2020	Hydrocephalus (Post trauma)	57 yr male	58 yr	11	No	No	No	No	Yes	Removal of distal VPS catheter, Proximal VPS catheter as EVD, Removal of proximal VPS catheter	Jejunum (No)	Nil	R	

										(re-VPS insertion not required)			
Calgaro <i>et al</i> [47], 2020	Hydrocephalus (Congenital)	2 mo male	7 mo	5	No	No	No	No	NA	Removal of entire VPS catheter, Immediate re-VPS insertion done	Stomach? (No)	Nil	R?
Najib <i>et al</i> [48], 2022	Hydrocephalus with NTD (Congenital)	Neonate male	8 mo	7	No	No	No	No	No	Removal of part of distal VPS catheter and re-positioning of remaining distal catheter into the peritoneal cavity	Stomach (Yes)	Nil	R

¹Site: Site of perforation.

CSF: Cerebrospinal fluid; EVD: External ventricular drainage; GI Surg: Gastrointestinal/abdominal surgery; NA: Not available/details not available; NTD: Neural tube defect; R: Recovered; VPS: Ventriculoperitoneal Shunt; VPS (R): Ventriculoperitoneal Shunt revision.

systematic review[17-62]. Forty-four manuscripts are published in the English language[17-19,21-40,42-62]. Only $n = 2$ manuscripts published and available in languages other than English are also included in the review. For the above two manuscripts, the desired details are obtained by translating them into the English language using Google Translate[20, 41]. All the $n = 46$ manuscripts included in the review are already published, and none are conference proceedings or unpublished. All the $n = 46$ manuscripts included for systematic review are full-text articles[17-62]. Thirty-five manuscripts described/detailed the isolated case[17,19,23-30,32,33,37-43,45,46,48-54,56-62]. Two of the manuscripts included in the review are original articles[35,44]. For one case, the details were extracted from a manuscript published as a case series[31]. Eight manuscripts are published and available under the headings of medical images, letters to the editor, correspondence, and technical notes[18,20-22,34,36,47,55]. Four manuscripts included $n = 5$ cases of the above-mentioned VPS complications were excluded from review due to the incomplete desired information[63-66].

This review included $n = 46$ cases ($n = 27$; 58.69% were males and $n = 19$; 41.3% were females). It was evident more in males, with a male-to-female ratio of 1.42:1. Group A included $n=32$ cases ($n = 20$; 62.5% male, and $n = 12$; 37.5% females) while Group B included $n=14$ cases ($n = 7$; 50% male, and $n = 7$; 50% females).

The indication for the primary VPS insertion was congenital hydrocephalus for approximately half of the entire cases ($n = 22$) cases and approximately sixty percent ($n = 19$) of the Group A cases. Post-infective hydrocephalus was also one of the indications for VPS insertion in approximately one-fifth ($n = 6$) of the Group A cases. Normal pressure hydrocephalus (NPH), idiopathic intracranial hypertension, and intracranial aneurysm with or without hemorrhage were the indications for the primary VPS catheter insertion for fifty percent of the Group B cases.

Group A cases were much younger than the Group B cases at the time of initial VPS placement. Two-thirds ($n = 22$) of Group A and one-fourth ($n = 4$) of Group B cases were infants, at the time of initial VPS placement. Three-fourths ($n = 9$) of Group B cases were > 40 years of age, at the time of initial VPS placement. Group A cases were much younger at the time of the diagnosis of VPS complications as well. More than half ($n=17$) of Group A cases were children ≤ 2 years of age at the time of diagnosis of the VPS complication mentioned above. One-fourths ($n = 4$) of Group B cases were children ≤ 5 years of age at the time of diagnosis of the VPS complication mentioned above. Seventy-two percent ($n = 23$) of Group A cases were ≤ 5 years of age, while more than half ($n = 8$) of Group B cases were > 40 years of age. Age was not a bar for the intra-gastric migration of the distal VPS catheter. A trans-oral extrusion of the distal VPS catheter was infrequently reported after 15 years, and only three cases were reported after the age of 15 years. Probably one of the reasons may be the age difference at the time of primary VPS insertion for both the Group cases and the second reason may be the difference in the indication for the initial VPS catheter insertion. The probable reason for a greater number of intra-gastric migrations clinically presented as trans-oral extrusion of the distal VPS catheter in children than in adult/older population may be because the number of VPS placements carried out in infants and children are many folds more than

Table 2 Demographics, clinical features, and outcome of the surgical procedures performed for the migration of the distal ventriculoperitoneal shunt catheter into the stomach without trans-oral extrusion (*n* = 14)

Ref.	Indication for VPS insertion	Age VPS insertion sex	Age gastric migration	Interval (mo)	VPS (R)	History GI Surg	Shunt tract infection	Peritonitis meningitis	CSF infection	Operative procedures executed	¹ Site repaired (Yes/No)	Complication	Outcome
Nishijima <i>et al</i> [49], 1980	Hydrocephalus (NPH)	69 yr female	71 yr	27	No	No	No	Meningitis	Yes	Distal VPS catheter found within the gastric lumen (Autopsy finding)	Stomach (Autopsy)	-	Death
Oi <i>et al</i> [50], 1987	Hydrocephalus (posttraumatic)	12 mo male	3 yr	24	Yes	No	Yes	Meningitis	Yes	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD, Delayed VPS revision done	Stomach (Glue)	Nil	R
Oshio <i>et al</i> [51], 1991	Hydrocephalus (Posttraumatic)	12 mo male	3 yr	24	No	No	Yes	Meningitis	Yes	Removal of part of distal VPS catheter, Proximal VPS catheter as EVD?, Delayed VPS revision done	Stomach (Glue)	Yes	R
Ho <i>et al</i> [52], 1992	Hydrocephalus (NPH)	68 yr male	72 yr	42	No	No	No	Meningitis	Yes	Distal VPS catheter found within the gastric lumen (Autopsy finding)	Stomach (Autopsy)	-	Death
Alonso-Vanegas <i>et al</i> [53], 1994	Hydrocephalus with NTD (Congenital)	Neonate female	4 mo	4	No	No	No	No	No	Removal of entire VPS catheter, Immediate ventriculo-atrial shunt	Stomach (Yes)	Nil	R
Christoph <i>et al</i> [54], 1995	Hydrocephalus (Congenital)	5 mo female	5 mo	1 d	No	Yes	No	No	No	Removal of distal VPS catheter from gastric lumen and converted as EVD, Delayed ventriculo-atrial shunt done	Stomach (NA)	Nil	R
Hart <i>et al</i> [55], 2001	Hydrocephalus (Congenital)	NA female	33 yr	NA	NA	No	No	No	No	Removal of distal VPS catheter from gastric lumen and relocation of distal catheter within the peritoneal cavity	Stomach (NA)	Nil	R
Masuoka <i>et al</i> [56], 2005	Hydrocephalus (Intracranial aneurysm)	47 yr male	51 yr	42	No	No	No	No	Yes	Removal of entire VPS catheter (re-VPS insertion not required)	Stomach (No)	Nil	R
Cheng <i>et al</i> [57], 2007	Hydrocephalus (Posttraumatic)	87 yr male	88 yr	8	No	No	No	No	Yes	Removal of entire VPS catheter (re-VPS insertion not done/required)	Stomach (Yes)	Nil	R
Cohen-Added <i>et al</i> [58], 2018	Hydrocephalus (Intracranial aneurysm)	65 yr male	72 yr	7 yr?	No	No	No	No	No	Surgical therapy not executed for intra-gastric migration of distal VPS catheter	Stomach (No)	--	R
Sidhu <i>et al</i> [59], 2019	Hydrocephalus (Intracranial aneurysm)	83 yr? male	84 yr	12?	No	Yes	No	No	No	Removal of entire VPS catheter (re-VPS insertion not required)	Stomach (NA)	Nil	R
Yala <i>et al</i> [60], 2019	Hydrocephalus (Intracranial aneurysm)	41 yr female	65 yr	36?	Yes	No	No	No	No	Removal of distal VPS catheter from gastric lumen and relocation of distal catheter within the peritoneal cavity	Stomach (Yes)	Nil	R
Chen <i>et al</i> [61], 2020	Hydrocephalus (Post infective)	44 yr female	54 yr	NA	Yes	No	No	No	Yes	Removal of entire VPS catheter, Placement of EVD, Delayed re-VPS insertion done	Stomach (Yes)	Nil	R

Scarascia <i>et al</i> [62], 2022	Hydrocephalus (IIH)	15 yr female	31 yr	16 yr?	No	No	No	No	No	Removal of entire VPS catheter (re-VPS insertion not done)	Stomach (Yes) Yes	R?
--------------------------------------	---------------------	--------------	-------	--------	----	----	----	----	----	---	-------------------	----

¹Site: Site of perforation.

CSF: Cerebrospinal fluid; EVD: External ventricular drainage; GI Surg: Gastrointestinal/abdominal surgery; IIH: Idiopathic intracranial hypertension; NA: Not available/details not available; NPH: Normal pressure hydrocephalus; NTD: Neural tube defect; R: Recovered; VPS: Ventriculoperitoneal Shunt; VPS (R): Ventriculoperitoneal Shunt revision.

done in adults and older age. Like the present findings, a recent review included $n = 210$ cases of the management of extrusion of the distal part of peritoneal catheter through the anal canal, also evidenced that in 73% of the cases, the age of the cases was ≤ 5 years of age[11]. For $n = 19$ of the Group A and $n = 9$ of the Group B cases, the details of the shunt type/which type of the VPS catheter implanted during the initial procedure was not available/not mentioned by the authors in the manuscripts[20,21,23-27,29-32,34,36,38,42,43,45,47,48,52,54,55,57-62]. “Chhabra slit n spring hydrocephalus VPS catheter” (Shahjahanpur, India) was used during the VPS implantation in $n = 8$ of the Group A cases[22,28,33,35,37,39,40,44]. For the remaining $n = 4$ Group A and $n = 5$ Group B cases, the shunt catheter used during VPS insertion were (1) Raimondi peritoneal catheter ($n = 3$); (2) Codman Hakim VPS system ($n = 5$); and (3) VPS catheter (Biomed valve, slit valve, silicon catheter, not spring type) ($n = 1$), respectively[17-19,41,46,49-51,53,56]. As in this review, in sixty percent ($n = 28$) cases, which type of VPS catheter implanted was not available, and therefore it is not clear whether any particular shunt catheter was responsible for the increased risk of gastric perforation.

For the entire Group A and Group B cases, the interval from the initial VPS insertion/VPS revision to the diagnosis of the VPS complication described above ranged from one day to 11 years. For the cases that had a history of VPS revision, for them, the interval was calculated from the date of the last VPS revision done. In seventy-two percent ($n = 33$) of the entire case, this complication was detected within 24 mo after the VPS insertion/shunt revision. In 60% ($n = 28$) of the entire case, it occurred within 12 mo of VPS insertion/last shunt revision. In one-fourths ($n = 12$) of the entire cases, it was detected within 6-months of VPS insertion/shunt revision. For Group A cases, the said complication was detected within a month to 24 mo in more than four-fifths ($n = 27$) of cases. For Group B cases, the complication was detected within a month to 24 mo in forty-three percent ($n = 6$) cases. In $n = 5$ of Group B cases, the interval from VPS insertion to the detection of the said VPS complication was 3 to 10 years. A recent systematic review (2022) of the $n = 210$ cases on the management of trans-anal extrusion of the distal VPS catheter also revealed that in 70% of the cases, it occurred within 12 mo after the VPS insertions[11]. Like the above finding, the present review also revealed that 60% of the entire cases and four-fifths of Group A cases were also diagnosed within 12 mo of the VPS insertion. In a recent systematic review (2022) of the $n = 37$ instances of the management of the perforation and intra-vesical (urinary bladder) migration of the distal part of the peritoneal catheter clinically presented with or without per-urethral extrusion identified that only onethird of the cases presented within 12 mo after the VPS insertion[12]. It means that urinary bladder perforation by the distal VPS catheter is a late complication than colonic or gastric perforation by the distal VPS catheter.

Peroral extrusion of the distal part of a VPS catheter was the chief complaint and clinical finding for Group A cases and it was evident in all the $n = 32$ cases reviewed. In the majority of the cases, the trans-oral extrusion of the distal VPS catheter was associated with a bout of vomiting of short duration. Mild abdominal pain/discomfort relating to the upper GI tract was also documented in some cases. A few Group A cases also had associated headaches and fever. Clinical presentation in Group B cases was vague, and not specific to the distal VPS catheter complication. The Group B cases mostly had symptoms relating to the CNS or gastrointestinal tract (GIT). Five cases presented with symptoms related to the CNS. Six cases presented predominantly with symptoms related to the upper GIT. Eight cases also had associated general symptoms like fever, weakness, and others.

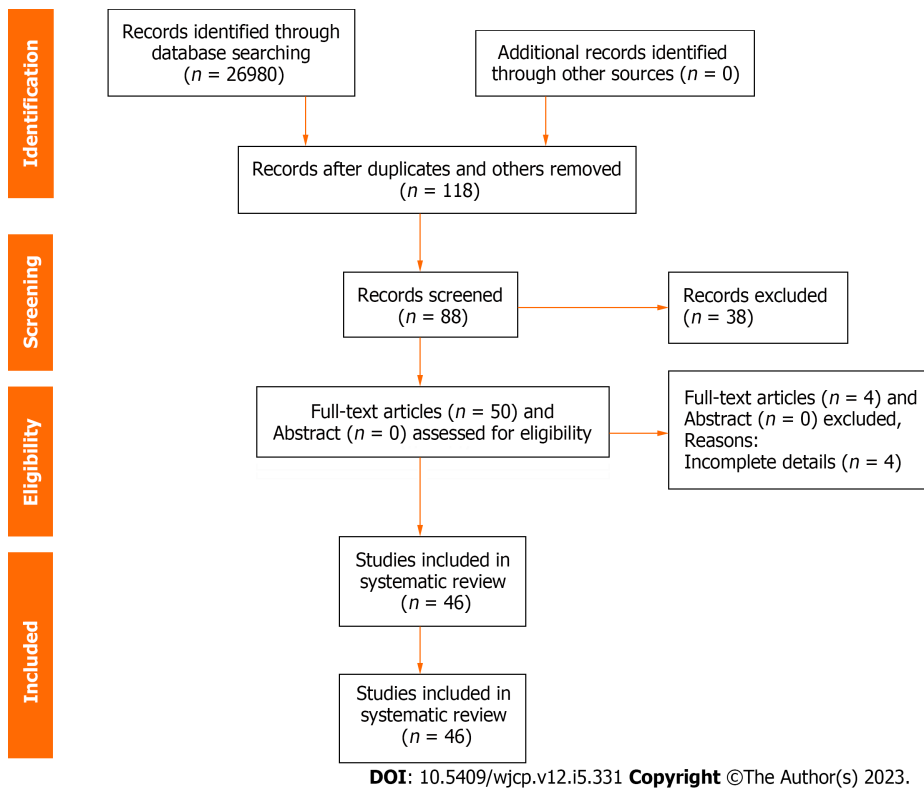


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for manuscripts screening and selection for the systematic review of the management of migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion.

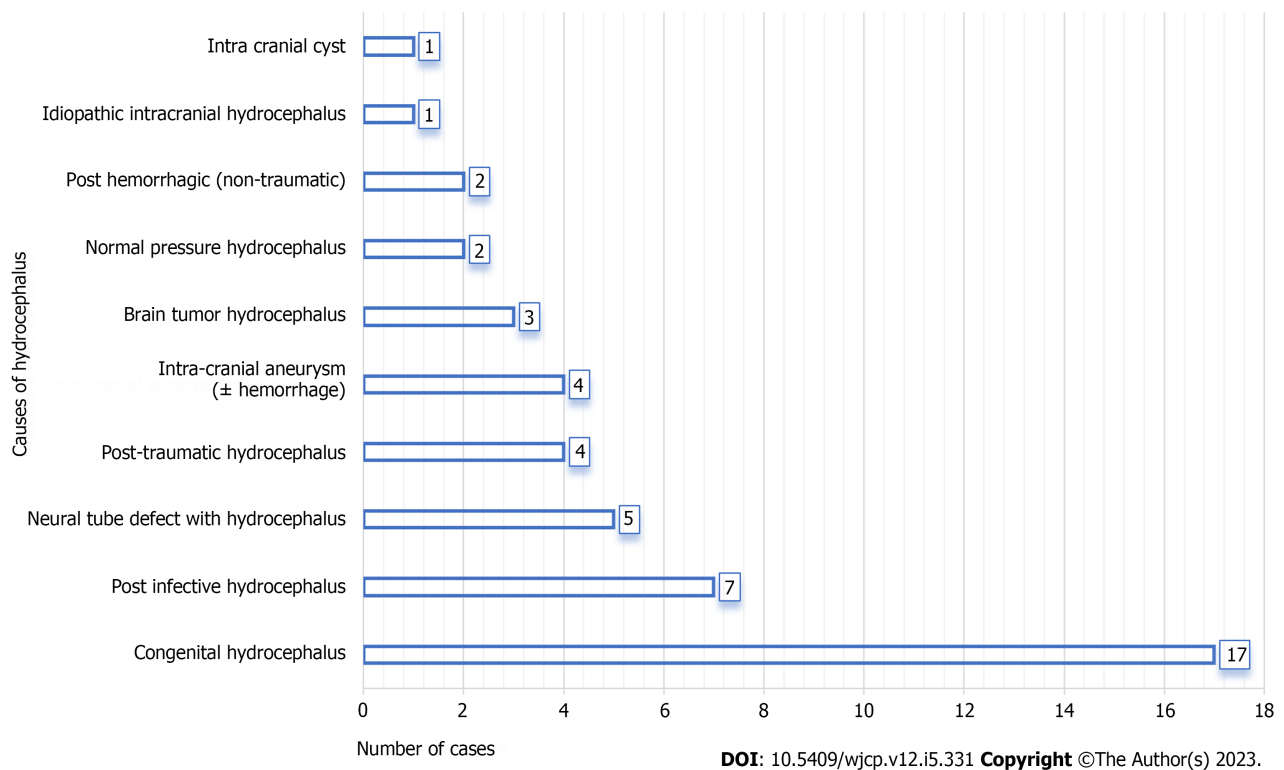


Figure 2 Indication (causes of hydrocephalus) for primary ventriculoperitoneal shunt insertion for entire cases ($n = 46$).

