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WJCP covers a variety of clinical medical topics, including fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, and evidence-based medicine and epidemiology. Priority publication will be given to articles concerning diagnosis and treatment of pediatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Vitamin D deficiency/insufficiency from childhood to adulthood: Insights from a sunny country

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Abstract

Vitamin D is known to be a key regulator of bone metabolism and is associated with muscle strength. Vitamin D deficiency is widely prevalent worldwide. In adults, vitamin D deficiency has been implicated in numerous health conditions including osteoporosis, cancer, diabetes, and autoimmune diseases. Considerable changes have occurred in lifestyles and childhood activities in the past years. Studies have shown that the children population is at high risks of vitamin D deficiency. The objective of this study was to learn about the extent of vitamin D deficiency in children worldwide and especially in sunny country like Israel. In this article we reviewed the extent and severity of vitamin D deficiency worldwide and especially in Israel, through a very comprehensive review of previous reports and research studies done during the last years. We found reports on vitamin D deficiency in children, which was associated with metabolic syndromes and obesity. It was more prevalent in children who spend less time on outdoor activities, in obese children, and in cases when there was imbalance between nutritional intakes and requirements. Vitamin D deficiency is common even in children living in sunny places like Israel. Health professionals should be aware of the fact that although vitamin D deficiency is prevalent in the elderly population, it is also common in children, and can be associated with different illnesses. We encourage supplementation of vitamin D to special populations (pregnant and lactating women, infants, and high risk groups). We also encourage implementation of international food fortification programs.

Key words: Vitamin D; Deficiency; Children; Obesity; Bone metabolism; Muscle strength; Osteoporosis; Non-skeletal diseases

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Core tip: Vitamin D is known to be a key regulator of bone metabolism and muscle strength. Vitamin D deficiency is widely prevalent worldwide. In this article we emphasize that vitamin D status may be also related to a number of non-skeletal diseases, including cardiovascular events, cancer, diabetes, and autoimmune diseases. Obesity has also been recently associated with vitamin D insufficiency. We demonstrate that the pediatric population is also at high risks of vitamin D deficiency. Studies that investigated the status of vitamin D deficiency in Israel, which is a known multi-cultural sunny country, revealed a high prevalence of vitamin D deficiency.

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INTRODUCTION

Vitamin D deficiency is widely prevalent worldwide. Low levels of 25-hydroxy vitamin D [25(OH)D], the primary circulating storage form of vitamin D, are present in 30%-50% of otherwise healthy middle-aged to elderly adults. Many studies have shown that the pediatric population is also at high risk of vitamin D deficiency^[1,2].

DEFINITIONS

Vitamin D deficiency is currently defined as serum 25(OH)D level less than 10 ng/mL (25 nmol/L) below which osteomalacia and rickets are commonly observed. In the osteoporotic/osteopenic adult population a general consensus is that 25(OH)D levels should be maintained above 30 ng/mL (75 nmol/L)^[3]. There is some controversy in the definition of vitamin D insufficiency and what target levels should be achieved in the general population. Blood levels below 30 ng/mL are considered by many as insufficient but the Institute of Medicine has set the cutoff at 20 ng/mL (50 nmol/L)^[4].

VITAMIN D AND BONE HEALTH

Vitamin D plays an important role in the regulation of bone metabolism and has great impact on muscle strength^[5,6].

Vitamin D has a positive effect on bone density and bone quality^[7]. Several studies indicate that vitamin D increases bone mineral density (BMD)^[8] and prevents fractures related to osteoporosis^[9,10]. Furthermore, having enough vitamin D reduces the risk of falling in the elderly^[11] by increasing muscle strength and improving muscle performance, whether these individuals are community-

dwelling or institutionalized^[6,12]. Thus, vitamin D lowers the risk of fracture in this population by improving both bone and muscle strength^[13].

On the other hand, several studies in adolescents and young adults described a direct link between vitamin D and bone mass^[14-17] while others have not^[18,19].

The association between vitamin D and bone strength may also be dependent on the genetic background of the population under study. For example, a recent study in adults found a positive correlation between circulating levels of 25(OH)D and BMD in Caucasian subjects, but not in African-American or Hispanic populations^[20].

VITAMIN D AND NON-SKELETAL DISEASES

In addition to the well-known effects on musculoskeletal system, vitamin D status is also related to a number of non-skeletal health problems^[7,13].

While there is strong and clear evidence for a beneficial effect of vitamin D on musculoskeletal health based on randomized controlled trials (RCTs)^[21] and large epidemiological studies^[22], studies on other health issues in humans are more controversial. A meta-analysis of 18 RCTs that included over 57000 individuals concluded that supplements of vitamin D were associated with decreased mortality^[23]. The mechanisms underlying this apparent beneficial effect on overall mortality may be multifactorial, affecting the cardiovascular system, the immune system and tumor progression, among others^[24-28].

Cardiovascular risks

Low levels of 25(OH)D appear to be an independent risk factor for cardiovascular events^[24]. However, the association between vitamin D deficiency and myocardial diseases is still inconclusive^[29].

For instance, in large studies, cardiovascular risk factors were not significantly improved by vitamin D^[27,28,30].

Although an adequate vitamin D status seemed to be associated with the prevention of arterial hypertension^[31,32], a recent meta-analysis didn't show any beneficial effect on either systolic or diastolic blood pressure.

From the mechanistic standpoint, it is noteworthy that both the vitamin D receptor (VDR) and the 1-alpha hydroxylase enzyme responsible for the activation of vitamin D are expressed in cardiomyocytes as well as in other cardiovascular system's cells^[33], suggesting a local influence of vitamin D on heart function. This is further supported by the adverse cardiovascular effects observed in VDR- and 1alpha hydroxylase-null mice^[34].

Likewise, other studies have shown that the active form of vitamin D 1 α ,25 dihydroxy-vitamin D [1 α ,25(OH)2D] reduces inflammation^[35], controls some metalloproteinases involved in vascular calcification^[36], and improves endothelial function^[37], therefore directly affecting the cardiovascular system. Indirectly, 1 α ,25 (OH)2D may also improve cardiovascular outcomes by modulating the

secretion of insulin and improving insulin sensitivity^[38,39], and decreasing parathyroid hormone (PTH) secretion^[40]. A recent meta-analysis seems to support the adverse role of PTH in cardiovascular outcomes^[41].

Autoimmune diseases

The role of vitamin D in autoimmune diseases has been investigated in animal models as well as in humans. Studies using animal models of several autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and inflammatory bowel diseases, have identified vitamin D as a potential key modulator of significant processes in the autoimmune reaction^[42-44]. However, the benefits of taking vitamin D supplements need additional supporting data.

Cancer

The role of vitamin D in cancer has been the subject of many studies in animal and human models. *In-vitro* data on a variety of cancer cells have clearly demonstrated that calcitriol [1,25(OH)₂D₃] directly stimulates apoptosis and inhibits proliferation of tumor cells^[45]. Calcitriol also inhibits angiogenesis, invasion and tumor progression^[46]. Animal models of cancer, particularly of breast cancer, have shown that vitamin D has a strong beneficial effect on tumor-initiation, tumor-progression and metastasis^[47].

Numerous studies suggest that circulating 25(OH)D levels are inversely associated with the risk of developing several types of cancer^[48]. Furthermore, some studies have reported an association between low 25(OH)D levels and cancer progression and recurrence^[49,50].

However, large human RCTs are lacking and the bulk of evidence comes from epidemiological data in breast, colon and prostate cancer^[51]. Small human trials have shown a beneficial effect or no effect at all, and recent meta-analyses have been inconclusive^[25,26]. An international effort is now underway to determine the effect of vitamin D on both cancer and cardiovascular outcomes^[52].

Obesity and fat distribution

Obesity has become an epidemic^[53]. For example, in the United States the combined percentage of overweight and obese children and adolescents is 32%, and for young adults is 66%^[54]. Vitamin D deficiency and vitamin D insufficiency are prevalent in these populations, especially in populations of low socioeconomic background^[54,55]. Several studies have shown an inverse correlation between obesity in adults and 25(OH)D levels^[56-62], and it has been argued that 1 α ,25(OH)₂D may be involved in the inhibition of adipogenesis^[63].

Interestingly, it has been noted that the 25(OH)D levels were substantially lower in obese adults who consumed supplemental vitamin D₂ and were exposed to UV light as compared to non-obese matched controls^[60].

Several studies in adults demonstrate that obesity is associated with vitamin D insufficiency^[56-60,62,64], and that low intake of vitamin D is an independent predictor

of obesity^[61]. Another study in postmenopausal women who consumed vitamin D reported a small but significant effect on weight gain prevention compared to placebo controls^[65].

The underlying mechanisms are still elusive but 1 α ,25(OH)₂D has been shown to lower leptin levels and may thus influence the body mass maintenance^[66].

In addition, vitamin D could also be trapped in fat tissues, thus body fat itself may be a factor which lowers the circulating 25(OH)D levels^[50,60]. Thus, obesity maybe a direct outcome of vitamin D insufficiency and/or may be a cause of vitamin D insufficiency^[7].

Kremer *et al*^[7] found a strong inverse correlation between body mass, weight and circulating vitamin D. A stronger association was found with visceral fat suggesting that fat distribution was affected by vitamin D. They also demonstrated that 25(OH)D was inversely correlated not only with total body fat, but also with specific features of visceral fat and sub cutaneous (SC) fat. This study showed a stronger association with visceral fat, suggesting that vitamin D targets more specifically a fat compartment related to cardiovascular complications.

Vitamin D and height

In their research population, Kremer *et al*^[7] described a positive correlation between circulating 25(OH)D and height. Although vitamin D is considered as an important factor in skeletal development and rickets may be associated with vitamin D deficiency^[17], none of the subjects in the study had any evidence of rickets (clinical or radiological).

Decreased height was also significant in adolescent girls, who had vitamin D deficiency without any clinical manifestation of rickets^[18]. The mechanism(s) underlying these unique observations remain(s) to be elucidated, and whether vitamin D has a direct or indirect effect on bone size and growth remains to be determined.

Overall, vitamin D insufficiency/deficiency has been associated with numerous health problems, such as osteoporosis, diabetes, rheumatoid arthritis, and even cancer^[67-69]. It has also been associated with increased body fat, which by itself carries a greater risk of diabetes and cancer^[70]. Consequently, vitamin D insufficiency/deficiency may play a significant role in the development of various and important clinical conditions through multiple mechanisms.

DEFICIENCY OF VITAMIN D IN CHILDREN

Breastfed infants are at higher risk of vitamin D deficiency because the content of vitamin D in the mother's milk is totally dependent of her vitamin D intake. The regular content of vitamin D in breast milk is normally insufficient to provide the baby with his daily requirements^[4,71].

The high prevalence of vitamin D insufficiency in the pediatric age group is surprising and likely to be multifactorial.

The rapid growth in childhood requires sufficient

nutrients, including vitamin D. Consequently, the children population has indeed a high risk of developing vitamin D deficiency, which was demonstrated by many studies^[1,2].

Considerable changes have occurred in lifestyles and childhood activities in the past 20 years. Children are now more sedentary and no longer routinely play outside for long periods. Voortman *et al*^[72] reported that children who spend less time on outdoor activities actually had lower serum levels of vitamin D.

In addition, children with obesity are more likely to have low vitamin D levels^[73]. This is partly attributable to lifestyle factors but also it is thought that vitamin D and its metabolic product, 25(OH)D, are sequestered in body fat, thereby making them unavailable when required^[60].

It has also been reported that in children, vitamin D deficiency is associated with metabolic syndromes^[73,74].

Weng *et al*^[55] reported that insufficiency of vitamin D was frequent in children living in the northeastern area of the United States. It was associated with the season of the year, ethnicity (black race), age, and level of vitamin D intake.

A study from Southeastern China^[75] evaluated the vitamin D status of 5571 young children aged 1-3 years living in Wuxi. Although there was a low prevalence of vitamin D deficiency in this population, the risk of vitamin D deficiency was increased as the children grew older, implying development of an imbalance between the nutritional intakes and requirements.

The observation that children and adolescents demonstrate an increased prevalence of both vitamin D insufficiency and obesity, implies that vitamin D may be an independent predictor of weight gain^[60,73]. As previously mentioned, several studies in the adult population have also demonstrated that insufficient levels of vitamin D are associated with obesity^[56-60,62,64], and that low intake of vitamin D may serve as an independent predictor of obesity^[61].

VITAMIN D DEFICIENCY IN ISRAEL

The status of vitamin D deficiency in Israel was investigated in about ten studies over the last decade, and demonstrated a considerably high prevalence of vitamin D deficiency and insufficiency. Several studies were carried out in the elderly population^[76], Ethiopians^[77,78] and Bedouins^[79].

One study compared vitamin D levels in orthodox and non-religious women and showed increased prevalence of low 25(OH)D levels in both populations, even in the summer, but orthodox women had significantly lower 25(OH)D levels^[80]. Vitamin D deficiency/insufficiency was also observed in soldiers^[81], in hospitalized patients^[82] and teenagers^[83]. In a study of Orthodox Yeshiva male students, severe vitamin-D deficiency was prevalent in ultra-Orthodox males^[84].

Additional research^[85] included 204 children in 2 clinics in Jerusalem. The vitamin D levels declined gradually with age, with the lowest levels observed mostly in the 10-19

years old age category.

In an ecological study made on a representative sample of the population of Israel in 2010^[86], it was found that 78% had vitamin D insufficiency (< 30 ng/mL). Vitamin D levels were higher in infants as compared to older age groups. As may be explained by the level of skin darkness, Israelis of Ashkenazi origin had higher vitamin D mean levels than those of Sephardic origin who, in turn, had higher vitamin D levels than Arab subjects (Table 1).

A large study^[87] among 198834 members (mostly adults) assessed vitamin D status among demographic subgroups in Israel. Vitamin D deficiency (vitamin D levels below 25 nmol/L), was detected in 14.4% of the subjects tested.

RECOMMENDATIONS

Historically, humans were designed to synthesize vitamin D naturally obtained through the action of the sun. However, this source of endogenous production of vitamin D proved to be inadequate due to the migration of populations to the Northern hemisphere and to the changes in cultural habits. Although vitamin D is present to various degrees in food products (oily fish, egg yolk, fortified cereals and spreads, Shitake mushrooms, etc.), these food products are not usually preferred by children. Thus, in children it would be difficult to implement recommendations based on nutrition alone in order to obtain the recommended daily amounts.

Furthermore, the natural vitamin D production through exposure of the skin to sunlight is prevented in several high risk populations. People with darker pigmented skin need considerably more exposure to the sun to generate the same vitamin D amounts due to the presence of melanin, which acts as a natural sunscreen. Increased prevalence of deficiency/insufficiency was identified in certain populations who wear clothing to cover the body for religious or cultural reasons^[88,89].

Finally, health promotion campaigns promoting safe sun exposure to lower the risk of skin malignancies may be contributing to reduced levels of vitamin D. Sunscreen with a factor of 8 or above blocks enough UVB rays to reduce the skin's ability to synthesize vitamin D by approximately 95%^[88].

In addition, fat malabsorption seen in individuals with Crohn's disease, certain liver conditions and gastric bypass surgery is associated with low vitamin D absorption by the small intestine and a higher risk of vitamin D deficiency^[44]. It is therefore important to identify those populations at increased risk and offer appropriate advice and supplementation (NICE 2014)^[90].

Simple and effective preventive measures could be implemented by providing vitamin D as oral preparations of vitamin D3 (cholecalciferol) derived from animal sources, or vitamin D2 (ergocalciferol) derived from vegetable sources.

Although Armas *et al*^[91] found that ergocalciferol is less easily absorbed, both forms can be prescribed. In

Table 1 Main reports on vitamin D deficiency in children

Prevalence	Age group	Place	Year	Ref.
In infants 0.4% - deficient (< 25 nmol/L) 33.6% - insufficient (< 75 nmol/L)	1 mo-16 yr	Hangzhou, China	2012	[1]
2-5 yr stage (preschool) 1.1% - deficient 68.6% - insufficient				
6-11 yr (school age) 2.0% - deficient 88.3% - insufficient				
Adolescents 3.3% - deficient 89.6% - insufficient				
86% - deficient (< 37 nmol/L) 38.3% - severely deficient (< 12.5 nmol/L) 91.7% - insufficient (< 50 nmol/L)	9-12 yr	Tehran, Iran	2007-2008	[2]
66.7% - insufficient (< 75 nmol/L), 23.6% - deficient 6.2% - severely deficient (< 25 nmol/L)	6 yr (school age)	The Netherlands	2015	[72]
Obese subjects 12.7% - deficient (< 30 nmol/L) 92% - insufficient (< 75 nmol/L)	6-16 yr	North Texas, United States	2012	[73]
Non-obese subjects 3.4% - deficient 68% - insufficient				
34% - insufficient 62.2% - deficient	8-16 yr	Izmir, Turkey	2012	[74]
31.0% - deficient 65.0% - insufficient	7-11 yr	Zanjan, Iran	2015	[71]
55% - insufficient (< 75 nmol/L) 5% - deficient (< 25 nmol/L)	6-21 yr	Northeastern United States	2007	[55]
55% - insufficient (< 75 nmol/L) 0.8% - deficient (< 30 nmol/L)	1-3 yr	Wuxi, China	2014-2015	[75]
Age < 5 yr 52.4% - insufficiency 19% - deficiency	1-50 yr	Israel	2008	[86]
Age > 5 and < 20 yr 79.4% - insufficiency 26.5% - deficiency				

Worldwide prevalence of vitamin D deficiency/insufficiency in infants, children and adolescents. Vitamin D deficiency was defined as 25(OH)D levels of $\leq$ 25 nmol/L and vitamin D insufficiency as 25(OH)D levels of $\leq$ 75 nmol/L.

subjects with decreased capacity of intestinal absorption or to improve compliance, cholecalciferol can be administered by intramuscular injection, using various regimens ranging from monthly to yearly injections^[92].

Recommendations from the Institute of Medicine of the National academies^[4] are as follows: 400 IU in newborn and infants from 0-13 mo, 600 IU from 1 to 70 years of age and 800 IU over 70 years of age.

The recommended doses for supplementation listed in the British National Formulary for Children are 400

IU daily for neonates and 400-600 IU daily for children aged one month to 18 years^[93].

However, implementation of these recommendations has been less successful than anticipated due to healthcare professionals' lack of knowledge and confusion over dosage and available products^[94-96]. There are preparations that contain also 100% of the recommended daily amount of vitamin A. Therefore, if the amount of vitamin D required is greater than 400 IU - alternative products should be considered in order to avoid vitamin A

toxicity.

Another possible complication can be caused in cases of prescribed products that not only provide vitamin D but are combined with calcium, especially in children over 12 years of age. In addition to the fact that calcium increases the unpalatability of the preparation, additional calcium supplements are not required for the great majority of children who obtain it in sufficient amounts from their diet. There may also be additional risks of calcium supplementation such as those reported on cardiovascular outcomes in adults^[97]. The risks appear to be moderate, but the long-term effects have not been investigated. Although the risk of hypercalcemia occurring during treatment with cholecalciferol is rare, and those incidents have occurred in infants or in children/adults receiving much higher doses than are normally prescribed^[98,99], the risk of hypercalciuria and kidney stones has not been thoroughly investigated even at lower doses^[100]. Consequently, in the absence of strong evidence for the added benefit of calcium and its inherent risks, calcium supplementation should be avoided.

A consensus statement from a group of leading experts on vitamin D and osteomalacia^[96] recommended the global adoption of the following: (1) Vitamin D supplements for all pregnant and lactating women; (2) Vitamin D supplements for all infants (as given in Israel for many years); (3) Vitamin D supplements for individuals in high-risk groups; and (4) Worldwide implementation of programs for food fortification to ensure nutritional sufficient amounts of vitamin D and calcium for the entire population.

The recommended amounts of preventive supplements of vitamin D currently advised according to the consensus statement are: (1) For all infants from birth to 12 mo of age - recommended dose of 400 IU/d (10 µg), which is adequate to prevent rickets, independently of their mode of feeding; (2) Beyond 12 mo of age, the nutritional requirement for vitamin D is at least 600 IU/d (15 µg), through diet and/or supplementation. The candidates for preventative vitamin D supplementation in this age group, in the absence of food fortification: Children with a history of symptomatic vitamin D deficiency who required treatment; and children and adults at high risk of vitamin D deficiency, with factors or conditions that reduce synthesis or intake of vitamin D; and (3) In healthy children, routine screening for 25(OH)D is not recommended, and therefore, no specific 25(OH)D threshold for vitamin D supplementation is targeted in this population.

SUMMARY

Vitamin D is known to play a significant role in bone metabolism, muscle strength, musculoskeletal health, and is also related to a number of non-skeletal diseases. Its deficiency has been related to many health conditions including osteoporosis, diabetes, rheumatoid arthritis and cancer.

Vitamin D deficiency is prevalent in the elderly population, but it can also appear in the pediatric population. This is mainly due to changes of lifestyles and childhood activities in the past decades. Children are now more sedentary and no longer routinely play outside for long periods.

We strongly support the recommendations published recently that encourage supplementation of vitamin D to special populations (pregnant and lactating women, infants, and high risk groups). We also recommend that international food fortification programs be implemented to ensure nutritional sufficiency of vitamin D and calcium for the entire population.

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Imaging of the pediatric thymus: Clinicoradiologic approach

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Abstract

The thymus is a lymphatic organ that undergoes dynamic

changes with age and disease. It is important to be familiar with these physiological changes in the thymus gland to be able to identify pathology and make an accurate diagnosis. The thymus may be involved in multisystem disorders or show focal isolated lesions. The aim of this article is to review the radiological anatomy of the thymus, normal variants, and pathology including hyperplasia and benign/malignant lesions involving the thymus gland in the pediatric age group. We also propose an algorithmic approach for imaging evaluation of a suspected thymic mass on the basis of morphologic features.

Key words: Thymus; Pediatric; Thymus hyperplasia; Thymus neoplasms; Mediastinum

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Core tip: It is important for clinicians to be able to identify normal variations in thymic appearance and avoid over-investigation. However, it is equally important to have a high index of suspicion for abnormal thymus especially in multisystem disorders. We discuss normal variants, hyperplasia and focal masses; and propose an algorithmic approach to the evaluation of a suspected thymic mass based on imaging morphology.

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INTRODUCTION

The thymus is a lymphatic organ which is responsible for T cell immunological function. It is the first of the lymphoid organs to be formed and grows considerably in infancy^[1]. It attains maximum weight at puberty and gradually becomes replaced by fat and involutes with age. Fibrofatty

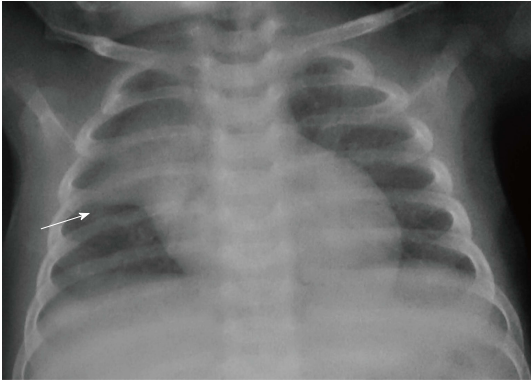


Figure 1 Frontal chest radiograph in an 11-mo-old boy with mild respiratory distress reveals normal thymus with characteristic “sail sign” (arrow).

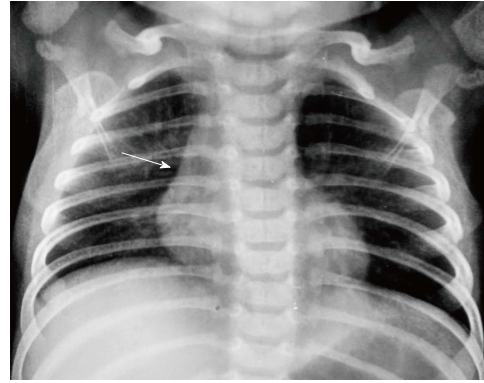


Figure 3 Frontal chest radiograph of a 2-year-old boy showing the inferior margin of the thymus merging with the cardiac silhouette - the “notch sign” (arrow).

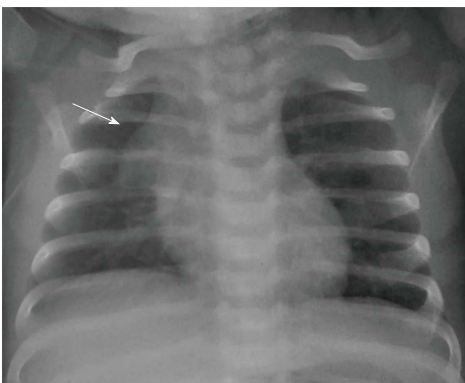


Figure 2 Frontal chest radiograph of a 2-mo-old girl with cough. The thymus gland is prominent but normal. Note the impression of the anterior ribs on the thymus producing the “wave sign” (arrow).

atrophy occurs more rapidly in young adult men than women^[2]. However, it can grow back at any time in life especially after periods of stress^[3].

As the thymus undergoes dynamic changes more so in the pediatric population, familiarity with the embryology, anatomy and pathology of the thymus gland is essential for radiologists to make an accurate diagnosis and avoid unnecessary biopsies and interventions.

The aim of this article is to review the radiological anatomy of the thymus, normal variants, and pathology including hyperplasia and benign/malignant lesions involving the thymus gland in the pediatric age group and propose an algorithmic approach for imaging evaluation of a suspected thymic mass.

IMAGING MODALITIES

Conventional radiography

The thymus gland is usually visible but difficult to differentiate from the cardiac silhouette on frontal chest radiographs in young children; and also may be mistaken for a mass lesion.

The normal thymus has a soft tissue density and smooth borders and numerous radiological signs have been described to aid its differentiation from a mediastinal

mass. The “thymic sail sign” is seen as a triangular extension of the normal thymus laterally. The right lobe of the thymus has a convex lateral margin and the straight inferior border gets demarcated by the minor fissure which gives the sail like appearance (Figure 1). The anterior reflections of the ribs produce a wavy contour of the thymus known as the “thymus wave sign” (Figure 2)^[4]. It has no mass effect on vascular structures or airway. The inferior margin of the thymus merges with the margin of the cardiac silhouette, producing the “notch sign” (Figure 3)^[5].

The imaging appearance of thymic masses on conventional radiographs can be variable from that of an anterior mediastinal mass to a hilar mass. Small masses may be seen as subtle mediastinal widening or a paratracheal bulge whereas larger masses can even extend up to the cardiophrenic angle.

Ultrasound

On ultrasound, the thymus appears homogenous with echo texture similar to the liver but less than the muscle^[6] and shows multiple echogenic foci or strands. These hyperchoic foci give a “starry sky” appearance (Figure 4) and help to identify thymic tissue^[3]. The characteristic ultrasound appearance is also helpful to identify normal anatomical variants like cervical or retrocaval extension of the thymus. The shape of the thymus can be seen to vary with cardiac and respiratory movements on real-time ultrasound, and this finding helps to differentiate it from solid tumors and infiltrative diseases^[3].

Ultrasound also helps to identify the solid or cystic nature of a suspected thymic mass and the presence of any fat or calcification within^[7]. It is also useful for image guided aspiration or biopsies of thymic masses. Being a low cost, portable and easily available modality with lack of ionizing radiation, sonography is useful as first line investigation for the evaluation of suspected thymic pathology^[8].