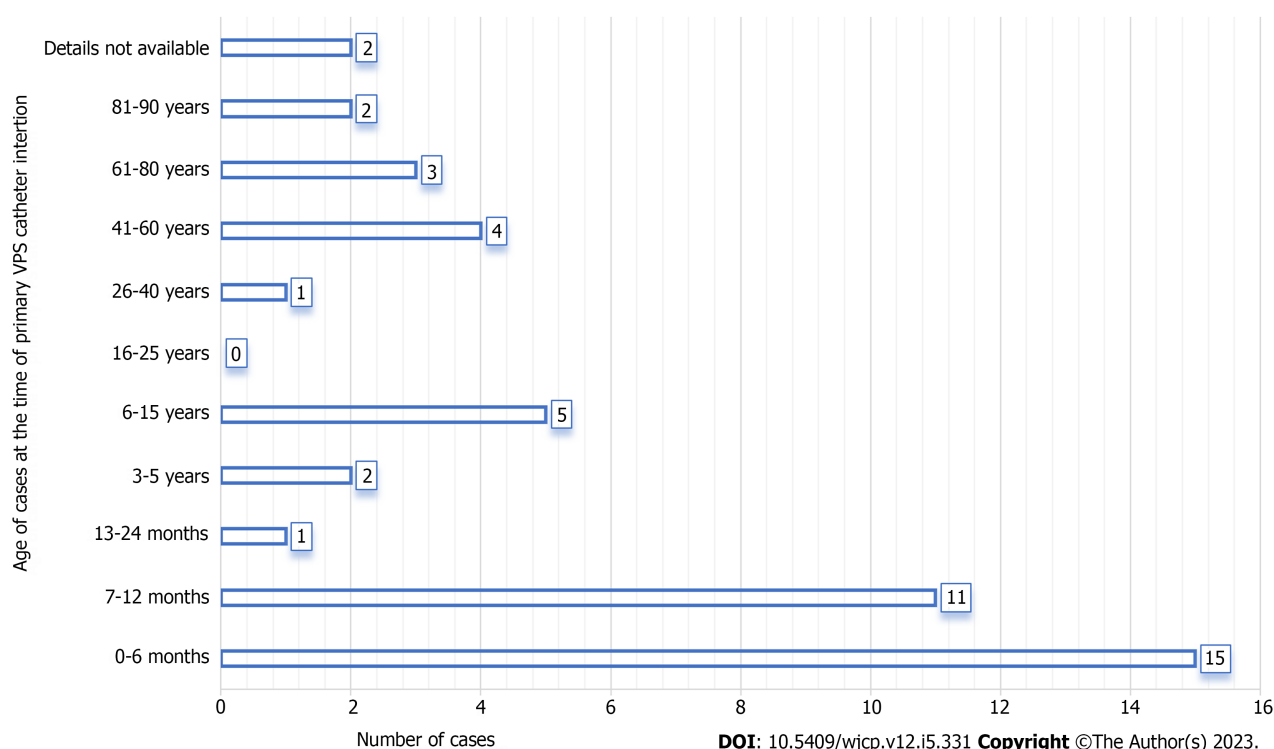


Figure 3 Age distribution (entire cases) at the time of primary ventriculoperitoneal shunt insertion ($n = 46$).

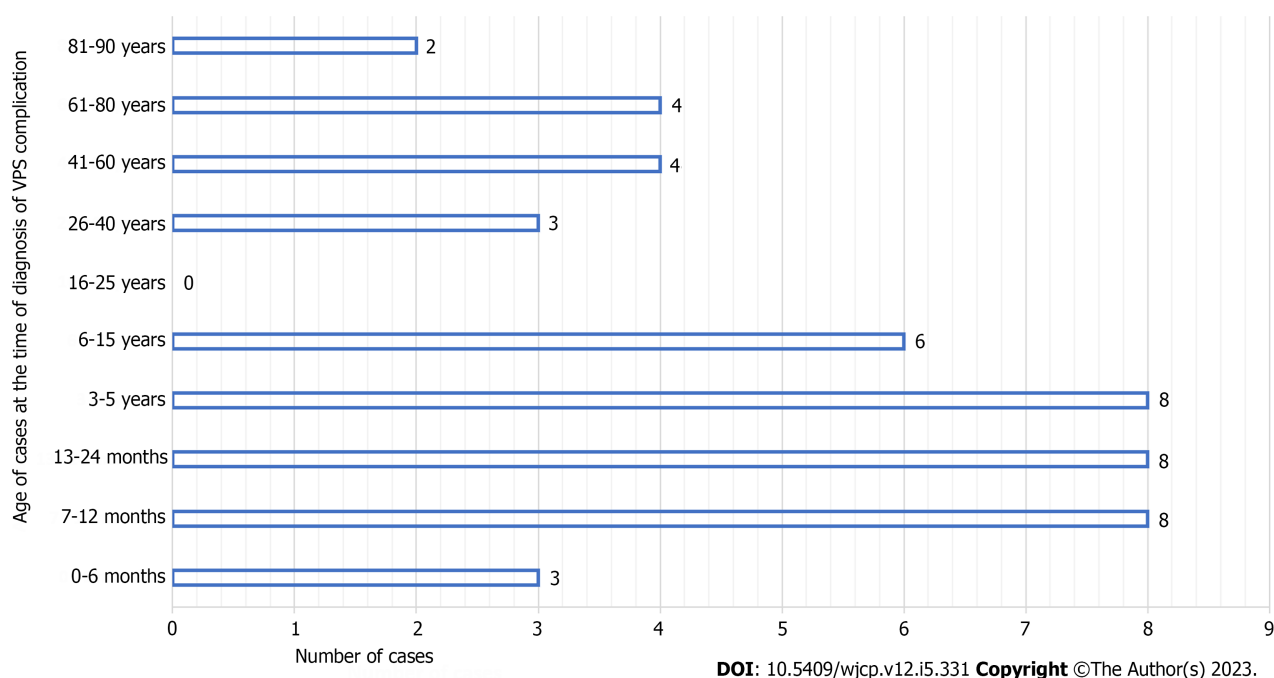


Figure 4 Age distribution (entire cases) at the time of diagnosis of migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion ($n = 46$).

In a 5-mo-old girl, an iatrogenic gastric perforation occurred during the initial/primary VPS insertion, but it was unnoticed. On the first postoperative day, the presence of a distal VPS catheter within the lumen of the stomach was detected, and it was treated successfully[54]. An 87-year-old man underwent investigation for upper GI bleeding/coffee-ground vomiting and the intra-gastric presence of his distal VPS catheter was detected during the upper GI endoscopy [57]. A 65-year-old woman was under investigation for iron deficiency anemia and the intra-gastric presence of her distal VPS catheter was detected during the upper GI endoscopic evaluation[60].

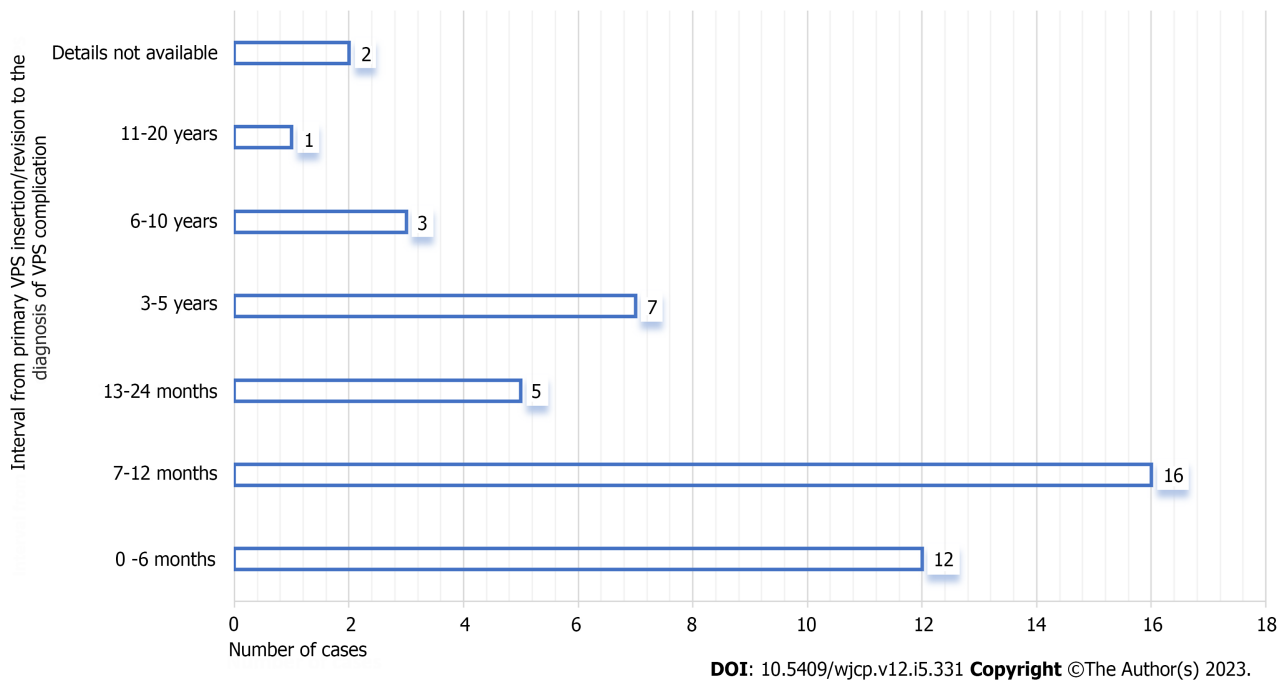


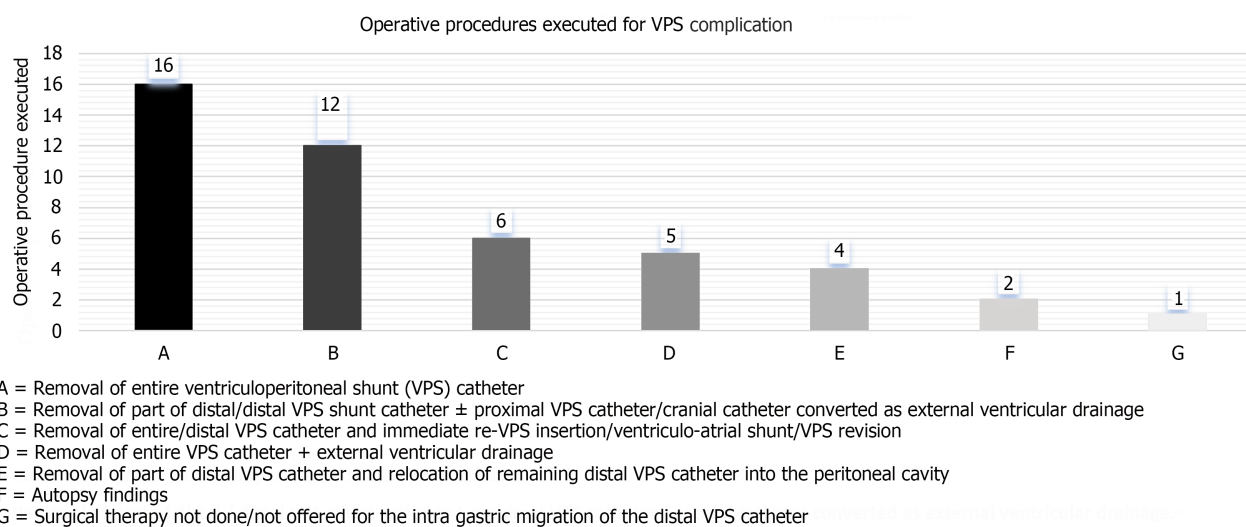
Figure 5 Interval (entire cases) from primary ventriculoperitoneal shunt catheter insertion/revision to the diagnosis of migration of the distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion ($n = 46$).



DOI: 10.5409/wjcp.v12.i5.331 Copyright ©The Author(s) 2023.

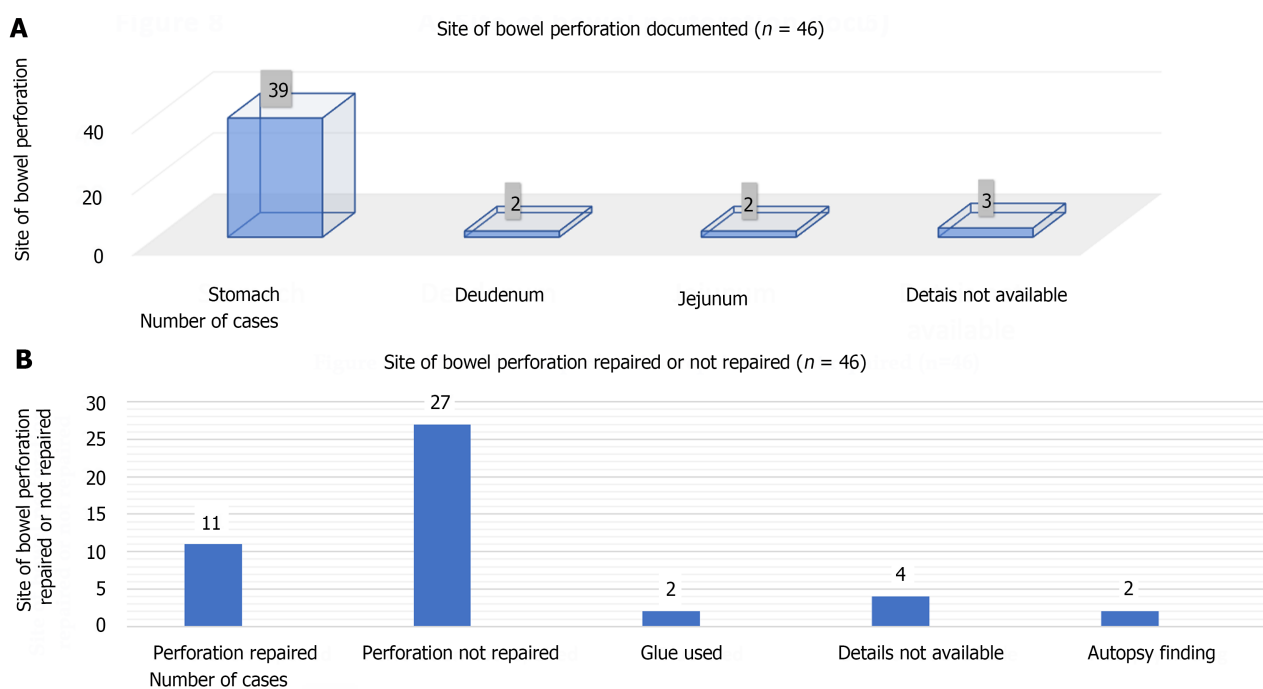
Figure 6 Clinical photograph of a 2 years-old-girl presented with trans-oral extrusion of the distal ventriculoperitoneal shunt catheter. This child was operated upon/managed by the author and published[37].

VPS catheter tract infection was not a frequent clinical finding. During the clinical examination, $n = 4$ (two from each Group) cases had features suggestive of shunt tract infection. Clinical features of peritonitis were not documented in any of the cases reviewed. The occurrence of peritonitis after the bowel/colon perforation by a distal VPS catheter is not a rule, and it was not reported in most cases. In a systematic review of trans-anal extrusion of the distal VPS catheter, peritonitis was documented only in 3.8% of the cases[11]. Possibly for similar reasons like colon perforation clinically



DOI: 10.5409/wjcp.v12.i5.331 Copyright ©The Author(s) 2023.

Figure 7 Operative procedures executed for the migration of distal ventriculoperitoneal shunt catheter into the stomach with or without trans-oral extrusion ($n = 46$).



DOI: 10.5409/wjcp.v12.i5.331 Copyright ©The Author(s) 2023.

Figure 8 The site of bowel perforation caused by the distal ventriculoperitoneal shunt catheter. A: Site of bowel perforation documented in the entire cases ($n = 46$); B: Site of bowel perforation repaired or not repaired ($n = 46$).

presented with per-rectal extrusion of VPS catheter, there was no peritonitis even though there was perforation and migration of distal VPS into the stomach in a present review. Clinical signs of meningitis were evident in $n = 4$ of Group B and none of the Group A cases. Cerebrospinal fluid (CSF) infection was documented in $n = 11$ cases. CSF infection was more frequently documented in Group B cases, as half of them had CSF infection. CSF infection was less frequent in Group A cases, as only $n = 4$ had CSF infection at the time of diagnosis of the VPS complication mentioned above.