Computed tomography

The thymus is seen in the anterior mediastinum as a

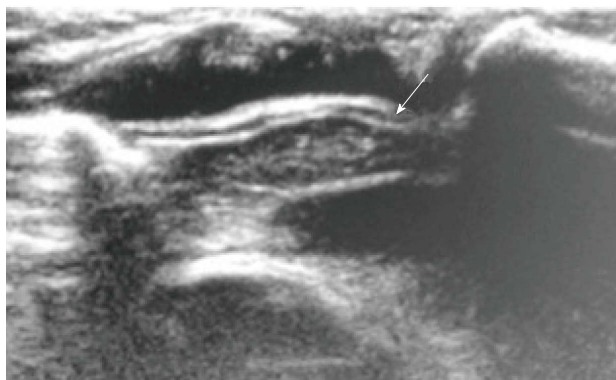


Figure 4 Normal sonographic (longitudinal view) appearance of the thymus gland in a 2-year-old boy with suspected mediastinal widening on chest radiograph. The thymus is hypoechoic with multiple internal echogenic foci giving the characteristic "starry sky" appearance (arrow).

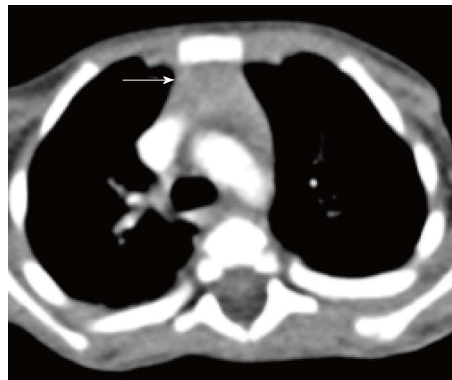


Figure 5 Normal appearance of the thymus on computed tomography scan of a 3-year-old boy. Axial contrast-enhanced computed tomography section shows homogenous soft tissue density structure (arrow) in the anterior mediastinum. Note that there is no compression of the vascular structures or airway.

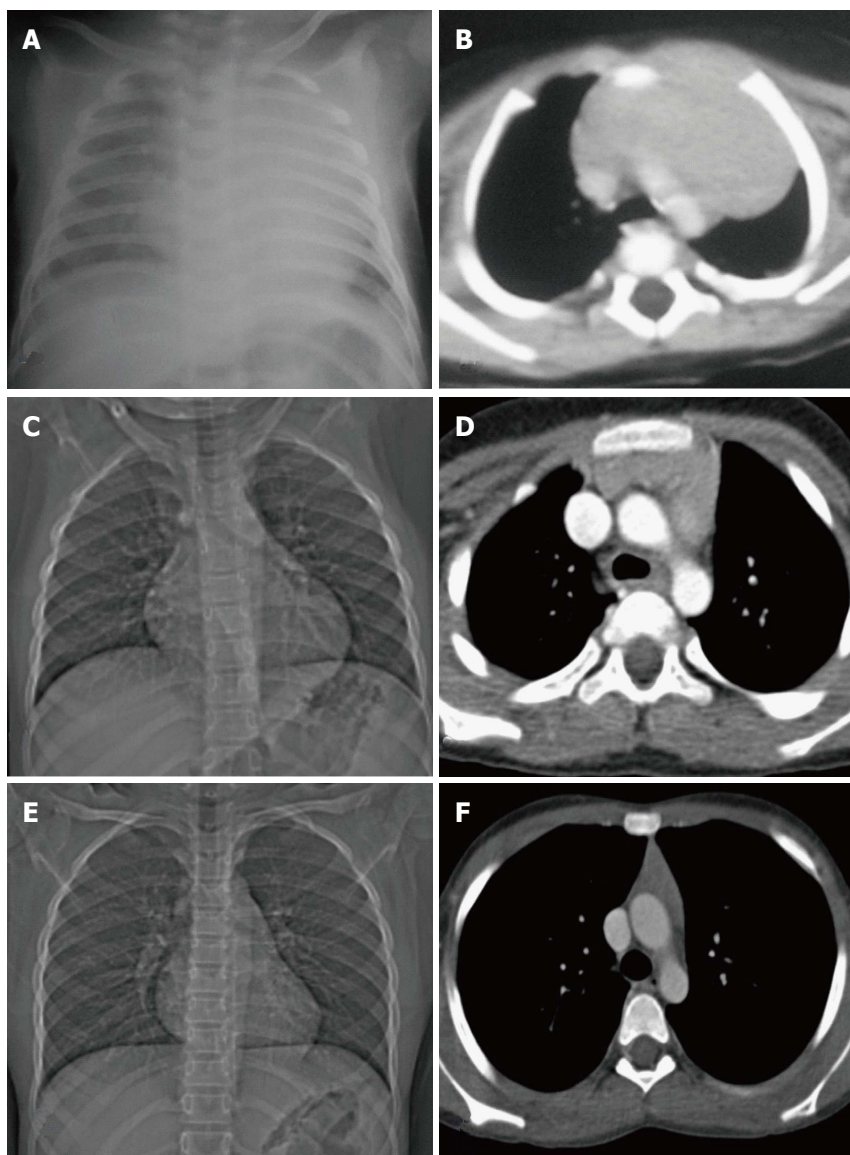


Figure 6 Normal variation in the appearance of the thymus with age. Frontal radiographs and CECT axial images at ages of (A, B) 2 mo, (C, D) 7 years and (E, F) 12 years. Note that the initial prominent bilobed thymus in a neonate assumes a quadrilateral shape with convex margins in early childhood. Gradually it assumes a triangular configuration with straight margins. The CT density also decreases with age with fatty replacement occurring in adults.

quadrilateral shaped soft tissue density structure with convex margins (Figure 5). It is located anterior to the proximal ascending aorta, the pulmonary outflow tract,

and the distal superior vena cava^[9]. With increasing age (Figure 6), it becomes triangular in shape with straight or concave margins.

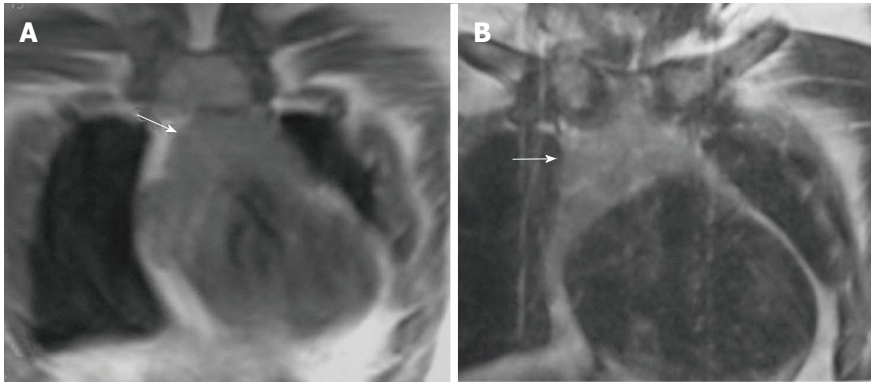


Figure 7 Normal appearance of the thymus on magnetic resonance imaging in a 1-year-old boy. Coronal T1WI (A) and T2WI (B) show that the signal intensity of the thymus gland is homogeneous (arrow in A and B), greater than that of the muscle on T1WI and isointense to that of fat on T2WI.

Table 1 Significance of imaging the thymus in various clinical settings

Clinical setting	Possible imaging finding(s)
Myasthenia gravis	Thymoma Thymic hyperplasia
Suspected immunodeficiency disorder	Thymic hypoplasia Thymic aplasia
Incidental detection while imaging for other causes	Thymic cyst Thymic hyperplasia Lymphangioma Vascular malformation Castleman's disease Thymolipoma
Fever evaluation	Lymphoma Abscess
Detected during evaluation of other multisystem disorders	Lymphoma Langerhans cell histiocytosis

The size of the thymus (Figure 6) also varies with age and has been extensively studied by cross-sectional imaging^[9,10]. The mean thickness of a normal thymus can vary from 0.5 to 1.1 cm as reported by Baron *et al*^[9]. Computed tomography (CT) density of the thymus has also been reported to decrease with age in children (from 80 HU to 56 HU) likely due to fatty replacement and cellular involution^[11].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) evaluation of the thymus includes T1- and T2-weighted image acquisition in the axial plane and either sagittal or coronal or both planes. Cardiac gating is usually not required. Appropriate coil as per the age of the patient is selected - quadrature knee coil for small infants, head coil for small children, or surface coils as needed^[8].

The signal intensity of the thymus gland appears homogeneous and is greater than that of the muscle on T1-weighted images and of intermediate signal intensity on T2-weighted images (Figure 7). Fat saturation does not decrease the signal intensity of the thymus; however, chemical shift imaging has been used to assess the fatty replacement of the thymus and identify infiltrative disorders^[12]. MRI is able to define size more accurately because of better contrast resolution. The thickness has

been found to be greater at MRI than CT scan (15-20 mm between ages 20 and 70 years) as reported by de Geer *et al*^[10].

THYMIC DISORDERS

Thymic lesions may be seen in systemic disorders or as a part of manifestation of specific disease entities (Table 1), like myasthenia gravis and immunodeficiencies. However, most of the thymic lesions are seen as incidental findings while imaging for other causes^[13].

We have classified thymic disorders into those presenting with small or enlarged thymus enabling the use of an imaging based approach (Table 2) in the diagnosis of thymic disorders.

SMALL THYMUS

In a neonate, the normal thymic shadow on the frontal radiograph should be more than twice the width of the third dorsal vertebra. Smaller dimensions characterize thymic involution or hypoplasia^[5].

Involution

Involution is seen normally as an age related decrease in the thymic size^[8]. When the normal size thymus gland decreases in size in response to any stress (*e.g.*, sepsis, major surgery, use of steroids or other immunosuppressants), it is known as thymic atrophy. It is usually transient and the thymus returns to normal after the stress resolves^[8]. The thymus may decrease in size up to 40% of its original volume varying according to the severity and duration of the stress^[14].

Thymic hypoplasia and aplasia

Thymic hypoplasia and aplasia indicate a small or absent thymus (Figure 8) seen in immune deficiencies^[15]. These terms are most commonly used with DiGeorge syndrome. DiGeorge syndrome is due to the abnormal development of the third and fourth pharyngeal pouches and is characterised by variable T-cell deficiency. Cross-sectional imaging in this setting is useful mainly for the evaluation of cardiovascular anomalies. Immunodeficiencies with T-cell abnormalities like ataxia telangiectasia or severe combined

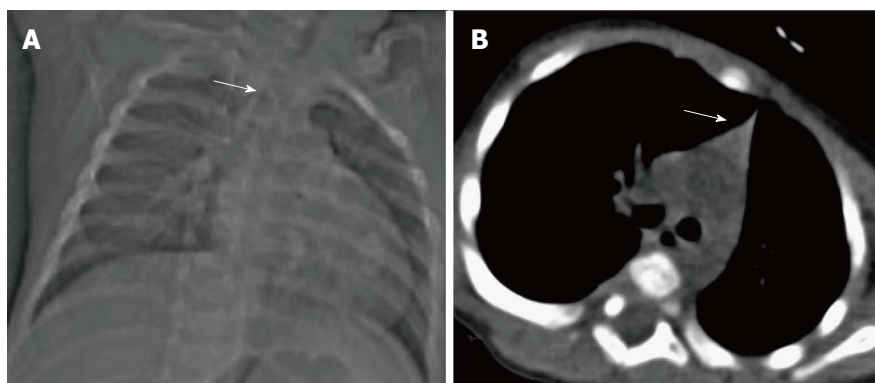


Figure 8 Thymic hypoplasia in a 3-mo-old male infant with primary immunodeficiency. CT scanogram (A) reveals small size of the thymus, i.e., less than twice the width of the third thoracic vertebra (arrow). NCCT chest axial section (B) shows triangular configuration of the thymus (arrow) with straight margins (normal appearance in adolescents). Compare this with the normal appearance of the thymus in a 2-mo-old infant (Figure 6A and B).

Table 2 Classification of thymic disorders according to the imaging appearance

Appearance/size of thymus	Diseases
Small thymus	Physiological Age related involution Treatment related atrophy Ectopic thymus Immunodeficiency disorders
	Hypoplasia Aplasia
Large thymus	Hyperplasia True hyperplasia Follicular hyperplasia
	Masses Cystic Thymic cyst Lymphatic malformation Germ cell tumor
	Solid Mild/moderate enhancement Lymphoma Thymoma Thymolipoma Thymic carcinoma
	Intense enhancement Hemangioma Castleman's disease Thymic carcinoid
	Mixed Infections (abscess/ tuberculosis) Germ cell tumor Langerhans cell histiocytosis

immunodeficiency syndrome are also associated with thymic aplasia or dysplasia^[16].

Ectopic and accessory thymic remnants

Ectopic and accessory thymic remnants can be found anywhere along the course of migration of the thymopharyngeal duct from the third and fourth branchial arches to the superior mediastinum. These can be solid or cystic in appearance and should be kept in the differentiation of pediatric neck swellings. In cases of ectopic location of the thymus, the mediastinal thymus may be small or absent. Accessory thymic tissue may be seen in the lower neck where anatomical contiguity with the relatively small mediastinal thymus can be established on imaging (Figure 9)^[3,12,13].

Table 3 Key morphologic features for differentiation of thymic hyperplasia from a thymic mass

Morphologic criteria	Hyperplasia	Mass
Enlargement	Diffuse, symmetric	Focal, asymmetric
Symmetrical		
Contour	Smooth	Nodular
Vessels	Normal	Random branching, encased
Necrosis	Absent	Maybe present
Calcification	Absent	May be present
Microscopic fat (on chemical shift MRI)	Present	Absent

Large thymus

Large thymus may be seen in hyperplasia or masses (which can be cystic, solid or mixed).

THYMIC HYPERPLASIA

There are two patterns of thymic hyperplasia histologically—true hyperplasia and lymphoid (follicular) hyperplasia.

True thymic hyperplasia

True thymic hyperplasia is characterized by an enlarged thymus gland which retains its organised structure. The shape of the gland may change from bilobed to oval^[17]. It is commonly seen in patients recovering from a recent stress such as infections, corticosteroid therapy, radiation therapy, chemotherapy, major surgery or burns. The thymus undergoes atrophy in response to stress; however, it can increase to its original size within 9 mo and may even increase in size to 50% or larger (Figure 10). This is known as rebound hyperplasia and is commonly seen in the pediatric population. True hyperplasia may also be seen in patients with systemic disorders like hyperthyroidism, sarcoidosis, or pure red cell aplasia^[14].

Lymphoid (follicular) hyperplasia

Lymphoid (follicular) hyperplasia is characterised by an increased number of lymphoid follicles and may not always be associated with thymic enlargement^[3]. It is associated with immunologically mediated disorders, including myasthenia gravis (Figure 11), systemic lupus erythematosus, rheumatoid arthritis, scleroderma, va-

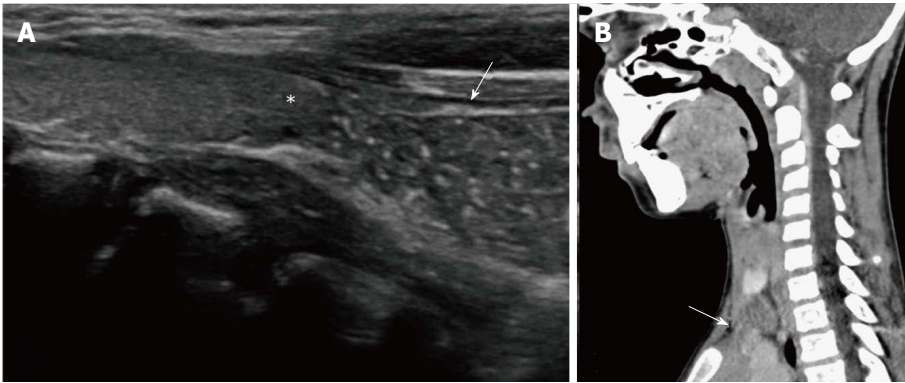


Figure 9 Cervical extension of the thymus in a 7-year-old male presenting with a lump in the neck. USG (A) shows the characteristic "starry sky appearance" of the left lower cervical swelling (arrow) lying near the inferior pole of the left lobe of the thyroid (asterisk). CECT sagittal reformatted image (B) documents the anatomical contiguity (arrow) of this swelling with the mediastinal thymus.

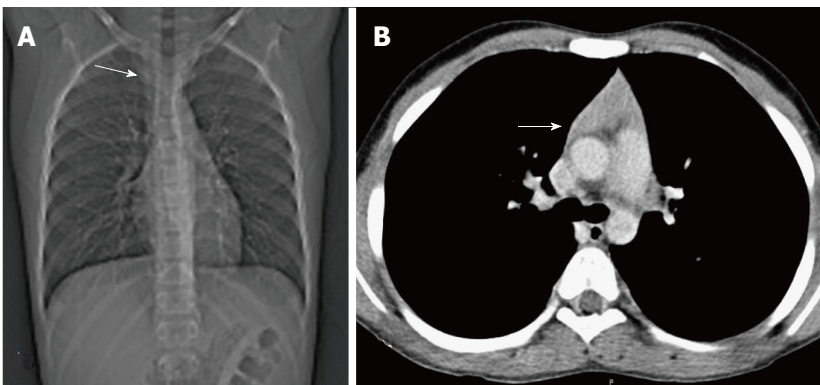


Figure 10 Thymic hyperplasia in a 12-year-old boy treated for Hodgkin's lymphoma for 8 mo. CT scanogram (A) shows subtle mediastinal widening (arrow). CECT axial section (B) shows mild thymic enlargement with convex margins and homogenous density (arrow) consistent with rebound hyperplasia.

sculitis, thyrotoxicosis, and Graves' disease^[3,12]. On conventional radiographs the thymus is usually of normal size and on CT it may appear normal (45% of cases), enlarged (35%) or as a focal mass (20%)^[14].

Identifying thymic hyperplasia and differentiating it from neoplasms

It is important to be able to identify thymic hyperplasia and differentiate it from neoplasms (Table 3). In thymic rebound hyperplasia there is a diffuse symmetric enlargement of the thymus gland, with a smooth contour and normal vessels. Thymic neoplasia, however, presents as a focal mass with nodular contour, contrast enhancement and heterogeneous appearance with areas of necrosis or calcification^[18].

The normal thymus and thymic hyperplasia have microscopic fat, which is detected on chemical shift MRI. Thymic hyperplasia thus demonstrates a decrease in signal on opposed-phase images when compared with in-phase images. Thymic tumours do not contain microscopic fat and there is no drop in signal on the opposed phase images^[2]. The chemical shift ratio (CSR) is calculated to assess the presence of microscopic fat and tissue within the same voxel and a CSR less than 0.9 is considered diagnostic for microscopic fat within a

thymic lesion^[19].

CYSTIC THYMIC MASSES

Thymic cyst

Thymic cysts are fluid containing lesions, usually found in adults. Of all the mediastinal masses in children, thymic cysts account for less than 1%^[8]. These can be congenital or acquired. The congenital cysts are found along the course of the thymopharyngeal duct in the neck or anterior mediastinum. Acquired cysts can be seen post radiotherapy for Hodgkin's lymphoma, after thoracotomy or as a cystic change in thymic tumours with inflammatory cysts usually seen in autoimmune disorders^[20]. On plain radiographs, thymic cysts are seen as homogenous, well-circumscribed masses of water density. CT reveals a homogenous fluid attenuating lesion with thin smooth walls and no solid component (Figure 12). There may be occasional internal septations or mural calcification. Presence of proteinaceous contents or hemorrhage results in increased attenuation and on MRI, an increase in T1 signal intensity^[12,14].

Lymphatic malformation

Lymphatic malformation (previously known as lymph-

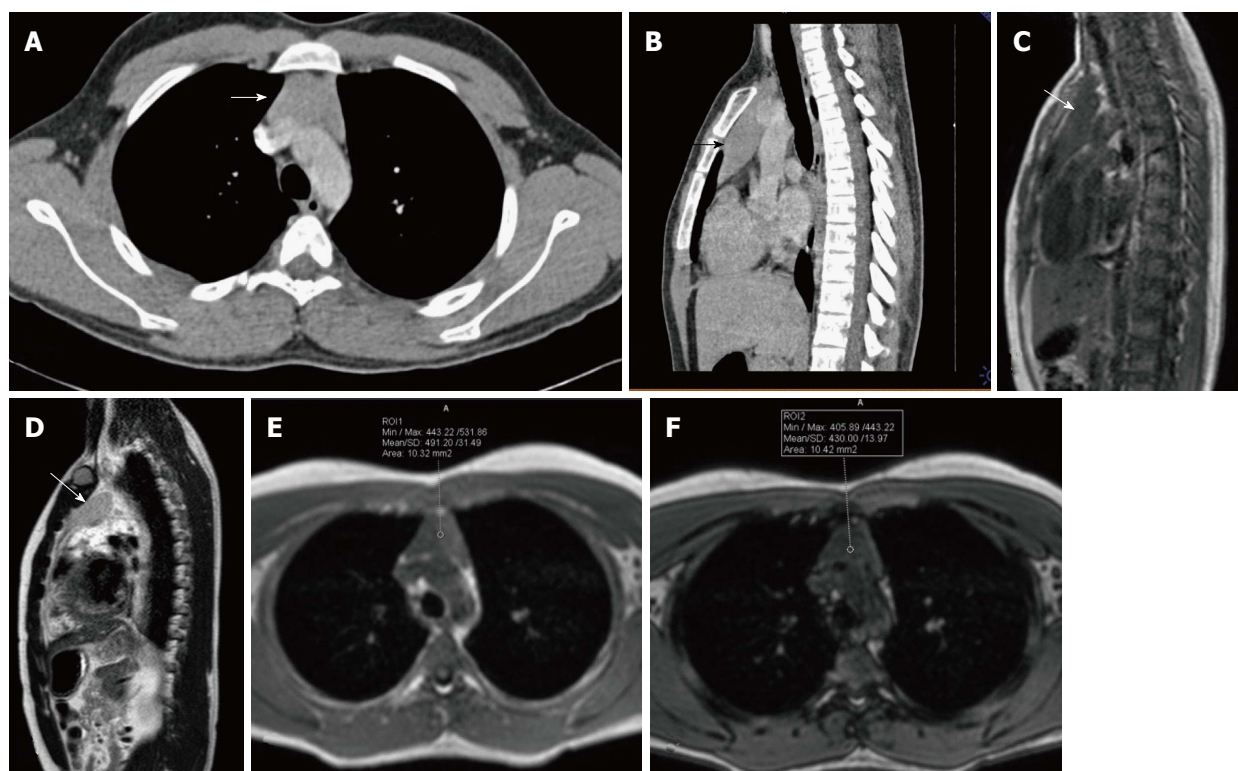


Figure 11 A 16-year-old male patient with myasthenia gravis. CECT axial (A) and sagittal (B) sections showing mild diffuse symmetric enlargement of the thymus gland with a smooth contour (arrow in A and B). Sagittal T1WI (C) and T2WI (D) of the chest show that the thymus (arrow in C and D) is of homogenous signal intensity (isointense to skeletal muscle on T1WI and hyperintense on T2WI). Axial T1WI show a decrease in signal on opposed-phase image (F) when compared with in-phase image (E). The findings are consistent with thymic hyperplasia.

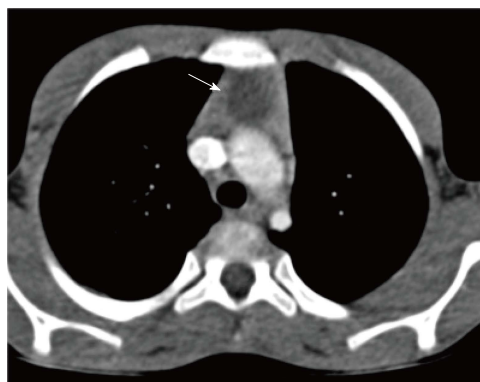


Figure 12 Thymic cyst in a 14-year-old boy treated for Hodgkin's lymphoma. CECT axial section reveals a small well-defined fluid-attenuating lesion (arrow) suggestive of cyst in the thymus.

angioma or cystic hygroma) consists of cysts lined by the endothelium and containing lymph. Commonly seen in the cervical region, these lesions present with neck swelling early in life. The cervical lesions may have a mediastinal extension with occasional involvement of the thymus. Cross sectional imaging shows a well-defined, multilocular cystic mass with multiple septations. CT density can be variable within the locules, with high density seen in case of hemorrhage or proteinaceous content (Figure 13). The signal intensity of such locules is high on T1WI and intermediate on T2WI. Post contrast imaging shows

enhancement of the wall and septations but not of the internal contents (Figure 14)^[21].

Mature germ cell tumour

Germ cell tumours arise from the primitive germ cells and can occur anywhere along their path of migration to the gonads. The most common location of extragonadal germ cell tumours is the anterior mediastinum, where they can develop within or near the thymus. It is believed that the cellular origin of mediastinal teratomas may lie within the embryonic thymic tissue^[22]. In the pediatric age group, germ cell tumours account for about 25% of the mediastinal tumours^[3]. Approximately 80% of these are benign or mature teratomas^[14].

Mature teratomas are usually asymptomatic and seen as an incidental finding on chest radiograph. However, symptoms may occur because of mass effect or complications. These include chest pain, hemoptysis, fever and rarely trichoptysis^[22].

On plain radiographs, both benign and malignant tumours are seen as round, lobulated and sharply margined masses located in the anterior mediastinum. Calcification, teeth or fat lucency may be identified within the mass^[3].

On cross sectional imaging, teratomas are seen as cystic masses with the presence of fat, teeth, bone or calcification. Mature teratomas are well-defined, lobulated fluid attenuating masses with a thin enhancing capsule

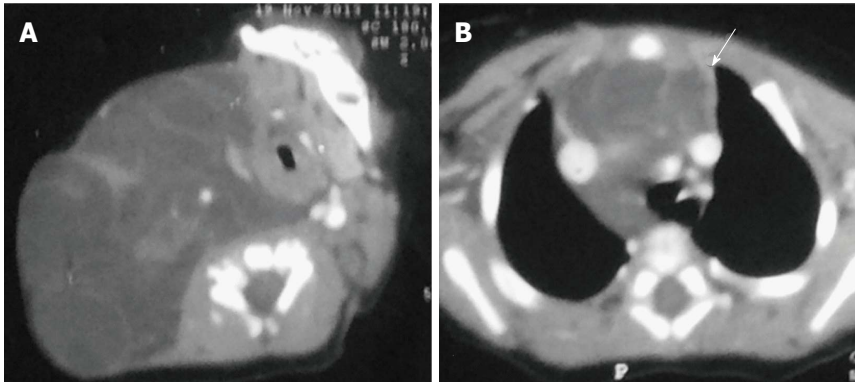


Figure 13 Thymic involvement by a large lymphatic malformation in a neonate diagnosed antenatally with cystic neck swelling. A: Contrast-enhanced CT scan shows a large right-sided poorly circumscribed, multiloculated low attenuation mass in the infrahyoid neck with extension into the posterior cervical and retropharyngeal space; B: Axial sections at the level of origin of arch vessels reveal involvement of the thymus (arrow) by this mass and extension into the anterior and middle mediastinum.

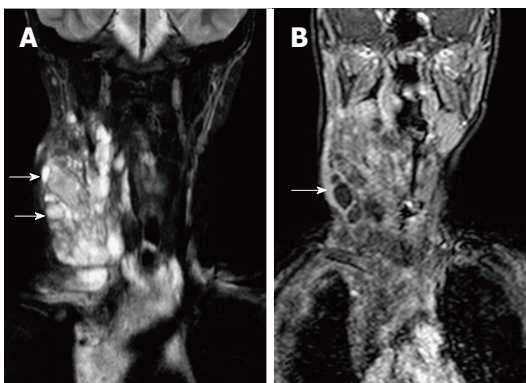


Figure 14 Lymphatic malformation in 13-year-old female patient. Coronal T2WI (A) shows a large, multilocular cystic neck mass with multiple septations. The mass is extending into the superior and anterior mediastinum. Note the variable signal intensity in different locules (arrows). On coronal post contrast T1WI (B), there is enhancement of the wall and internal septations (arrow).

and fat/calcification on CT. On MRI, the signal intensity varies according to the internal contents. Fat component has a high T1 and intermediate T2 signal intensity whereas fluid has a low T1 and high T2 signal^[3]. Calcific foci show evidence of blooming on gradient images.

Spontaneous rupture into the lung, tracheobronchial tree, pleural or pericardial space can occur, resulting in adjacent consolidation, atelectasis, pleural or pericardial effusion (Figure 15). In addition to these findings, the presence of internal inhomogenous densities within the mass, irregular tumor margins and bursting configuration of fat globules should raise the possibility of rupture^[23,24]. It is important for radiologists to identify these signs of rupture and guide clinicians in planning proper surgical management^[25].

Teratomas are well encapsulated lesions and usually can be completely resected. Surgical resection is indicated even in asymptomatic patients with incidentally detected mediastinal teratomas. This is because of the potential of pulmonary extension or rupture. Rupture of teratomas usually leads to adjacent inflammation and adhesions, which may complicate the surgery. Chemotherapy or radiotherapy is given in cases of malignant teratomas and imaging is required for evaluation of residual or recurrent disease^[22].

SOLID MASSES WITH MILD/ MODERATE ENHANCEMENT

Lymphoma

Lymphoma is the most common primary tumor in the pediatric age group followed by germ cell neoplasm^[26,27].

Thymic involvement in lymphomas and leukemias is rare and mostly associated with a systemic disease. It is more commonly seen in Hodgkin's disease compared to non-Hodgkin's lymphoma^[2,3].

Patients with Hodgkin's lymphoma have intrathoracic involvement in approximately 85% of cases. This can be in the form of nodal involvement, multiple pulmonary nodules or areas of consolidation. However, intrathoracic involvement is seen in only about 50% of cases of non-Hodgkin's lymphoma. Along with the enlarged mediastinal nodes there may be associated pulmonary nodules, consolidation, interstitial thickening, pleural effusion and pleural masses^[21].

When infiltrated by lymphomatous cells, the thymus gland is homogeneously enlarged. Imaging findings include diffuse thymic enlargement, solitary mass or multiple masses in the presence of mediastinal and hilar lymphadenopathy (Figure 16). In approximately 20% of cases, cystic change and calcification may be detected by pretreatment CT^[14].

On MRI, lymphomas are of low signal intensity on T1 and variable signal intensity on T2 weighted images^[14]. Usually, thymic involvement and nodal masses resolve after chemotherapy. However, in cases of a residual mass, low T2 signal intensity is suggestive of fibrosis and high signal intensity is suggestive of a residual tumour.

It is difficult to differentiate between a recurrent tumour and thymic rebound hyperplasia. Usually, thymic rebound hyperplasia has a symmetrical, smooth and homogenous appearance whereas a recurrent tumor is nodular and heterogeneous^[3].

Thymoma

Thymoma is a thymic epithelial tumor usually benign or of low-grade malignancy. It is usually seen in adults and is rare in children, accounting for less than 5% of the pediatric mediastinal tumours^[27].

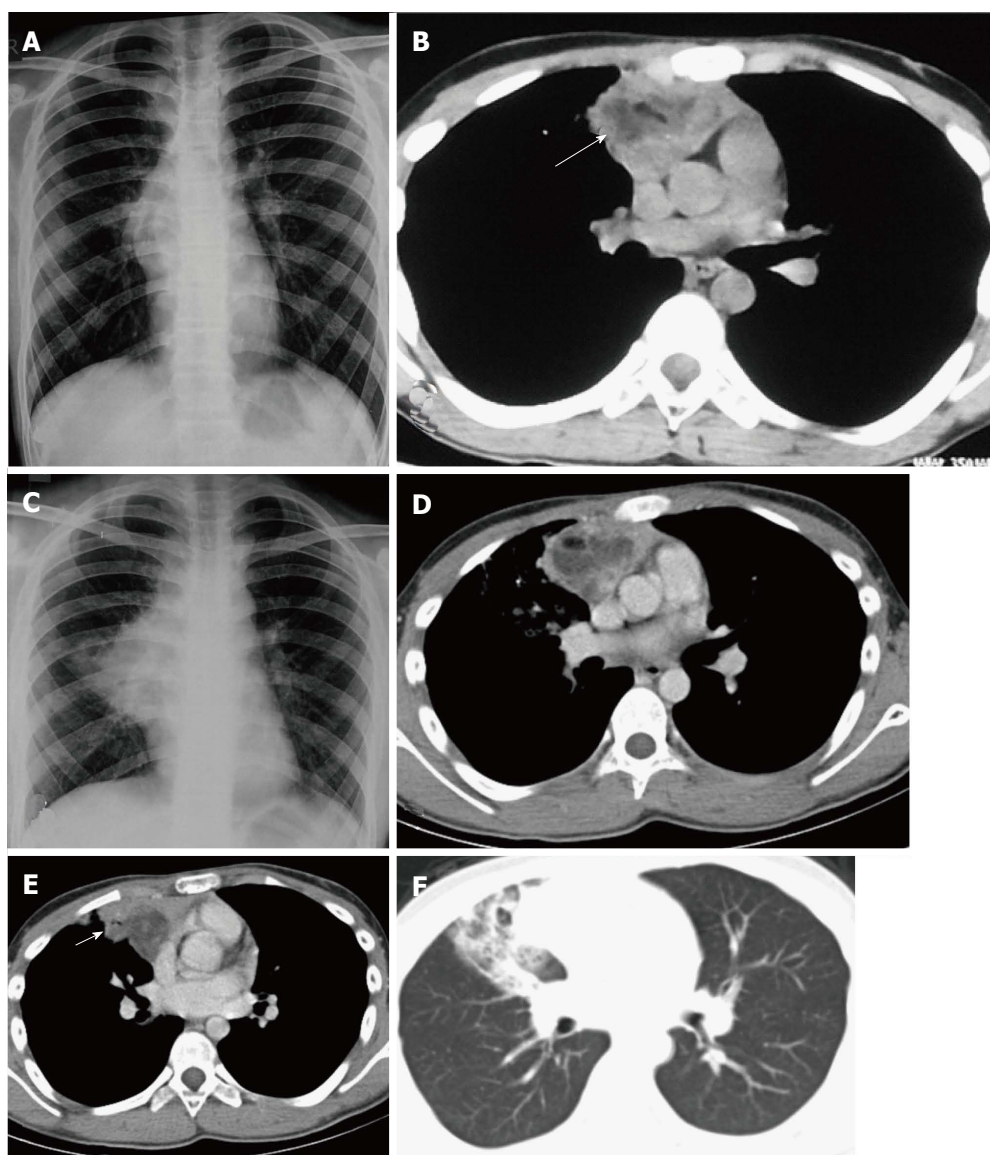


Figure 15 Ruptured anterior mediastinal teratoma in a 14-year-old male. Chest radiograph (A) shows a lobulated soft tissue mass in the right hilar region with obscured inferior margin. CECT axial section (B) shows a heterogenous mass in the anterior mediastinum with soft tissue, fluid and fat suggestive of anterior mediastinal teratoma. The patient refused surgery and presented 5 mo later, with complaint of cough and expectoration of foul smelling material. Chest radiograph (C) shows a large right hilar mass with irregular margins and patchy consolidation in the adjacent right mid zone. CECT (D) also demonstrates the increase in the size of the mass and irregular margins. There is evidence of small air foci (arrow in E) within this mass with adjacent consolidation suggestive of rupture into the tracheobronchial tree. Axial CT lung window (F) shows the adjacent ground glass and consolidation in the right middle lobe.

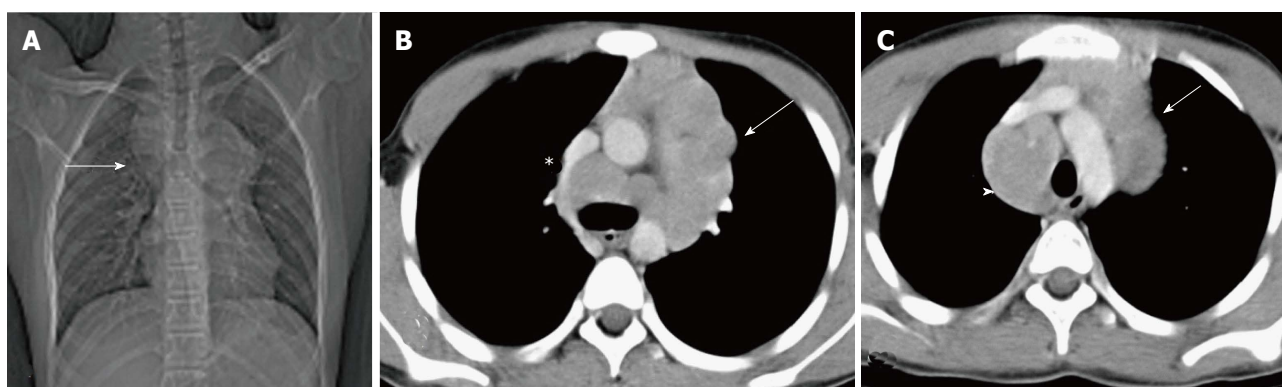


Figure 16 Hodgkin lymphoma in a 12-year-old boy presenting with fever and weight loss for 6 mo. CT scanogram (A) shows mediastinal widening (arrow) with lobulated contour. Axial CECT sections (B and C) reveal multiple, enlarged, homogenous lymph nodes in the region of the thymus (arrow in B and C) and paratracheal location (arrowhead in C). Note mild compression of SVC by this anterior mediastinal nodal mass (asterisk in B).

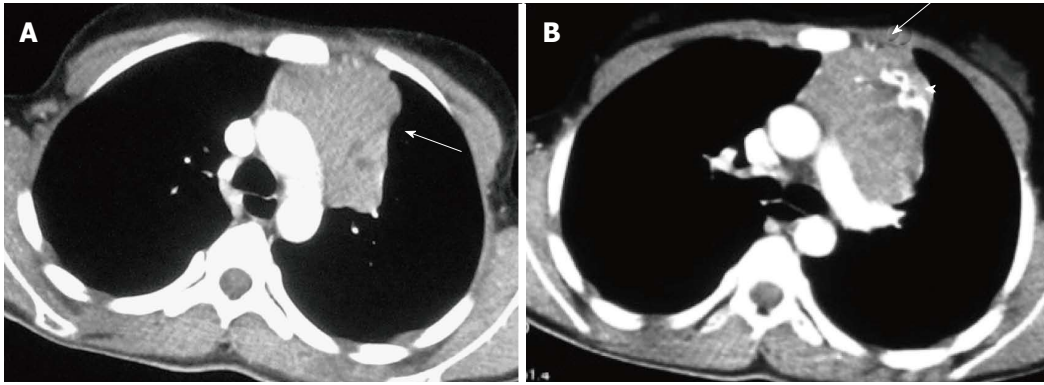


Figure 17 Invasive thymoma in a 13-year-old girl presenting with cough and chest pain. CECT axial images reveal a heterogeneously enhancing anterior mediastinal mass with irregular margins (arrow in A) and peripheral calcification (arrowhead in B). There is evidence of focal area of extension to subpleural region anteriorly (arrow in B).

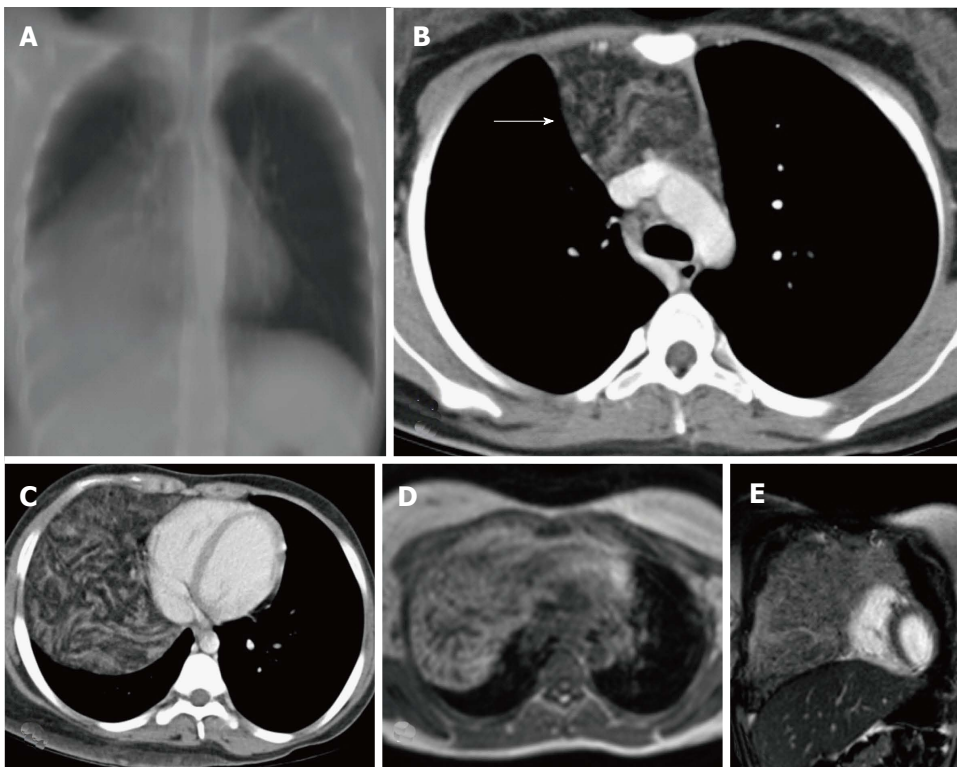


Figure 18 Thymolipoma in 17-year-old female. Thick MPR (multiplanar reconstruction) in the coronal plane (A) shows a large anterior and middle mediastinal mass with low attenuation and sharp margins. CECT axial images (B and C) reveal a large anterior mediastinal mass lesion extending into the right hemithorax. The mass is predominantly of fat attenuation (arrow in A). Note that there is no displacement of the heart or great vessels. Axial T1WI (D) and coronal T2WI (E) show a large heterogenous fat containing mass with intervening fibrous septa. The mass has predominantly hyperintense signal on T1WI and intermediate signal on T2WI consistent with fat.

Usually asymptomatic, thymomas are picked up as an incidental finding on chest radiographs. Association with myasthenia gravis is seen in 5% to 15% of the pediatric patients^[28]. Other associated conditions include pure red cell aplasia, hypogammaglobulinemia, connective tissue diseases and inflammatory bowel disease^[14].

On plain radiographs, thymoma appears as a well-defined mass of increased opacity in the retrosternal location with lobulated margins. CT reveals a homogenous, soft tissue density mass with sharp margins (Figure 17). The shape may be oval, round or lobulated. Calcification and cystic degeneration may occasionally be seen.

It is clinically important to differentiate invasive from non-invasive thymomas, as invasive thymomas require neo-adjuvant chemotherapy. The CT findings, which suggest invasion, include ill-defined margins, an irregular tumour-lung interface, encasement of vessels

and other mediastinal structures, and nodular pleural thickening. Intra-abdominal extension may occur *via* the retrocrural space^[29]. It is difficult to differentiate invasive thymomas from thymic carcinomas. Thymic carcinomas are more aggressive with lymphadenopathy and distant metastases being more common than in thymomas^[3].

On MR imaging, thymomas are of low signal intensity on T1 and high signal intensity on T2 weighted images with homogenous enhancement post contrast.

Thymomas are FDG avid and PET imaging can be used in detection of metastases and postoperative recurrence. However, FDG-PET scanning is not able to differentiate between normal thymus, thymic hyperplasia and thymoma as all show FDG uptake^[30].

Thymolipoma

Thymolipomas are rare tumours seen in any age group

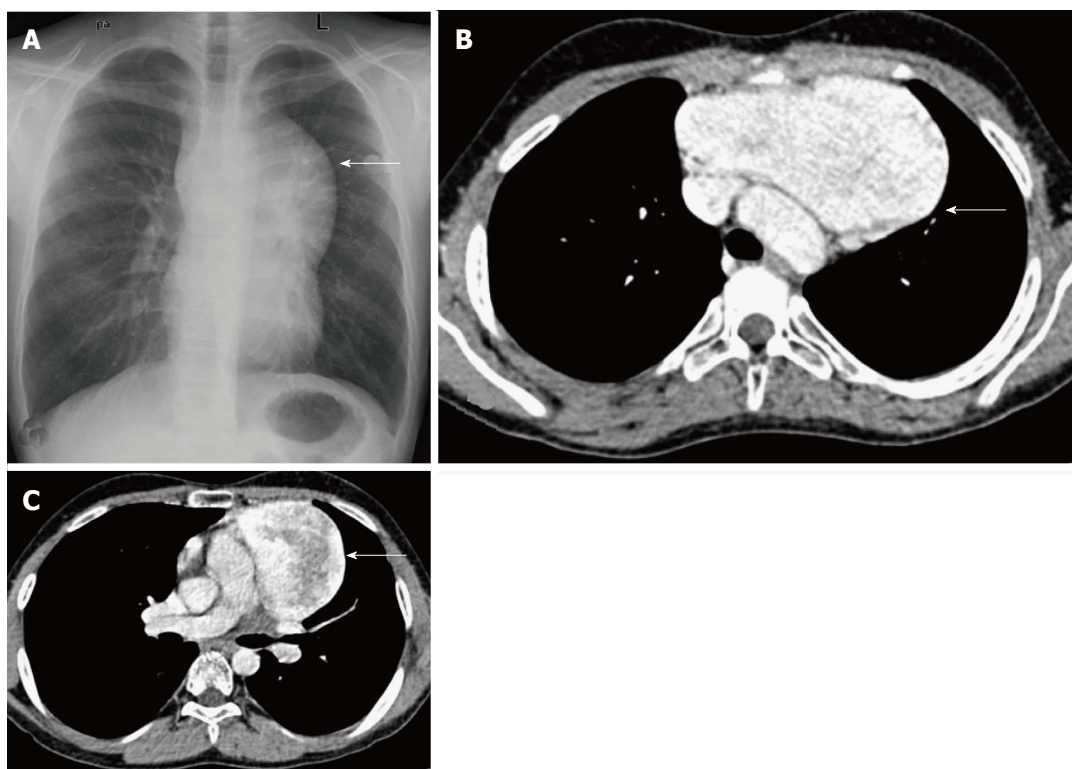


Figure 19 Incidentally detected cavernous hemangioma in 16-year-old male. Frontal chest radiograph (A) reveals a well-defined, lobulated soft tissue density mass (arrow) with broad base towards the mediastinum and positive hilum overlay sign. CECT axial sections (B and C) show a sharply margined mass lesion (arrow in B) anterior to the arch of the aorta. Note the intense post contrast enhancement with central heterogeneity (arrow in C).

with a mean age of 21 years^[3]. They are soft, pliable tumors with predominant fatty content. They can be very large, occupying the entire hemithorax (Figure 18). On plain radiographs, the density of the mass is less than that of soft tissue. On CT, they are of fat attenuation with intervening fibrous septa and normal thymic tissue. MRI reveals an anterior mediastinal mass with high T1 and T2 signal intensity with intervening low signal intensity fibrous strands^[3].

Thymic carcinoma

Thymic carcinomas are rare in children and usually present in the fifth to sixth decades^[3]. They are more aggressive than thymomas and 50%-65% of patients have metastases at the time of diagnosis^[31].

SOLID MASSES WITH INTENSE ENHANCEMENT

Hemangioma

Infantile hemangioma in the anterior mediastinum involving the thymus is rare. It is usually seen in infants and young children. The imaging findings include a well defined, echogenic mass with internal vascularity and high diastolic flow on ultrasonography (USG). On CT, it is a lobulated, noncalcified mass with intense post contrast enhancement (Figure 19). The mass is isointense on T1WI and hyperintense on T2WI with internal flow voids and marked enhancement^[13]. Cavernous hemangiomas

in older children also shows intense enhancement but can have central heterogeneity. The differential differentiation of such avidly enhancing mass would include metastases from hypervascular primaries (thyroid, neuroendocrine tumours, and renal cell carcinoma) and Castleman's disease.

Castleman's disease

Castleman's disease is a nonclonal lymph node hyperplasia with approximately 70% of cases occurring in the chest^[32]. On imaging it is seen as an intensely enhancing mediastinal nodal mass with associated prominent feeding vessels. Calcification may be seen in 10% of the cases and is usually coarse or in a branching pattern^[33].

Thymic carcinoid

Thymic carcinoids are rare neuroendocrine tumors arising from cells of neural crest origin. They are usually seen in adults and patients can present with endocrine abnormalities like Cushing syndrome or syndrome of inappropriate secretion of anti-diuretic hormone^[31,34]. They are more aggressive tumors with a poor prognosis and non-specific imaging features.

MIXED DENSITY MASSES

Infections

The thymus may be involved as a part of mediastinitis with heterogenous appearance on imaging. Focal abscess

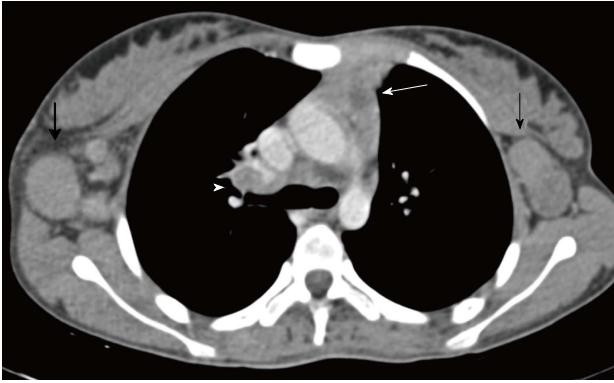


Figure 20 Tuberculosis in a 12-year-old girl presenting with fever and loss of weight and appetite for 3 mo. CECT axial section reveals heterogenous appearance of the thymus with central low attenuation areas (arrow). There is presence of necrotic right hilar lymph node (arrowhead) and enlarged bilateral axillary lymph nodes (black arrows).

is seen as a rim enhancing lesion with surrounding hypodensity suggestive of edema.

Tuberculosis

Tuberculosis is commonly seen in mediastinal lymph nodes and can secondarily involve the thymus gland. Multiple nodes may be involved with evidence of matting and conglomeration. They are hypodense with peripheral rim enhancement and central necrosis (Figure 20). Tuberculosis of the thymus is rare and is seen as an inhomogenously enhancing mass lesion in the region of the thymus gland^[35]. It is important to keep it in the differential differentiation of heterogenous thymus, especially with evidence of tuberculosis elsewhere.

Immature germ cell tumors

Approximately 20% of the mediastinal germ cell tumors are immature teratomas^[14]. These are malignant or potentially malignant masses and usually demonstrate a solid enhancing component on imaging. On conventional radiographs, it is difficult to differentiate these from mature teratomas. However, on cross-sectional imaging (Figure 21), immature teratomas have a nodular outline, more solid component and areas of haemorrhage or necrosis. These tend to invade the surrounding structures rather than displace them as is seen in the case of mature teratomas^[21,22].

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a rare multi-system disease characterised by the proliferation of monoclonal dendritic cells. Thymic involvement (Figure 22) can present as an increase in size with a nodular outline and heterogenous appearance (due to cystic change and calcification). In a study by Lakatos *et al*^[36], it was concluded that the presence of calcifications and /or cysts in a normal or enlarged thymus in a case of biopsy proven LCH is diagnostic for thymic involvement. They recommended screening USG for thymic involvement in

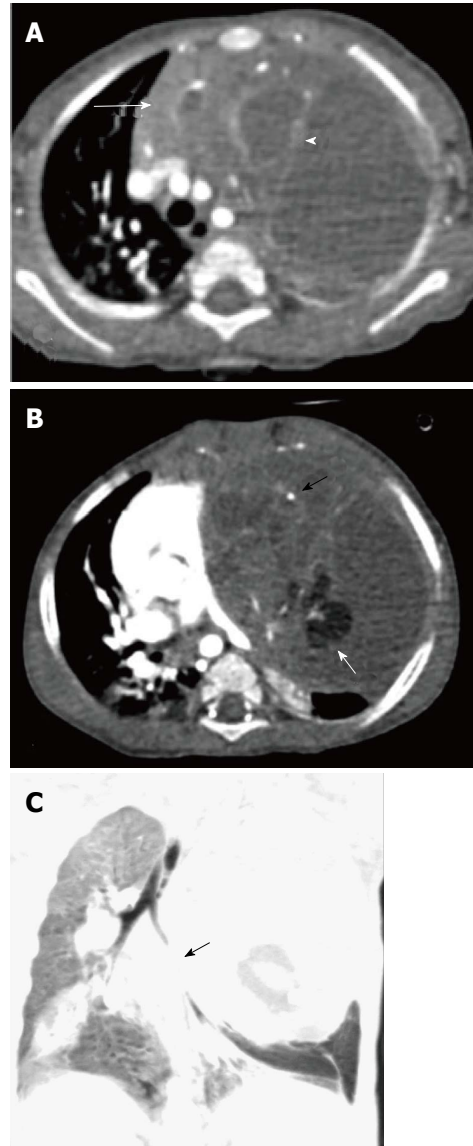


Figure 21 Immature teratoma in a 1-year-old boy. CECT axial sections (A and B) reveal a large cystic mass in the anterior mediastinum. The mass has enhancing solid component (arrow in A), internal septations (arrowhead in A), fat (white arrow in B), and calcific foci (black arrow in B). Note the mass effect on heart and mediastinal vascular structures. Coronal minimum intensity projection image (C) shows the narrowing of left lower lobe bronchus (arrow) and basal atelectasis.

all patients with diagnosed LCH. These findings usually resolve after chemotherapy^[3,36].

CONCLUSION

It is important for clinicians to be able to identify normal variations in thymic appearance and avoid over-investigation. However, it is equally important to have a high index of suspicion for abnormal thymus especially in multisystem disorders. We discuss normal variants, hyperplasia and focal masses; and propose an algorithmic approach (Figure 23) to the evaluation of a suspected thymic mass based on imaging morphology.

The normal thymus has a variable appearance and

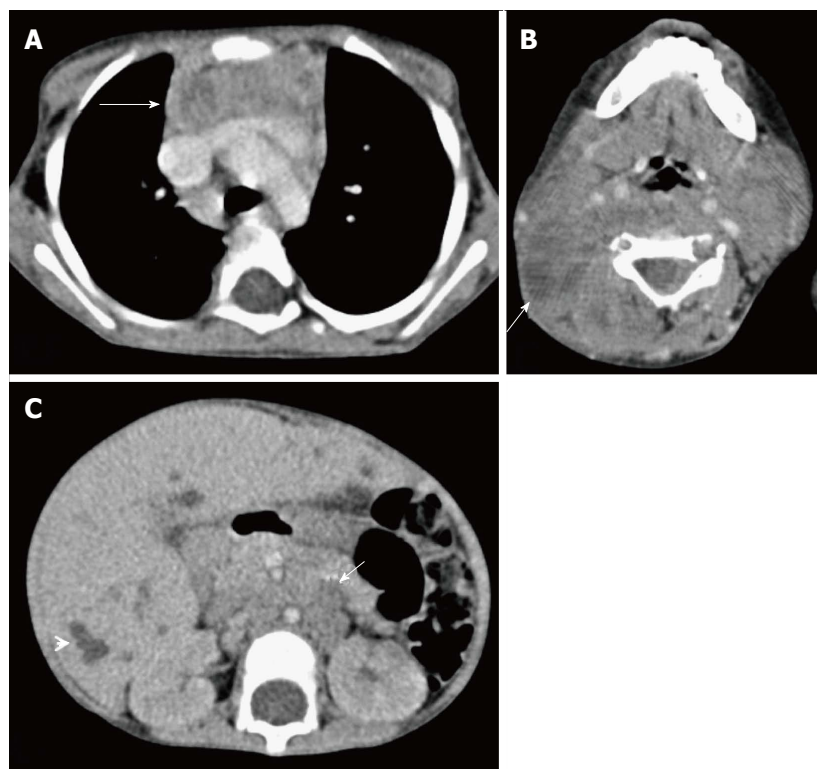


Figure 22 Thymic involvement in systemic Langerhans cell histiocytosis in a 2-year-old girl. CECT axial section at the level of the arch of the aorta (A) shows heterogeneous appearance of the thymus with a nodular outline (arrow). Axial section of the suprahyoid neck (B) shows multiple bilateral enlarged lymph nodes with cystic change (arrow). CECT of the abdomen (C) reveals hepatomegaly with multiple small focal hypodense lesions (arrowhead) in both lobes of the liver and enlarged retroperitoneal lymph nodes (arrow).