The clinical diagnosis of peroral extrusion of the distal part of a VPS catheter was evident for the entire Group A cases. Various investigations were required for the diagnosis of Group B cases. Varieties of investigations were needed and carried out to confirm or exclude the continuity of the VPS catheter, the presence or absence of gas under the diaphragm, peritoneal fluid collections, and evaluation of the ventricular system. A skiagram of the head, abdomen, and chest was one of the commonly advised investigations. Cranial computed tomography (CT) scan was ordered in $n = 15$ cases ($n = 10$ for Group A and $n = 5$ for Group B) for the confirmation of the position of the ventricular catheter within the ventricle and the understanding of the hydrocephalus/ventricles[23,24,28,32,37,38,40,42,43,46,51,58,59,61,62]. CT scan of the abdomen was ordered for $n = 9$ cases[26,46,55,56,58,59,60-62]. It was only ordered for $n = 2$ of the Group A cases[26,46].

CT scan of the abdomen was ordered for $n = 7$ of the Group B cases for the confirmation of the intra-gastric position of the distal VPS catheter[55,56,58,59,60-62]. Shuntogram ($n = 3$) and dye studies ($n = 3$) were performed/done during the investigations[33,34,50,51,53]. Upper gastrointestinal endoscopic evaluation was carried out in $n = 12$ cases[19,32,34,38,55-62]. Eight of the Group B cases were evaluated by the upper GI endoscopy, which was helpful in the confirmation of the intra-gastric location of the distal VPS catheter[55-62].

Much progress has taken place not only in the field of better understanding of the etiopathogenesis of the hydrocephalus, but also in the field of physiology of CSF circulation, development of shunt devices/shunt systems, use of newer technology, perioperative and postoperative care, and management of the shunt related complications[67-69]. VPS catheter implantation is among the most frequently performed surgical procedures in the management of hydrocephalus, caused by various etiology, and performed across the globe for all ages. Many VPS-related complications also require shunt revisions[70-74]. The insertion of the peritoneal/distal VPS catheter within the peritoneal cavity for primary VPS insertion or shunt revision surgery can be done *via* mini-laparotomy, using a trocar or laparoscopic technique with the advantages and disadvantages of each of the surgical techniques[75-77]. A recent international survey carried out for the preference of the distal VPS catheter insertion within the peritoneal cavity found that most of the responded neurosurgeons preferred doing so *via*/through a mini-laparotomy, and it was frequently preferred by the surgeons over the laparoscopic methods[78].

Management of the intra-gastric migration of the distal VPS catheter with or without trans-oral extrusion is three-fold: (1) The removal of intra-gastric migrated distal VPS catheter; (2) treatment of the gastric perforation caused by the distal VPS catheter; and (3) shunt revision, if required. It differs from case to case, depending upon the presence or absence of shunt or shunt tract infection, CSF infection/meningitis, peritonitis, and the general condition of the patient. Various surgical procedures were offered for the management of the above-described complication in $n = 43$ cases of both Groups. One-third ($n = 16$) of the entire case was treated by the removal of the entire VPS catheter. One-fourth ($n = 12$) of the entire case was treated by the removal of the part of the peritoneal/distal VPS catheter with or without conversion to EVD. In six cases ($n = 5$ Group A and $n = 1$ Group B), the entire/distal VPS catheter was removed and shunt revision was carried out during the same operative procedure. In five cases ($n = 4$ Group A and $n = 1$ Group B), the entire VPS catheter was removed and an EVD was inserted. Four cases ($n = 2$ Group A and $n = 2$ Group B) were managed by the relocation of the distal/remaining distal VPS catheter within the peritoneal cavity. In two instances/cases, the intra-gastric presence of the distal VPS catheter was detected during the autopsy[49,52]. In one of the cases, the surgical therapy was deferred as he was clinically stable and did not have symptoms related to the intra-gastric migration of the distal VPS catheter[58]. Percutaneous surgical removal of the entire/distal VPS catheter with or without an EVD was the procedure of choice and was preferred in $n = 27$ ($n = 24$ Group A and $n = 3$ Group B) cases. Exploratory laparotomy was carried out for the management of the above-described distal VPS catheter complication in $n = 11$ ($n = 7$ of Group A and $n = 4$ of Group B) cases[18,22,32,39,41,42,43,53,54,59,61]. The laparoscopic technique was applied in $n = 5$ cases and was carried out in $n = 4$ Group B cases[34,55,57,60,62].

The functional status of the VPS catheter was not mentioned/not provided in the literature reviewed for $n = 22$ of Group A and $n = 11$ of Group B cases[17,19-23,26,27,30-32,34-36,41-49,51-54,57-62]. The distal end of the VPS catheter was draining CSF, confirming that the VPS catheter was functioning well in $n = 6$ of Group A and $n = 2$ of Group B cases, respectively[18,24,25,29,37,39,50,55]. The authors also documented that the VPS catheter was not functional, and it was not draining CSF at the distal end in $n = 4$ of Group A and $n = 1$ of Group B cases, respectively[28,33,38,40,56].

Crust formation at the tip of the distal VPS catheter was not detected/documentated in any of the Group A cases managed for the transoral extrusion of the distal VPS catheter[17-48]. Crust formation at the tip of the distal VPS catheter was not detected/documentated during the radiological/endoscopic evaluation and operative procedures executed for the management of intragastric migration of the distal peritoneal catheter/distal VPS catheter $n = 11$ of the Group B cases[50,51,53-57,59-62]. Only in one of the Group B cases, during the autopsy, a white stone-like structure was detected at the tip of the distal VPS catheter, although the other drainage holes/perforations of the distal VPS catheter were patent. The intragastric part of the distal VPS catheter was like a rigid coiled spring catheter[52]. In this case, the stone/crust formation at the tip of the distal VPS catheter that happened either before the intragastric migration or afterward was also not explained/not clear[52].

The literature review documented/revealed the use of the stomach as the site for the insertion of the distal VPS catheter for CSF diversion in the treatment of hydrocephalus[79-82]. In 1965, Alther described a direct insertion of the distal VPS catheter into the stomach through a Witzel-type fistula[79,80]. In 1972, Lamesch reported/published the use of a gastric tube for the insertion of a distal CSF shunt catheter in seven mongrel dogs. He experimented and performed ventriculogastrostomy by means of the creation of the pedunculated gastric pouch and insertion of the distal shunt catheter within the gastric pouch. In the same paper, he also reported the first successful result of a ventriculogastrostomy that was performed by him on a 3-year-old boy. The operation was performed by him on April 22, 1970. He further reported that the boy was doing well at the follow-up done 10 mo after the operation[80]. In 1975, Weiss *et al*[81] also reported ventriculogastrostomy as an alternative means for CSF diversion as a preliminary study. They experimented with the technique in eight of the mongrel dogs. They also performed ventriculogastrostomy on a 3-wk-old child for the treatment of hydrocephalus. In 1977, Duff *et al*[82] reported their experience with ventriculo-gastric shunts and the role of gastroscopy in shunt evaluation and revision. They reported their experience of ventriculo-gastric shunts, that was performed on six patients, and their age ranged from three weeks to nine years. Two of their cases developed distal shunt obstruction and were evaluated and successfully treated by means of gastroscopy.

The stomach was the site of perforation by the distal VPS catheter $n = 25$ of the Group A and all ($n = 14$) the Group B cases. The duodenum was perforated by the distal VPS catheter in two of the Group A cases[42,43]. The jejunum was perforated by the distal VPS catheter in two of the Group A cases[22,46]. The site of perforation by the distal VPS catheter was not mentioned/not provided in the manuscripts for three cases. Repair of the bowel perforation caused by the distal

VPS catheter is not always required. A systematic review of $n = 210$ cases of bowel perforation by the distal part of the VPS catheter clinically presented with the extrusion of the same *via* the anal canal revealed that colon/bowel perforation was repaired only in one-fourth of the cases. In the remaining, three-fourths cases, the colon/bowel perforation healed spontaneously, after the removal of the migrated/extruded VPS catheter[11]. In the present systematic review of $n = 46$ cases of gastric perforation by the distal VPS catheter only one-fourth ($n = 11$; $n = 6$ Group A and $n = 5$ Group B) of the cases, the perforation site was surgically repaired. In two cases, the perforation site was sealed by the fibrin glue application. In more than half ($n = 27$) cases, the gastric perforation caused by the distal VPS catheter was not repaired and healed spontaneously.

Shunt revision was also an integral part of the management of the intra-gastric migration of a distal VPS catheter clinically presented with or without peroral extrusion of the distal end of VPS catheter. In the present review of $n = 46$ cases of the trans-gastric migration of the distal VPS catheter, the details for $n = 25$ ($n = 20$ Group A and $n = 5$ Group B) cases are available regarding the shunt revision procedures. Delayed re-VPS insertion/VPS revision or VA shunt placement was preferred over the immediate shunt revision. The advantages of delayed reVPS insertion/VPS revisions or VA shunt insertion were that the optimal treatment was provided for meningitis/CSF infection, if present, and it was also possible to evaluate the cases for the requirement of shunt revision. Delayed re-VPS insertion/VPS revision or conversion to a VA shunt was carried out in $n = 19$ ($n = 15$ Group A and $n = 4$ Group B) cases. For the Group A cases; delayed re-VPS insertion in $n = 11$, VPS revision in $n = 2$, and VA shunt placement in $n = 2$, were preferred by the authors. In six ($n = 5$ Group A and $n = 1$ Group B) cases, the shunt revision procedure was executed immediately after removing the entire/distal VPS catheter. The authors performed an immediate re-VPS insertion in $n = 3$, VPS revision in $n = 1$, and an immediate VA shunt insertion in $n = 2$ cases. In the present review, authors also documented that re-VPS insertion/VPS revision or VA shunt insertion was not required in $n = 10$ ($n = 7$ Group A and $n = 3$ Group B) cases, neither during the immediate postoperative nor during the followup period.

The exact cause and mechanism of why and how the distal VPS catheter perforates the stomach, migrated within the stomach, and in some of them extruded trans-orally and not extruded in other cases. Possible factors that were responsible for the above in the present review were; the younger age of cases (infants and children younger than 5 years), redundant intra-peritoneal distal VPS catheter in children, history of VPS revisions, and history of abdominal/GI surgery. One-fourth ($n = 11$) underwent VPS revision in the past, and $n = 8$ of the cases had a history of abdominal/GI surgery in the past and were also the possible factors responsible for the migration of the distal VPS catheter into the stomach. The presence of meningitis ($n = 4$) and CSF infection ($n = 11$) in the present study was most probably the result of ascending infection, and may not be the factor responsible for the VPS complication discussed. The perforation of the gastric wall by the distal VPS catheter may be a result of the continuous friction effect. Once there is a small perforation, it is sealed off without producing clinical peritonitis. The distal VPS catheter is forced within the stomach due to the variation in the size of the stomach, the force of abdominal wall movements, and changes in the intra-abdominal pressure. Once it is within the stomach, why some of them extruded trans-orally is not very clear. Most probably, the presence of redundant extra length of the distal VPS catheter within the peritoneal cavity/stomach (especially in children) is responsible for the peroral extrusion of the distal part of a VPS catheter. The intra-gastric distal VPS catheter acts as a foreign body and is expelled per-orally by forceful regurgitation/vomiting. The combination of forceful upward movement of the stomach, increased intra-peritoneal pressure, and forceful abdominal wall movement during nausea/vomiting are responsible for the trans-oral extrusion/protrusion of the distal VPS catheter. The length of the distal VPS/peritoneal catheter is not much extra or redundant in adults and older people and may be the reason for the migration of the distal VPS catheter within the stomach only, and clinically not presenting as trans-oral extrusion of the same.

In the present review, a total of five cases documented complications that were detected during the immediate and late postoperative period. The complications revealed were brain stem herniation ($n = 1$), CSF infection ($n = 2$), meningitis ($n = 1$), and VPS catheter extrusion from the abdominal wound ($n=1$). During the management of the cases of the intra-gastric migration of the distal VPS catheter, this study revealed a total of four (8.69%) deaths, two from each Group[17,23,49,52]. In a 9.3-year-old girl, a VPS catheter was inserted for post-infective hydrocephalus. She also required a feeding gastrostomy for inadequate oral nutritional intake. Three months after VPS insertion, she presented with trans-oral extrusion of her distal VPS catheter, without the clinical features of peritonitis or meningitis, and her CSF also did not detect any organisms. Her VPS complication was treated with EVD and placement of a VA shunt. One month after the VA shunt insertion, she developed acute brain stem herniation and died of the same[17]. A two-year-old boy was diagnosed with congenital hydrocephalus and associated neural tube defect (NTD). His NTD was repaired and a VPS catheter was also placed at the age of 9 mo. Fifteen months after the VPS insertion at the age of two years, he presented with trans-oral extrusion of his distal VPS catheter, without the clinical features of meningitis and peritonitis. His VPS complication was treated with the removal of part of the peritoneal/distal VPS catheter and conversion of the proximal VPS catheter as an EVD. He had a CSF infection and developed ventriculitis that failed to respond well to the antibiotics, and finally died of the same during the treatment[23]. Two of the Group B cases died due to the intra-gastric migration of the distal VPS catheter and the related complication[49,52]. A 69 years-old female developed meningitis 7 mo after VPS insertion that was done for normal pressure hydrocephalus. She was treated conservatively and finally, she died of pneumonia 27 mo after the VPS insertion[49]. A 68-year-old man was diagnosed with NPH and a VPS catheter was implanted. His CNS condition deteriorated further. He was also detected with CSF infection and was treated with antibiotics and other supportive measures, but died of the same[52]. In the above two cases, the intra-gastric migration of the distal VPS catheter was detected during the autopsy[49,52].

Limitations

This systematic review revealed/obtained a limited number of published literature/manuscripts, and it is one of the limitations of this review. Four manuscripts that included five cases were excluded from review for various reasons[63-

66]. There was no uniformity in the treatment of the cases, treated by surgical techniques ranging from simple percutaneous removal of the entire/distal VPS catheter to exploratory laparotomy. For $n = 4$ (8.69%) cases, the entry site in the bowel by the distal VPS catheter is also not known/not available. The exact cause and the mechanism for the perforation of the stomach and intra-gastric migration of the distal VPS catheter is also not known.

CONCLUSION

Intra-gastric migration of the peritoneal end of a VPS catheter is one of the rare complications of VPS catheter implantation done for the treatment of hydrocephalus across all age groups. Intra-gastric migration with trans-oral extrusion of the distal VPS catheter was twice more commonly reported than the intra-gastric migration of the distal VPS catheter without trans-oral extrusion. It was more frequently reported in children, although also reported in adults and older people. Intra-gastric migration of the distal VPS catheter without transoral extrusion was more frequent in adults and older age groups. Formal exploration of the abdomen for the management of the VPS complication described above was neither done nor required in 70% of cases. In two-thirds of cases, the repair of the stomach/bowel perforation caused by the distal VPS catheter was not done and it healed after the removal of the distal shunt catheter from the stomach/bowel. A very high degree of clinical suspicion is required for the diagnosis of the intra-gastric migration of the distal VPS catheter, clinically presenting without trans-oral extrusion.

ARTICLE HIGHLIGHTS

Research background

Intra-gastric migration of the distal ventriculoperitoneal shunt (VPS) catheter clinically presenting with or without trans-oral extrusion is one of the rare complications of VPS catheter insertion.

Research motivation

To know more about the intra-gastric migration of the distal VPS catheter.

Research objectives

This systematic review of the literature aims to highlight the demographics, clinical characteristics, and outcome of the surgical procedures performed for the intra-gastric migration of the distal VPS catheter, clinically presented with or without trans-oral extrusion of the distal end of peritoneal/VPS catheter.

Research methods

An online search was carried out for extraction/retrieval of published literature about the intra-gastric migration of the distal VPS catheter. PubMed, PubMed Central, ResearchGate, Google Scholar, and Google Images databases were searched using various terminology relating to the VPS complications. Manuscripts were retrieved from 1980 to December 2022. The selection of literature for the present review was done by assessing the titles, abstracts, and full texts of the manuscripts.

Research results

A total of $n = 46$ cases of intra-gastric migration of the distal VPS catheter clinically presented with or without peroral extrusion were recruited for the systematic review and were retrieved from the $n = 46$ manuscripts. Approximately sixty percent of them were children ≤ 5 years of age at the time of diagnosis of the complication mentioned above. In seventy-two percent of cases, this complication was detected within 24 mo after the VPS insertion/last shunt revision. Removal of the entire VPS catheter/removal of part of the distal/distal VPS catheter with or without external ventricular drainage was preferred by the authors. Percutaneous surgical removal of the entire or the distal VPS catheter with or without external ventricular drainage was a procedure of choice and was opted for $n = 27$ cases. For the management of VPS complications mentioned above, formal laparotomy was carried out only in $n = 11$ cases. In eighty-five percent of cases, the site of bowel perforation was the stomach. The site of bowel perforation was repaired only in $n = 11$ cases.

Research conclusions

Intra-gastric migration of the peritoneal end of a VPS catheter is one of the rare complications of VPS catheter implantation done for the treatment of hydrocephalus across all age groups. It was more frequently reported in children, although also reported in adults and older people. Formal exploration of the abdomen for the management of the VPS complication described above was neither done nor required in 70% of cases. In two-thirds of cases, the repair of the stomach/bowel perforation caused by the distal VPS catheter was not done and it healed after the removal of the distal shunt catheter from the stomach/bowel.