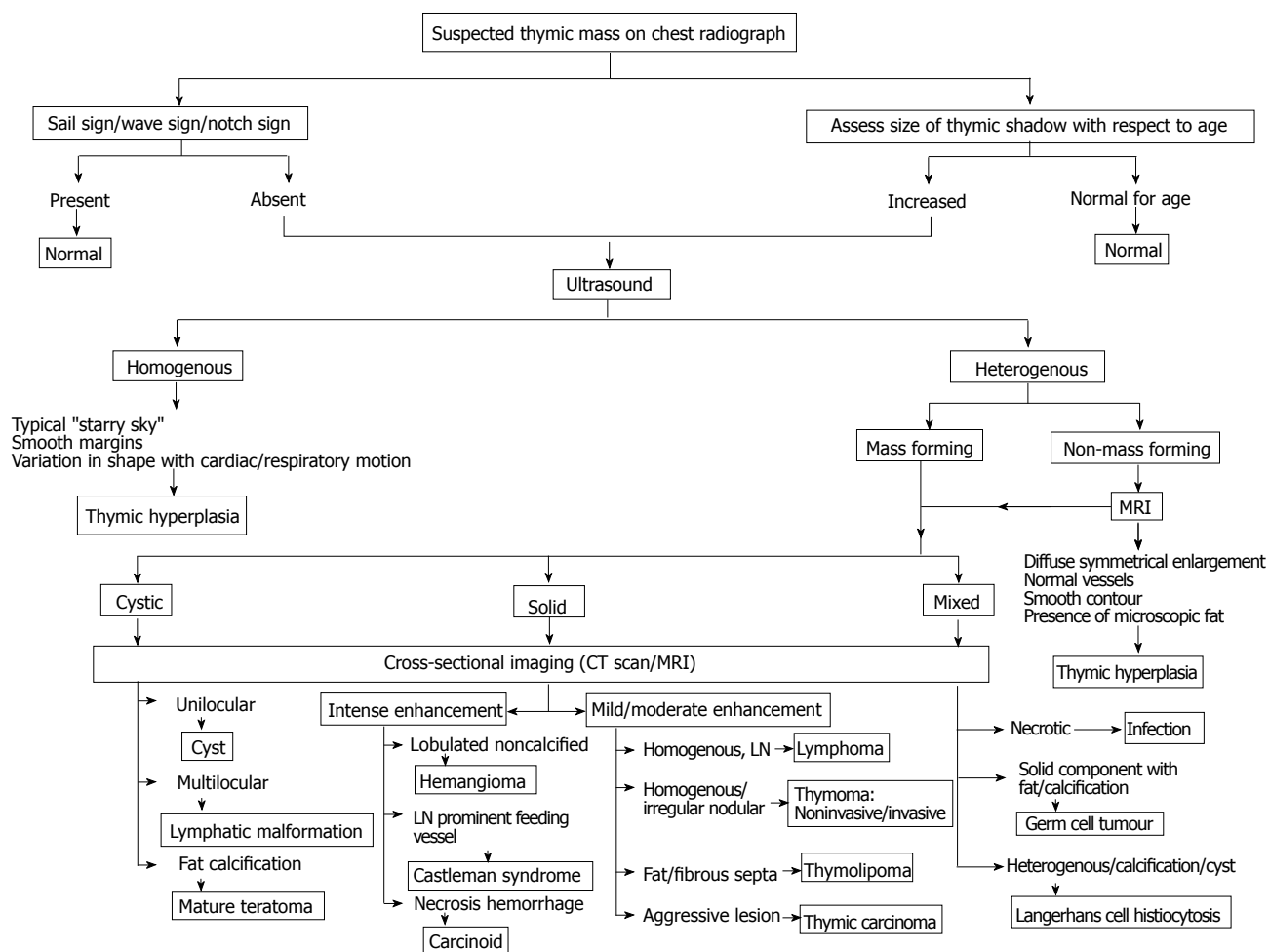


Figure 23 Imaging approach to the evaluation of a suspected thymic mass.

awareness of these anatomical variations is important to prevent unnecessary investigations and invasive procedures. The thymus may be involved in benign and malignant conditions and it is essential to know this spectrum of involvement to be able to make an accurate diagnosis.

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Retrospective Cohort Study

Language and cognitive outcome for high-risk neonates at the age of 2-3 years - experience from an Arab Country

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Abstract

AIM

To investigate the effect of different neonatal risk factors on different language parameters as well as cognitive abilities among Arabic speaking Egyptian children at the age of two to three years of life and to find out which risk factor(s) had the greatest impact on language and cognitive abilities.

METHODS

This retrospective cohort study was conducted on 103 children with age range of 2-3 years (median age 31 mo). They were 62 males and 41 females who were exposed to different high-risk factors in the perinatal period, with exclusion of metabolic disorders, sepsis/meningitis, congenital anomalies and chromosomal aberrations. The studied children were subjected to a protocol of language assessment that included history taking, clinical and neurological examination, audiological evaluation, assessment of language using modified preschool language scale-4, IQ and mental age assessment and assessment of social age.

RESULTS

The studied children had a median gestational age of 37 wk, median birth weight of 2.5 kg. The distribution of the high-risk factors in the affected children were prematurity in 25 children, respiratory distress syndrome

in 25 children, hypoxic-ischemic encephalopathy in 15 children, hyperbilirubinemia in 10 children, hypoglycemia in 13 children, mixed risk factors in 15 children. The results revealed that high-risk neonatal complications were associated with impairment of different language parameters and cognitive abilities ($P < 0.05$). The presence of prematurity, in relation to other risk factors, increases the risk of language and cognitive delay significantly by 3.9 fold.

CONCLUSION

Arabic-speaking children aged 2-3 years who were exposed to high-risk conditions in the perinatal period are likely to exhibit delays in the development of language and impairments in cognitive abilities. The most significant risk factor associated with language and cognitive impairments was prematurity.

Key words: High-risk neonates; Prematurity; Arabic language; Cognition; Child disability

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Core tip: The aim of this retrospective cohort study was to evaluate the effect of different neonatal risk factors on different language parameters as well as cognitive abilities among Arabic speaking Egyptian children at the age of two to three years and to find out which risk factor(s) had the greatest impact on language and cognitive abilities. The results revealed that Arabic-speaking children who were exposed to high-risk conditions in the perinatal period are likely to exhibit delays in the development of language and impairments in cognitive abilities. The most significant risk factor associated with language and cognitive impairments was prematurity.

Abou-Elsaad T, Abdel-Hady H, Baz H, ElShabrawi D. Language and cognitive outcome for high-risk neonates at the age of 2-3 years - experience from an Arab Country. *World J Clin Pediatr* 2017; 6(1): 24-33 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/24.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.24>

INTRODUCTION

High-risk neonates are defined as neonates who are more liable to morbidity or mortality due to the exposure to high-risk factors which include preconceptional, pre-natal, natal, or postnatal conditions or circumstances that interfere with the normal birth process or impede adjustment to extrauterine growth and development^[1,2]. Those risk factors include prematurity, hyperbilirubinemia, hypoglycemia, hypoxic-ischemic encephalopathy (HIE) and respiratory distress syndrome (RDS)^[3]. Babies who were exposed to high-risk factors before birth, during birth or during their neonatal periods are likely to have adverse outcomes. They are more liable to an increasing

risk of behavioral problems, intellectual deficits and a lag in language acquisition^[4]. Advances in perinatal care and establishment of improved neonatal services have increased the survival rates of many high-risk neonates in developing countries. Those neonates can experience significant short-term and long-term sequela.

The first three years of life; when the brain is developing and maturing, is the most intensive period of acquiring speech and language skills. There appear to be critical periods for speech and language development in infants and young children when the brain is best able to absorb language. If these critical periods are allowed to pass without exposure to language, it will be more difficult to learn^[5]. Most of the neonatal risk factors cause language and cognitive delays through impairments of the neural development and integrity of the brain functions resulting in affection of the language area and higher functions of the brain.

Language difficulties are prevalent in high-risk children and include expressive language delays that manifest themselves as poor vocabulary and grammar in addition to articulation problems. Difficulties with phonological awareness are also common and predict later poor reading and writing skills. High-risk neonates are likely to have long-term sequelae affecting linguistic development beyond preschool. In addition, such babies are also at an increasing risk of lower IQ scores below 70, attention-deficit-hyperactivity disorders and negative emotionality^[6,7]. Developmental delay describes children who present with delays in meeting developmental milestones during early childhood and have lower scores in neurodevelopmental testing. The delay is often in more than one system, including gross and fine motor functions, language, social, communication, and visuo-spatial functions^[8,9].

The aim of this cohort study was to evaluate the effect of different neonatal risk factors on different language parameters as well as cognitive abilities among Arabic speaking Egyptian children at the age of two to three years and to find out which risk factor(s) had the greatest impact on language and cognitive abilities.

MATERIALS AND METHODS

This study was done on 103 Arabic speaking Egyptian children with their ages ranged between 24 to 37 mo (median age was 31 mo). They were 62 males and 41 females. All the studied children were admitted to the neonatal intensive care unit (NICU) at Mansoura University Children's Hospital with history of neonatal high-risk conditions and followed-up at the Phoniatric outpatient clinic at Mansoura University Hospitals in the period from January 2013 to November 2014. Children with a history of neonatal high-risk conditions accompanied with metabolic disorders, sepsis/meningitis, chromosomal aberrations, genetic disorders or multiple congenital anomalies were excluded. All parents/legal guardians provided informed written consent prior to

study enrollment. The study was approved by Institutional Review Board of the Faculty of Medicine, Mansoura University, Mansoura, Egypt.

All patients included in the study were subjected to the following protocol of assessment.

Elementary diagnostic procedures

Parent/legal guardian interview: Parent/legal guardian interview for recording information about socio-demographic data of the studied children. The information on child's age, birth order, gestational age, place and mode of delivery, birth weight, presence of neonatal disorders such as neonatal HIE, postnatal hyperbilirubinemia, infections, hypoglycemia, seizures, admission to NICU (causes and duration of admission to NICU and history of assisted ventilation techniques or oxygen supplementation), milestone of development, illnesses of early childhood were recorded. The included cases of Neonatal hyperbilirubinemia in the study were full-term neonates with serum bilirubin level exceeding that is required for treatment by phototherapy according to the guidelines of American Academy of Pediatrics^[10]. Neonatal hypoglycemia was defined as a plasma glucose level less than 40 mg/dL.

Assessment of parents-child interaction: A short semi-objective questionnaire was designed to evaluate parent-child linguistic interactions during the first two to three years of child's life. The questions were: (1) Did you spend a substantial time to communicate verbally with your child? (2) Did you wait for your child to communicate? (3) Did you participate and talk to your child during his/her daily activities? and (4) Did you reward your child when pronounced a new word? If the parents responded yes to any of the afore-mentioned questions; it was considered a positive parent-child interaction. The two-point score was assigned where (0) = no parent-child verbal interaction and (1) = positive parent-child verbal interaction.

General, vocal tract and full neurological examinations: General, vocal tract and full neurological examinations were performed for each child.

Clinical diagnostic aids

Formal testing: Formal testing for psychometric evaluation using Stanford Binnet Intelligence Scale 4th Arabic version for determination of IQ^[11]. Assessment of social age by Vineland social maturity scale^[12] and Language assessment using the Standardized Arabic Language test (Modified preschool language scale) (for determination of receptive, expressive and total language ages)^[13].

Audiological evaluations: To evaluate hearing sensitivity through pure tone audiometry, Auditory Brain Stem Evoked Response (ABR) and tympanometry.

Additional instrumental measures

Electroencephalography and computed tomography and magnetic resonance imaging of the brain were done only when indicated.

Statistical analysis

The results were collected, tabulated, and analyzed using SPSS Statistical Package Version 17 (SPSS Inc. SPSS Statistics for Windows, Chicago, IL, United States). Descriptive data were expressed as median/range (Minimum - maximum) for quantitative non-parametric data, Mean $\pm$ SD for quantitative parametric data and frequency (number/percent). Mann-Whitney test was used to compare between two groups of numerical (non-parametric) data. Kruskal-Wallis test was used to compare between more than two groups of numerical (non-parametric) data. Inter-group comparison of categorical data was performed by using χ^2 test. Some investigated parameters were entered into a logistic regression model to determine which of the factors would be considered as a significant risk factor and identify its odds ratio. Also, some investigated parameters were entered into forward logistic regression to detect a binary response based on one or more predictor variables (risk factors). All parameters were entered into *post hoc* analysis model. *P* value was considered statistically significant if < 0.05 .

RESULTS

Descriptive data

The current retrospective cohort study was conducted on 103 Arabic speaking Egyptian children with their ages ranged between 24 to 37 mo (median age was 31 mo) with history of high risk conditions to assess their language and cognitive outcomes. The demographic data of the studied children and their mothers are summarized in Table 1. The distribution of the high risk factors in the affected children and the maternal risk factors are summarized in Table 2. Eight children had history of intra-ventricular hemorrhage, 7 children had history of peri-ventricular leukomalacia, 5 had history of retinopathy of prematurity and 5 had history of intra-uterine growth retardation (IUGR). All the children with hyperbilirubinemia were born full term with the serum level ranged between 18-24 mg/dL.

Among the 103 studied children, 68 of them demonstrated delayed language development (DLD) (66%) with underlying different etiological factors (Table 3). The rest of the studied children ($n = 35$) (34%) demonstrated no language delay.

Reliability of questionnaire for assessment of parents-child interaction

Reliability testing of the questionnaire used for assessment of parents-child interaction using Cronbach's alpha coefficient demonstrated a value of 0.87 which indicated

Table 1 Demographic data of the studied children/their mothers

Demographic data of children	Median	Range	Number	%
Age (mo)	31	24-37		
Gestational age (wk)	37	24-38		
Birth weight (kg)	2.5	0.75-5		
Outcome of pregnancy				
Single			79	76.7
Twin			15	14.6
Triplet			9	8.7
Order of birth				
First			54	52.4
Second			32	31.1
Third			10	9.7
Fourth			7	6.8
Sex				
Male			62	60.2
Female			41	39.8
Demographic data of the mothers				
Maternal age (yr)	25	18-40		
Maternal age groups				
≤ 18			2	1.9
18-35			95	92.2
≥ 35			6	5.8
Maternal risk factors ¹				
Yes			48	46.6
No			55	53.4

¹Maternal risk factors as diabetes mellitus, hypertension, pre-eclampsia, antepartum hemorrhage, chorioamnionitis, premature rupture of membranes, etc.

excellent reliability of the questionnaire.

Correlative analysis

A number of correlative analyses were done between gestational age and birth weight vs cognitive abilities (IQ and social age) and language parameters (receptive, expressive and total). The results demonstrated statistically significant positive correlations between gestational age and expressive language score, total language age, and social age ($P < 0.05$). On the other hand, no statistically significance correlations were found between the other language parameters and IQ score (Table 4). Statistically significant positive correlations were found between birth weight and receptive language age, expressive language score, expressive language age, total language score, total language age, and social age ($P < 0.05$). On the other hand, no statistical significance correlations were detected between receptive language age and IQ score (Table 4).

Comparison analysis

The association between different peri-natal risk factors regarding the different language parameters and cognitive abilities revealed statistically significant differences in receptive language age, expressive language score, expressive language age, total language age, mental age and social age ($P < 0.05$). On the other hand; there were no statistical significant differences as regard receptive language score, total language score and IQ. *Post hoc* analyses between different peri-natal risk factors and the various language and cognitive parameters were summarized in Table 5.

Table 2 The distribution of risk factors in the studied children and their mothers

	Number	%
The neonatal risk factors		
Prematurity	25	24.3
RDS	25	24.3
Hypoxic-ischemic encephalopathy	15	14.6
Hyperbilirubinemia	10	9.7
Hypoglycemia	13	12.6
Mixed risk factors	15	14.6
The maternal risk factors		
PROM	12	25
Anemia	8	16.70
Pre-eclampsia	10	20.80
DM	10	20.80
Assisted fertilization techniques	8	16.70

RDS: Respiratory distress syndrome; PROM: Premature rupture of membrane; DM: Diabetes mellitus.

Table 3 Underlying causes of delayed language development among studied children

Causes of DLD	Number of children	%
Mental retardation	26	38.2
Environmental deprivation	12	17.6
Below average mentality	10	14.7
Specific language impairment	6	8.8
Cerebral palsy	5	7.4
Hearing impairment	5	7.4
ADHD (inattentive)	2	2.9
ASD - autism	2	2.9

DLD: Delayed language development; ADHD: Attention deficit hyper-activity disorder; ASD: Autism spectrum disorder.

Table 4 Correlation between gestational age and birth weight of high risk children vs different language parameters and cognitive abilities

		Gestational age	Birth weight
Receptive language score	R	0.054	0.112
	P	0.591	0.26
Receptive language age (mo)	R	0.189	0.241
	P	0.055	0.014 ^a
Expressive language score	R	0.231	0.309
	P	0.019 ^a	0.001 ^a
Expressive language age (mo)	R	0.168	0.289
	P	0.09	0.003 ^a
Total language score	R	0.192	0.239
	P	0.051	0.015 ^a
Total language age (mo)	R	0.197	0.286
	P	0.046 ^a	0.003 ^a
IQ score	R	0.125	0.178
	P	0.208	0.072
Social age (mo)	R	0.214	0.322
	P	0.030 ^a	0.001 ^a

^a $P < 0.05$. R: Spearman's rho correlation coefficient.

No statistically significant differences were detected between the presence or the absence of maternal risk factors regarding all different language parameters, IQ and

Table 5 Association between high-risk factors regarding language parameters and cognitive abilities

	Hyperbilirubinemia	Hypoglycemia	Hypoxic-ischemic encephalopathy	Prematurity	Respiratory distress syndrome	Mixed risk factors	P-value
Receptive language score							
Median	76.5	76	53	63	82	72	0.5
Range	51.0-110.0	51.0-110.0	52.0-110.0	51.0-105.0	53.0-115.0	51.0-105.0	
Receptive language age (mo)							
Median	21.5	24	20.0 ²	20.0 ²	30.0 ^{3,5}	20	0.027 ^a
Range	1.0-36.0	12.0-39.0	1.0-39.0	1.0-36.0	2.0-43.0	1.0-37.0	
Expressive language score							
Median	58.5	57	52.0	52.0 ²	62.0 ⁵	53.0 ²	0.049 ^a
Range	50.0-105.0	52.0-105.0	50.0-93.0	50.0-78.02	50.0-112.0	50.0-93.0	
Expressive language age (mo)							
Median	21.5	25	16.0 ²	18.00 ²	21.00 ⁴	15.00 ²	0.037 ^a
Range	10.0-35.0	15.0-39.0	1.0-39.0	1.0-36.0	1.0-41.0	1.0-36.0	
Total language score							
Median	57.5	56	50	50	71	51	0.11
Range	50.0-110.0	50.0-124.0	50.0-96.0	50.0-92.0	50.0-117.0	50.0-96.0	
Total language age (mo)							
Median	22	26	18	17.02	24.0 ⁵	17.0 ²	0.03 ^a
Range	4.0-35.0	13.0-39.0	1.0-39.0	1.0-32.0	1.0-39.0	1.0-36.0	
IQ score							
Median	79	85	67	78	74	75	0.38
Range	54.0-90.0	64.0-95.0	54.0-33.0	54.0-94.0	53.0-33.0	29.0-90.0	
Social age (mo)							
Median	30	36	29.0 ²	27.0 ²	31.0 ⁵	27.0 ²	0.004 ^a
Range	24.0-39.0	24.0-41.0	24.0-37.0	19.0-38.0	24.0-44.0	12.0-41.0	
Mental age (mo)							
Median	25.5	24	24	21.0 ¹	28.0 ^{4,5}	24.0	0.005 ^a
Range	15.0-36.0	18.0-36.0	18.0-36.0	12.0-36.0	17.0-36.0	12.0-34.0	

Kruskal-Wallis test. ^a $P < 0.05$. ¹Significance relative to hyperbilirubinemia; ²Significance relative to hypoglycemia; ³Significance relative to hypoxic-ischemic encephalopathy; ⁴Significance relative to mixed risk factors; ⁵Significance relative to prematurity.

Table 6 Comparison between presence vs absence of maternal risk factors regarding language parameters and cognitive abilities

	Maternal risk factors				P-value
	Absence		Presence		
	Median	Range	Median	Range	
Receptive language score	66	51.0-115.0	77	51.0-115.0	0.3
Receptive language age (mo)	22	1.0-43.0	22.5	1.0-37.0	0.8
Expressive language score	53	50.0-105.0	53.5	50.0-112.0	0.6
Expressive language age (mo)	20	1.0-39.0	19	1.0-41.0	0.9
Total language score	51	8.0-124.0	52	50.0-117.0	0.7
Total language age (mo)	23	1.0-39.0	19.5	1.0-39.0	0.9
IQ score	78	53.0-133.0	78	29.0-110.0	0.78
Social age (mo)	31	19.0-44.0	28	12.0-41.0	0.008 ^a
Mental age (mo)	24	12.0-6.0	24	12.0-6.0	0.3

Test used: Mann-Whitney; ^a $P < 0.05$.

mental age. On the other hand; there was a statistically significant difference with social age ($P < 0.05$) (Table 6).

On comparing the delayed language group and non-delayed ones; there was no statistically significant difference regarding age at assessment, gestational age, maternal age, order of birth, outcome of pregnancy, maternal risk factors and consanguinity ($P > 0.05$) (Table 7). On the other hand, there were statistically significant differences as regard all language parameters, IQ and social age ($P < 0.05$) (Table 8).

The results demonstrated statistically significant

differences between parent-child interactions and receptive language score, expressive language score, total language score and IQ ($P < 0.05$). On the other hand, there were statistically non-significant differences between parent-child interactions and receptive language age, expressive language age, total language age, and social age ($P > 0.05$) (Table 9).

Regression analysis

Using univariate logistic regression analysis, the presence of prematurity in relation to other risk factors increases the risk

Table 7 Comparison between delayed language development and non-delayed language development groups as regard demographic data

	DLD group <i>n</i> = 68		<i>n</i> (%)	Non-DLD <i>n</i> = 35		<i>n</i> (%)	<i>P</i> -value
	Median	Range		Median	Range		
Age (mo)	29	24-36		31	24-37		0.17
Maternal age (yr)	25	18-39		25	19-40		0.38
Gestational age (wk)	37	24-38		36.5	27-38		0.2
Birth weight (kg)	2.75	0.75-5		2.5	0.75-4.5		0.027 ^a
Sex							
Male			14 (40.0%)			48 (70.6%)	0.003 ^a
Female			21 (60.0%)			20 (29.4%)	
Order of birth							
1			20 (57.1%)			34 (50.0%)	0.6
2			10 (28.6%)			22 (32.4%)	
3			4 (11.4%)			6 (8.8%)	
4			1 (2.9%)			6 (8.8%)	
Outcome of pregnancy							
Single			28 (80.0%)			51 (75.0%)	0.8
Twin			4 (11.4%)			11 (16.2%)	
Triple			3 (8.6%)			6 (8.8%)	
Consanguinity							
Negative			27 (77.1%)			53 (77.9%)	0.9
Positive			8 (22.9%)			15 (22.1%)	
Maternal risk factors							
No			19 (54.3%)			36 (52.9%)	0.9
Yes			16 (45.7%)			32 (47.1%)	

Test used: Mann-Whitney; ^a*P* < 0.05. DLD: Delayed language development.

Table 8 Comparison between delayed language development and non-delayed language development groups as regard different language parameters and cognitive abilities

	DLD group <i>n</i> = 68		Non-DLD <i>n</i> = 35		<i>P</i> -value
	Median	Range	Median	Range	
Receptive language score	54.0	51.0-105.0	94.0	76.0-115.0	< 0.001 ^a
Receptive language age (mo)	18.5	1.0-37.0	32.0	22.0-43.0	< 0.001 ^a
Expressive language score	52.0	50.0-71.0	84.0	50.0-112.0	< 0.001 ^a
Expressive language age (mo)	15.0	1.0-36.0	28.0	15.0-41.0	< 0.001 ^a
Total language score	50.0	50.0-75.0	89.0	8.0-124.0	< 0.001 ^a
Total language age (mo)	17.0	1.0-35.0	30.0	23.0-39.0	< 0.001 ^a
IQ score	67.0	29.0-90.0	87.0	74.0-133.0	< 0.001 ^a
Social age (mo)	29.0	12.0-40.0	34.0	24.0-44.0	0.002 ^a

Test used: Mann-Whitney; ^a*P* < 0.05. DLD: Delayed language development.

of language and cognitive delay significantly by 3.9 fold. The presence of other risk factors, namely hyperbilirubinemia, hypoglycemia, hypoxia and RDS increases the risk of language and cognitive delay by 1.3 folds, 7.8%, 21.9% and 40.1% respectively, but not to a significant level (Table 10).

In multivariate stepwise forward logistic regression analysis, it was found that in step 1 total language score had 0.83 risk (95%CI: 0.78-0.9) (*P* ≤ 0.0001) which means that the increase in total language score lowered the risk of DLD by 16.3%. On other hand, in step 2 regression; total language score had 0.84 risk (95%CI: 0.79-0.9) (*P* ≤ 0.0001) and parent-child interactions 0.16 risk (95%CI: 0.02-0.7) (*P* = 0.02) which means that the increase in total language score lowered the risk of DLD by 15.5% and children with positive parents-child interactions had lowered

the risk of DLD by 89.4% (Table 11).

DISCUSSION

Children who were exposed to neonatal risk factors, which include prematurity, hyperbilirubinemia, hypoglycemia, HIE and RDS as well as children with history of maternal risk factors, including pre-eclampsia, hypertension, diabetes mellitus, anemia and assisted fertilization technique, are more liable to increase the risk of behavioral problems, intellectual deficits and a lag in language acquisition^[4]. The present retrospective cohort study evaluated different language parameters (receptive, expressive and total language) and cognitive outcome (IQ, mental age and social age) in 103 Arabic speaking Egyptian children with a history of neonatal risk factors at the age of two to three

Table 9 Comparison between different parents-child interactions regarding language parameters and cognitive abilities

	Parent-child interactions				<i>P</i> -value
	Negative (<i>n</i> = 41)		Positive (<i>n</i> = 62)		
	Median	Range	Median	Range	
Receptive language score	58.0	51.0-105.0	82.0	51.0-115.0	0.003 ^a
Receptive language age (mo)	20.0	1.0-37.0	24.0	1.0-43.0	0.6
Expressive language	53.0	50.0-78.0	67.5	50.0-112.0	0.02 ^a
Expressive language age (mo)	19.0	1.0-35.0	21.0	1.0-41.0	0.3
Total language score	51.0	50.0-90.0	76.5	50.0-124.0	0.009 ^a
Total language age (mo)	19.0	1.0-35.0	23.0	1.0-39.0	0.4
IQ score	70.0	53.0-90.0	85.0	29.0-133.0	< 0.001 ^a
Social age (mo)	30.0	20.0-40.0	30.0	12.0-44.0	0.6

^aP < 0.05.**Table 10** Univariate logistic regression for different neonatal risk factors

	P-value	95%CI for OR		
		OR	Lower	Upper
Hyperbilirubinemia	0.714	1.307	0.313	5.457
Hypoglycemia	0.799	0.922	0.492	1.725
Hypoxic-ischemic encephalopathy	0.671	0.781	0.25	2.444
Respiratory distress syndrome	0.256	0.599	0.247	1.451
Prematurity	0.023 ^a	3.937	1.21	12.813

^aP < 0.05.**Table 11** Forward logistic regression

		B	P-value	OR	95%CI for EXP(B)	
					Lower	Upper
Step 1	Total language	-0.178	0.000 ^a	0.837	0.783	0.895
Step 2	Total language	-0.168	0.000 ^a	0.845	0.793	0.902
	Parents interaction	-2.246	0.019 ^a	0.106	0.016	0.695

^aP < 0.05.

years.

There were significant correlations between different language parameters, social ages of the studied children and their gestational age. Similar results were obtained by Gatti *et al.*^[14], Reidy *et al.*^[15], and Duncan *et al.*^[16], who reported a significant association between language delay and a smaller gestational age especially preterm babies less than 32 wk gestation as compared to full term babies. On the other hand, we found no significant correlation between IQ and gestational age in our studied children. This finding did not come in agreement with the Aarnoudse-Moens *et al.*^[17] study who reported a significant correlation between high-risk children with a gestational age less than 30 wk and IQ. This could be explained by a higher gestational age of children included in our study (median age 37 wk) relative to children included in the later study.

Another significant correlation was detected between different language parameters, social age and birth weight in our studied children. Similar results were reported by

Schirmer *et al.*^[18], and Foster-Cohen *et al.*^[19], who also reported impaired cognitive parameters including the IQ. They reported that the presence of white matter abnormalities in such very low-birth-weight babies impairs the integrity of the brain and affects the higher functions resulting in low IQ results. We did not find significant correlation between birth weight and IQ in our studied children which may be due to their higher birth weights (median 2.5 kg) compared to the birth weights of the later studies which were less than 1.5 kg. Moreover, we found no statistically significant association between different neonatal risk factors and IQ in our studied children. Morsing *et al.*^[20] reported a statistically significant association between high-risk neonates (preterm/IUGR) and cognitive functions as assessed by IQ testing with scores less than 70. Such difference may be attributed to the lower gestational age included in the later study (their median gestational age was 26.9 wk), while in our study it was about 31 wk which might decreased the associated risk on IQ.

Among the various risk factors examined in the study, prematurity showed a statistically significant association with language delay in all language parameters. On logistic-regression analysis, prematurity in relation to other neonatal risk factors increases the risk of language and cognitive delay by 3.9 folds. These results come in agreement with most reported literature^[5,14,21,22] that had studied the effect of high-risk neonatal conditions on language outcome. They reported that prematurity is significantly associated with language and cognitive delays.

We found no statistically significant association between neonatal hyperbilirubinemia and different language parameters and cognitive outcome in our studied children. However, the presence of hyperbilirubinemia in relation to other risk factors increased the risk of language and cognitive delay by 1.3 folds, but not to a statistically significant level. Johnson *et al*^[23] and Bhutani *et al*^[24] reported a significant correlation between neonatal hyperbilirubinemia and language delay. Such difference may be due to the small number of cases included in our study and the presence of other risk factors as prematurity in their studies in contrast to ours where all cases of neonatal hyperbilirubinemia were full-term.

In the current study, there was a statistically significant association between neonatal hypoglycemia and expressive language age, total language age and social age, whereas, it was not associated with other language and cognitive parameters. The presence of hypoglycemia in relation to other risk factors increases the risk of language and cognitive delay by 7.8%, but not to a statistically significant level. The receptive language was not delayed in our studied children due to the fact that most of the cases of neonatal hypoglycemia were diagnosed as specific language impairment in which the IQ was more than 90, and in such circumstances; the receptive language is usually intact. These results come in agreement with the results reported by Akçay *et al*^[25] who reported that neonatal hypoglycemia causes severe and permanent but preventable neurological sequelae and may lead to poor neurodevelopmental outcome that may causes poor cognitive and language development.

We found no statistically significant association between neonatal HIE and different language and cognitive parameters in our studied children. On regression analysis, the presence of HIE in relation to other risk factors increases the risk of language and cognitive delay by 21.9%, but not to a statistically significant level. Marlow *et al*^[26], and Perez *et al*^[27], reported in their study a significant association between neonatal HIE and language and cognitive outcomes. Such differences in the outcomes may be due to the severity of HIE in the later studies which were moderate and severe, while our studied children were affected by mild to moderate HIE with only two cases with cerebral palsy and a single case with severe mental retardation. There are some accumulating data that long-term neurodevelopmental outcome depends on the severity of HIE, with rare adverse outcomes in children with mild HIE, more common in children with moderate HIE, and invariably

present in children with severe HIE^[28,29].

We found a statistically significant association between neonatal RDS and receptive language age and mental age and no statistically significant association with other language parameters and cognitive outcome. Such differential affection of the receptive vs expressive language outcomes may be due to the deteriorating effect of brain anoxia on higher brain functions and neural development with consequent mentality affection. Such affection results in impairment of receptive more than expressive language. Regression analysis demonstrated that the presence of RDS in relation to other risk factors increases the risk of language and cognitive delay by 40.1, but not to a statistically significant level. It comes in agreement with Anderson and Doyle^[30] who reported that neonatal RDS is associated with a strong possibility of delayed language development, particularly with regards to receptive language skills. Moreover, five out of 25 full-term children with RSD in our study demonstrated moderate sensory neural hearing loss (SNHL). D'Souza *et al*^[31], stated that perinatal asphyxia resulted in SNHL by lesions in the dorsal and ventral cochlear nuclei and in the cochlea.

The comparison of the DLD group vs the non-DLD group regarding parent-child interactions demonstrated a statistically significant association between language delay and subnormal IQ and lack of parent-child interactions. Moreover, forward logistic regression revealed that the total language score improved significantly by 89.4% in the presence of positive parent-child interaction. This comes in agreement with the results reported by Meijssen *et al*^[32] and Stolt *et al*^[33], who stated that the quality of mother-child interaction was associated significantly with later language development in high risk children. The importance of parent-child interaction was not only in its existence or not, but by the quality of such interaction which should positively affect language development. Parents of such high risk children should be aware of these interactions to provide a language thriving environment for their children.

It can be stated that Arabic-speaking children who were exposed to high-risk conditions in the perinatal period are likely to exhibit delays in the development of language and impairments in cognitive abilities. The multivariate stepwise forward logistic regression demonstrated that the risk of DLD increased with the increase of risk factors affecting neonates and *vice versa*. In general, the neonatal risk factors cause a delay in the total language score by 16.3%. Also when the parent-child interactions increased, the risk of delayed language development decreased. Those findings were in accordance with those of Sidhu *et al*^[34], study who highlighted the complex relationship between risk factors and language outcome in children. They reported that the language quotients of the children decrease as the number of risk factors increase. So the results of our study on high risk Arabic speaking children were consistent with the results of the before-mentioned studies on high risk non-Arabic speaking children which reported that poor language outcomes in young children

are affected by the increased stress of multiple risk factors rather than the nature of any particular risk. Prematurity was found to be the most significant risk factor among the studied risk factors that are associated with such delays. In fact, most, but not all, of the studied children who were exposed to high-risk factors showed delayed language and cognitive developments. This suggests that other factors may modify the effect of such factors which necessitates further studies, *e.g.*, the quality and quantity of parent-child interactions. Moreover, a further study should be planned to follow these patients at school age to check the long term effect and whether they need special teaching and learning strategies on the long run.

Howard *et al.*^[35], reported that poor expressive and receptive language skills at the age of two years are a significant predictor of poor expressive and receptive language skills at the age of five years. Prevention is one aspect of a Phonetician's/speech language therapist scope of practice in communication disorders that has been neglected in our Arabic countries. Eliminating pre-term birth through adequate prenatal care is one crucial step for preventing efforts. However, even with adequate prenatal care; preterm birth occurs. Many efforts are needed to focus on providing the earliest and proper care, beginning in the NICU, for reducing the risk of language and cognitive deficits. Waiting until a child is two years old for diagnosis and intervention related to their language abilities is not early enough. Awareness of the Pediatricians and parents for early intervention of high risk neonates specifically the premature ones that have potential risk of language and cognitive deficits is warranted.

Limitations of the study

A longer period of follow-up is needed to re-assess the language and cognitive delay vs the deficit cases.

Some limitations related to the age of the study group (2-3 years) as we were able to assess only language and cognition, while other abilities were not amenable for assessment as speech disorders and learning disabilities.

In conclusions, Arabic-speaking children who were exposed to high-risk conditions in the perinatal period are likely to exhibit delays in the development of language and impairments in cognitive abilities. The most significant risk factor associated with language and cognitive impairments was prematurity.

COMMENTS

Background

The first three years of life; when the brain is developing and maturing, is the most intensive period of acquiring speech and language skills. There appear to be critical periods for speech and language development in infants and young children when the brain is best able to absorb language. If these critical periods are allowed to pass without exposure to language, it will be more difficult to learn. Most of the neonatal risk factors cause language and cognitive delays through impairments of the neural development and integrity of the brain functions resulting in affection of the language area and higher functions of the brain.

Research frontiers

The aim of this retrospective cohort study was to evaluate the effect of different neonatal risk factors on different language parameters as well as cognitive abilities among Arabic speaking Egyptian children at the age of two to three years and to find out which risk factor(s) had the greatest impact on language and cognitive abilities.

Innovations and breakthroughs

Arabic-speaking children aged 2-3 years who were exposed to high-risk conditions in the perinatal period are likely to exhibit delays in the development of language and impairments in cognitive abilities. The most significant risk factor associated with language and cognitive impairments was prematurity. The presence of prematurity in relation to other risk factors increases the risk of language and cognitive delay significantly by 3.9 fold. The presence of other risk factors, namely hyperbilirubinemia, hypoglycemia, hypoxia and respiratory distress syndrome increases the risk of language and cognitive delay by 1.3 folds, 7.8%, 21.9% and 40.1% respectively, but not to a significant level. We also found that children with positive parents-child interactions had lowered the risk of delayed language development by 89.4%.

Applications

Many efforts are needed to focus on providing the earliest and proper care, beginning in the neonatal intensive care unit, for reducing the risk of language and cognitive deficits. Waiting until a child is two years old for diagnosis and intervention related to their language abilities is not early enough. Awareness of the pediatricians and parents for early intervention of high risk neonates specifically the premature ones that have potential risk of language and cognitive deficits is warranted.

Terminology

High-risk neonates are defined as neonates who are more liable to morbidity or mortality due to the exposure to high-risk factors which include preconceptional, prenatal, natal, or postnatal conditions or circumstances that interfere with the normal birth process or impede adjustment to extrauterine growth and development.

Peer-review

This is a good paper analyzing association between perinatal factors and delay language development in the following life. Manuscript preparation and language are in standard for academic presentation.

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Retrospective Study

Pediatric asthma severity score is associated with critical care interventions

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Institutional review board statement: This study was reviewed and approved by the Institutional Review Board at the Indiana University School of Medicine.

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Abstract

AIM

To determine if a standardized asthma severity scoring system (PASS) was associated with the time spent on continuous albuterol and length of stay in the pediatric intensive care unit (PICU).

METHODS

This is a single center, retrospective chart review study at a major children's hospital in an urban location. To qualify for this study, participants must have been admitted to the PICU with a diagnosis of status asthmaticus. There were a total of 188 participants between the ages of two and nineteen, excluding patients receiving antibiotics for pneumonia. PASS was calculated upon PICU admission. Subjects were put into one of three categories based on PASS: ≤ 7 (mild), 8-11 (moderate), and ≥ 12 (severe). The groups were compared based on different variables, including length of continuous albuterol and PICU stay.

RESULTS

The age distribution across all groups was similar. The median length of continuous albuterol was longest in the severe group with a duration of 21.5 h (11.5-27.5), compared to 15 (7.75-23.75) and 10 (5-15) in the moderate and mild groups, respectively ($P = 0.001$). The

length of stay was longest in the severe group, with a stay of 35.6 h (22-49) compared to 26.5 (17-30) and 17.6 (12-29) in the moderate and mild groups, respectively ($P = 0.001$).

CONCLUSION

A higher PASS is associated with a longer time on continuous albuterol, an increased likelihood to require noninvasive ventilation, and a longer stay in the ICU. This may help safely distribute asthmatics to lower and higher levels of care in the future.

Key words: Asthma; Noninvasive ventilation; Critical care; Albuterol

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Core tip: This is a single center retrospective study designed to determine whether or not the pediatric asthma severity score was associated with critical care interventions. It was found that patients with a higher (more severe) severity score were more likely to require continuous albuterol for longer ($P = 0.001$) and were more likely to have a longer length of pediatric intensive care unit stay compared to those with less severe scores ($P = 0.001$). It was also determined that patients with a higher severity score were more likely to require other critical care interventions, including noninvasive positive pressure ventilation and amiodarone. This may help safely distribute asthmatics to higher and lower levels of care in the future.

Maue DK, Krupp N, Rowan CM. Pediatric asthma severity score is associated with critical care interventions. *World J Clin Pediatr* 2017; 6(1): 34-39 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/34.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.34>

INTRODUCTION

Asthma is the one of the most common chronic pediatric medical condition in the United States^[1,2] and accounts for approximately 150000 hospitalizations per year^[3,4]. It is estimated that upwards of 30% of pediatric emergency department visits due to asthma result in hospitalization^[5]. A portion of these patients are admitted to the pediatric intensive care unit (PICU), although the rate of ICU admission varies widely by institution. A recent study in New Jersey showed that while admission rates for status asthmaticus are overall on the decline, there has been an increase in ICU admission for these patients from 4% in 1992 to 35% in 2006, which also led to an increase in cost to treat patients with status asthmaticus from 6.6 million in 1992 to 9.5 million in 2006^[6]. PICU admissions are very stressful for families^[7] and are expensive. PICU beds can be limited, particularly during respiratory seasons.

Hospital systems across the nation are making difficult decisions to triage those who truly are in need of critical care services, to optimize ICU bed availability for the sickest patients^[8]. In making initial bed assignment decisions, however it is prudent to ensure that patients who are admitted to floor level care are unlikely to clinically decompensate after admission, thus requiring later ICU transfer.

Asthma severity scores have been developed, validated, and used in various settings of pediatric care. The PASS (Pediatric Asthma Severity Score) was developed and validated in the early 2000's^[9,10]. In at least one study, the PASS was superior to spirometry at predicting the need for further treatment^[10]. Severity scores have generally been used in the emergency department to help determine whether a patient requires hospital admission or can be safely discharged home^[9-13]. However, there are no published studies to date that examine the effectiveness of a pediatric asthma scoring system in triage to ICU vs ward treatment.

The aim of this study is to determine whether the PASS is associated the length of continuous albuterol usage, and higher level respiratory support that often requires PICU level care. The hypothesis is that PASS symptom stratification (mild, moderate, or severe respiratory compromise) can be used to help identify patients most likely to require critical care interventions.

MATERIALS AND METHODS

Approval for this study was obtained from the Indiana University institutional review board prior to data collection. This is a single center, retrospective chart review of patients admitted to the PICU from July 2012-June 2013 with an admitting diagnosis of status asthmaticus. Inclusion criteria were age two through nineteen years, admitted to Riley Hospital for Children PICU *via* the emergency department or direct admission to the PICU. Patients transferred from the ward or receiving antibiotics for bacterial pneumonia were excluded. The data was obtained from the electronic medical record system. Patients were identified based on those admitted to the PICU with the primary diagnosis code for status asthmaticus. Data points collected include: Demographics, medical history, admitting diagnosis, medications for asthma care (inpatient and outpatient), vital signs, level of respiratory support, clinical assessments by respiratory therapy, nursing and physicians, times of ICU admission, transfer, and medication changes. It was also noted whether patients were already followed in the Riley Hospital High Risk Asthma Clinic prior to admission, which is an intensive outpatient management program. Prior to data analysis, a time of greater than or less than 6 h of continuous albuterol was determined to be a collection point. This time frame was chosen as it seemed to be a reasonable time frame to attempt weaning of continuous albuterol in the emergency department or ward setting.

PASS scores were calculated retrospectively at admission to the PICU, at the end of continuous bronchodilator

Table 1 Pediatric asthma severity score calculation table

Score	1	2	3
Respiratory rate			
2 to 3 yr	≤ 34	35 to 39	≥ 40
4 to 5 yr	≤ 30	31 to 35	≥ 36
6 to 12 yr	≤ 26	27 to 30	≥ 31
Older than 12 yr	≤ 23	24 to 27	≥ 28
Oxygen requirements	> 90% on room air	85%-90% on room air	< 85% on room air
Auscultation	Normal breath sounds or end-expiratory wheeze only	Expiratory wheezing	Inspiratory and expiratory wheezing or diminished breath sounds
Retractions	≤ One site	Two sites	≥ Three sites
Dyspnea	Speaks in sentences, coos and babbles	Speaks in partial sentences, short cry	Speaks in single words/short phrases/grunting

Table 2 Demographic information

Characteristic	Subgroup	Total <i>n</i> (%)	Mild <i>n</i> (%)	Moderate <i>n</i> (%)	Severe <i>n</i> (%)	<i>P</i> value
Gender	Male	112 (59.6)	26 (65.0)	68 (58.1)	18 (58.1)	0.18
	Female	76 (40.4)	14 (35.0)	49 (41.9)	13 (41.9)	
Race/ethnicity	Caucasian	44 (23.4)	5 (12.5)	29 (24.8)	10 (32.3)	0.18
	African American	130 (69.1)	33 (82.5)	79 (67.5)	18 (58.1)	
	Hispanic	10 (5.3)	2 (5.0)	7 (6.0)	1 (3.2)	
	Other	4 (2.1)	0 (0)	2 (1.7)	2 (6.4)	
Asthma history	Uses controller medication	137 (72.9)	35 (87.5)	78 (66.7)	24 (77.4)	0.03
	Patient in high risk asthma clinic	61 (32.4)	16 (40.0)	33 (28.2)	12 (38.7)	0.25

treatment, and at the first interval bronchodilator treatment. The PASS calculation can be found in Table 1. This was accomplished by reviewing nursing vitals and respiratory therapy (RT) documentation. The first set of vitals and RT documentation after arrival to the PICU was used to calculate the admission score. The total length of time on continuous albuterol was calculated from charting on the medication administration record. The total length of time in the PICU was calculated from the first set of vitals charted by the PICU nurse to the time transfer orders were written. Groups were assigned as follows based on clinical guidelines utilized at other institutions for bronchodilator weaning: mild respiratory compromise were defined as PASS ≤ 7; moderate respiratory compromise PASS 8-11; severe respiratory compromise PASS ≥ 12^[14].

Descriptive statistics using medians and interquartile ranges were calculated for continuous variables. Comparison of continuous variables between risk groups was done using Kruskal-Wallis test. Categorical variables were compared using χ^2 or Fisher exact test where appropriate. Statistical significance was set at a value of 0.05. We used Statistical Package of the Social Science (SPSS) Statistical software for Windows, Version 20.0 (SPSS Inc., Chicago, IL, United States) and Microsoft Office Excel (Microsoft Corporation, Redmond, WA).

RESULTS

Patient characteristics

A total of 188 subjects with the admission diagnosis of status asthmaticus were included in the study. The

mean age at admission was 7.2 ± 4.0 years (range 2-19 years). African American race and male gender accounted for the majority of the study population. Additional demographic information can be found in Table 2.

PASS ranges

In total, there were 40 subjects that fell into the mild respiratory compromise group, 117 in the moderate group, and 31 in the severe group.

Respiratory support

The degree of respiratory support required for each patient was documented, specifically high flow nasal cannula, noninvasive positive pressure ventilation (NIPPV), intubation, and extracorporeal membrane oxygenation (ECMO). In total, 6 subjects required high flow nasal cannula, 6 required NIPPV, 1 was intubated, and none were on ECMO. The breakdown of the number in each group that required each form of respiratory support is found in Table 3. Not surprisingly, those in the severe group were more likely to receive NIPPV.

Medication usage

Medication use for the 188 patients as a whole and per group is displayed in Table 3. The severe respiratory compromise group was more likely to receive continuous albuterol for more than 6 h as well as aminophylline. The medium and high risk groups were more likely to receive scheduled ipratropium. There was no significant difference among the groups with terbutaline or magnesium sulfate. The difference is shown below in Table 4.

Table 3 Medication usage by each severity group

Medication	Total received all groups (%)	Mild compromise number received (%)	Moderate compromise number received (%)	Severe compromise number received (%)	P value
Systemic steroids	187 (99.5)	40 (100)	116 (99.1)	31 (100)	0.737
Magnesium sulfate	126 (67.0)	26 (65)	77 (65.8)	23 (74.1)	0.646
Aminophylline	4 (2.1)	0	0	4 (12.9)	< 0.001
Terbutaline	4 (2.1)	0	2 (1.7)	2 (6.5)	0.155
Scheduled ipratropium	146 (77.7)	21 (55.3)	100 (86.2)	25 (83.3)	< 0.001
Continuous albuterol > 6 h	139 (73.9)	23 (57.5)	88 (75.2)	28 (90.3)	0.007

Total *n* (%) reported per severity group, *P* value obtained from extend fisher exact or χ^2 where appropriate.

Table 4 Respiratory support required for each severity group

Respiratory support	Mild	Moderate	Severe	Pearson χ^2
High flow nasal cannula	1 (2.6)	4 (3.4)	1 (3.2)	0.96
Noninvasive positive pressure ventilation	0	2 (1.7)	4 (12.9)	0.003
Invasive mechanical ventilation	0	0	1 (3.2)	0.078

Breakdown of respiratory support required in each severity group, total *n* (%) reported, *P* value obtained from extended fisher exact.

Length of time on continuous albuterol

The moderate and severe group was on continuous albuterol longer. The mild group received continuous albuterol for a median of 10 h (IQR 5-15), moderate group for 15 h (IQR 7.75-23.75) and the severe group for 21.5 h (IQR 11.5 – 27.5) ($P = 0.001$). The difference among the groups is shown in Figure 1.

Total length of time in the pediatric ICU

The severe group was in the Pediatric ICU for a longer period of time. The mild group had a median length of stay of 17.6 h (IQR 13-29), the moderate group 26.5 h (17.3-39.4), and the severe group 35.6 h (22.2-49.6) ($P = 0.001$). The difference among the groups is demonstrated in Figure 2.

DISCUSSION

To our knowledge, this is the first study that associates an asthma clinical severity score with PICU interventions and outcomes. Our high number of patients at a large pediatric hospital, recent study period, and common standard practices for status asthmaticus make the results generalizable to many children's hospitals in the United States.

The most reassuring result of our study is the significant difference among severity groups with regards to length of time on continuous albuterol and length of PICU stay. Based on these results, a patient's admission PASS could help clinicians predict how long a patient could need ICU resources, and their risk of requiring intensive pharmacologic treatment such as aminophylline. Particularly in times of high utilization of critical care resources, the ability to identify those that will not require

continuous albuterol for extended periods of time and have a lower risk of requiring higher levels of respiratory support can be an exceedingly useful triage tool. Since the mild respiratory compromise group was less likely to receive prolonged continuous albuterol, it is feasible that these patients could be weaned to intermittent albuterol in the emergency room in a reasonable amount of time. The ability to objectively identify these patients during times of limited PICU bed availability can help ensure those that are likely to have the highest need for critical care obtain the resources first. This will not only improve patient safety but assist with patient flow through the emergency department. It may also assist accepting hospitals in triage of referred patients from outside facilities.

In this study, 99.5% of patients received systemic steroids, and there was no significant difference among the groups. It is also clear that magnesium sulfate is often used in asthmatics that are deemed critically ill, requiring PICU admission. Regardless of PASS score, there was no difference in this intervention when comparing severity groups. It is not particularly surprising that we did not see a significant difference in the use of most of medications among the different groups. Magnesium sulfate is commonly used at many institutions, including ours, in both the emergency department as well as the PICU. It has been shown to reduce bronchoconstriction and has been shown to help avoid hospitalization. The toxicity rates are also relatively low so it is considered safe to use^[15].

There was a significant difference with aminophylline, with patients in the severe group more likely to receive it. At our institution, aminophylline use is restricted to the ICU setting, due to the potential for significant toxicity, and is reserved for patients with persistent respiratory distress despite other modalities. The fact that aminophylline use was seen only in the severe group base on PASS speaks to the congruence of the PASS to more subjective estimation of clinical status. The fact that the moderate group (PASS 8-11) had no aminophylline use at all during their clinical course is notable, in that the patients in this severity category did not decompensate to the point of requiring this particular intervention. Admittedly, there were only a total of four patients in the study that received aminophylline so it is difficult to make generalizations based on this data. The data on aminophylline is mixed with a recent study showing that, while it did improve lung

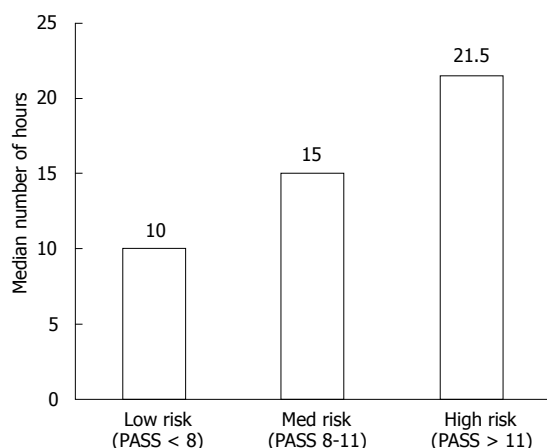


Figure 1 Length of time on continuous albuterol based on admission pediatric asthma severity score illustration of the difference in length of time on continuous albuterol among the three severity groups. The mild compromise group received continuous albuterol for 10 h (IQR: 5-15), moderate compromise group for 15 h (IQR: 7.75-23.75), and the severe compromise group for 21.5 h (IQR: 11.5-27.5) ($P = 0.001$).

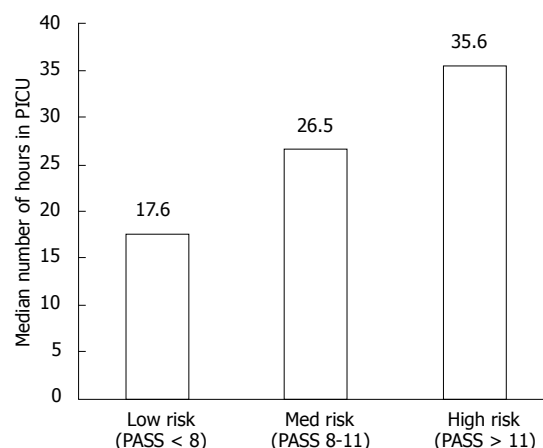


Figure 2 Length of time in the intensive care unit based on admission pediatric asthma severity score. This figure shows the difference in length of time in the intensive care unit among the three severity groups. For the mild compromise group, the median length of time in the pediatric intensive care unit was 17.6 h (IQR: 13-29), moderate compromise group for 26.5 h, with a (IQR: 17.3-39.4), and the severe compromise group for 35.6 h (IQR: 22.2-49.6) ($P = 0.001$).

function at six hours, there was no reduction in number of nebulized treatments as well as being inconclusive on whether or not it reduced length of stay or complications such as mechanical ventilation. There is also significant toxicity associated with aminophylline^[16,17]. Therefore, most providers reserve it for patients who have a severe case when they are not responding to traditional treatments.