Research perspectives

This systematic review revealed that the intra-gastric migration of the peritoneal end of a VPS catheter was more commonly reported in children than adults and older people. Intra-gastric migration with peroral extrusion of the distal

VPS catheter was twice as commonly reported than the intra-gastric migration of the distal VPS catheter clinically presented without peroral extrusion. A high degree of clinical suspicion is required for the diagnosis of cases of an intra-gastric migration of the distal VPS catheter clinically presenting without trans-oral extrusion. The exact mechanism for the intra-gastric migration of the peritoneal end of the VPS catheter is not known and requires some specific experimental studies.

FOOTNOTES

Author contributions: All authors have read and approved the final, revised manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009/2021 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: India

ORCID number: Rajendra Kumar Ghritlaharey 0000-0003-0407-1810.

S-Editor: Liu JH

L-Editor: A

P-Editor: Cai YX

REFERENCES

- Hochstetler A, Raskin J, Blazer-Yost BL. Hydrocephalus: historical analysis and considerations for treatment. *Eur J Med Res* 2022; **27**: 168 [PMID: 36050779 DOI: 10.1186/s40001-022-00798-6]
- Srinivas D, Tyagi G, Singh GJ. Shunt Implants - Past, Present and Future. *Neurol India* 2021; **69**: S463-S470 [PMID: 35103003 DOI: 10.4103/0028-3886.332263]
- Pande A, Lamba N, Mammi M, Gebrehiwet P, Trenary A, Doucette J, Papatheodorou S, Bunevicius A, Smith TR, Mekary RA. Endoscopic third ventriculostomy versus ventriculoperitoneal shunt in pediatric and adult population: a systematic review and meta-analysis. *Neurosurg Rev* 2021; **44**: 1227-1241 [PMID: 32476100 DOI: 10.1007/s10143-020-01320-4]
- Chalasani R, Goonathilake MR, Waqar S, George S, Jean-Baptiste W, Yusuf Ali A, Inyang B, Koshy FS, George K, Poudel P, Mohammed L. The Outcome of Surgical Intervention (Ventriculoperitoneal Shunt and Endoscopic Third Ventriculostomy) in Patients With Hydrocephalus Secondary to Tuberculous Meningitis: A Systematic Review. *Cureus* 2022; **14**: e25317 [PMID: 35637922 DOI: 10.7759/cureus.25317]
- Reddy GK, Bollam P, Caldito G. Long-term outcomes of ventriculoperitoneal shunt surgery in patients with hydrocephalus. *World Neurosurg* 2014; **81**: 404-410 [PMID: 23380280 DOI: 10.1016/j.wneu.2013.01.096]
- Merkler AE, Ch'ang J, Parker WE, Murthy SB, Kamel H. The Rate of Complications after Ventriculoperitoneal Shunt Surgery. *World Neurosurg* 2017; **98**: 654-658 [PMID: 27826086 DOI: 10.1016/j.wneu.2016.10.136]
- Desai VR, Sadrameli SS, Jenson AV, Asante SK, Daniels B, Trask TW, Britz G. Ventriculoperitoneal shunt complications in an adult population: A comparison of various shunt designs to prevent overdrainage. *Surg Neurol Int* 2020; **11**: 269 [PMID: 33033631 DOI: 10.25259/SNI_38_2020]
- Paff M, Alexandru-Abrams D, Muhonen M, Loudon W. Ventriculoperitoneal shunt complications: a review. *Interdisciplinary Neurosurgery* 2018; **13**: 66-70 [DOI: 10.1016/j.inat.2018.04.004]
- Harischandra LS, Sharma A, Chatterjee S. Shunt migration in ventriculoperitoneal shunting: A comprehensive review of literature. *Neurol India* 2019; **67**: 85-99 [PMID: 30860103 DOI: 10.4103/0028-3886.253968]
- Morosanu CO, Nicolae L. Gastrointestinal complications following ventriculoperitoneal shunt insertion for pediatric hydrocephalus. *J Pediatr Neurosci* [Epub ahead of print] [cited 2023 June 10] [DOI: 10.4103/jpn.jpn_190_21]
- Ghritlaharey RK. Systematic literature review of the management of transanal extrusion of distal ventriculoperitoneal shunt catheter: 1966–2020. *Med J DY Patil Vidyapeeth* 2022; **15**: 629-659 [DOI: 10.4103/mjdrdypu.mjdrdypu_149_21]
- Ghritlaharey RK. Systematic review of migration of distal ventriculoperitoneal shunt catheter into the urinary bladder with or without per-urethral extrusion. *Med J DY Patil Vidyapeeth* 2022; **15**: 840-853 [DOI: 10.4103/mjdrdypu.mjdrdypu_547_20]
- Ghritlaharey RK. Management of trans-vaginal extrusion of the distal ventriculoperitoneal shunt catheter: a systematic literature review from 1973 to 2021. *Int J Res Med Sci* 2021; **9**: 3416-3423 [DOI: 10.18203/2320-6012.ijrms20214096]
- Ghritlaharey RK. Review of the Management of Peroral Extrusion of Ventriculoperitoneal Shunt Catheter. *J Clin Diagn Res* 2016; **10**: PE01-PE06 [PMID: 28050444 DOI: 10.7860/JCDR/2016/23372.8920]
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**: 1006-1012 [PMID: 19631508 DOI: 10.1016/j.jclinepi.2009.06.005]
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD. The PRISMA 2020 statement: an updated guideline for reporting

- systematic reviews. *Syst Rev* 2021; **10**: 89 [PMID: 33781348 DOI: 10.1186/s13643-021-01626-4]
- 17 **Griffith JA**, DeFeo D. Peroral extrusion of a ventriculoperitoneal shunt catheter. *Neurosurgery* 1987; **21**: 259-261 [PMID: 3309717 DOI: 10.1227/00006123-198708000-00028]
 - 18 **Danismend N**, Kuday C. Unusual complication of ventriculoperitoneal shunt. *Neurosurgery* 1988; **22**: 798 [PMID: 3374797 DOI: 10.1097/00006123-198804000-00035]
 - 19 **Park CK**, Wang KC, Seo JK, Cho BK. Transoral protrusion of a peritoneal catheter: a case report and literature review. *Childs Nerv Syst* 2000; **16**: 184-189 [PMID: 10804056 DOI: 10.1007/s003810050491]
 - 20 **Jiménez Moya A**, Penela Vélez De Guevara T, Gracia Remiro R, Romero Escós D, Santana Rodríguez C, Reig Del Moral C, Martín MH. Extrusion of a ventriculoperitoneal shunt catheter through the mouth. *An Esp Pediatr* 2001; **54**: 609-610 (Spanish) [DOI: 10.1016/s1695-4033(01)77609-6]
 - 21 **Kothari PR**, Shankar G, Kulkarni B. Extruded ventriculo-peritoneal shunt: An unusual complication. *J Indian Assoc Pediatr Surg* 2006; **11**: 255-256 [DOI: 10.4103/0971-9261.29616]
 - 22 **Odeh TO**. Jejunal perforation and peroral extrusion of a peritoneal shunt catheter. *Br J Neurosurg* 2007; **21**: 235-236 [PMID: 17453796 DOI: 10.1080/02688690701264346]
 - 23 **Berhouma M**, Messerer M, Houissa S, Khaldi M. Transoral protrusion of a peritoneal catheter: a rare complication of ventriculoperitoneal shunt. *Pediatr Neurosurg* 2008; **44**: 169-171 [PMID: 18230935 DOI: 10.1159/000113123]
 - 24 **Murali R**, Ravikumar V. Transoral migration of peritoneal end of ventriculoperitoneal shunt: A case report of a rare complication and review of literature. *J Pediatr Neurosci* 2008; **3**: 166-168 [DOI: 10.4103/1817-1745.43651]
 - 25 **Sridhar K**, Karmarkar V. Peroral extrusion of ventriculoperitoneal shunt: case report and review of literature. *Neurol India* 2009; **57**: 334-336 [PMID: 19587479 DOI: 10.4103/0028-3886.53283]
 - 26 **Sinnadurai M**, Winder MJ. Silicone spaghetti. *J Clin Neurosci* 2009; **16**: 1348-1350 [PMID: 19577477 DOI: 10.1016/j.jocn.2008.12.029]
 - 27 **Low SW**, Sein L, Yeo TT, Chou N. Migration of the abdominal catheter of a ventriculoperitoneal shunt into the mouth: a rare presentation. *Malays J Med Sci* 2010; **17**: 64-67 [PMID: 22135552]
 - 28 **Dua R**, Jain R. Peroral extrusion of ventriculoperitoneal shunt: a case report and review of the literature. *Cent Eur Neurosurg* 2011; **72**: 107-108 [PMID: 20865650 DOI: 10.1055/s-0030-1262828]
 - 29 **Agarwal M**, Adhana R, Namdev H, Yadav YR, Agrawal T. Transoral extrusion of the ventriculo-peritoneal shunt: A case report and review of literature. *J Pediatr Neurosci* 2011; **6**: 149-151 [PMID: 22408670 DOI: 10.4103/1817-1745.92847]
 - 30 **Gupta M**, Digra NC, Sharma N, Goyal S, Agrawal A. Peroral extrusion of the peritoneal catheter in an infant. *N Am J Med Sci* 2012; **4**: 290-292 [PMID: 22754883 DOI: 10.4103/1947-2714.97214]
 - 31 **Kundal VK**, Gajdhar M, Sharma C, Agrawal D, Kundal R. Wandering distal end of ventriculo-peritoneal shunt: Our experience with five cases and review of literature. *J Nepal Paediatr Soc* 2012; **32**: 266-269 [DOI: 10.3126/jnps.v32i3.6935]
 - 32 **Yilmaz MB**, Egemen E, Tonge M, Kaymaz M. Transoral protrusion of a peritoneal catheter due to gastric perforation 10 years after a ventriculoperitoneal shunting: case report and review of the literature. *Turk Neurosurg* 2013; **23**: 285-288 [PMID: 23546921 DOI: 10.5137/1019-5149.JTN.4904-11.1]
 - 33 **Gupta R**, Mala TA, Gupta A, Paul R, Malla SA, Gupta AK. Transoral migration of peritoneal end of ventriculoperitoneal shunt with perforation of gastro-esophageal junction: a case report of a rare complication. *Bangladesh J Med Sci* 2014; **13**: 492-495 [DOI: 10.3329/bjms.v13i4.20654]
 - 34 **Mandhan P**, Wong M, Samarakkody U. Laparoendoscopic removal of peroral extrusion of a ventriculoperitoneal shunt. *Asian J Endosc Surg* 2015; **8**: 95-97 [PMID: 25598065 DOI: 10.1111/ases.12157]
 - 35 **Thiong'o GM**, Luzzio C, Albright AL. Ventriculoperitoneal shunt perforations of the gastrointestinal tract. *J Neurosurg Pediatr* 2015; **16**: 36-41 [PMID: 25837887 DOI: 10.3171/2014.11.PEDS14347]
 - 36 **Sohal AP**, Whittle V, Nicholson C, Kisler J. Where did the oral tube originate from? *J Paediatr Child Health* 2015; **51**: 738, 740 [PMID: 26135149 DOI: 10.1111/jpc.12576]
 - 37 **Ghritlaharey RK**. Extrusion of ventriculoperitoneal shunt catheter through mouth in a two-year-old girl: A case report. *Int J Clin Pediatr Surg* 2015; **1**: 1-4 [DOI: 10.11648/j.ijcps.20150101.11]
 - 38 **Shah AS**, Singh D, Loomba P, Singh H, Mittal A, Srivastava S. Peroral extrusion of ventriculoperitoneal shunt: An unusual complication and review of literature. *Indian J Neurosurg* 2016; **5**: 196-201 [DOI: 10.1055/s-0036-1584586]
 - 39 **Sharma DD**, Meena A, Shukla AK, Sharma P, Raipuria G. Trans-oral migration of VP shunt tube through gastric perforation with review of literature. *Int J Med Res Prof* 2017; **3**: 303-305 [DOI: 10.21276/ijmrp.2017.3.3.062]
 - 40 **Al Fauzi A**, Suryaningtyas W, Wahyuhadi J, Parenrengi MA, Turchan A, Wijaya MC, Jonatan M, Mahyudani, Setyono H. Upward migration and peroral extrusion of a peritoneal shunt catheter: Case report and review of the literature. *Surg Neurol Int* 2017; **8**: 178 [PMID: 28868190 DOI: 10.4103/sni.sni_138_17]
 - 41 **Reyes MJ**, Díaz KA, Prada CA. Migración del catéter de derivación ventriculoperitoneal con protrusión por cavidad oral: Reporte de un caso y revisión de la literatura. *Neurociencias Journal* 2017; **24**: 153-160
 - 42 **Badri M**, Gader G, Belkahla G, Kallel J, Zammel I. Transoral migration of the inferior end of a ventriculoperitoneal shunt: A case report with literature review. *Neurochirurgie* 2018; **64**: 203-205 [PMID: 29709372 DOI: 10.1016/j.neuchi.2018.02.005]
 - 43 **Romuald K**, Dominique NO, Guy V. Transoral migration of the inferior end of a peritoneal catheter: A rare complication of ventriculoperitoneal shunt. *Int J Sci Res* 2018; **7**: 1629-1632
 - 44 **Ezzat AAM**, Soliman MAR, Hasanain AA, Thabit MA, Elshitany H, Kandel H, Abdel-Bari SH, Ghoul AMF, Abdullah A, Alsawy MFM, Ghaleb AA, Al Menabbawy A, Marei AA, El Razik BA, Schroeder HWS, Marx S, Zohdi A, El Refaee E. Migration of the Distal Catheter of Ventriculoperitoneal Shunts in Pediatric Age Group: Case Series. *World Neurosurg* 2018; **119**: e131-e137 [PMID: 30031953 DOI: 10.1016/j.wneu.2018.07.073]
 - 45 **Bemora JS**, Yu Song MT, Rakotondraibe WF, Ratovondrainy W, Rabarijaona M, Andriamamonjy C. A rare complication of ventriculoperitoneal shunt: gastric perforation. *Journal of Advance Research in Medical & Health Science* 2019; **5**: 744 [DOI: 10.53555/nmhs.v5i6.744]
 - 46 **Feeney V**, Ansar N, Donaldson-Hugh B, Alalade AF. Transoral Protrusion of a Ventriculoperitoneal Catheter Caused by Jejunal Perforation in an Adult: Rare Case Report and Review of the Literature. *World Neurosurg* 2020; **137**: 200-205 [PMID: 32058122 DOI: 10.1016/j.wneu.2020.02.009]
 - 47 **Calgaro S**, Colangelo AC, Otchirov S, Pizzol D, Antunes M. Failed ventriculoperitoneal shunt as treatment of infantile hydrocephalus. *World J*