It is interesting that our study did not show any significant difference among the groups in terms of heated humidified high flow nasal cannula (HHFNC). This may be reflective of the trend to use HHFNC more commonly, even on general wards. It may also be due to the fact many patients on HHFNC were on it prior to arrival to the PICU, thus improving their work of breathing and improving their PASS. Recent studies have shown that when used correctly, HHFNC is safe to use on a general pediatric ward as long as there is a Pediatric ICU bed available should worsening respiratory failure or other complications ensue^[18].

There are a few limitations with this study, mostly related to the retrospective nature of the study. Data sources to identify admission and discharge times and to calculate the PASS were consistent among all patients, which may mitigate some of the retrospective limitation. Another limitation is the lack of data surrounding PASS scores at arrival to the emergency department. As PASS is not a standard part of emergency department care at our institution, there was not enough detail in the retrospective charts to obtain this information uniformly for all patients. It is possible that some patients could have initially had a more severe PASS and then with treatment could have improved substantially before arriving to the PICU. Future studies will work to address this.

Our study finds that PASS ranges are associated with the use of critical care interventions. Patients that fall into the severe range were more likely to require a longer time on continuous albuterol as well as a longer time in the

PICU. They were also more likely to require NIPPV as well as other medications typically reserved for severe status asthmaticus. Future prospective studies investigating PASS ranges as a triage tool would be needed to fully understand its utility in patients admitted to the hospital with asthma.

COMMENTS

Background

Asthma is the most common chronic condition of childhood and status asthmaticus is a very frequent admitting diagnosis in the pediatric intensive care unit (PICU). These patients come to the PICU because it can be very serious and life threatening, and some patients are sicker than others. At the authors' institution, the decision of whether or not to increase or decrease support is based on subjective exam of the patient. In previous studies, asthma severity scores have been studied in the ER as to whether or not they can predict if a patient needs to be admitted or safely discharged. In their study, we look at whether or not an asthma severity score (PASS, or Pediatric Asthma Severity Score) is predictive of the need for critical care services, specifically length of time on continuous albuterol and length of time in the PICU.

Research frontiers

There have been studies in the past looking at asthma severity scores and patient outcomes. Previous studies have mainly looked at using these scores in the emergency department and predicting whether or not a patient needs to be admitted or could be discharged. Healthcare is changing and many institutions are striving to standardize care, and using these scores could be another way to do so.

Innovations and breakthroughs

To their knowledge, this is the first study that has studied whether or not a patient's asthma severity score (in this case, PASS) can be predictive of their need for critical care interventions. Their study found that if a patient fell into the severe group, he/she was more likely to be on continuous albuterol for longer and need the PICU longer. These patients were also more likely to require noninvasive positive pressure ventilation and be on aminophylline.

Applications

This study could be applied in the future in multiple ways. It could be used to help PICU physicians predict which patients will need more intensive treatment

or could safely have treatment de-escalated. It could also potentially be used to decide whether or not a patient needs PICU admission or could be safely treated on a general floor.

Terminology

PASS: Pediatric asthma severity score - a score that is determined by different variables (oxygen requirement, respiratory rate, work of breathing, retractions, auscultation) that "scores" how severe an asthma exacerbation is at that point in time.

Peer-review

The paper is well-written.

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Retrospective Study

Cystic meconium peritonitis with jejunoileal atresia: Is it associated with unfavorable outcome?

Kin Wai Edwin Chan, Kim Hung Lee, Hei Yi Vicky Wong, Siu Yan Bess Tsui, Yuen Shan Wong, Kit Yi Kristine Pang, Jennifer Wai Cheung Mou, Yuk Him Tam

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Institutional review board statement: The study was reviewed and approved by the Joint CUHK-NTEC Clinical Research Ethics Committee (CREC) (CRE Ref. No. 2016.225).

Informed consent statement: As anonymized administrative and clinical data were used for this study, specific written consent was not required to use patient information stored in hospital databases.

Conflict-of-interest statement: The authors declare that there is no conflict of interest to disclose.

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Abstract

AIM

To compare the outcome between patients with jejunoileal atresia (JIA) associated with cystic meconium peritonitis (CMP) and patients with isolated JIA (JIA without CMP).

METHODS

A retrospective study was conducted for all neonates with JIA operated in our institute from January 2005 to January 2016. Demographics including the gestation age, sex, birth weight, age at operation, the presence of associated syndrome was recorded. Clinical outcome including the type of operation performed, operative time, the need for reoperation and mortality were studied. The demographics and the outcome between the 2 groups were compared.

RESULTS

During the study period, 53 neonates had JIA underwent operation in our institute. Seventeen neonates (32%) were associated with CMP. There was no statistical difference on the demographics in the two groups. Patients with CMP had earlier operation than patients with isolated JIA (mean 1.4 d vs 3 d, $P = 0.038$). Primary

anastomosis was performed in 16 patients (94%) with CMP and 30 patients (83%) with isolated JIA ($P = 0.269$). Patients with CMP had longer operation (mean 190 min *vs* 154 min, $P = 0.004$). There were no statistical difference the need for reoperation (3 *vs* 6, $P = 0.606$) and mortality (2 *vs* 1, $P = 0.269$) between the two groups.

CONCLUSION

Primary intestinal anastomosis can be performed in 94% of patients with JIA associated with CMP. Although patients with CMP had longer operative time, the mortality and reoperation rates were low and were comparable to patients with isolated JIA.

Key words: Meconium; Peritonitis; Atresia; Jejunoileal

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Core tip: Owing to the adhesive and vascular nature of the meconium cyst, difficult operation is expected in patients with jejunoileal atresia associated with cystic meconium peritonitis. However, whether the overall mortality and morbidity is higher when compare to patients with isolated jejunoileal atresia is not known. Our results showed primary intestinal anastomosis could be performed in majority of neonates with cystic meconium peritonitis without an increase in morbidity and mortality.

Chan KWE, Lee KH, Wong HYV, Tsui SYB, Wong YS, Pang KYK, Mou JWC, Tam YH. Cystic meconium peritonitis with jejunoileal atresia: Is it associated with unfavorable outcome? *World J Clin Pediatr* 2017; 6(1): 40-44 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/40.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.40>

INTRODUCTION

Jejunoileal atresia (JIA) is a common cause of neonatal intestinal obstruction that required operation. With the improvement in neonatal intensive care, timely surgical intervention and parental nutrition, the mortality rate dropped from over 90% to 11%^[1]. Cystic meconium peritonitis (CMP) is a result of *in-utero* perforation of intestine^[2]. Although the meconium is sterile, it will lead to secondary inflammation to the peritoneal cavity resulting in fibrosis, calcification and cyst formation^[3].

Neonates with JIA associated with CMP required early surgical intervention in view of the coexisting intestinal obstruction. However, in the presence of inflammation and fibrosis, surgery may be difficult as a result of the bleeding and adhesion^[4]. In this study, we aim to review the characteristics of patients with JIA and in particular with patients with associated CMP. We would like to study if the presence of CMP has any adverse effect on the clinical outcome.

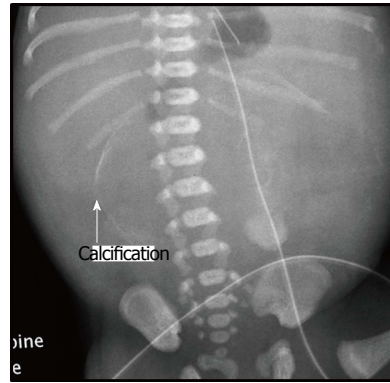


Figure 1 Plain abdominal radiograph showing eggshell calcification compatible with cystic meconium peritonitis.

MATERIALS AND METHODS

From January 2005 to January 2016, 53 neonates had JIA operated in our institute. Seventeen neonates (32%) were associated with CMP. A retrospective review was performed on the antenatal diagnosis, gestation age, sex, birth weight, age at operation and the presence of associated syndrome in all neonates with JIA. Clinical outcome including the type of operation performed, operative time, the need for reoperation and mortality were studied. Comparison was made on the demographics and outcome between neonates with JIA associated with CMP and neonates with isolated JIA (JIA without CMP).

Statistical analysis

Statistical analysis was accomplished using the SPSS program for Windows 21.0 (SPSS, Chicago, Illinois, United States). The Mann-Whitney U Test was used to compare the continuous data. Fisher exact test was used to compare the categorical data. $P < 0.05$ was considered statistically significant. The statistical methods of this study were reviewed by Yuk Him Tam from the Prince of Wales Hospital.

RESULTS

Thirty three male and 20 female neonates with JIA were operated in the study period. The median gestation age was 36 wk (range 26-41 wk). Twenty-seven patients were born prematurely. The median birth weight was 2.8 kg (range 0.82-3.9 kg). Twenty-seven patients had abnormal antenatal ultrasonography (USG). Dilated bowel loop was detected in antenatal USG in 21 patients. Regarding the 17 patients with CMP, 11 patients had abnormalities detected on antenatal USG. USG detected pseudocyst in 5 patients and another 6 patients had dilated bowel shadow without pseudocyst. Calcification was present in the plain radiograph in seven (41%) neonates with CMP (Figure 1). Out of the 35 patients, 7 had associated anomalies (Malrotation

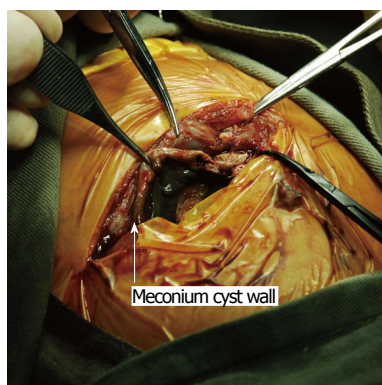


Figure 2 Operative photo showing the fibroadhesive meconium cyst wall in cystic meconium peritonitis.

Table 1 Demographics in neonates with jejunoileal atresia

	JIA with CMP (<i>n</i> = 17)	Isolated JIA (<i>n</i> = 36)	<i>P</i> value ¹
Antenatal diagnosis	11 (65%)	16 (44%)	0.139
Sex, M:F	10:07	23:13	0.476
Prematurity	10 (59%)	17 (47%)	0.311
Birth weight, kg (mean ± SD)	2.59 ± 0.92	2.71 ± 0.66	0.841
Associated anomalies	1 (6%)	6 (20%)	0.269

¹*P* < 0.05 was considered statistically significant. M: Male; F: Female; JIA: Jejunoileal atresia; CMP: Cystic meconium peritonitis.

of intestine in 3, Meckel's diverticulum in 2, congenital diaphragmatic hernia in 1, absent toes in 1). No patient had cystic fibrosis. There was no statistical difference on the demographics in the two groups (Table 1).

The mean age at operation was 2.5 d (range 0-18 d). Neonates with CMP had earlier operation than neonates with isolated JIA (mean 1.3 d vs 3.0 d, *P* = 0.039). The type of initial operation including primary intestinal anastomosis (*n* = 46), fashioning of stoma (*n* = 6) or drainage procedure (*n* = 1). Primary intestinal anastomosis was performed in 94% (16/17) of neonates with CMP and 83% (30/36) of neonates with isolated JIA. One patient with CMP had drainage done. She was born prematurely because of maternal sepsis. She was diagnosed to have CMP antenatally. She had sepsis at birth and drainage procedure was performed.

The mean operative time was 166 min. In the presence of fibroadhesion, difficult surgical dissection was experienced in neonates with CMP (Figure 2). They had a significantly longer operative time than neonates with isolated JIA (190 min vs 155 min, *P* = 0.004) (Table 2).

Regarding the outcome after primary operation, nine neonates (CMP in 3, isolated JIA in 6) required reoperation after primary intestinal anastomosis [intestinal obstruction in 8 and necrotizing enterocolitis (NEC) in 1] (Table 2).

Two patients with CMP died after operation. The first patient underwent primary intestinal anastomosis but was complicated with intestinal obstruction. Stoma was fashioned but the patient died because of sepsis and TPN related liver failure. The second patient was the one

Table 2 Surgery related data and outcome in neonates with jejunoileal atresia

	JIA with CMP (<i>n</i> = 17)	Isolated JIA (<i>n</i> = 36)	<i>P</i> value ¹
Age at operation, d (mean ± SD)	1.35 ± 1.54	3.00 ± 3.78	0.0391
Primary anastomosis	16 (94%)	30 (83%)	0.269
Operative time, min (mean ± SD)	190.38 ± 42.02	154.86 ± 45.26	0.0041
Reoperation	2 (12%)	6 (20%)	0.493
Mortality	2 (12%)	1 (2.7%)	0.238

¹*P* < 0.05 was considered statistically significant.

with drainage procedure performed. The sepsis was not controlled despite drainage and she passed away at the same day of operation.

One neonate with isolated JIA died because of sepsis and TPN related liver failure. He underwent primary intestinal anastomosis but complicated with intestinal obstruction and required fashioning of stoma. On a median follow-up of 63 mo (range 6 to 123 mo), no patient suffered from short bowel syndrome.

DISCUSSION

The prevalence of JIA is 0.7 per 10000 births and the prevalence rate of meconium peritonitis is 1 in 30000 livebirth^[5,6]. In this review, we studied the characteristics of neonates with CMP, which is a complicated type of meconium peritonitis with the presence of pseudocyst^[3]. Our study showed 32% of neonate with JIA has CMP. Unlike in western countries, CMP may be associated with cystic fibrosis^[7]. In this study, no patient had cystic fibrosis. It is corresponding to the low incidence of cystic fibrosis in the local population^[8].

JIA can be diagnosed antenatally. The presence of maternal polyhydramnios and dilated bowel loops are suggestive features of JIA. The antenatal diagnosed rate (ADR) was reported to be around 30%^[9]. In this study, the overall ADR is 51%, which may reflected the more routine use of antenatal ultrasonography in second and third trimester. Besides maternal polyhydramnios and dilated bowel loops, fetus with CMP may have pseudocyst or calcification detected in antenatal ultrasonography^[1,8,10]. This additional specific feature reflected the higher ADR rate in neonate with CMP and JIA than in neonate with isolated JIA (65% vs 44%).

In this study, neonates with CMP had earlier operation than neonates with isolated JIA. One of the reasons may be associated with the higher ADR. Moreover, in the presence of the cyst, the abdomens were distended at birth. This alarming feature may lead to early referral to the surgical unit. On the other hand, the clinical features of patients with isolated distal ileal atresia may be more subtle. Abdomen distension may be absent at birth and this may lead to a delay in

presentation.

Surgery in neonates with cystic meconium peritonitis is expected to be difficult in view of the underlying fibroadhesion, inflammation and bleeding^[4]. We did experience difficulty in surgical dissection and isolation of the intestine from the adherent cyst. Our study confirmed the operative time in patients with CMP was significantly longer than patients with isolated JIA. There were controversies in the literature on the initial approach of patient with CMP^[4,11,12]. Some advised for primary drainage procedure in view of the expected difficult operation^[12], while other suggested primary intestinal anastomosis should be the treatment of choice^[4,11].

Regarding our surgical approach, we opt for primary anastomosis in patients with JIA, no matter it is associated with CMP or not. Despite the difficulty in operation in neonate with CMP, we managed to perform primary intestinal anastomosis in the rest of the cases (93%, 16/17). On the other hand, we performed primary intestinal anastomosis in 83% (30/36) cases only in neonate with isolated JIA.

In primary intestinal anastomosis, the principle of surgery is to excise the dilated aperistaltic proximal intestine and perform the anastomosis^[13]. In case there is a marked discrepancy in the diameter between the proximal and distal intestine, stoma will be fashioned. In neonate with CMP, since the perforation of intestine had occurred antenatally and the bowel content was already drained into the peritoneal cavity, the obstructed proximal intestine was partially decompressed. We postulated the decompression led to a less dilated or hypertrophic proximal intestine, which may decreased the discrepancy in diameter between the proximal and distal intestine. In this study, drainage procedure was only performed in one neonate with CMP. She was one of the mortality cases in this study. She was in critical condition after birth and we could only manage to insert a drain soon after delivery and she succumbed on the same day.

The reoperation or mortality rates were comparable between the two groups. Two neonates with CMP had intestinal obstruction and one developed NEC. Six neonates with isolated JIA developed post-operative intestinal obstruction. Our reoperation rate was comparable to other series in literatures^[11,13,14]. Despite the preexisting peritoneal adhesions in neonates with CMP, there was no increase in post-operative intestinal obstruction rate. One patient in each group died in the early study period of this series because of total parental nutrition (TPN) related liver failure. With the introduction of fish oil based lipid preparation in TPN in recent years, we did not experience any TPN related liver failure^[15] in patients with JIA.

In conclusion, despite longer operative time in patients with JIA associated with CMP, it was not associated with an unfavorable outcome when compare with patients with isolated JIA. With delicate surgical technique, advance in antenatal diagnosis and postnatal care, the morbidity and mortality rate in neonates with JIA remained low.

COMMENTS

Background

Cystic meconium peritonitis (CMP) is a result of *in-utero* bowel perforation. It will lead to secondary inflammation to the peritoneal cavity resulting in fibrosis, calcification and cyst formation. Difficult surgery is expected as a result of the fibroadhesion and inflammation.

Research frontiers

Controversies still exist on the initial approach in the management of CMP. Some advocated for primary anastomosis while others suggested for drainage procedure. In addition, whether CMP associated with jejunoileal atresia (JIA) had poorer outcome when compare with patients with isolated JIA is not known.

Innovations and breakthroughs

This study showed primary intestinal anastomosis can be performed in 94% of patients with CMP. When compare with patients with isolated JIA, there is no increase in morbidity and mortality.

Applications

Despite longer operation time in patients of CMP as a result of the fibroadhesion, primary intestinal anastomosis is safe and feasible.

Terminology

Cystic meconium peritonitis (CMP): *In utero* perforation of intestine leading to secondary inflammation of the peritoneal cavity and resulting in fibrosis, calcification and cyst formation. Jejunoileal atresia: Congenital intestinal atresia involving the jejunum or ileum.

Peer-review

This is a very good paper about an important neonatal surgical condition. Paper is well written, methods are ok, results are well described and conclusion is supported by the data.

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Observational Study

Culturally adapted pictorial screening tool for autism spectrum disorder: A new approach

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Informed consent statement: All parents participating in the study gave informed consent verbally. Identity of parents and child was accessible only to the researchers and all data were held in strict confidentiality. Informed written consent was obtained from all parents who agreed to be photographed with their children for the pictorial scale. All children photographed were typically developing children.

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Data sharing statement: No additional data is available on participating children, except data on clinical intervention, which are confidential and cannot be shared.

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Abstract

AIM

To assess the performance of a newly designed, culturally adapted screening tool for autism spectrum disorder (ASD).

METHODS

Items for the screening tool were modeled from already documented checklists and diagnostic criteria for ASD. Each item in text was paired with a photograph that illustrated the written content, which was in the 2 main local languages. The final product had 21 items and was named the pictorial autism assessment schedule (PAAS). Performance of PAAS was tested on a clinical sample of 18-48 mo old children, diagnosis naïve, presenting with developmental deficits. Mothers completed PAAS checklist.

Based on clinical diagnosis, which was taken as the gold standard, children were later grouped into ASD (Group 1) and non-ASD developmental disorders (Group 2). Mothers of a control sample of typically developing children also completed PAAS (Group 3).

RESULTS

A total of 105 children (Group 1-45, Group 2-30, Group 3-30) participated in the study. Mean age of Group 1 and Group 2 were 36 and 40 mo respectively. Majority were male in all 3 groups. Performance of PAAS in discriminating between ASD and non-ASD developmental disorders was sensitivity 88.8%, specificity 60.7%, positive predictive value (PPV) 78.4%, negative predictive value (NPV) 77.2%, likelihood ratio (LR+) 2.26, and LR- 0.18. Performance of PAAS in discriminating between ASD and typical development was sensitivity 88.0%, specificity 93.3%, PPV 95.2%, NPV 84.0%, LR+ 13.3 and LR- 0.12. The results indicated that that a positive result from PAAS was 2.26 times more likely to be found in a child with ASD than in a child with non-ASD developmental disorder. A positive result from PAAS was 13.3 times more likely to be found in a child with ASD than in a child with typical development.

CONCLUSION

PAAS is an effective tool in screening for ASD. Further study is indicated to evaluate the feasibility of using this instrument for community screening for ASD.

Key words: Autism spectrum disorder; Screening tool; Culture; Ethnicity; Parent self-assessment; Pictorial

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Core tip: Two previous studies in Sri Lanka showed that mothers had difficulty in comprehending and accurately responding to symptom of autism spectrum disorder (ASD) given in written text in a screening tool. The possible reason was cultural, where mothers did not perceive social deficits. To overcome this barrier, a screening tool was designed where each item on the checklist of key features of ASD was paired with a compatible photograph to improve comprehension. The new tool was tested on children with ASD, non-ASD developmental disorders and typically developing children. The new tool showed high sensitivity in discriminating between ASD and the other 2 groups.

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INTRODUCTION

Autism spectrum disorder (ASD) is neurodevelopmental

in nature, where deficit in social interaction and social communication is the most prominent behavioral feature. ASD is a biological disorder and therefore, the diagnostic criteria are similar irrespective of ethnic and racial differences. However, description of behavioral symptoms of ASD, their interpretation, and the level of acceptance is known to vary widely across cultures^[1]. As a result, culture can influence the outcome in surveillance and screening and arriving at a valid diagnosis. It has been suggested that some cultures may not recognize ASD as a disorder or may group individuals with ASD under another diagnostic category^[1]. Although supportive evidence is available in this regard, systematic research is limited^[1].

ASD is considered the commonest developmental disorder and the importance of early identification and intervention is well accepted. Several screening and diagnostic tools for early detection are available for use in community and clinical settings. Almost all these instruments were developed in high-income countries and were not designed to consider cultural and ethnic variables or influences in using them^[2]. Hence, their use in culturally diverse populations has been a challenge, with an added risk in adversely affecting the true estimates in epidemiological studies^[1,2]. Even in the United States, marked disparity has been shown in diagnosis of ASD in different ethnic groups on community based screening. This difference in rates was attributed to parental reporting, level of availability of services for ethnic minorities, socioeconomic status and heterogeneity of presentation^[3-5]. Other similar studies concluded that ascertainment issues, environmental risk factors, and genetic susceptibility may have influenced the observed differences^[1]. Findings that contradict these facts are also available. A long term follow up of birth cohorts in the United States failed to find any differences in prevalence rates between racial and ethnic groups^[6]. Also, early childcare providers in underserved communities using a screening tool, effectively identified young children for ASD in preschool/daycare settings, thus providing early diagnosis and access to intervention^[7]. Among Asian populations, delay in seeking help for a child with ASD is explained on cultural beliefs of parents and family. When compared to the median age of 15-19 mo for seeking treatment in the West, that for a Sri Lankan and Indian clinical cohorts were 35.8 mo and 25.7 mo respectively^[8,9]. In a four country (United States, United Kingdom, South Korea, Israel) study that compared relationship between culture and symptoms of comorbid psychopathology in those with ASD, the authors concluded that cultural factors, such as views about typical behaviour should be taken into account when examining symptoms of comorbidity in children with ASD^[10].

Comparison of sensitivity and specificity of screening tools for ASD have shown that their accuracy is moderate, which limits their use in isolation and in making decisions on diagnosis^[11]. At the same time, formal screening tools and general developmental testing

provide critical data as brief clinical observations may not reliably detect ASD risk where atypical behaviors are present^[12]. Although diagnostic and screening instruments have been translated into many languages and used in ethnically diverse populations, the effect of potential cultural confounds on the validity and reliability of these instrument have not been thoroughly assessed^[1]. Also, most widely available development, communication and behavior screening tools for young children, such as Ages and Stages Questionnaire (ASQ-3), Parents Evaluation of Developmental Status (PEDS) and Child Development Inventory among others, lack the sensitivity to screen for ASD.

The Modified Autism Checklist for Toddlers (M-CHAT) is the most commonly studied screening instrument^[13]. M-CHAT is a 23 item checklist of symptoms and is used for screening of 16-30 mo olds. It is available as a free on-line version and is self-administered to parents/guardians and interpreted by pediatric providers in the context of developmental surveillance^[14]. More recent revised and follow-up version (M-CHAT-R/F) claims to reduce false positive rates and better detection than the original M-CHAT^[15]. A positive predictive value of 50% has been found with M-CHAT-R/F when used in community settings. M-CHAT has been translated to several languages. Some have shown satisfactory reliability when used in culturally varied populations while some did not^[16-23]. For example, in a large community survey, an Arabic validation of M-CHAT failed to identify a substantial proportion of children, 18-24 mo of age suspected to have ASD^[16]. However, a Chinese version showed sensitivity as high as 93% on a similar age group^[21]. Training of professionals to use existing tools was feasible and effective in an Iranian study for screening of preschool children^[24]. Q-CHAT is another related tool found to be effective and reliable in screening at 18-24 mo^[25]. Adapted versions of existing tools have been criticized for their flawed research methods as a reason for poor performance. Differences between the psychometric properties of the original and adapted versions were common, indicating the need to obtain normative data on populations to increase the utility of the translated tools^[26]. Also, in a systematic review on the cultural adaptation of autism screening in ten languages, it was found that the cultural adaptation process was not always clearly outlined and often did not follow the recommended guidelines^[1].

Our study investigated the sensitivity and specificity of a new screening tool for ASD. Justification for development of such a tool came from two previous research outcomes. First was in using a translated M-CHAT in a total population screening at 18-24 mo of age^[27]. The study found that sensitivity of M-CHAT was only 25%. Second was a study on the presenting complaints in a clinical cohort of children later diagnosed with ASD. Abnormal play behavior and social un-connectedness were presented as key problems in only in 1.2%, which was in marked contrast to 82.3% seeking help for delayed speech development^[8]. Possible

reasons for both findings were considered as socio-cultural influence where parents attributed less importance or failed to notice deficits in social behavior. The alternative was to develop a tool that may reduce these cultural barriers to screening.

MATERIALS AND METHODS

Development of the screening tool

The checklist of items for the screening tool was adopted from several sources, but was not directly translated. The main source was diagnostic criteria for ASD in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM V)^[28]. Others were selected from M-CHAT^[13] and "First Signs" from American Academy of Neurology and the Child Neurology Society^[29]. The applicability to an age group of 18-48 mo and cultural factors that may influence the responses to ASD related enquiry were given due consideration when selecting and constructing the items of the checklist. Each item on the scale was worded as a question, for example: "Does your child bring over things to show you?" These items were originally written in Sinhala language and also translated into Tamil. Sinhala and Tamil are the 2 main languages spoken in Sri Lanka. All items were checked for accuracy of meaning, clarity and cultural appropriateness by experts in English and Sinhala/Tamil languages.

Design of pictorial scale

Each item on the checklist was paired with a photograph that illustrated the message in text. All photographs were taken on typically developing children together with an adult, either mother or father, where relevant. Informed written consent was obtained from the parent following which, the children and adults were initially coached on participating for the requirement of the photograph.

The written items and the matching photographs (facing each other on the opposing pages) were compiled into a manual. The end product was a list of 21 items where 20 items carried photographs to match. The last item was in text only (item 21) as it was difficult to convey meaning in a photograph. The self-assessment responses by parent were recorded on a separate sheet giving the numbered items in text with a choice of "yes" or "no" as the response. A "Yes" response to items 15, 16 and 21, and a "No" response to all other items was taken as positive indicators for ASD. Four or more positive indicators according the above scoring were taken as positive for ASD. Appropriate response to each item in support of ASD was counted as one.

Table 1 gives the English translation of items of PAAS. Clarity and comprehensibility of the text items and the compatibility of the text to the accompanying photograph in the compiled manual was further reviewed by a random sample of different grades of healthcare personnel and members of the general public. This was done on request and changes were made as necessary.

The completed scale was named Pictorial autism

Table 1 English translation of items of Pictorial autism assessment schedule

Does your child bring over things to show you
Does your child enjoy being thrown up and down on your lap
Does your child enjoy playing hide and seek
Does your child show pretend play
Does your child point to request
Does your child play with toys appropriately rather than mostly mouth or break them
Does your child attempt to imitate your actions
Does your child show an interest in other children
Does your child show willingness to share toys with others
Does your child look at your face when you hold an object in front of you
Does your child imitate your facial gestures
Does your child reciprocate affectionate gestures from you
Does your child look directly at your face on request
If you point at something far away, does your child look in that direction
Does your child watch rotating objects such as a fan or wheels for long periods
Does your child show repetitive purposeless finger movements
Does your child respond when called by name
If you point at something nearby, does your child look in that direction
Does your child join in a play of another child
Does your child point and show something that interests him
Does your child often appear as if he is in his own world

assessment schedule (PAAS).

Assessment of performance of scale

Performance of PAAS was evaluated on children selected from consecutive new referrals to a specialist developmental and child mental health outpatient service in a tertiary care pediatric hospital. They were either self-referrals or referrals from other pediatric services. The child was included in the sample if he/she was: (1) 18-48 mo of age; (2) was seeking help for a developmental problem; and (3) not had a developmental assessment or intervention prior to entry into the study. The last inclusion criterion was applied to avoid bias in responding to PAAS from exposure to ASD specific information from previous assessments. Mothers of all children included in the sample completed PAAS prior to the clinical assessment of the child. The mothers were unaware of the child's diagnosis at the time. Detailed information gathering from mother, observation of child's behavior and DSM V criteria was used to include or exclude ASD. The clinical diagnosis of ASD or non-ASD developmental disorder, which was carried out by a team of senior clinicians, was taken as the gold standard. In addition, those children diagnosed with ASD were assessed on Childhood autism Rating Scale (CARS) to further establish the clinical decision and estimate the severity. Diagnosis of developmental disorder was also made on clinical assessment and laboratory investigations where indicated.

Study and control samples

The sample was divided into 2 groups, based on the

diagnosis. Group 1 - consisted of children who earned a diagnosis of ASD; Group 2 - were children diagnosed with a developmental disorder but not ASD. A control group of children, 18-48 mo of age, with typical development (Group 3) were randomly selected from general pediatric outpatient clinics at the same hospital. Absence of developmental problems in Group 3 children was established from their clinical records. Children with any doubt about their developmental status in the records were excluded from the sample. Mothers of the control group children also completed PAAS.

Statistical analysis

Frequency distribution of data was analyzed using SPSS version 16. Sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios was calculated on performance of PAAS in detecting ASD and discriminating from non-ASD. Approval was obtained from the institutional ethical review committee of the Lady Ridgeway Hospital for Children, where the study was conducted.

RESULTS

Characteristics of the study population

A total of 105 children whose parents completed PAAS, 45 were later diagnosed with ASD (Group 1), 30 with non-autistic developmental delay (Group 2), and 30 had typical development (Group 3).

Table 2 gives the characteristics of children who participated in the study.

Performance of the scale

Table 3 gives the performance of PAAS in discriminating between ASD, non-ASD developmental delay/disorder and typical development

These results indicate that a positive outcome from PAAS was 2.26 times more likely to be found in a child with ASD than in a child with non-ASD developmental disorder. A positive result from PAAS was 13.3 times more likely to be found in a child with ASD than in a child with typical developmental. Similarly, a negative result from PAAS was 0.18 time and 0.12 times more likely to be found with ASD than with non-ASD developmental disorder and typical development respectively.

CARS scores on Group 1 ranged from 33-45 (mean 39.4, SD 3.988) indicating that all were in moderate to severe range for ASD. Test-retest reliability of PAAS was 95.7%. The time taken by mothers to complete PAAS was 15-20 min.

DISCUSSION

PAAS was an attempt to overcome a cultural barrier to identifying symptoms of ASD by adding a visual aid to facilitate recognition. When compared to a text only scale, pairing the item with a photograph improved the comprehension and identification of the symptom and better accuracy of responses by mothers. Also, PAAS had

Table 2 Characteristics of children who participated in the study

Variable	Group 1 <i>n</i> = 45	Group 2 <i>n</i> = 30	Group 3 <i>n</i> = 30
Mean age in months (range, SD)	36.5 (18-48, 12.02)	40.2 (18-48, 12.82)	31.8 (19-44, 9.77)
Sex			
Male	38 (84.4)	22 (73.3)	17 (56.7)
Female	7 (15.6)	8 (26.7)	13 (43.3)
Screening positive (%)	40 (88.8)	9 (30.0)	1 (3.33)
Screening negative (%)	5 (11.1)	21 (70.0)	29 (96.7)
Maternal education			
Primary education	3 (6.7)	2 (6.7)	6 (20.0)
Secondary education	19 (42.2)	22 (73.3)	22 (73.3)
Tertiary education	23 (51.1)	6 (20.0)	2 (6.7)

an administration time of 15-20 min, which increased its user friendliness. The nature of the cultural barriers that were overcome in PAAS is not entirely clear. However, it was inferred in a previous study on community-based screening in Sri Lanka that a disregard for social interactional deficits, stigma, and an over-riding wish for the child to be normal may all contribute to a false-negative result in screening for ASD^[27].

Our results showed that PAAS performed well in identifying ASD. This was evident from a sensitivity of 88.8% in discriminating between ASD and non-ASD developmental disorder, and 88.0% between ASD and typical development. In comparison, in the previous community based study, the respective results for M-CHAT were sensitivity of 25%, specificity of 71%, PPV of 0.13 and NPV of 0.85^[27]. These discrepancies were evident despite the fact that item lists in both M-CHAT and PAAS are directly related to core behaviors of ASD. The high LR+ of 13.3 in the current study indicated a good discriminatory power of PAAS between ASD and typical development, with a specificity of 93.3%. In comparison, at a specificity of 60.7% and LR of 2.26, performance of PAAS was less satisfactory in discriminating between ASD and non-ASD developmental disorders. The possible explanation is that some children with other developmental disorders in the sample may have had comorbid ASD like behavior.

In developing the tool, cultural adaptation was implemented in several ways. Firstly, the photographs used were that of local children. Secondly, the items for the checklist were conceptualized and worded in the local language in the first instance, rather than translated from English. All items were ASD specific, giving the tool the required face validity. Also, the high sensitivity of the tool indicated satisfactory construct validity against the gold standard of clinical assessment. Other similar adaptations to improve performance of ASD screening in different cultural settings are known. In a Japanese study, using a list of most discriminative in a short form screener improved performance of M-CHAT^[30]. Also, the Indian scale for assessment of autism (ISAA) and INCLIN diagnostic tool for autism Spectrum disorder (INDT-ASD) are culturally adapted new screening tools^[31,32].

Table 3 Performance of Pictorial autism assessment schedule in discriminating between autism spectrum disorder, non-autism spectrum disorder developmental delay/disorder and typical development

Result	Group 1 (<i>n</i> = 45) vs Group 2 (<i>n</i> = 30)	Group 1 (<i>n</i> = 45) vs Group 3 (<i>n</i> = 30)
Sensitivity	88.80%	88.00%
Specificity	60.70%	93.30%
PPV	78.40%	95.20%
NPV	77.20%	84.00%
LR+	2.26	13.3
LR-	0.18	0.12

Use of picture based illustrations in assessment and screening tools to facilitate comprehension is well known. For example, line-drawings and clip-art are used in scales for assessment of pain, body-image and anxiety, especially in children. However, such scales are few when compared to the vast number in written text alone. More recent studies have used pictorial scales where accurate comprehension is compromised by literacy level of the respondents, or the traditional instrument took too long to complete^[33-35]. Some of these scales have used only pictures and no text. With regard to ASD, a pictorial scale is available for assessment of joint attention in infants and preschoolers, which shows good validity^[36].

Using an arbitrary rather than a calculated cut-off score of 4 positive items is a limitation of our scale. However, in M-CHAT, positive response for only 2 critical items or 3 of the others is taken as positive for ASD. Similarly, in keeping with M-CHAT and other similar screening tools, "Yes/No" responses were implemented rather than a Likert scale. The tool was tested on an age group of 18-48 mo. This does not guarantee its performance on older children. The reason is that although core symptoms are that of social communication and social interaction, there is a wide variation in symptoms and behavior according to age, cognitive level, and severity. The sample being hospital based and small in size are other shortcomings. To be useful as a screening tool, PAAS should ideally be tested in primary healthcare setting and on a larger sample. The mother's education level especially of the Group 1 children was relatively high, which may not match that of a community-based sample. Hence, its performance and feasibility in using in the community is yet to be examined, although high sensitivity and PPV indicate good potential value.

In conclusion, PAAS is an effective tool in screening for ASD. The addition of a visual aid in the form of photographs improved its sensitivity. Further study is indicated to evaluate the feasibility of using this instrument for community screening for autism.

COMMENTS

Background

Inconsistency of performance of screening tools for autism spectrum disorder (ASD) in culturally diverse populations is a challenge to accurate estimation

of epidemiological data. There is limited research on applicability of screening instruments in such varied groups.

Research frontiers

Use of suitable modifications based on the knowledge about specific cultural values and beliefs in order to improve performance of screening tools is indicated.

Innovations and breakthroughs

The use of photographs to illustrate the text items in this screening instrument for ASD produced a high sensitivity and discriminatory power up to 13 times with non-ASD developmental disorders and typical development.

Applications

This tool was used in a hospital-based setting. In view of its high sensitivity, positive predictive value and positive likelihood ratio, the possibility exists in using it in hospital-based developmental clinics to screen ASD. However, further study is indicated before use in community setting.

Terminology

Screening for ASD in young children is actively promoted due to clear benefit of early intervention. However, culturally diverse populations do not always respond accurately to existing screening tools. Hence, developing culturally adapted tools is useful.

Peer-review

The paper is very interesting.

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Prospective Study

Off-label-use of sulfur-hexafluoride in voiding urosonography for diagnosis of vesicoureteral reflux in children: A survey on adverse events

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Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

Conflict-of-interest statement: Thorsten Bley: Consultancy for GSK and MSD; Speakers bureau: Bayer, Bracco, GE, Guerbet, HeartFlow, Siemens; Research funding: Deutsche Forschungsgesellschaft DFG: BL 1132/1-2; Research cooperation: Siemens, Noras, Rapid. The remaining authors of this manuscript have no conflicts of interest to disclose.

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Abstract

AIM

To evaluate the risk profile of sulfur hexafluoride in voiding urosonography (VUS) based on a large cohort of children.

METHODS

Since 2011 sulfur hexafluoride (SH, SonoVue®, Bracco, Italy) is the only ultrasound contrast available in the European Union and its use in children has not been approved. Within a 4-year-period, 531 children with suspected or proven vesicoureteral reflux (f/m = 478/53; mean age 4.9 years; 1 mo-25.2 years) following parental informed consent underwent VUS with administration of 2.6 ± 1.2 mL SH in a two-center study. A standardized

telephone survey on adverse events was conducted three days later.

RESULTS

No acute adverse reactions were observed. The survey revealed subacute, mostly self-limited adverse events in 4.1% (22/531). The majority of observed adverse events (17/22) was not suspected to be caused by an allergic reaction: Five were related to catheter placement, three to reactivated urinary tract infections, five were associated with perineal disinfection before voiding urosonography or perineal dermatitis and four with a common cold. In five patients (0.9%) hints to a potential allergic cause were noted: Perineal urticaria was reported in three interviews and isolated, mild fever in two. These were minor self-limited adverse events with a subacute onset and no hospital admittance was necessary. Ninety-six point two percent of the parents would prefer future VUS examinations with use of SH.

CONCLUSION

No severe adverse events were observed and indications of self-limited minor allergic reactions related to intravesical administration of SH were reported in less than 1%.

Key words: Voiding urosonography; Ultrasound contrast agent; Vesicoureteral reflux; SonoVue; Adverse events; Sulfur hexafluoride

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Core tip: This was a two-center study on 531 children with suspected or proven vesicoureteral reflux undergoing off-label voiding urosonography using sulfur hexafluoride (SH). We investigated the SH risk profile with intravesical administration. No acute allergic adverse event was observed with the off-label-use of SH for radiation free assessment of vesicoureteral reflux. Only a few subacute, minor-to-moderate adverse events were reported (4.1%). Hints of self-limited minor allergic reaction related to intravesical administration of sulfur hexafluoride were reported in less than 1%. This underlines the demand for an approval of SH in pediatric applications.

Sauer A, Wirth C, Platzer I, Neubauer H, Veldhoen S, Dierks A, Kaiser R, Kunz A, Beer M, Bley T. Off-label-use of sulfur-hexafluoride in voiding urosonography for diagnosis of vesicoureteral reflux in children: A survey on adverse events. *World J Clin Pediatr* 2017; 6(1): 52-59 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/52.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.52>

INTRODUCTION

The role of vesicoureteral reflux (VUR) in the pathophysiology of renal damage is controversially discussed^[1,2]. Voiding urosonography (VUS) is a radiation-free imaging

modality and has become an established alternative to the most common radiological modality for detection of VUR, that is fluoroscopic voiding cystourethrography (VCUG)^[3-7]. Recent studies have demonstrated its equal or higher sensitivity when compared to VCUG, especially in cases of high grade VUR^[3,8,9]. Known negative effects of ionizing radiation underline the demand for VUS to replace VCUG for assessment of VUR in children (Figure 1).

First generation urosonography contrast agents (US-CA) consisted of stabilized galactose-based air-filled microbubbles. Until its withdrawal in 2011, Levo-vist® (Bayer-Schering, Berlin, Germany) was approved for pediatric application and was commonly used for VUS, which is the most frequent pediatric application of US-CA^[10]. Since that time, sulfur hexafluoride (SH, SonoVue® Bracco, Milan, Italy) remains as the only US-CA available in the European Union. To date, it has not been approved for the use in children. SH is a second-generation US-CA composed of a stabilized aqueous suspension of sulfur hexafluoride microbubbles with a phospholipid shell^[11,12]. Due to the clinical demand it has gained widespread off-label acceptance in Europe. VUS implies the intravesical administration of SH and saline solution using a trans-urethral catheter. While scanning the bladder and kidneys during filling and voiding, the observer assesses whether microbubbles ascend to the ureters and/or the renal collecting system (Figure 2).

To date there are only few studies evaluating the safety profile of intravesical application of SH in children. These studies mainly address diagnostic efficacy of VUS using SH^[13-15] and only additional limited data concerning adverse reactions were reported on the side. Severe side effects were not reported in any of these studies. Riccabona^[16] underlined these results in a survey among European departments of radiology concerning adverse events associated with SH in intracavity use: No adverse reaction was recorded. Additionally, Papadopoulou *et al*^[17] reported no adverse allergic event in VUS with SH application in a single Pediatric Medical Center.

To date, there is no prospective multicenter study focusing on SH related adverse events in VUS. The aim of this prospective two-center-study was to evaluate the risk profile of SH in VUS based on a large cohort of children with suspected or proven VUR.

MATERIALS AND METHODS

Within a 4-year period, 531 children with suspected or proven VUR (f/m = 478/53; mean age 4.9 years; range 1 mo-25.2 years) underwent VUS in one of the two participating study hospitals ($n = 487$ in tertiary care hospital and $n = 44$ in secondary care hospital), which perform VUS in daily routine for several years. Indications for VUS were history of recurrent febrile urinary tract infections (UTI) or follow-up of previously detected VUR under conservative treatment or after surgical therapy, as recommended in the guidelines of the European Association of Urology/European Society for Pediatric

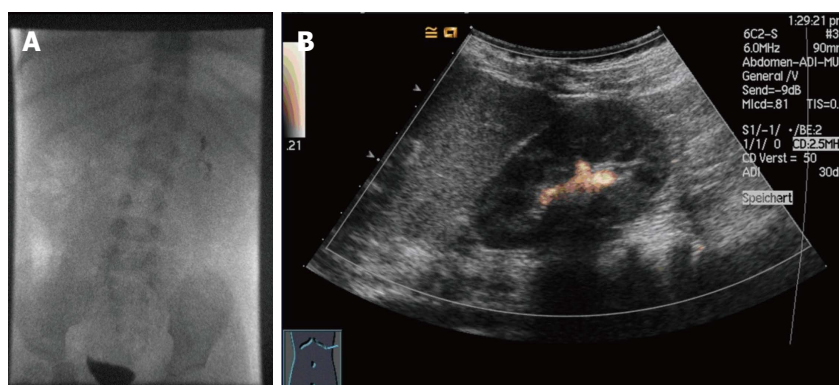


Figure 1 Voiding cystourethrography (A) vs voiding urosonography (B) of a two-year-old male patient with proven vesicoureteral reflux left at the left kidney (grade II). The voiding urosonography scan shows the urosonography contrast agent microbubbles in the left renal pelvis (agent detection mode).

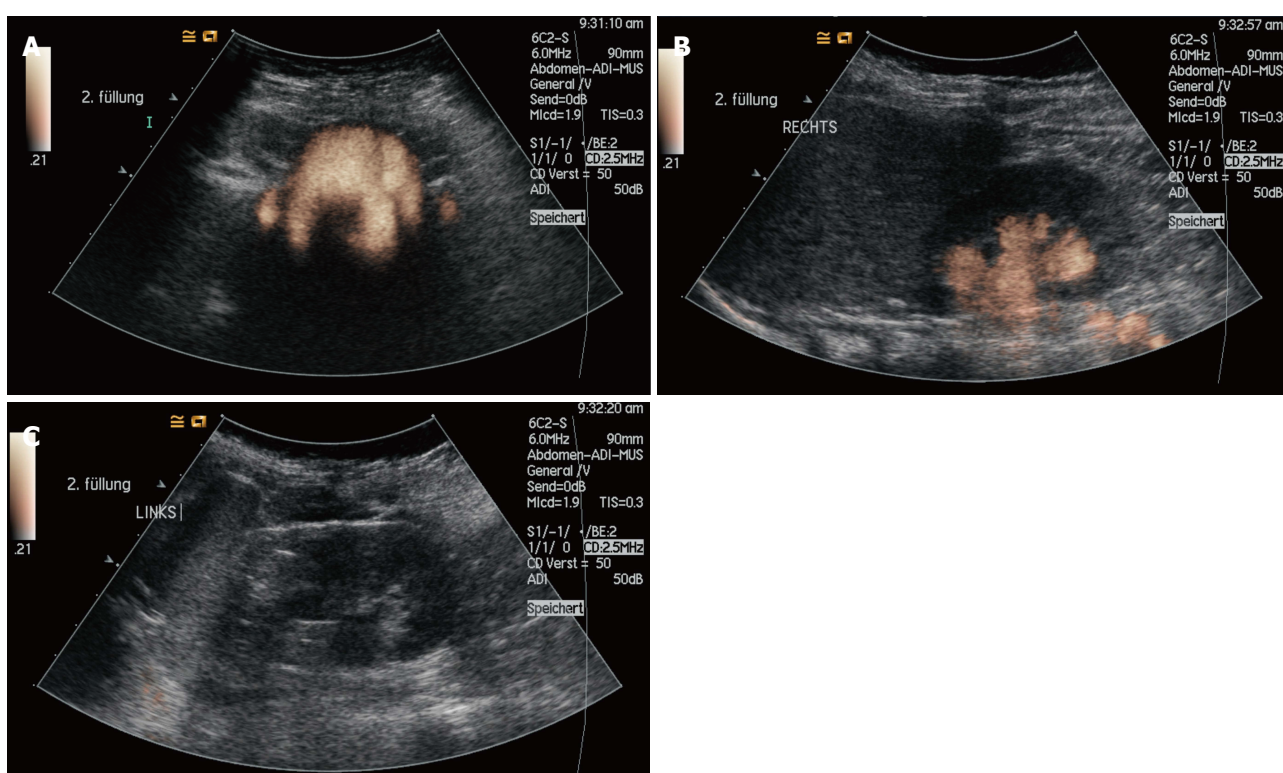


Figure 2 Voiding urosonography of a 6-year-old girl with proven, bilateral vesicoureteral reflux (grade I left and grade III right). The voiding urosonography scan shows the urosonography contrast agent microbubbles in both ureters and in the left renal pelvis (A: Bladder and distal ureters; B: Right kidney and proximal ureter; C: Left kidney).

Urology. In case of follow-up, a continuous oral antibiotic prophylaxis was performed in 370 children.

All legal guardians were informed about the off-label use of SH and their informed written consent was obtained prior to the examination. All study work was conducted in accordance with the Helsinki Declaration. Parents were asked to take part in a standardized telephone survey after VUS.

VUS examination

Ultrasound of the urinary tract was conducted in supine and prone position with a 5/6-MHz convex abdominal transducer (Acuson-Sequoia 512, Siemens Healthcare, Erlangen, Germany or Aplio 400, Toshiba Medical Systems, Neuss, Germany). Then the bladder was catheterized under aseptic conditions by using a 5/6 CH infant

feeding tube (Unomedical, Birkerød, Denmark) coated with anaesthetic gel (Instillagel, Farco-Pharma, Cologne, Germany) and fixed with a hypoallergenic, adhesive strip (Leukostrip, Smith and Nephew, Hamburg, Germany). Thereafter a urine test was performed and only in the absence of signs of acute UTI the examination was continued. The catheter was connected with a three-way valve. Target bladder capacity was calculated according to the following formula: Bladder volume (mL) = (Age in years + 2) × 30^[18].

First, the bladder was filled up to approximately one third of its capacity with 0.9% saline solution. Then, 0.5 mL-1 mL of SH was slowly administered and the bladder was subsequently filled with saline solution until maximum bladder capacity was reached or the child started voiding. SH was always prepared according to

the manufacturer's recommendation and was applied in a sterile manner. Meanwhile, the distribution of the UCA was observed and recorded in bladder, ureters and kidneys by ultrasound during filling and voiding. In order to increase the reflux detection rate this procedure was repeated at least twice. The average amount of administered SH was 2.6 ± 1.2 mL per patient and individually adapted to achieve the best diagnostic contrast. During the contrast-specific examination mode the mechanical index was turned to a low level (0.4) to minimize possible ultrasound-related disruptions of the microbubbles^[19]. All examinations were digitally recorded and performed/supervised by one specialized pediatric radiologist (in the tertiary care university hospital) and one trained pediatrician (in the secondary care hospital).

Documentation of adverse reactions

During the examination and until 30 min thereafter, all children were observed for any perineal skin or mucosal tissue reactions, generalized hypersensitivity or anaphylactoid reactions (*i.e.*, urticaria, pruritus, nausea, vomiting, abdominal pain, respiratory problems). Parents were instructed to monitor their child for three days and inform a doctor in case of any adverse event. After three days, parents were contacted for a standardized telephone survey comprising six specific items (skin rash, itching, wheals, fever, shortness of breath, consultation of a doctor) with dichotomic answers. Furthermore, they were asked for any onset of unspecific symptoms (*i.e.*, discomfort due to catheterization). Finally, a question concerning the willingness to have VUS with SH repeated, if clinically necessary for possible future examinations completed the survey.

Type, duration and onset of adverse events were recorded and classified as minor, moderate or severe event based on the World Health Organization Draft Guidelines for Adverse Event Reporting and Learning Systems^[20].

Statistical analysis

Mann-Whitney-*U* test was used for statistical analysis. A *P*-value < 0.05 was considered statistically significant.

RESULTS

No signs of acute hypersensitivity, generalized allergy or anaphylactoid reaction were observed during the examination and over the ensuing 30 min. The parents of all 531 children participated in the standardized telephone survey. Some adverse event was reported in 22 children (4.1% with 20 cases in the tertiary and two in the secondary care hospital; mean age 2.6 years; range 1 mo-6.2 years).

The majority of adverse events noted by the parents (17/22) did not reveal any association with potential allergic reactions: In three cases (0.6%), parents reported a new onset dysuria and mild fever, most likely due to an acute episode of chronic UTI. In a 6.2-year-

old girl, a medical consultation was attended and successful antibiotic therapy was performed. In a 1-month-old boy, hospital admittance was necessary for successful treatment of multiple antibiotic resistant bacterial UTI. In a 3-year-old girl, symptoms were self-limited. Duration of symptoms in all three cases was longer than 24 h. In 5 children (0.9%), a discomfort due to bladder catheterization (4 females and 1 male, 2 mo-5.8 years) and in four cases (0.7%) symptoms of a common cold (3 females and 1 male, 1.3 years-4.5 years) were reported. In 5 children (4 females, 1 male; 1 mo-2.4 years; 0.9%), a self-limited, perineal erythema was described. In one case (male, 21 mo), a spell of pruritus was reported and self-limitation was observed within 48 h.

Only a minority of the observed adverse events (5/22) were suggestive of potential allergic reaction. All of them (0.9%, 4 females and 1 male, 5 mo-6.2 years) were minor adverse events with a subacute onset and self-limitation within 24 h. Perineal urticaria was reported in approximately 0.5% (*n* = 3, 2 females and 1 male, 6 mo-3.8 years) and an isolated, mild fever was seen in 0.4% (*n* = 2, 2 females, 2-6.2 years). In one case with isolated fever (female, 2 years) a medical consultation took place. No hospital admittance was necessary due to any reported potential allergic adverse event (Table 1).

In the present study cohort in 224/531 (42.2%) children a VUR was detected. In those cases with described adverse events in 8/22 (36.4%) children a VUR was observed. In those children with potential allergic reaction a VUR was detected in 2/5 (40%).

We compared the mean amount of administered SH between those children showing adverse events and those without by using a Mann Whitney-*U* test (group 1: Patients with adverse events, *n* = 22; group 2: Patients without adverse events, *n* = 509). There was no significant difference (*P* > 0.05) between the two groups.

Ninety-six point two percent (*n* = 511) of the parents stated that, if clinically necessary, they would prefer further VUS examinations with the use of SH for their child over an X-ray voiding study.

DISCUSSION

No severe allergic adverse events were noted in this prospective, two-center survey on adverse events after intravesical administration of SH. In 0.9% of the study population, subacute minor adverse events were reported, which may have been caused by self-limited minor allergic reactions.

Recent studies have demonstrated an equal or higher sensitivity of VUS when compared to VCUG, especially in cases of high grade VUR^[3,8,9]. In a metaanalysis Darge *et al*^[6] described a sensitivity of 57%-100%, a specificity of 85%-100%, positive/negative predictive values of 58%-100%/87%-100%, respectively, and a diagnostic accuracy of 78%-96%. Moreover Kis *et al*^[13] examined a total of 183 children using VCUG and VUS in parallel. They detected VUR with VUS in 34.4% and with VCUG in

Table 1 Description of adverse events reported after 531 voiding urosonography in children

Adverse event	Severity	Total (n, %)	Age (range)	Gender (f/m, n)	Duration	Onset
Urinary tract infection	Minor/moderate	3 (0.6%)	1 mo-6.2 yr	f (2), m (1)	24-72 h	Subacute
Perineal erythema	Minor	5 (0.9%)	1 mo-2.4 yr 21 mo	f (4), m (1)	< 24 h 24-48 h	Subacute Subacute
Discomfort due to catheterization	Minor	5 (0.9%)	2 mo-5.8 yr	f (4), m (1)	< 24 h	Subacute
Symptoms of a common cold	Minor	4 (0.7%)	1.3-4.5 yr	f (3), m (1)	< 24 h	Subacute
Hints for hypersensitivity						
Perineal urticaria	Minor	3 (0.5%)	6 mo-3.8 yr	f (2), m (1)	< 24 h	Subacute
Isolated, mild fever	Minor	2 (0.4%)	2-6.2 yr	f (2)	< 24 h	Subacute

28.1%. Reflux was detected by both methods in 24.3%. VCUg missed cases of high-grade reflux whereas VUS missed only low-grade reflux. They suggest - based on their study results - that contrast-enhanced harmonic VUS using SH is superior to VCUg in the detection and grading of VUR.