- Pediatr Surg* 2020; **3**: e000123 [PMID: 36474922 DOI: 10.1136/wjps-2020-000123]
- 48 **Najib C**, Abdellaoui H, Othmane A, Abdelhalim M, Khalid K, Youssef B. Transoral protrusion of a ventriculo-peritoneal shunt catheter in an 8-month-Old. *J Pediatr Surg Case Rep* 2022; **76**: 102112 [DOI: 10.1016/j.epsc.2021.102112]
- 49 **Nishijima M**, Ohyama H, Higuchi H. [Gastric perforation in ventriculo-peritoneal shunt--a case report (author's transl)]. *No Shinkei Geka* 1980; **8**: 679-683 [PMID: 7413011]
- 50 **Oi SZ**, Shose Y, Asano N, Oshio T, Matsumoto S. Intra gastric migration of a ventriculoperitoneal shunt catheter. *Neurosurgery* 1987; **21**: 255-257 [PMID: 3309715 DOI: 10.1227/00006123-198708000-00026]
- 51 **Oshio T**, Matsumura C, Kirino A, Go M, Bando Y, Manabe Y, Nakagawa Y. Recurrent perforations of viscus due to ventriculoperitoneal shunt in a hydrocephalic child. *J Pediatr Surg* 1991; **26**: 1404-1405 [PMID: 1765921 DOI: 10.1016/0022-3468(91)91047-3]
- 52 **Ho KJ**. Recurrent meningitis associated with intra gastric migration of a ventriculoperitoneal shunt catheter in a patient with normal-pressure hydrocephalus. *South Med J* 1992; **85**: 1145-1148 [PMID: 1439958 DOI: 10.1097/00007611-199211000-00021]
- 53 **Alonso-Vanegas M**, Alvarez JL, Delgado L, Mendizabal R, Jiménez JL, Sanchez-Cabrera JM. Gastric perforation due to ventriculo-peritoneal shunt. *Pediatr Neurosurg* 1994; **21**: 192-194 [PMID: 7803310 DOI: 10.1159/000120834]
- 54 **Christoph CL**, Poole CA, Kochan PS. Operative gastric perforation: a rare complication of ventriculoperitoneal shunt. *Pediatr Radiol* 1995; **25** Suppl 1: S173-S174 [PMID: 8577518]
- 55 **Hart AL**, Hollanders D. 98 unusual cases and technical notes. *Endoscopy* 2001; **33**: 98 [PMID: 11205000 DOI: 10.1055/s-2001-17405]
- 56 **Masuoka J**, Mineta T, Kohata T, Tabuchi K. Peritoneal shunt tube migration into the stomach--case report--. *Neurol Med Chir (Tokyo)* 2005; **45**: 543-546 [PMID: 16247243 DOI: 10.2176/nmc.45.543]
- 57 **Cheng JY**, Lo WC, Liang HH, Kun IH. Migration of ventriculoperitoneal shunt into the stomach, presenting with gastric bleeding. *Acta Neurochir (Wien)* 2007; **149**: 1269-1270 [PMID: 17999030 DOI: 10.1007/s00701-007-1413-9]
- 58 **Cohen-Addad DI**, Hewitt K, Bell D. A ventriculoperitoneal shunt incidentally found in the stomach. *Radiol Case Rep* 2018; **13**: 1159-1162 [PMID: 30233750 DOI: 10.1016/j.radcr.2018.08.004]
- 59 **Sidhu JS**, Mandal A, Kafle P, Chaulagai B, Gayam V. Ventriculoperitoneal shunt migration inside the gastric lumen: A rare case report. *Cureus* 2019; **11**: e4453. [DOI: 10.7759/cureus.4453]
- 60 **Yala KR**, Shilpa L, Nazneen A. Peritoneal shunt catheter migration into the stomach: Case report and review of literature. *Adv Res Gastroenterol Hepatol* 2019; **12**: 75-76 (555844) [DOI: 10.19080/argh.2019.12.555844]
- 61 **Chen YH**, Hsieh CT, Sun JM, Chang SI. Gastric perforation by a ventriculoperitoneal shunt in an adult. *Neurosciences (Riyadh)* 2020; **25**: 144-147 [PMID: 32351252 DOI: 10.17712/nsj.2020.2.20190118]
- 62 **Scarascia A**, Atallah E, Pineda MA, Rosenwasser R, Judy K. Gastric perforation from a migrating ventriculoperitoneal shunt: A case report and review of literature. *Radiol Case Rep* 2022; **17**: 4899-4902 [PMID: 36281285 DOI: 10.1016/j.radcr.2022.09.064]
- 63 **Fermin S**, Fernández-Guerra RA, Sureda PJ. Extrusion of peritoneal catheter through the mouth. *Childs Nerv Syst* 1996; **12**: 553-555 [PMID: 8906372 DOI: 10.1007/BF00261610]
- 64 **Tamlikha A**, Shukri F, Zahari Z. Transoral migration of ventriculoperitoneal shunt: A rare presentation. *GMJ* 2021; **32**: 131-134 [DOI: 10.12996/gmj.2021.28]
- 65 **Faheem M**, Jaiswal M, Prajapati HP, Kumar R, Saba Nu, Ojha BK. Unusual complications of ventriculoperitoneal shunt surgery: Tertiary care experience. *J Pediatr Neurosci* [Epub Ahead of print] [Cited 2023 June 11] [DOI: 10.4103/jpn.JPN_150_20]
- 66 **Pant N**, Singh S, Singh G, Kumar A, Rai RK, Rawat J, Waklu A. The wandering ventriculoperitoneal shunt and the scope of its salvage. *Childs Nerv Syst* 2021; **37**: 2613-2618 [PMID: 33963923 DOI: 10.1007/s00381-021-05198-5]
- 67 **Symss NP**, Oi S. Is there an ideal shunt? A panoramic view of 110 years in CSF diversions and shunt systems used for the treatment of hydrocephalus: from historical events to current trends. *Childs Nerv Syst* 2015; **31**: 191-202 [PMID: 25547875 DOI: 10.1007/s00381-014-2608-z]
- 68 **Miyake H**. Shunt Devices for the Treatment of Adult Hydrocephalus: Recent Progress and Characteristics. *Neurol Med Chir (Tokyo)* 2016; **56**: 274-283 [PMID: 27041631 DOI: 10.2176/nmc.ra.2015-0282]
- 69 **Texakalidis P**, Tora MS, Wetzel JS, Chern JJ. Endoscopic third ventriculostomy versus shunt for pediatric hydrocephalus: a systematic literature review and meta-analysis. *Childs Nerv Syst* 2019; **35**: 1283-1293 [PMID: 31129704 DOI: 10.1007/s00381-019-04203-2]
- 70 **Frassanito P**, Tamburrini G, Di Rocco C. Surgical treatment of hydrocephalus based on CSF shunt devices. In: Di Rocco C, Pang D, Rutka J (eds) *Textbook of Pediatric Neurosurgery*. Springer, Cham 2018 [DOI: 10.1007/978-3-319-31512-6_25-1]
- 71 **Sobana M**, Halim D, Aviani JK, Gamayani U, Achmad TH. Neurodevelopmental outcomes after ventriculoperitoneal shunt placement in children with non-infectious hydrocephalus: a meta-analysis. *Childs Nerv Syst* 2021; **37**: 1055-1065 [PMID: 33479825 DOI: 10.1007/s00381-021-05051-9]
- 72 **Hasanain AA**, Abdullah A, Alsawy MFM, Soliman MAR, Ghaleb AA, Elwy R, Ezzat AAM, Al Menabbawy A, Marei AA, Abd El Razik B, El Hamaky MI, Schroeder HWS, Fleck S, El Damaty A, Marx S, Nowak S, Baldauf J, Zohdi A, El Refaee EA. Incidence of and Causes for Ventriculoperitoneal Shunt Failure in Children Younger Than 2 Years: A Systematic Review. *J Neurol Surg A Cent Eur Neurosurg* 2019; **80**: 26-33 [PMID: 30508865 DOI: 10.1055/s-0038-1669464]
- 73 **Rizvi I**, Garg RK, Malhotra HS, Kumar N, Sharma E, Srivastava C, Uniyal R. Ventriculo-peritoneal shunt surgery for tuberculous meningitis: A systematic review. *J Neurol Sci* 2017; **375**: 255-263 [PMID: 28320142 DOI: 10.1016/j.jns.2017.02.008]
- 74 **Muram S**, Isaacs AM, Sader N, Holubkov R, Fong A, Conly J, Hamilton MG. A standardized infection prevention bundle for reduction of CSF shunt infections in adult ventriculoperitoneal shunt surgery performed without antibiotic-impregnated catheters. *J Neurosurg* 2023; **138**: 494-502 [PMID: 35916085 DOI: 10.3171/2022.5.JNS22430]
- 75 **He M**, Ouyang L, Wang S, Zheng M, Liu A. Laparoscopy versus mini-laparotomy peritoneal catheter insertion of ventriculoperitoneal shunts: a systematic review and meta-analysis. *Neurosurg Focus* 2016; **41**: E7 [PMID: 27581319 DOI: 10.3171/2016.5.FOCUS1637]
- 76 **Ding Q**, Wang J, Fan H, Jiang W, Guo H, Ji H, Song T, Xu S, Liu B. Introduction and comparison of three different fixation methods in the suprahepatic space in laparoscopy-assisted ventriculoperitoneal shunt for hydrocephalus. *Sci Rep* 2023; **13**: 6231 [PMID: 37069252 DOI: 10.1038/s41598-023-33566-5]
- 77 **Greuter L**, Ruf L, Guzman R, Soleman J. Open versus laparoscopic ventriculoperitoneal shunt placement in children: a systematic review and meta-analysis. *Childs Nerv Syst* 2023; **39**: 1895-1902 [PMID: 37225936 DOI: 10.1007/s00381-023-05966-5]
- 78 **Ruf L**, Greuter L, Guzman R, Soleman J. Distal shunt placement in pediatric ventriculoperitoneal shunt surgery: an international survey of practice. *Childs Nerv Syst* 2023; **39**: 1555-1563 [PMID: 36780037 DOI: 10.1007/s00381-023-05855-x]

- 79 **Alther E.** [The gastric valve. A new surgical technic for the treatment of infantile hydrocephalus]. *Schweiz Med Wochenschr* 1965; **95**: 234-236 [PMID: [14259753](#)]
- 80 **Lamesch A.J.** Ventriculogastrostomy by means of a gastric tube for the treatment of hydrocephalus: a preliminary report. *J Pediatr Surg* 1972; **7**: 55-59 [PMID: [5013126](#) DOI: [10.1016/0022-3468\(72\)90404-6](#)]
- 81 **Weiss MH, Jane JA, Apuzzo ML, Heiden JS, Kurze T.** Ventriculogastrostomy, an alternative means for CSF diversion: a preliminary study. *Bull Los Angeles Neurol Soc* 1975; **40**: 140-144 [PMID: [1233088](#)]
- 82 **Duff TA, Rosenthal J, Jane JA.** Evaluation and revision of ventriculo-gastric shunts by gastroscopy. *Neurochirurgia (Stuttg)* 1977; **20**: 28-31 [PMID: [840355](#) DOI: [10.1055/s-0028-1090352](#)]

Warburg effect mimicking inborn errors of metabolism in childhood hematologic malignancies: A case-based systematic review

Khanittha Permtawee, Maliwan Tengsujaritkul, Chane Choed-Amphai, Supapitch Chanthong, Kanittha Mankhemthong, Lalita Sathitsamitphong, Rungrote Natesirinilkul, Pimlak Charoenkwan

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Jeong KY, South Korea; Sultana N, Bangladesh

Received: July 22, 2023

Peer-review started: July 22, 2023

First decision: September 4, 2023

Revised: September 9, 2023

Accepted: September 26, 2023

Article in press: September 26, 2023

Published online: December 9, 2023



Khanittha Permtawee, Maliwan Tengsujaritkul, Chane Choed-Amphai, Supapitch Chanthong, Lalita Sathitsamitphong, Rungrote Natesirinilkul, Pimlak Charoenkwan, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

Kanittha Mankhemthong, Department of Pediatrics, Nakornping Hospital, Chiang Mai 50180, Thailand

Corresponding author: Chane Choed-Amphai, MD, Doctor, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, No. 110 Intawarorot road, Sriphum, Muang, Chiang Mai 50200, Thailand. chane.c@cmu.ac.th

Abstract

BACKGROUND

Type B lactic acidosis and hypoglycemia can occur in various pediatric conditions. In young children with a history of fasting preceding these metabolic derangements, inborn errors of metabolism should be primarily considered. However, the Warburg effect, a rare metabolic complication, can also manifest in children with hematologic malignancies. Only a few reports of this condition in children have been published in the literature.

AIM

To identify the clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis.

METHODS

We performed a comprehensive search of the PubMed, Scopus, and Cochrane databases without any time restriction but limited to English language articles. The databases were last accessed on July 1st, 2023.

RESULTS

A total of 20 publications were included in the analysis, all of which were case reports or case series. No higher quality evidence was available. Among children with hematologic malignancies and Warburg effect, there were 14 cases of acute lymphoblastic leukemia and 6 cases of non-Hodgkin's lymphoma including our illustrative case. Lactic acidosis occurred in 55% of newly diagnosed cases and 45% of relapsed cases. The mean age was 10.3 ± 4.5 years, and 80% of cases were male. The mean serum lactate was 16.9 ± 12.6 mmol/L, and 43.8% of the cases had concomitant hypoglycemia. Lactic acidosis initially subsided in 80% of patients

receiving chemotherapy compared to 60% in the contrast group. The mortality rate of newly diagnosed cases was 45.5%, while the relapsed cases represented a 100% mortality rate. All 8 patients reported before 2001 died from disease-related complications. However, patients described in reports published between 2003 and 2023 had a 54.5% rate of complete remission.

CONCLUSION

This complication has historically led to fatal outcome; however, patients who received chemotherapy showed a more favorable response. Therefore, it is crucial to promptly initiate specific treatment in this context.

Key Words: Warburg effect; Lactic acidosis type B; Inborn errors of metabolism; Leukemia; Lymphoma; Children

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In children with a history of fasting preceding lactic acidosis, inborn errors of metabolism (IEM) should be considered. However, we describe a case of 10-year-old boy with Burkitt leukemia who exhibited Warburg effect mimicking IEM. The most recent review on lactic acidosis in pediatric leukemia/lymphoma was published in the journal *Cancer* in 2001. All cases published to that date experienced worsening or recurrence of lactic acidosis, with a mortality rate of 100%. However, this updated systematic review has shown improved outcomes for children with this complication over the past two decades. Newly diagnosed patients and those who received chemotherapy displayed more favorable outcomes.

Citation: Permtawee K, Tengsujaritkul M, Choed-Amphai C, Chanthong S, Mankhemthong K, Sathitsamitphong L, Natesirinilkul R, Charoenkwan P. Warburg effect mimicking inborn errors of metabolism in childhood hematologic malignancies: A case-based systematic review. *World J Clin Pediatr* 2023; 12(5): 350-358

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/350.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.350>

INTRODUCTION

Leukemia and lymphoma are the most common childhood cancers worldwide[1]. These hematologic malignancies have been known to develop several complications, such as tumor lysis syndrome, hyperleukocytosis, and superior vena cava syndrome[2]. In terms of metabolic derangements, hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia commonly occur in patients with active disease. In a minority of cases, another form of metabolic complication in children with cancer is lactic acidosis[3].

Normal lactic acid production is mainly derived from glucose metabolism *via* the glycolytic pathway, and its utilization primarily occurs in the liver. When abnormal lactate accumulates in the body, it can lead to metabolic acidosis. A serum lactate between 2 mmol/L and 5 mmol/L represents hyperlactatemia, whereas lactic acidosis is commonly found when lactate levels are greater than 5 mmol/L[4]. Lactic acidosis usually occurs when there is an imbalance between oxygen delivery and oxygen demand in type A lactic acidosis. In contrast, type B lactic acidosis results from an impairment of oxidative phosphorylation, which is associated with various conditions, including inborn errors of metabolism (IEM), exposure to drugs/toxins, and malignancies. The latter form, which is presented in patients with cancer, could be defined as the “Warburg effect”.

Unlike normal cells, which primarily rely on mitochondrial oxidative phosphorylation to generate the energy required for cellular processes, most cancer cells instead rely on aerobic glycolysis[5]. Various factors influence this phenomenon such as oncogene activation, loss of function of tumor suppressors, and effects of transcription factors[6]. This is a rare and unusual metabolic complication in children with hematologic malignancies. Few pediatric case series and case reports of this condition have been published. A previous literature review in 2001 showed that cases with lactic acidosis were more commonly observed in relapsed disease with specific clinical manifestations related to bone marrow, hepatosplenic, or lymph node involvement, and were associated with a poor outcome[3]. However, we encountered a case of newly diagnosed Burkitt leukemia in a 10-year-old boy with hypoglycemia and lactic acidosis which mimicked an IEM disorder. The patient achieved complete remission after treatment with a combination of rituximab and multiagent chemotherapy. Furthermore, we performed an updated systematic review in order to identify the overall profile of clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis from recent decades.

Illustrative case

A 10-year-old boy presented with poor appetite and vomiting that had persisted for 2 d. The physical examination did not show any masses, lymphadenopathy, or hepatosplenomegaly. Complete blood count and peripheral blood smear were within normal limits. A critical blood sample demonstrated the following values: Sodium of 142 mmol/L (normal range: 136-143 mmol/L); potassium of 4.0 mmol/L (normal range: 3.8-4.9 mmol/L); chloride of 109 mmol/L (normal range: 101-107 mmol/L); HCO₃ of 9 mmol/L (normal range: 17-26 mmol/L); anion gap of 24 mmol/L (normal range: 10-

14 mmol/L); blood urea nitrogen of 17 mg/dL (normal range: 7.3-21 mg/dL); creatinine of 1.1 mg/dL (normal range: 0.31-0.61 mg/dL); venous pH of 7.3 (normal range: 7.35-7.45); base excess of -15.2 mmol/L [normal range: (-2)-(+2) mmol/L]; and glucose of 49 mg/dL (normal range: 70-100 mg/dL). Further laboratory studies showed increased serum lactate (3.7 mmol/L; normal range: 1-2 mmol/L), serum ketone (2.7 mmol/L; normal range: 0-1 mmol/L), uric acid (12.5 mg/dL; normal range: 3.4-7.0 mg/dL), and triglycerides (354 mg/dL; normal range: 0-200 mg/dL), while serum cortisol and blood ammonia were normal (20.9 µg/dL and 50 µmol/L, respectively).

Based on the patient's clinical signs and symptoms, wide anion gap metabolic acidosis with ketotic hypoglycemia, IEM especially gluconeogenesis defects, glycogen storage disorders, and organic acidemia were considered. Subsequently, a specific test for plasma amino acids was performed, but only a nonspecific increase in cystathionine of 8.1 nmol/mL (normal range: 0-3 nmol/mL) and β-aminoisobutyric acid of 598.0 nmol/mL (normal range: 0-2 nmol/mL), which is a product of pyrimidine metabolism, was demonstrated. Urine organic acid testing showed an increased excretion of lactic acid and 4-hydroxyphenylactic acid. These findings explained that lactic acidosis was the cause of the wide anion gap metabolic acidosis without any supporting evidence of those IEM.

During admission, the patient developed hypertension and seizure. Computed tomography scan of the brain was performed, which revealed posterior reversible encephalopathy syndrome. The results of the metabolic workup showed that he had hyperuricemia, hyperphosphatemia, hypocalcemia, and acute kidney injury, along with markedly elevated levels of lactate dehydrogenase. These abnormal findings were consistent with tumor lysis syndrome.

Further computed tomography scan of the chest and abdomen was performed to evaluate the cause of hypertension and metabolic derangement, which demonstrated a posterior gastric wall thickening, and infiltrative soft tissue thickening of peritoneum and omentum without hepatic involvement. In addition, lobulated multifocal hypo-enhancing lesions were found scattered throughout the bilateral enlarged renal parenchyma. The patient underwent esophago-gastroduodenoscopy for gastric tissue biopsy, and histological pathology revealed a monotonous, intermediate-size lymphoid cells with starry sky appearance. These cells showed round nuclei with finely clumped chromatin and several paracentral nucleoli. Tingible body macrophages phagocytizing apoptotic debris were also observed. The immunohistochemistry testing was positive for CD20, CD79a, CD10, c-MYC, and Ki67 (> 95%), leading to the definitive diagnosis of Burkitt lymphoma.

After the procedure, the patient experienced disease progression characterized by progressive cytopenia with abnormal cells observed on peripheral blood smear. As part of disease staging, a bone marrow examination was performed, which revealed a lymphomatous involvement of 30%. The final diagnosis was Burkitt leukemia. A combination of rituximab and multiagent chemotherapy was administered following the St. Jude Mature B-Cell lymphoma and leukemia study III group c protocol. The patient responded well to the treatment, and the metabolic derangement was rapidly resolved. As of June 2023, the patient has been in complete remission for 1 year and 3 mo.

MATERIALS AND METHODS

Data sources and searches

Three authors (Permtawee K, Choed-Amphai C, and Chanthong S) independently conducted searches of the PubMed, Scopus, and Cochrane databases without any time restrictions. The following keywords were used for the search: "lactic acidosis"; "Warburg"; "pediatric"; "child"; "leukemia"; and "lymphoma". For PubMed, the specific search-term strategy was: ["acidosis, lactic" (MeSH Terms) or "acidosis" (All Fields) and "lactic" (All Fields) or "lactic acidosis" (All Fields) or "lactic" (All Fields) and "acidosis" (All Fields) or "warburg" (All Fields) or "warburg's" (All Fields)] and ["paediatrics" (All Fields) or "pediatrics" (MeSH Terms) or "pediatrics" (All Fields) or "paediatric" (All Fields) or "pediatric" (All Fields) or "child" (MeSH Terms) or "child" (All Fields) or "children" (All Fields) or "child's" (All Fields) or "children's" (All Fields)] and ["leukaemia" (All Fields) or "leukemia" (MeSH Terms) or "leukemia" (All Fields) or "leukaemias" (All Fields) or "leukemias" (All Fields) or "leukemia's" (All Fields) or ["lymphoma" (MeSH Terms) or "lymphoma" (All Fields) or "lymphomas" (All Fields) or "lymphoma's" (All Fields)] or ["haematologic malignancy" (All Fields) or "hematologic neoplasms" (MeSH Terms) or "hematologic" (All Fields) and "neoplasms" (All Fields) or "hematologic neoplasms" (All Fields) or "hematologic" (All Fields) and "malignancy" (All Fields) or "hematologic malignancy" (All Fields)]. Only articles published in English language were considered for selection.

Article selection

Inclusion criteria were as follows: Type B lactic acidosis in children with hematologic malignancies (including leukemia and lymphoma); and presence of data on clinical course, treatment strategies, and outcomes. Articles which did not meet these criteria were excluded. Summarization of the inclusion and exclusion criteria for this systematic review is presented in Table 1. The study followed the preferred reporting items for systematic reviews and meta-analysis 2020 guideline[7].

Data extraction

Extracted data included demographic and disease characteristics, laboratory parameters, clinical course, treatment strategies, and outcomes.

Data analysis

A qualitative systematic analysis was conducted using descriptive statistics. Due to differences among individual cases and small sample sizes, a meta-analysis could not be performed.

Table 1 Inclusion and exclusion criteria

Criteria
Inclusion
Children, 0 to 18 yr
Diagnosis of hematologic malignancy, including leukemia and lymphoma
Presence of lactic acidosis
Availability of clinical course, treatment, and outcome data
Exclusion
Adults, > 18 yr
Diagnosis of other solid tumors
Presence of other causes of metabolic acidosis without lactic acidosis
Incomplete information regarding clinical courses, treatment, and outcomes

RESULTS

Search results and article inclusion

A total of 115 publications were obtained through the search. Thirty-five abstracts were screened. The publications were limited to English language articles that provided detailed information about the clinical courses of type B lactic acidosis in children with leukemia or lymphoma resulting in the inclusion of 18 articles. A further two publications were discovered from manually searching the references of prior articles (Figure 1). The 20 included publications were case reports and case series, and there was no higher quality evidence available for this rare complication. These could be categorized into three groups according to cause of type B lactic acidosis, including Warburg effect, thiamine deficiency, and medications. Table 2 summarizes the clinical and laboratory parameters, treatments, and outcomes of the previously reported cases[3,8-26].

Demographic and disease characteristics

Among the pediatric cases with hematologic malignancies and the Warburg effect, there were 14 of acute lymphoblastic leukemia (ALL), including 7 with B-ALL, 4 with T-ALL, and 3 with unknown cell type, as well as 6 cases of non-Hodgkin's lymphoma (NHL), which consisted of 5 of Burkitt leukemia/lymphoma and 1 of T-NHL. Lactic acidosis occurred in 11 cases with newly diagnosed leukemia/lymphoma (55%), while the remaining cases had relapsed disease (45%). The mean age of the patients was 10.3 ± 4.5 years, and 80% of the cases were male.

Clinical manifestations and laboratory parameters

The most common clinical manifestations were dyspnea (44.4%), symptoms related to cytopenia (38.9%), fever (27.8%), weight loss (27.8%), and splenomegaly (27.8%). Hepatic involvement, which included patients with hepatomegaly, impaired hepatic synthetic function, cholestasis, or imaging-proven infiltrative disease, was found in 62.5% of cases (10 out of 16 patients). Renal involvement, which was defined as patients with imaging-proven infiltrative disease, occurred in about half of the cases (8 out of 14 patients). Patients with renal failure that might have resulted from other specific causes, such as tumor lysis syndrome, were excluded. The mean serum lactate was 16.9 ± 12.6 mmol/L, and 43.8% of the cases had concomitant hypoglycemia.

Treatment strategies

Almost all cases received sodium bicarbonate infusion (85%) in addition to general management protocols such as delivery of intravenous fluids and glucose. Renal replacement therapies, including continuous renal replacement therapy and peritoneal dialysis, were provided in only 20% of cases. Chemotherapy was given to three-quarters of the patients as a specific treatment.

Clinical courses and outcomes

Lactic acidosis initially subsided in about 80% of patients receiving chemotherapy compared to 60% in the contrast group. Furthermore, patients treated with chemotherapy had a more favorable response (complete remission of 40% *vs* 0%, respectively). The disease status may also affect the long-term outcome. The mortality rate of patients with newly diagnosed hematologic malignancies and lactic acidosis was 45.5%, while the relapsed patients had a 100% mortality rate. Warburg effect accounted for 23.1% of the causes of death. This review also highlighted that patients in the last two decades have experienced better outcomes than those in the previous review. Prior to 2001, patients diagnosed with leukemia or lymphoma-associated lactic acidosis had extremely poor outcomes. Six out of eight cases died from the disease-related conditions, while the other two cases experienced uncontrolled infections. However, publications between 2003 and 2023 revealed that 54.5% of cases achieved complete remission. In the minority of cases, patients with type B

Table 2 Demographics, treatments, and outcomes of previously reported children with leukemia/lymphoma and type B lactic acidosis

Ref.	Primary diagnosis	Age in yr, Sex	Clinical manifestation	Initial lactate in mmol/L	Blood glucose in mg/dL	Hepatic involvement	Renal involvement	Treatment	Clinical course	
									Lactic acidosis	Outcome
Type B lactic acidosis-Warburg effect										
Field <i>et al</i> [8]	Relapsed ALL	4, M	Bleeding, hepatosplenomegaly	20.2	NR	Yes	NR	Bicarbonate, radiotherapy, chemotherapy	Improved but recurred	Death from disease
	ALL	8, M	NR	9.9	NR	NR	NR	Bicarbonate, chemotherapy	Improved but recurred	Death from infection
Coleman <i>et al</i> [9]	Relapsed T-ALL	2, M	Lymphadenopathy, splenomegaly, dyspnea	24.6	74	No	NR	Bicarbonate, thiamine, insulin, methylglyoxal	Improved but recurred	Death from disease
Ali <i>et al</i> [10]	Relapsed B-ALL	12, M	Poor appetite, weight loss, abdominal pain	12.0	NR	No	Yes	Bicarbonate, chemotherapy	Improved but recurred	Death from infection
Révész <i>et al</i> [11]	Relapsed Burkitt lymphoma	8, M	Seizure, altered mental status, dyspnea, polydipsia, polyuria	24.0	93	No	Yes	Bicarbonate, thiamine, chemotherapy, radiotherapy	Improved but recurred	Death from disease
Sillos <i>et al</i> [3]	Relapsed T-ALL	11, F	Altered mental status	10.8	47	Yes	No	Bicarbonate, CRRT, chemotherapy	Improved but recurred	Death from disease
	Relapsed T-ALL	17, M	Altered mental status, dyspnea, edema	16.0	132	No	No	Bicarbonate	Worsened	Death from disease
	T-NHL	18, F	Fever, weight loss, lymphadenopathy, splenomegaly, dyspnea	15.4	44	Yes	No	Bicarbonate, chemotherapy	Resolved but recurred	Death from disease
Hayek and Srinivasan [12]	B-ALL	7, M	Anemia, lymphadenopathy, hepatosplenomegaly	8.4	96	Yes	Yes	Bicarbonate, PD, chemotherapy	Resolved after chemotherapy	CR
Rastogi <i>et al</i> [13]	Burkitt lymphoma, HIV	11, M	Fever, hepatosplenomegaly, periorbital and pedal edema	4.2	26	Yes	NR	Bicarbonate, glucagon	Improved	Death from disease
Luscri <i>et al</i> [14]	Relapsed B-ALL	7, M	Fever, ascites, dyspnea	5.5	33	Yes	NR	Bicarbonate, CRRT	Worsened	Death from LA, disease
Kulkarni <i>et al</i> [15]	Burkitt lymphoma	12, M	Dyspnea, hepatomegaly, abdominal pain	21.0	Normal	Yes	Yes	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Terpe <i>et al</i> [16]	B-ALL	11, M	Nausea, dyspnea, lymphadenopathy, abdominal pain, pancytopenia	21.0	48	Yes	Yes	Bicarbonate, chemotherapy	Worsened	Death from LA, ACS
Gökçe <i>et al</i> [17]	B-ALL	13, M	Weight loss, nausea, bone pain	62.0	97	Yes	Yes	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Schuh <i>et al</i> [18]	Relapsed B-ALL	12, M	Fever, abdominal pain, bicytopenia	14.8	80	Yes	Yes	Chemotherapy	Worsened	Death from disease
Narayani <i>et al</i> [19]	ALL	2, M	Fever, pancytopenia	13.5	96	NR	No	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Khera <i>et al</i> [20]	T-ALL	11, F	Poor appetite, weight loss, nausea, dyspnea, bicytopenia	20.0	104	No	No	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
O'Rourke <i>et al</i> [21]	Burkitt leukemia	13, M	NR	NR	Low	NR	NR	Chemotherapy	Worsened	Death from LA

Hui <i>et al</i> [22]	Relapsed B-ALL	17, F	Poor appetite, weight loss, bicytopenia	15.0	NR	NR	No	Bicarbonate CRRT	Improved	NR
This study	Burkitt leukemia	10, M	Poor appetite, nausea, vomiting	3.7	49	No	Yes	Rituximab, chemotherapy	Resolved after chemotherapy	CR
Type B lactic acidosis-thiamine deficiency										
Oriot <i>et al</i> [23]	Relapsed ALL, on TPN without vitamin	3, M	Altered mental status, fever, dyspnea, hepatomegaly	30.0	43	Yes	No	Bicarbonate, PD, thiamine	Resolved	CR
Svahn <i>et al</i> [24]	B-ALL, on TPN without vitamin	0.9, F	Altered mental status	18.6	NR	NR	NR	Bicarbonate, multivitamin including thiamine	Resolved	CR
Didisheim <i>et al</i> [25]	ALL, post-sepsis	13, M	Fever, abdominal pain, hypotension	19.6	NR	NR	NR	ECMO, thiamine	Resolved	CR
Type B lactic acidosis-medication (s)										
Smolka <i>et al</i> [26]	Relapsed B-ALL, pneumonia (antibiotics including linezolid)	9, F	Altered mental status, dyspnea	19.0	NR	Yes	NR	Bicarbonate, withdraw linezolid	Improved	CR

ACS: Abdominal compartment syndrome; ALL: Acute lymphoblastic leukemia; CR: Complete response; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; F: Female; LA: Lactic acidosis; M: Male; NR: Not reported; PD: Peritoneal dialysis.

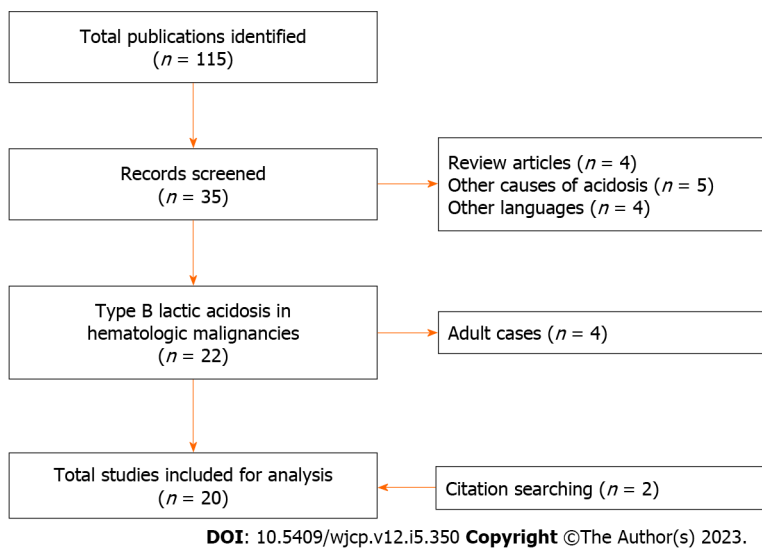


Figure 1 Preferred reporting items for systematic reviews and meta-analysis flowchart for study selection.

lactic acidosis from thiamine deficiency and linezolid treatment had excellent outcomes, with a 100% complete remission rate.

DISCUSSION

In the pediatric population, especially young children, an IEM disorder should be considered as a potential differential diagnosis in patients with a history of fasting or poor intake followed by hypoglycemia, and lactic acidosis with or without ketosis. The specific disorders of carbohydrate metabolism that can present with hyperlactatemia include glycogen storage diseases, gluconeogenesis defects, and organic acidemia. Findings from personal history taking, family history taking, and physical examination should be evaluated. Another crucial investigation in these diseases is a critical blood sampling taken during hypoglycemia episodes and including analysis of lactate, ammonia, blood gas analysis, insulin, cortisol, and ketones. Additional plasma amino acid and urine organic acid tests should be performed depending on the clinical suspicion[27,28]. After a comprehensive evaluation in our case, there was no evidence to support these

diseases. However, the patient later developed clinical symptoms of hypertensive emergency, tumor lysis syndrome and cytopenia, which led to the final diagnosis of Burkitt leukemia.

Type B lactic acidosis is an uncommon complication in patients with cancer, although there are several precipitating causes such as thiamine deficiency and medications. Cancer itself can lead to this form of metabolic acidosis. The proposed pathophysiology of this condition was first described by Warburg[29] in 1925. Since then, several studies have explored cancer metabolism and Warburg effect, which can be summarized into four main functions, as follows: Cell signaling; rapid adenosine triphosphate synthesis; biosynthesis; and tumor microenvironment[5]. Contrary to the publications on adult cases, the most recent review of lactic acidosis in pediatric leukemia and lymphoma was published in 2001 [3]. Sillos *et al*[3] summarized a total of 9 pediatric cases of hematologic malignancies with lactic acidosis, comprising 2 with lymphomas (1 Burkitt lymphoma and 1 T cell-non-Hodgkin's lymphoma) and 7 with ALLs. All cases experienced worsening or recurrence of lactic acidosis, and the outcome was extremely poor, with a 100% mortality rate. However, this updated review demonstrated that outcomes have improved in the last two decades, possibly due to increased understanding of disease pathophysiology, advances in treatment, and improvements in supportive care. Patients with newly diagnosed leukemia/lymphoma and those who received a specific treatment with chemotherapy appeared to have a better outcome. These findings also differ from those in the adult population. In the past decade, adults with hematologic malignancies who experienced lactic acidosis still had a mortality rate of more than 80%[30,31]. Despite the same pathophysiology of this complication in the pediatric and adult populations, disease status and response to treatment may explain the dismal outcome in adults. According to the United States' surveillance, epidemiology, and end results program database, survival rates according to age of diagnosis (all patients) at 17 years, 20 years, and 70 years were 75%, 48%, and 15%, respectively. Different treatment regimens and responses were determined to have played significant roles in this survival cliff drop-off[32]. This systematic review is limited by the rarity of this complication, with only a few case reports and case series available.

When compared to the other pediatric reports, our case presented with only nonspecific symptoms (a less common clinical manifestation). The patient had hypoglycemia with slightly elevated serum lactate levels, which is usually described as hyperlactatemia. However, further comprehensive investigations were performed and demonstrated that hyperlactatemia was the only remaining cause of the wide anion gap metabolic acidosis in this patient. One of the different management approaches used for this patient was administration of rituximab, a monoclonal antibody to CD20, which elicited a rapid response when combined with conventional chemotherapy. The lactic acidosis was abruptly resolved, and the patient has remained in complete remission.

CONCLUSION

Historically, Warburg effect in childhood hematologic malignancies has led to absolute fatal outcome, but over the past two decades about half of the cases have achieved complete remission. Specific treatment should be promptly initiated in this context. Furthermore, our case illustrates this uncommon metabolic derangement in childhood Burkitt leukemia. While IEM are one of the causes of metabolic acidosis in young children, Warburg effect in hematologic malignancies should also be considered in older children.

ARTICLE HIGHLIGHTS

Research background

Type B lactic acidosis is a rare metabolic complication in children with hematologic malignancies which can mimic inborn errors of metabolism (IEM). There have been few pediatric case series and case reports published on this specific condition. Moreover, the most recent review was conducted over two decades ago, in 2001.

Research motivation

The illustrative case of a 10-year-old boy with Burkitt leukemia who exhibited Warburg effect mimicking IEM was the basis of our systematic review. The previous review of this metabolic complication showed an extremely poor outcome. In recent years, however, advancements in cancer treatments may have led to the overall improvement in the clinical course.

Research objectives

To identify the clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis.

Research methods

We performed a comprehensive search of the PubMed, Scopus, and Cochrane databases without any time restrictions to identify children with leukemia/lymphoma and type B lactic acidosis. The publications considered for inclusion were limited to English language articles.

Research results

Lactic acidosis initially subsided in 80% of patients receiving chemotherapy compared to 60% in the contrast group. The mortality rate of newly diagnosed cases was 45.5%, while the relapsed cases had a 100% mortality rate. All 8 cases reported before 2001 died from disease-related complications, while cases reported between 2003 and 2023 showed a 54.5% rate of complete remission.

Research conclusions

Historically, this complication has led to fatal outcome; however, patients who received chemotherapy showed a more favorable response. Therefore, it is crucial to promptly initiate specific treatment in this context.

Research perspectives

This systematic review has revealed an improvement in the clinical course and outcomes compared to the past. Future studies in this context might include a larger scale of cases involving multicenter research. Retrospective study on prognostic factors or therapeutic research in the era of immunotherapy and targeted therapy could also be performed in this population.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Ms. Somjai Sittiprechachan for her contribution to the care of our patient.

FOOTNOTES

Author contributions: Permtawee K, Tengsujaritkul M and Choed-Amphai C drafted the manuscript; Permtawee K, Tengsujaritkul M, Choed-Amphai C, Chanthong S, Mankhemthong K, Sathitsamitphong L, Natesirinilkul R and Charoenkwan P participated in patient management and data collection; Permtawee K, Choed-Amphai C and Chanthong S contributed to the systematic review; All authors contributed to the article and approved the submitted version.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Thailand

ORCID number: Chane Choed-Amphai 0000-0002-2520-1162; Supapitch Chanthong 0009-0001-0975-0081; Lalita Sathitsamitphong 0000-0003-4774-259X; Rungrote Natesirinilkul 0000-0002-9840-3443; Pimlak Charoenkwan 0000-0002-9123-9177.

S-Editor: Qu XL

L-Editor: A

P-Editor: Yuan YY

REFERENCES

- 1 Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). *Cancer* 2008; **112**: 416-432 [PMID: 18074355 DOI: 10.1002/cncr.23169]
- 2 Prusakowski MK, Cannone D. Pediatric Oncologic Emergencies. *Hematol Oncol Clin North Am* 2017; **31**: 959-980 [PMID: 29078932 DOI: 10.1016/j.hoc.2017.08.003]
- 3 Sillos EM, Shenep JL, Burghen GA, Pui CH, Behm FG, Sandlund JT. Lactic acidosis: a metabolic complication of hematologic malignancies: case report and review of the literature. *Cancer* 2001; **92**: 2237-2246 [PMID: 11745277 DOI: 10.1002/1097-0142(20011101)92:9<2237::aid-cncr1569>3.0.co;2-9]
- 4 Seheult J, Fitzpatrick G, Boran G. Lactic acidosis: an update. *Clin Chem Lab Med* 2017; **55**: 322-333 [PMID: 27522622 DOI: 10.1515/cclm-2016-0438]
- 5 Padda J, Khalid K, Kakani V, Cooper AC, Jean-Charles G. Metabolic Acidosis in Leukemia. *Cureus* 2021; **13**: e17732 [PMID: 34659946 DOI: 10.7759/cureus.17732]
- 6 Vaupel P, Multhoff G. Revisiting the Warburg effect: historical dogma versus current understanding. *J Physiol* 2021; **599**: 1745-1757 [PMID: 33347611 DOI: 10.1113/JP278810]

- 7 **Page MJ**, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71 [PMID: [33782057](#) DOI: [10.1136/bmj.n71](#)]
- 8 **Field M**, Block JB, Levin R, Rall D. Significance of blood lactate elevations among patients with acute leukemia and other neoplastic proliferative disorders. *The American Journal of Medicine* 1966; **40**: 528-47 [DOI: [10.1016/0002-9343\(66\)90117-3](#)]
- 9 **Coleman RA**, Sommerville HM, Friedman HS, Falletta JM, Kinney TR. Insulin therapy for ketolactic acidosis complicating malignancy. *J Pediatr* 1982; **100**: 584-587 [PMID: [7038079](#) DOI: [10.1016/s0022-3476\(82\)80759-2](#)]
- 10 **Ali AA**, Flombaum CD, Brochstein JA, Gillio AP, Bussel JB, Boulard F. Lactic acidosis and renal enlargement at diagnosis and relapse of acute lymphoblastic leukemia. *J Pediatr* 1994; **125**: 584-586 [PMID: [7931878](#) DOI: [10.1016/s0022-3476\(94\)70013-3](#)]
- 11 **Révész T**, Obeid K, Mpofu C. Severe lactic acidosis and renal involvement in a patient with relapsed Burkitt's lymphoma. *Pediatr Hematol Oncol* 1995; **12**: 283-288 [PMID: [7640182](#) DOI: [10.3109/08880019509029570](#)]
- 12 **Hayek M**, Srinivasan A. Acute lymphoblastic leukemia presenting with lactic acidosis and renal tubular dysfunction. *J Pediatr Hematol Oncol* 2003; **25**: 488-490 [PMID: [12794529](#) DOI: [10.1097/00043426-200306000-00012](#)]
- 13 **Rastogi MV**, Desai N, Quintos JB. Non-islet-cell tumor hypoglycemia and lactic acidosis in a child with congenital HIV and Burkitt's lymphoma. *J Pediatr Endocrinol Metab* 2008; **21**: 805-810 [PMID: [18825882](#) DOI: [10.1515/jpem.2008.21.8.805](#)]
- 14 **Luscri N**, Mauer M, Sarafoglou K, Moran A, Tolar J. Lactic acidosis and hypoglycemia with ALL relapse following engrafted bone marrow transplant. *Pediatr Blood Cancer* 2009; **53**: 223-225 [PMID: [19405138](#) DOI: [10.1002/pbc.22010](#)]
- 15 **Kulkarni K**, Kaur S, Sibal A, Jerath N, Arya LS. Severe lactic acidosis, hypertriglyceridemia, and extensive axial skeleton involvement in a case of disseminated Burkitt's lymphoma. *Int J Hematol* 2010; **91**: 546-548 [PMID: [20213117](#) DOI: [10.1007/s12185-010-0534-8](#)]
- 16 **Terpe F**, Siekmeyer M, Bierbach U, Siekmeyer W, Kratzsch J, Till H, Wittekind C, Kiess W. Fulminant and fatal course of acute lymphoblastic leukemia due to lactic acidosis and suspected abdominal compartment syndrome. *J Pediatr Hematol Oncol* 2012; **34**: e80-e83 [PMID: [22134616](#) DOI: [10.1097/MPH.0b013e31822d4e8c](#)]
- 17 **Gökçe M**, Unal S, Gülşen H, Başaran O, Cetin M, Gümrük F, Beşbaş N, Gürgey A. A rare metabolic complication of acute lymphoblastic leukemia in childhood: lactic acidosis. *Türk J Pediatr* 2012; **54**: 61-63 [PMID: [22397045](#)]
- 18 **Schuh AM**, Leger KJ, Summers C, Uspal NG. Lactic Acidosis in a Critically Ill Patient: Not Always Sepsis. *Pediatr Emerg Care* 2018; **34**: e165-e167 [PMID: [30180106](#) DOI: [10.1097/PEC.0000000000001603](#)]
- 19 **Narayani S**, Balu P, Santhanam R, Scott JX. Type B Lactic Acidosis: A Rare Initial Presentation of Childhood Acute Lymphoblastic Leukemia. *Indian J Nephrol* 2019; **29**: 71-73 [PMID: [30814800](#) DOI: [10.4103/ijn.IJN_181_16](#)]
- 20 **Khera S**, Pramanik SK, Kalra S, Dwivedi A. Type B lactic acidosis due to Warburg effect in a child presenting with T cell acute lymphoblastic leukaemia: a milder phenotype. *BMJ Case Rep* 2020; **13** [PMID: [32188616](#) DOI: [10.1136/bcr-2019-233941](#)]
- 21 **O'Rourke E**, Malone A, O'Marcaigh A, Storey L, Betts D, McDermott M, Smith OP. Burkitt Lymphoma/Leukaemia in Children & Young Adolescents. *Ir Med J* 2020; **113**: 6 [PMID: [32298568](#)]
- 22 **Hui WF**, Hon KL, Leung AKC, Leung KKY, Ku SW, Cheng FWT. Continuous Renal Replacement Therapy (CRRT) for Nonrenal Indications among Critically Ill Children with Malignancy. *Case Rep Pediatr* 2021; **2021**: 6660466 [PMID: [33791137](#) DOI: [10.1155/2021/6660466](#)]
- 23 **Oriot D**, Wood C, Gottesman R, Huault G. Severe lactic acidosis related to acute thiamine deficiency. *JPEN J Parenter Enteral Nutr* 1991; **15**: 105-109 [PMID: [1901099](#) DOI: [10.1177/0148607191015001105](#)]
- 24 **Svahn J**, Schiaffino MC, Caruso U, Calvillo M, Minniti G, Dufour C. Severe lactic acidosis due to thiamine deficiency in a patient with B-cell leukemia/lymphoma on total parenteral nutrition during high-dose methotrexate therapy. *J Pediatr Hematol Oncol* 2003; **25**: 965-968 [PMID: [14663281](#) DOI: [10.1097/00043426-200312000-00012](#)]
- 25 **Didisheim C**, Ballhausen D, Choucair ML, Longchamp D, Natterer J, Ferry T, Perez MH, Amiet V. Severe Lactic Acidosis in a Critically Ill Child: Think About Thiamine! A Case Report. *J Pediatr Intensive Care* 2021; **10**: 307-310 [PMID: [34745706](#) DOI: [10.1055/s-0040-1713382](#)]
- 26 **Smolka V**, Rohanova M, Ludikova B, Novak Z, Zapalka M, Pospisilova D, Volejnikova J. Severe linezolid-induced lactic acidosis in a child with acute lymphoblastic leukemia: A case report. *J Infect Chemother* 2020; **26**: 1316-1318 [PMID: [32859497](#) DOI: [10.1016/j.jiac.2020.07.018](#)]
- 27 **Saudubray JM**, Garcia-Cazorla A. Inborn Errors of Metabolism Overview: Pathophysiology, Manifestations, Evaluation, and Management. *Pediatr Clin North Am* 2018; **65**: 179-208 [PMID: [29502909](#) DOI: [10.1016/j.pcl.2017.11.002](#)]
- 28 **Weinstein DA**, Steuerwald U, De Souza CFM, Derks TGJ. Inborn Errors of Metabolism with Hypoglycemia: Glycogen Storage Diseases and Inherited Disorders of Gluconeogenesis. *Pediatr Clin North Am* 2018; **65**: 247-265 [PMID: [29502912](#) DOI: [10.1016/j.pcl.2017.11.005](#)]
- 29 **Warburg O**. The Metabolism of Carcinoma Cells I. *The Journal of Cancer Research* 1925; **9**: 148-63 [DOI: [10.1158/jcr.1925.148](#)]
- 30 **De Raes EA**, Benoit DD, Depuydt PO, Offner F, Nollet J, Vantilborgh AK, Steel E, Noens LA, Decruyenaere JM. Early recognition of malignant lactic acidosis in clinical practice: report on 6 patients with haematological malignancies. *Acta Clin Belg* 2012; **67**: 347-351 [PMID: [23189542](#) DOI: [10.2143/ACB.67.5.2062688](#)]
- 31 **Brault C**, Zerbib Y, Delette C, Marc J, Gruson B, Marolleau JP, Maizel J. The Warburg Effect as a Type B Lactic Acidosis in a Patient With Acute Myeloid Leukemia: A Diagnostic Challenge for Clinicians. *Front Oncol* 2018; **8**: 232 [PMID: [29974036](#) DOI: [10.3389/fonc.2018.00232](#)]
- 32 **Siegel SE**, Stock W, Johnson RH, Advani A, Muffly L, Douer D, Reed D, Lewis M, Freyer DR, Shah B, Luger S, Hayes-Lattin B, Jaboin JJ, Coccia PF, DeAngelo DJ, Seibel N, Bleyer A. Pediatric-Inspired Treatment Regimens for Adolescents and Young Adults With Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Review. *JAMA Oncol* 2018; **4**: 725-734 [PMID: [29450465](#) DOI: [10.1001/jamaoncol.2017.5305](#)]



Situs inversus totalis in an asymptomatic adolescent - importance of patient education: A case report

Lauren C. Hayashi, Ratna Acharya

Specialty type: Pediatrics

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: MD XM, China

Received: June 6, 2023

Peer-review started: June 6, 2023

First decision: August 30, 2023

Revised: September 9, 2023

Accepted: September 26, 2023

Article in press: September 26, 2023

Published online: December 9, 2023



Lauren C. Hayashi, Department of Pediatrics, University of Florida College of Medicine, Gainesville, FL 32608, United States

Ratna Acharya, Division of General Pediatrics, Department of Pediatrics, University of Florida, Gainesville, FL 32608, United States

Corresponding author: Lauren C. Hayashi, MS, Researcher, Department of Pediatrics, University of Florida College of Medicine, No. 1104 Newell Drive, Gainesville, FL 32608, United States. lauren.hayashi@ufl.edu

Abstract

BACKGROUND

Situs inversus totalis (SIT) may be an incidental finding in asymptomatic children. Patients may not understand the implications of this condition and the importance of relaying the diagnosis to their healthcare providers.

CASE SUMMARY

We report an asymptomatic seventeen-year-old adolescent with previously-diagnosed SIT who presented for a routine well-child visit. During history taking, he denied any past medical conditions, including cardiovascular conditions. Only when physical exam revealed point of maximal impulse and heart sounds on the right side, did he convey that he had been diagnosed with SIT incidentally at age of 12 years. He was not aware of associated conditions or the potential implications of his diagnosis, nor did he realize it is pertinent medical history to be relayed to healthcare providers. Chest X-ray confirmed dextrocardia and abdominal X-ray showed right-sided stomach. Abdomen sonogram showed left-sided liver and right-sided spleen. Echocardiogram showed normal valvular structure and function. A comprehensive discussion was provided to address the patient's lack of understanding that SIT is a medical diagnosis with potential implications.

CONCLUSION

While SIT is rare and mostly asymptomatic, affected patients may not comprehend the importance of the diagnosis and its potential ramifications. Recognition of the patient's lack of awareness allows the healthcare provider to educate the patient and hopefully can prevent potential medical and surgical complications.

Key Words: Situs inversus; Dextrocardia; Adolescent; Education; Case report

Core Tip: Situs inversus totalis (SIT) is a rare and mostly asymptomatic condition. This care report describes a previously-diagnosed seventeen-year-old adolescent who presented for a routine healthcare visit. During history taking, he denied any past medical conditions, including cardiovascular issues, until physical exam showed heart sounds on the right. He then revealed that he had been diagnosed with SIT incidentally at age 12, but did not realize that it is a significant condition. Patients with SIT may not understand the importance of the diagnosis and its potential ramifications. Healthcare workers must recognize that this lack of understanding of their diagnosis exists and educate them. Our patient was counseled that his diagnosis, although asymptomatic, should be relayed to healthcare teams.

Citation: Hayashi LC, Acharya R. Situs inversus totalis in an asymptomatic adolescent - importance of patient education: A case report. *World J Clin Pediatr* 2023; 12(5): 359-364

URL: <https://www.wjgnet.com/2219-2808/full/v12/i5/359.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v12.i5.359>

INTRODUCTION

Situs inversus totalis (SIT) is a rare congenital anomaly in which the abdominal and thoracic organs are transposed across the sagittal midline with complete mirror-image reversal of laterality[1]. Situs solitus totalis is the term used to describe the normal left-right asymmetry with respect to midline in the arrangement of internal organs. Situs ambiguus, also called heterotaxy syndrome, involves a disturbance in the usual left-right distribution of the thoraco-abdominal organs which does not entirely correspond to the complete mirror image, unlike in SIT[2]. An example would be isolated dextrocardia, in which the heart has reverse orientation without concomitant laterality shift of thoracoabdominal organs. In some of these ambiguous cases, normally asymmetric structures like the lung (2 left lobes *vs* 3 right) and kidneys (different vascular branching patterns) tend toward symmetry[2]. SIT refers to complete, 180 degree reversal of left-to-right orientation, such that the heart, stomach and spleen are located on the right side, liver on the left side, and the paired lungs and kidneys also display reversal of left-right characteristics[1]. However, given that most of these cases are discovered incidentally during the work-up for another condition and are mostly asymptomatic, patients and their families may not realize the importance of this condition. Here, we report such a lack of awareness in a 17-year-old male with SIT who presented for a routine health care examination visit in a primary care provider's office.

CASE PRESENTATION

Chief complaints

Patient is a 17-year-old male who presents to the adolescent clinic in the southeastern United States for a sports physical examination and well-child visit.

History of present illness

Patient is accompanied by his mother, who is from South America and does not speak English. Patient and mother report that he is "completely healthy with no medical conditions." He exercises regularly for 90 min daily, encompassing both strength training and cardiovascular fitness.

History of past illness

The patient initially reports no medical history, including when directly asked about cardiac conditions or symptoms of chest pain, shortness of breath, dyspnea at rest or on exertion, palpitations, ascites, or leg edema. However, when physical exam revealed right-sided heart sounds, the patient revealed that he had been diagnosed incidentally at the age of 12 years following an X-ray performed for unrelated abdominal pain. He subsequently had two appointments with a cardiologist in South America with no reported symptoms or complications. Since moving to the United States two years ago, he has not had medical care. He denies history of sinopulmonary infections or decreased olfaction. When asked why the patient and mother did not disclose this diagnosis when queried about cardiac conditions, their answer was that it was not important information since he is healthy and SIT does not affect him; their understanding was that he did not have a disease, just a mirror-image flip and was essentially normal. The patient and his mother were surprised by these questions and were unaware that this condition may be associated with other syndromes or that there may be potential ramifications for his medical treatment in the future.

Personal and family history

The patient's personal and family history were otherwise unremarkable for cardiovascular conditions or sudden deaths.

Physical examination

Physical examination revealed stable vital signs with manual blood pressure 120/74 mmHg (< 95th percentile for age, height and gender), pulse 86 beats per minute, temperature 96.2° F, and body mass index of 24.5 kg/m². Cardiovascular examination was significant for point of maximal impulse palpated on the right at the 5th intercostal space at the midclavicular line. Rate and rhythm were regular with no murmurs, rubs or gallops. Skin had two benign-appearing dark nevi with well-defined borders (approximately 2-3 mm) along posterior axillary line bilaterally. There were no surgical scars detected. Abdominal examination was significant for inferior border of liver palpated 2 cm beneath left costal margin. There were normal bowel sounds with no rebound or guarding.

Laboratory examinations

Investigations showed borderline decreased high-density cholesterol of 27 mg/dL (23-92 mg/dL), and otherwise unremarkable lipid studies. Complete blood count showed hemoglobin of 16 g/dL. Renal and hepatic function was normal.

Imaging examinations

Chest X-ray showed dextrocardia with situs inversus (Figure 1). Abdominal radiograph showed stomach on the right upper quadrant (Figure 2). Transthoracic echocardiogram showed heart located in the right chest with cardiac apex pointing to the right. There was atrial situs inversus with atrio-ventricular concordance and ventriculo-arterial concordance. The pulmonary veins drained normally to the right sided morphologic left atrium. The superior and inferior vena cava drained normally to the left sided morphologic right atrium. There was normal valvular structure and function. Abdominal sonogram report from South America mentioned liver on the left, spleen on the right, and mirror image configuration of aorta and inferior vena cava.

FINAL DIAGNOSIS

The final diagnosis was SIT with dextrocardia.

TREATMENT

No specific treatment for this condition was necessary.

OUTCOME AND FOLLOW-UP

Given that the patient was asymptomatic with otherwise stable chest X-ray and normal echocardiogram, no further workup was deemed necessary. The main intervention consisted of counseling the patient and his mother about SIT, including how it is a medical condition that should be included when relaying his history. The patient was asked to follow up at next well-child visit for routine check-up. It was suggested that no scheduled follow up with cardiology is necessary unless symptoms arise.

DISCUSSION

In this report, we describe an asymptomatic adolescent male with a history of incidentally found SIT who, upon relaying his medical history, initially denied cardiac conditions, including when directly asked about congenital heart conditions. The patient was unaware that SIT is a diagnosis that should be communicated to his providers as part of his history. It was only when heart sounds were auscultated on his right side that he mentioned his diagnosis. He explained that from his understanding, SIT would not impact his health. He was unaware that it may be associated with other syndromes and was thus confused when further questioned about symptoms that could be associated with SIT. It is critical to educate these patients about their condition and potential implications. This case report is the first to our knowledge to highlight the lack of patient understanding of their SIT diagnosis and to focus upon the importance of patient education.

Reverse orientation of thoracoabdominal organs was first documented in human beings in the 17th century[3]. In 1888, the condition was documented with illustrations of physical exam findings. Finally, in 1897, Vehsemeyer was the first to demonstrate transposition by X-ray, which in addition to ultrasound has since been the diagnostic method of choice[4]. The incidence of SIT has been reported to be 1:6500 to 1:25000[1].

Laterality is established in utero around day 22 when embryological cardiac tubes rotate rightward, known as looping [5]. The apex of the heart migrates to the left thorax over the following two weeks, such that the heart is located on the left side of the chest[6]. Dextrocardia is a heart with the apex directed to the right[7]. When the abnormal rotation of the cardiac tubes leftward is also accompanied by a similar rotation of the lungs and visceral organs, SIT results. The embryological cascade which dictates laterality is believed to involve over a hundred genes, including those coding for signaling, cell adhesion and motor peptides. While most cases of abnormal laterality are sporadic, there are also



DOI: 10.5409/wjcp.v12.i5.359 Copyright ©The Author(s) 2023.

Figure 1 Chest X-ray reveals dextrocardia with situs inversus. Heart size and hila are normal. Stomach gas is noted in the right upper quadrant.



DOI: 10.5409/wjcp.v12.i5.359 Copyright ©The Author(s) 2023.

Figure 2 Situs inversus is seen with stomach in the right upper quadrant. There is no evidence of abnormal bowel dilation or obstruction. There is moderate amount of fecal matter noted in the colon and rectum.

hereditary cases[8].

It is important to note that SIT may occur with other anomalies or as a part of broader syndromes. The most common is primary ciliary dyskinesia, also known as immotile cilia or Kartagener syndrome, which can involve a triad of situs inversus, bronchiectasis and sinusitis. About half of the individuals with a diagnosis of Kartagener's syndrome have SIT. The underlying dysmotility in cilia and flagella results in recurrent sinopulmonary infections, anosmia and infertility in males[9].

Rates of congenital heart disease increase with left-right malformation. Cardiac anomalies occur in 3%-9% of patients with SIT and 80% with situs ambiguous, compared to 0.6% without a laterality condition[10]. Up to 25% of patients with situs ambiguous may not be diagnosed until adulthood, especially those with mild cardiac abnormalities[1]. Caval vein disorders are also common, which may lead to higher rates of deep vein thrombosis[11]. When situs ambiguous disrupts splenic development, it can cause either asplenia (double right-side anatomy or right isomerism) or polysplenia (double left-side anatomy or left isomerism)[12]. Asplenia is associated with severe cardiac and pulmonary abnormalities, leading to a mortality rate up to 80% in the first year[13,14]. It is important to take a careful history about syndromic or congenital heart disease symptoms and following up the abnormal physical examination findings with imaging to differentiate among these laterality diagnoses.

Our patient falls into the majority of SIT patients who are asymptomatic with an incidental diagnosis. Even though he was previously diagnosed, he did not realize this information is pertinent medical history and was unaware that his presentation could be part of a broader syndrome.

An understanding of their disease is of especial importance in pediatric adolescent patients as they transition to adult care. Of the handful of studies that address this topic in adolescents with congenital heart conditions, participants have shown a poor understanding of their disease. One study in adolescents (median 13 years of age) with a wide spectrum of heart disease (not including SIT), illustrated that 78% of participants did not know the medical name of their condition and 36% had a poor understanding or wrong concept about their disease. There was no association between understanding and severity of the congenital heart disease but there was a positive correlation between understanding and increasing age[15]. Another study (median age 17 years of age) replicated a poor knowledge, including < 50% correctly knowing name of their heart defect (also not including SIT), reasons for follow-up, effects on competitive sports and future implications[16]. These studies illustrate an incomplete knowledge that, if addressed, could help adolescents take greater responsibility for their own health.

Having an understanding of SIT and communicating the diagnosis is of particular importance in emergent settings such as acute abdomen, since SIT patients may have atypical symptom locations[17]. Patients who present with left sided abdominal pain in the setting of appendicitis are more likely to have delayed diagnosis and treatment[18]. One report described a 46-year-old with a family history of SIT who presented with left upper quadrant pain[19]. Because the patient volunteered the SIT family history, clinical suspicion for SIT was high and thus atypical differential diagnoses were considered. Indeed, the work-up revealed both a new SIT diagnosis and acute cholecystitis, which might have otherwise been misdiagnosed and mistreated as gastritis. Another report described a patient who was diagnosed incidentally during exploratory laparotomy in the setting of trauma[20]. Visceral surgery in SIT patients poses a unique challenge; the common guidance for surgery in SIT patients includes diligent preoperative planning and selection of experienced surgeons who can adapt to technical modifications for the reverse anatomy[21].

Our case report illustrates a poor understanding of SIT in a previously-diagnosed adolescent. Given the patient was a new international patient to our clinic, his previous medical records from South America were unavailable. We were thus relying on his and his mother's history, in which they failed to convey his SIT diagnosis until it was revealed by physical exam. He subsequently showed a lack of knowledge about the disease or its potential implications. After our patient had a stable X-ray and echocardiography to rule out congenital abnormalities, he was deemed clear for sports and counseled about his condition. This surprise diagnosis in an outpatient setting had little health consequence, but could have added confusion and costly time to diagnosis or surgical challenges in the context of urgent care or trauma.

The main limitation of this case is that the patient had an incentive to present himself as a healthy individual with no medical conditions, since he was seeking medical clearance for high school sports. It is possible this led him to downplay his diagnosis; yet it is also possible that he truly had an inaccurate understanding of his disease. If this misperception is genuine, it may be that his previous cardiologist's reassurances that SIT is not immediately life-threatening led to this patient's idea that it is not a medical disease. To fully understand the extent of incomplete comprehension about SIT within asymptomatic patients, more research is needed in pediatric patients outside of the medical-clearance context.

Because SIT is so rare and most physicians will encounter only a few cases in their careers[4], the medical profession has not recognized this lack of awareness within adolescent SIT patients, let alone SIT patients in general. There are currently no guidelines about how to counsel patients with this condition. This case report highlights a knowledge gap within the medical literature on the extent to which patients with SIT understand their disease. Further research on this topic may help guide clinical practice in counseling patients with SIT and enable patients, especially adolescents, to safeguard their health.

CONCLUSION

SIT is a congenital anomaly with potential health implications. This case report highlights the poor understanding of the disease in a previously diagnosed adolescent and the importance of patient education. For an adolescent approaching adulthood, it is of particular importance that he comprehend and can communicate his own medical history, especially with a diagnosis of SIT. This understanding can help avert diagnostic and therapeutic confusion, especially in the setting of trauma or emergent surgeries, where a thorough review of past medical records is not always feasible. The patient was counseled that his SIT diagnosis, although asymptomatic, must be relayed to future healthcare teams as it could affect his medical care.

FOOTNOTES

Author contributions: Hayashi LC and Acharya R were involved in the acquisition of the clinical data, analysis, writing, interpretation and revision.

Informed consent statement: Informed consent was obtained from the parent of the patient by Dr. Acharya for publication of the information.

Conflict-of-interest statement: Both authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE checklist, and the manuscript was prepared and revised according to the CARE checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United States

ORCID number: Lauren C. Hayashi 0009-0001-1678-2567.

S-Editor: Lin C

L-Editor: A

P-Editor: Yuan YY

REFERENCES

- Eitler K, Bibok A, Telkes G. Situs Inversus Totalis: A Clinical Review. *Int J Gen Med* 2022; **15**: 2437-2449 [PMID: 35264880 DOI: 10.2147/IJGM.S295444]
- Spoon JM. Situs inversus totalis. *Neonatal Netw* 2001; **20**: 59-63 [PMID: 12143842 DOI: 10.1891/0730-0832.20.1.63]
- Wood GO, Blalock A. Situs inversus totalis and disease of biliary tract: survey of literature and report of case. *Arch Surg* 1940; **40**: 885-896 [DOI: 10.1001/archsurg.1940.04080040067007]
- Blegen HM. Surgery in Situs Inversus. *Ann Surg* 1949; **129**: 244-259 [PMID: 17859304 DOI: 10.1097/00000658-194902000-00009]
- Splitt MP, Burn J, Goodship J. Defects in the determination of left-right asymmetry. *J Med Genet* 1996; **33**: 498-503 [PMID: 8782051 DOI: 10.1136/jmg.33.6.498]
- Izpisua Belmonte JC. How the body tells left from right. *Sci Am* 1999; **280**: 46-51 [PMID: 10349731 DOI: 10.1038/scientificamerican0699-46]
- Evans WN, Acherman RJ, Collazos JC, Castillo WJ, Rollins RC, Kip KT, Restrepo H. Dextrocardia: practical clinical points and comments on terminology. *Pediatr Cardiol* 2010; **31**: 1-6 [PMID: 19727926 DOI: 10.1007/s00246-009-9516-0]
- Peeters H, Devriendt K. Human laterality disorders. *Eur J Med Genet* 1999; **49**: 349-362 [DOI: 10.1016/j.ejmg.2005.12.003]
- Popatia R, Haver K, Casey A. Primary Ciliary Dyskinesia: An Update on New Diagnostic Modalities and Review of the Literature. *Pediatr Allergy Immunol Pulmonol* 2014; **27**: 51-59 [PMID: 24963453 DOI: 10.1089/ped.2013.0314]
- Merklin RJ, Varano NR. Situs inversus and cardiac defects. A study of 111 cases of reversed asymmetry. *J Thorac Cardiovasc Surg* 1963; **45**: 334-342 [PMID: 13935010]
- Batouty NM, Sobh DM, Gadelhak B, Sobh HM, Mahmoud W, Tawfik AM. Left superior vena cava: cross-sectional imaging overview. *Radiol Med* 2020; **125**: 237-246 [PMID: 31823296 DOI: 10.1007/s11547-019-01114-9]
- Asplenia, Polysplenia Syndromes. In: Baert AL editors. *Encyclopedia of Diagnostic Imaging*. Berlin: Springer, 2008 [DOI: 10.1007/978-3-540-35280-8_179]
- Maldjian PD, Saric M. Approach to dextrocardia in adults: review. *AJR Am J Roentgenol* 2007; **188**: S39-49; quiz S35 [PMID: 17515336 DOI: 10.2214/AJR.06.1179]
- Applegate KE, Goske MJ, Pierce G, Murphy D. Situs revisited: imaging of the heterotaxy syndrome. *Radiographics* 1999; **19**: 837-52; discussion 853 [PMID: 10464794 DOI: 10.1148/radiographics.19.4.g99jl31837]
- Veldtman GR, Matley SL, Kendall L, Quirk J, Gibbs JL, Parsons JM, Hewison J. Illness understanding in children and adolescents with heart disease. *Heart* 2000; **84**: 395-397 [PMID: 10995408 DOI: 10.1136/heart.84.4.395]
- Van Deyk K, Pelgrims E, Troost E, Goossens E, Budts W, Gewillig M, Moons P. Adolescents' understanding of their congenital heart disease on transfer to adult-focused care. *Am J Cardiol* 2010; **106**: 1803-1807 [PMID: 21126624 DOI: 10.1016/j.amjcard.2010.08.020]
- Oh JS, Kim KW, Cho HJ. Left-sided appendicitis in a patient with situs inversus totalis. *J Korean Surg Soc* 2012; **83**: 175-178 [PMID: 22977765 DOI: 10.4174/jkss.2012.83.3.175]
- Akbulut S, Ulku A, Senol A, Tas M, Yagmur Y. Left-sided appendicitis: review of 95 published cases and a case report. *World J Gastroenterol* 2010; **16**: 5598-5602 [PMID: 21105193 DOI: 10.3748/wjg.v16.i44.5598]
- Herrera Ortiz AF, Lacouture JC, Sandoval Medina D, Gómez Meléndez LJ, Uscategui R. Acute Cholecystitis in a Patient With Situs Inversus Totalis: An Unexpected Finding. *Cureus* 2021; **13**: e15799 [PMID: 34306867 DOI: 10.7759/cureus.15799]
- Olaschinde O, Owojuyigbe AM, Adisa AO, Awowole IO. Incidental finding of complete situs inversus in a polytraumatized adult. *Afr J Med Med Sci* 2014; **43**: 183-186 [PMID: 25474996]
- Enciu O, Toma EA, Tulin A, Georgescu DE, Miron A. Look beyond the Mirror: Laparoscopic Cholecystectomy in Situs Inversus Totalis-A Systematic Review and Meta-Analysis (and Report of New Technique). *Diagnostics (Basel)* 2022; **12** [PMID: 35626419 DOI: 10.3390/diagnostics12051265]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