To date, there are only few studies concerning the intravesical use of SH in children. Most of them focus on the diagnostic efficacy in VUS and experiences with adverse events are only additionally reported^[9,13-15,20]. In case of additional VCUg with intravesical application of an iodinated contrast agent during the same session, sufficient correlation of adverse events to one of the administered contrast agents was not possible^[9,13,15,20]. Duran *et al.*^[14] conducted a diagnostic study focusing on VUS with exclusive administration of SH. Thus, potential adverse events could be related to SH. None of the above noted studies (Table 2) reported any adverse event. In a single Pediatric Medical Center, Papadopoulou *et al.*^[17] focused on the safety profile of intracavity use of SH. They reported 37 cases (f/m = 18/19; 1 mo-8.9 years; 3.7%) of adverse events, which were mainly attributed to the bladder catheterization rather than to the administration of SH in a total of 1010 (f/m = 5/4; mean age: 2.9 years; range 15 d-17.6 years) children. Papadopoulou *et al.*^[17] described no signs of acute hypersensitivity or generalized allergic reaction, which is in line with the findings from our own study. The present study described a comparable frequency of adverse events, as noted in 4.1% of our patients.

Self-limited or successfully treated UTIs were observed in 0.6% that is in two children who had already been on prophylactic antibiotic therapy. Papadopoulou *et al.*^[17] reported UTIs with a lower frequency of only 0.1%, a discrepancy which may be explained by the standardized oral 3-d prophylactic antibiotic therapy prior to VUS administered to all their study participants. In the present study, and as recommended in the guidelines of the European Association of Urology/European Society for Pediatric Urology, children received a continuous oral antibiotic prophylaxis only in case of previously detected VUR (69% of all patients). In contrast to Papadopoulou *et al.*^[17], an additional short-time, prophylactic antibiotic therapy was not performed, which enables the detection of adverse events solely related to SH without being

compounded by additional antibiotic therapy. The comparably small incidence of subsequent UTIs in both studies raises the question whether a prophylactic antibiotic therapy to prepare patients for the VUS examination is indeed beneficial, also keeping in mind the concerns about the spread of antimicrobial resistances across bacterial strains^[21]. The results reported by Papadopoulou *et al.*^[17] in comparison to our own study suggest a VUS-related increase of 0.5% in mild UTI when no antibiotics are used as preparation.

The present study showed self-limited, subacute discomfort due to catheterization in five patients (0.9%). In contrast, Papadopoulou *et al.*^[17] described this in 2.6%. The difference could be related to the smaller number of male patients undergoing catheterization (f/m = 478/53) in the present study, boys being more susceptible for discomfort after catheterization due to anatomical conditions of the urethra and a possibly more difficult catheterization. This unequal sex ratio is related to the established diagnostic algorithm for the assessment of VUR in the participating study hospitals: The primary imaging modality in girls is VUS, whereas in boys, VCUg is routinely used on first referral due to a better delineation of the urethra in order to exclude urethral valves. For follow-up, VUS is the first choice in boys, as it is in girls.

A self-limited, perineal erythema was reported in five children, which was most likely related to a new onset of dermatitis (all children were diapered) or to disinfection in VUS procedure.

Unlike previous studies which reported no cases of allergic reactions, five unclear cases (three cases of urticaria and two cases of mild isolated fever) with hints for a potential allergic cause were observed: All of them were minor, subacute adverse events and self-limited. In four of five patients, the potential allergic reaction was reported by the parents during the telephone interview and suspected allergic aetiology was based solely on subjective parental assessment. In a 2-year-old girl with isolated fever, the parents consulted the family doctor who could not identify a clear reason for the fever episode. Therefore, a more detailed conclusion is not possible and the described symptoms have to be rated as possible hints for minor allergic reaction. Moreover, none of the parents contacted the study doctors at the onset of the described events. Maybe

Table 2 Overview of studies reporting a safety profile for intravesical use of sulfur hexafluoride in voiding urosonography

Ref.	Total	gender (f/m)	Age (range)	+ VCUG	Adverse events	Severity
Ascenti <i>et al</i> ^[15]	80	44/36	3 mo-5 yr	Yes	None	None
Papadopoulou <i>et al</i> ^[19]	228	105/123	6 d-13 yr	Yes	None	None
Kis <i>et al</i> ^[13]	183	89/94	2 d-44 mo	Yes	None	None
Ključevšek <i>et al</i> ^[20]	66	31/35	5 d-1 yr	Yes	None	None
Duran <i>et al</i> ^[14]	295	153/154	13 d-18 yr	No	None	None
Papadopoulou <i>et al</i> ^[17]	1010	563/447	15 d-17.6 yr	No	37	Minor
Present study	531	478/53	1 mo-25.2 yr	No	20	Minor
					2	Moderate

VCUG: Voiding cystourethrography.

additional laboratory data and a physical examination after 24 h could be helpful to rule out these potential hints for an allergic reaction in future studies.

Contrary to recent studies^[9,13-15,20] the average amount of used SH was higher (2.6 ± 1.2 mL vs 0.5-1.0 mL) which was most likely due to the higher mean age (4.9 years vs 5.1 mo-2.9 years). Therefore, a higher dose of SH was necessary to gain a sufficient bladder contrast. Moreover, at least two voiding cycles were performed in each patient and additional scans were done in unclear cases. In accordance to Papadopoulou *et al*^[17] no dependency of adverse events from the amount of administered SH and children's age were described.

Although we report on a two-center study, the evaluation of a large heterogeneous cohort of children is limited by an unequal distribution between the participating hospitals with the tertiary care hospital contributing far more patients. Nevertheless, there was a comparable amount of observed adverse events in both institutions (4.1% in the tertiary and 4.5% in the secondary care hospital) with potential hints for an allergic reaction only reported in the tertiary care hospital.

In contrast to SH, Levovist® was approved for the intravesical use in children in Europe until its withdrawal. Therefore the evaluation of its safety-profile in clinical practice within studies focusing on Levovist® was only secondary. In 2013 Darge *et al*^[12] published a review on safety of CE-US in children for non-cardiac applications. In this meta-analysis of eight studies^[19,22-28], 17 of 1062 children presented with minor adverse events after intravesical administration of Levovist®^[19,22], most likely related to the placement of the catheter and with a comparable frequency, as reported from VUS using SH.

Zerin *et al*^[29] described postprocedural symptoms in 35.1% of the children ($n = 228$) undergoing VCUG, radionuclide cystography or diuretic renal scintigraphy. The frequency of postprocedural symptoms was nearly identical in the VCUG group and the two other groups. Dysuria was the most common symptom (32.9%). Symptoms disappeared within 24 h in 40%. They concluded that most postprocedural symptoms could be attributed to the discomforting, minimally invasive procedure of bladder catheterization itself as well as its psychological impact on the children, rather than the contrast agent. Weese *et al*^[30] report 2 cases (0.3%)

of anaphylactoid reactions during VCUG or retrograde pyelography in a retrospective review of 783 patients.

This survey revealed that 96.2% of parents would favor further radiation-free VUS examinations utilizing SH for detection of potential vesicoureteral reflux. The remaining 3.8% disagreeing to further VUS examinations felt uncomfortable due to its off-label-use.

In summary, the off-label-use of SH for radiation-free assessment of VUR provides a good safety profile. The present study did not reveal any acute severe allergic adverse event. Minor-to-moderate adverse events were observed in 4.1% and had hints for an allergic cause in less than 1% of the study population. Accordingly, the off-label-use had a high level of acceptance among the interviewed parents. The study results underline the demand for an approval of SH in pediatric applications.

COMMENTS

Background

The role of vesicoureteral reflux (VUR) in the pathophysiology of renal damage is controversially discussed. Voiding urosonography (VUS) entails the intravesical administration of an urosonography contrast agent (US-CA) for the diagnosis of VUR. VUS is now recognized as a practical, radiation-free modality with comparable or higher sensitivity than voiding cystourethrography (VCUG). First generation US-CA consisted of stabilized galactose-based air-filled microbubbles. Until its withdrawal in 2011, Levovist® (Bayer-Schering, Berlin, Germany) was approved for pediatric application and was commonly used for VUS. Since that time, sulfur hexafluoride (SH, SonoVue®, Bracco, Milan, Italy) remains as the only US-CA available in the European Union. To date, it has not been approved for the use in children. SH is a second-generation US-CA composed of a stabilized aqueous suspension of sulfur hexafluoride microbubbles with a phospholipid shell. Due to the clinical demand it has gained widespread off-label acceptance in Europe.

Research frontiers

To date there are only few studies evaluating the safety profile of intravesical application of SH in children. These studies mainly address diagnostic efficacy of VUS using SH and only additional limited data concerning adverse reactions were reported on the side. The aim of this prospective two-center-study was to evaluate the risk profile of SH in VUS based on a large cohort of children with suspected or proven VUR.

Innovations and breakthroughs

To date there is no prospective multicenter study focusing on SH related adverse events in VUS. This is the first two-center-study which evaluates the risk profile of SH in VUS based on a large cohort of children with suspected or proven VUR. The authors did not address diagnostic efficacy of VUS using SH, also they did not focus on a comparison to VCUG. Therefore the authors performed no additional VCUG with intravesical application of an iodinated

contrast agent during the same session to gain sufficient correlation of adverse events to the administered SH. In a single Pediatric Medical Center, Papadopoulou *et al* focused on the safety profile of intracavity use of SH. They reported 37 cases of adverse events, which were mainly attributed to the bladder catheterization rather than to the administration of SH in a total of 1010 children. The present two-center-study described a comparable frequency of adverse events. But in contrast to Papadopoulou *et al*, in this study a minority of the observed adverse events were suggestive of potential allergic reaction. Tough none of the observed events were acute or severe and no hospital admittance was necessary.

Applications

In summary, the off-label-use of SH for radiation-free assessment of VUR provides a good safety profile. The study results underline the demand for an approval of SH in pediatric applications.

Terminology

VUR is a condition in which urine flows retrograde from the bladder into the ureters/kidneys. VUS is a radiation-free imaging modality and has become an established alternative to the most common radiological modality for detection of VUR that is fluoroscopic VCUG. SH (SonoVue®) is a second-generation US-CA composed of a stabilized aqueous suspension of sulfur hexafluoride microbubbles with a phospholipid shell.

Peer-review

The authors conducted a survey on adverse events of SH in VUS in children. This paper is well-written and has valuable information.

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Prospective Study

Understanding academic clinicians' intent to treat pediatric obesity

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Abstract

AIM

To examine the extent to which the theory of planned behavior (TPB) predicts academic clinicians' intent to treat pediatric obesity.

METHODS

A multi-disciplinary panel iteratively devised a Likert scale survey based on the constructs of the TPB applied to a set of pediatric obesity themes. A cross-sectional electronic survey was then administered to academic clinicians at tertiary care centers across Canada from January to April 2012. Descriptive statistics were used to summarize demographic and item agreement data. A hierarchical linear regression analysis controlling for demographic variables was conducted to examine the extent to which the TPB subscales predicted intent to treat pediatric obesity.

RESULTS

A total of 198 physicians, surgeons, and allied health

professionals across Canada (British Columbia, Alberta, Manitoba, Saskatchewan, Nova Scotia, Ontario and Quebec) completed the survey. On step 1, demographic factors accounted for 7.4% of the variance in intent scores. Together in step 2, demographic variables and TPB subscales predicted 56.9% of the variance in a measure of the intent to treat pediatric obesity. Perceived behavioral control, that is, confidence in one's ability to manage pediatric obesity, and subjective norms, congruent with one's context of practice, were the most significant predictors of the intent to treat pediatric obesity. Attitudes and barriers did not predict the intent to treat pediatric obesity in this context.

CONCLUSION

Enhancing self-confidence in the ability to treat pediatric obesity and the existence of supportive treatment environments are important to increase clinicians' intent to treat pediatric obesity.

Key words: Pediatric obesity; Therapeutics; Intention; Decision Making; Behavior

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Core tip: Clinicians play an integral role in diagnosing and managing childhood obesity. This study examined how the theory of planned behavior (TPB) predicted academic clinicians' intent to treat pediatric obesity. Demographic variables and TPB subscales predicted 56.9% of the variance in intent scores amongst health professionals to treat pediatric obesity. One's practice context (subjective norms) and confidence in one's ability to manage pediatric obesity (perceived behavioral control) were the most significant predictors of intent. Attitudes and barriers did not predict intent. The TPB can be applied to strengthen clinical training programs targeted towards management of obesity in children.

Frankfurter C, Cunningham C, Morrison KM, Rimas H, Bailey K. Understanding academic clinicians' intent to treat pediatric obesity. *World J Clin Pediatr* 2017; 6(1): 60-68 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/60.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.60>

INTRODUCTION

Pediatric obesity is considered to be one of the greatest public health threats of the twenty-first century. In the last three decades, obesity amongst infants and young children has reached epidemic proportions^[1]. It is estimated that the total of 42 million children under the age of five who were overweight or obese as of 2013 will evolve into a magnitude of 70 million by 2025 if current trends persist^[2]. Presently, upper-middle income countries experience the highest prevalence of overweight children, yet rates are rising in all countries,

with the highest rate of growth in lower-middle income nations^[1].

The metabolic and physiological changes that accompany an increased body mass index are diverse and complex. Children who are classified as overweight and obese are not only at an increased risk of remaining overweight or obese as they progress into adulthood, but also face a range of medical sequelae including hyperlipidemia, hypertension, glucose intolerance, coronary heart disease, and psychosocial disorders^[3,4]. Obese children are more likely to experience an impaired quality of life, bearing not only a significant social and psychological burden, but also an increased risk of premature mortality^[5,6].

The obesity phenomenon is multifactorial and complex in its etiology and course. Governmental policies, community and family environments, and lifestyle all play a significant role in shaping the body mass index of infants and children. Particularly important actors in not only the management, but also the prevention of pediatric obesity, are healthcare professionals. They can identify children at high risk for becoming overweight or obese, engage children and their families in appropriate and vital interventions, as well as contribute to public health prevention efforts^[7]. In spite of the recent expansion in the availability of pediatric weight management programs and physicians' ability to connect patients with available community resources such as dietitians and physical activity counselling, the overall management of obesity by health care professionals is still sub-optimal^[8,9]. A large percentage of overweight and obese children remain clinically undiagnosed, suggesting that the window for early interventions is being missed and behavioral obesity-related risk factors are not being adequately screened for^[10-13].

Many clinicians feel they do not have the qualifications to treat obese patients and report a lack of adequate training to provide weight management counseling^[14]. Self-reported competence regarding obesity treatment has been consistently reported as poor^[15-17]. Experience with failure in managing patients' weight in the past is likely discouraging current clinicians from actively participating in obesity management^[17-19]. Given strong support amongst physicians for better counseling tools to guide patients toward lifestyle modification, there is a need for supplementary education and training in pediatric weight management to improve patient care^[14,19].

The decision of clinicians to engage in pediatric obesity management is influenced by a multitude of psychological factors, many of which are encapsulated within major theories of behavior. The theory of planned behavior (TPB) is one such model used extensively to predict human intent and behavior^[20]. It posits that attitudes, perceived behavior control, and subjective norms result in the formation of behavioral intentions that, in turn, serve as proximal causes of behavior. Attitudes are defined as expectations about an intervention's benefits

and effectiveness. Perceived behavior control refers to personal beliefs about one's own abilities, whereas subjective norms are considered to be the views of others with regard to a certain behavior and one's motivations to act in synchrony with these views^[20-22]. An individual's estimation of the costs of an action ("barriers") can additionally be utilized as a fourth subscale to strengthen the predictive ability of the TPB model^[22]. Intent, defined as a proxy of an individual's readiness to engage in a particular behavior, has been identified as the strongest correlate of actual behavior, and according to the TPB, is a cumulative function of four subscales: (1) attitudes; (2) subjective norms; (3) perceived behavioral control; and (4) barriers^[23]. The TPB has been recognized as an appropriate model for predicting the behavior of healthcare professionals^[23-26].

There is a compelling case for the treatment of pediatric obesity and strong evidence identifying intent as a proximal predictor of behavior. Understanding which dimensions within the TPB best predict the intent to treat would better inform strategies that would mobilize clinicians to engage in active pediatric obesity management. Such strategies may include educational programs and campaigns shifting clinical culture within academic institutions. Though past literature has examined the reported attitudes and competency levels of physicians towards obesity treatment^[15,18,27], to our knowledge, there has been no evidence addressing what factors play a significant role in influencing clinicians' intent to treat obesity within the pediatric population. There has been a call for research exploring the extent to which physician attitudes and health system factors are associated with clinical practice patterns of obesity care, as this information is important to catalyze effective health professional obesity diagnosis and management, and ultimately enhance health outcomes for children with obesity^[18,28].

The objective of this study was to determine the extent to which the TPB subscales (attitudes, subjective norms, perceived behavioral control, and barriers) predict variation in academic clinicians' intent to treat pediatric obesity. We hypothesized that all four aforementioned subscales significantly predict the intent of clinicians to treat pediatric obesity. This knowledge will be valuable in informing the design of more effective and innovative strategies to improve the care of infants and children with obesity.

MATERIALS AND METHODS

Setting and participants

This study was conducted at academic tertiary care centers affiliated with medical schools across Western Canada (British Columbia, Alberta, Manitoba, Saskatchewan), Eastern Canada (Nova Scotia), Ontario, and Quebec. We recruited health professionals affiliated with academic institutions as they are the ones involved in the training of the next generation of clinicians who will be treating pediatric patients.

Liaisons with the academic heads of pediatrics,

Table 1 Psychometric properties of the theory of planned behavior subscales

Subscales	No. of items	Cronbach's α
Attitudes	6	0.93
Subjective norms	6	0.76
Perceived behavioral control	10	0.87
Barriers	7	0.60
Intent	9	0.85

family medicine, and pediatric general surgery at 16 academic hospitals across the nation were established. Academic heads who agreed to participate in the survey then circulated the electronic survey link to all health professionals *via* email using their department mailing list. The survey was administered according to the Dillman method over a 4-mo period from January to April 2012^[28].

Study design

An electronic survey for this study was devised according to a framework specific to the creation of a TPB questionnaire^[29]. Themes that influence clinical decision-making with respect to obesity were identified in our previous qualitative study, in which 24 physicians from across Canada were interviewed^[30]. A multi-disciplinary panel consisting of a psychologist, pediatric endocrinologist, pediatric surgeon, and clinical epidemiologist iteratively then devised a Likert scale survey based on the constructs of the TPB applied to the identified pediatric obesity themes until consensus was reached. The final survey consisted of 38 items assessing the TPB constructs in relation to the management and treatment of pediatric obesity, and is available upon request. Intent and the 4 TPB constructs (attitudes, subjective norms, perceived behavioral control, and barriers) were assessed with 5-point Likert scale questions, where 1 was defined as strong disagreement and 5 indicated strong agreement. For example, when measuring intent, participants were presented with the starting phrase, "I would be willing to": And then asked to individually rate 9 items on the 5-point Likert scale. Data on participants' sex, age, birth, native language, education, practice setting, years of professional experience, and years of experience treating pediatric obesity were also collected. Basic psychometric properties of the survey are summarized in Table 1. All survey responses were anonymous; identifying information and IP addresses were not collected (Table 2).

This cross-sectional survey, administered as a sub-section of a larger questionnaire under the "ACT NOW" study, explored attitudes of clinicians towards obesity treatment through behavioral questions using a conjoint-based methodology^[31]. The entire questionnaire required approximately 30 min for completion, with the TPB questions located near the start of the survey and representing about one quarter of the entire question set. The study received ethics approval from the Hamilton Integrated Research Ethics Board (11-167). Informed consent was obtained prior to the start of the

Table 2 Agreement level for subscale items (*n* = 198)

	Percentage (%)				
	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
Attitudes/benefits					
When obesity is managed or treated, children and adolescents will be less likely to develop:					
Diabetes	1.5	0.5	2.0	39.4	56.6
Cardiovascular disease	1.5	0.0	4.0	43.4	51.0
High blood pressure	1.5	0.5	3.0	44.9	50.0
Musculoskeletal problems	1.5	1.5	3.5	49.5	43.9
Elevated LDL cholesterol levels	2.0	1.5	9.1	52.0	35.4
Mental health problems	1.5	3.5	15.7	54.0	25.3
Subjective norms					
What would encourage you to manage or treat pediatric obesity?					
Patients requesting treatment	0.0	4.5	12.1	38.4	44.9
Parents requesting that a child or adolescent be treated	0.0	5.6	21.2	49.5	23.7
Clinical practice guidelines	0.0	3.5	15.2	58.1	23.2
Colleagues who found treatment was successful	0.0	3.5	24.7	55.6	16.2
Policies in your organization	0.5	10.1	36.4	42.4	10.6
Meta-analyses showing treatment was successful	0.0	2.5	8.1	52.5	36.9
Self-efficacy/barriers					
What would make it difficult for you to manage or treat pediatric obesity?					
Families do not support pediatric obesity treatment	2.0	16.7	19.7	40.4	21.2
Patients do not adhere to pediatric obesity treatments	0.0	7.6	18.2	53.5	20.7
I don't have enough expertise in the treatment of pediatric obesity	5.6	18.7	22.7	37.4	15.7
It would be hard to find the time	5.6	23.2	29.8	27.8	13.6
I don't have access to consultation regarding the treatment of pediatric obesity	8.6	32.8	22.7	30.8	5.1
Difficulty billing for pediatric obesity treatment	9.1	36.4	36.9	14.1	3.5
My colleagues would not support pediatric obesity treatment	15.2	42.4	27.3	13.1	2.0
Perceived behavioral control					
With respect to pediatric obesity, I have the skills to:					
Conduct an assessment	4.5	16.2	15.2	47.0	17.2
Estimate the risks associated with pediatric obesity	4.5	18.2	19.7	48.0	9.6
Counsel patients and families regarding treatment options	6.1	22.2	19.7	43.4	8.6
Deal with children and adolescents who do not adhere to treatment	10.1	36.4	18.7	29.3	5.6
Deal with families who do not support treatment	12.1	35.4	21.7	27.8	3.0
Provide psychosocial treatment	17.7	44.4	19.2	16.2	2.5
Provide long term treatment follow-up	16.2	24.2	18.7	35.4	5.6
Evaluate the usefulness of different approaches to treatment	7.6	26.3	22.7	38.9	4.5
Treat or manage obesity with medication	25.3	48.0	12.6	12.1	2.0
Provide surgical treatment	66.7	22.2	4.0	4.0	3.0
Intent					
I would be willing to:					
Refer a pediatric patient for obesity treatment	2.5	2.0	3.0	41.9	50.5
Assess obesity in children	7.1	10.6	8.1	50.5	23.7
Assess obesity in adolescents	6.1	9.6	11.1	48.5	24.7
Counsel families regarding obesity treatment options	7.1	11.6	13.6	52.5	15.2
Accept referrals of children and adolescents who have difficulty with obesity	23.2	25.3	14.1	25.3	12.1
Provide psychosocial treatments for obesity in adolescents	19.7	37.4	15.2	22.7	5.1
Provide psychosocial treatments for obesity in children	22.2	35.4	16.2	22.7	3.5
Treat obesity with medication	19.2	38.9	18.2	21.7	2.0
Provide surgical treatments for obesity	56.1	23.2	9.1	9.1	2.5

The order of questions within subscales was randomized in each survey. LDL: Low-density lipoprotein.

survey. Data were collected in a confidential password-protected database without personal identifiers.

Statistical analysis

Statistical analysis was conducted using SPSS v.20.0. Descriptive statistics were used to summarize demographic and item agreement data. Pearson correlations were computed to determine the magnitude of the associations between the TPB variables. Hierarchical linear regression analysis was conducted to examine the extent

to which the TPB subscales predicted the intent to manage pediatric obesity. To control for demographic variables, and to examine the relationship between demographic variables and the intent to treat pediatric obesity, we entered years of experience, birth country, and sex in step one of the hierarchical linear regression equation. The four TPB subscales were entered in step two. Participants who did not complete the entire survey were excluded from the analysis. *P*-values of less than 0.05 were considered significant. The statistical methods of this study were

Table 3 Demographic and practice characteristics of participants (*n* = 198)

Variable	<i>n</i> (%)
Sample Size	198 (100)
Gender	
Male	73 (37)
Female	125 (63)
Age	
26-35	38 (19)
36-55	127 (64)
≥ 56	33 (17)
Years of experience treating pediatric obesity	
0-5	119 (60)
6-15	48 (24)
≥ 16	31 (16)
Birth country	
Canada	131 (66)
Other country	67 (34)
First language	
English	158 (80)
French	23 (12)
Other	17 (9)
Educational background	
Allied health	11 (6)
Physician	149 (75)
Surgeon	38 (19)
Setting	
Walk-in/individual practice/community hospital	14 (7)
Group practice	19 (10)
University teaching hospital	165 (83)
Professional experience	
0-5 yr	43 (22)
6-15 yr	81 (41)
≥ 16 yr	74 (37)
Province	
West	52 (26)
Ontario	98 (50)
Quebec	19 (10)
East	29 (15)

reviewed by Dr. David Streiner from University of Toronto.

RESULTS

Of 341 participants who opened the survey, 291 consented to participate, and 198 completed the entire survey and were included in the analysis. This sample consisted of 149 physicians, 38 surgeons, and 11 allied health professionals (e.g., nurse practitioners, dieticians, etc.). Demographic characteristics of this sample are summarized in Table 3. A greater proportion of respondents were female (63%), worked as physicians (75%), and were employed in a teaching hospital setting (83%).

Survey results

The results of the survey regarding levels of agreement for each of the TPB subscales are illustrated in Table 2. There was strong agreement on benefits of obesity management and treatment. Over 75% of respondents either agreed or strongly agreed that obesity management would result in children being less likely to develop all listed co-morbidities (diabetes, cardiovascular disease,

high blood pressure, musculoskeletal problems, elevated LDL levels, and mental health problems). Agreement with subjective norms items was likewise high. The surveyed health professionals would be most notably encouraged to treat pediatric obesity if meta-analyses showed that treatment was successful (89%) and patients requested treatment (83%). A total of 72% reported an inclination to treat if they encountered colleagues who found treatment to be successful. A lack of patient adherence and family engagement were reported as the biggest barriers by 74% and 62% of respondents. Agreement on perceived behavioral control was low. A total of 62% respondents reported that they did not have the skills to provide psychosocial treatment, 73% did not know how to treat obesity with medication, and 48% reported not having skills to deal with families who did not support treatment. From an overall management perspective, 74% were willing to assess obesity in children, 73% were willing to assess obesity in adolescents, and 92% were willing to refer a pediatric patient for obesity treatment.

Predictors of intent

The correlations between demographic variables and TPB subscales are presented in Table 4. Length of experience was directly related to greater perceived behavioral control, fewer barriers, and a higher intent to treat pediatric obesity. The results of the full hierarchical linear regression analysis are summarized in Table 5. In step one of the equation, sex, birth country and years of experience treating pediatric obesity accounted for only 7.4% of the variance in intent scores [$F(3,194) = 6.29, P < 0.001$, adjusted $R^2 = 0.074$]. In step two, perceived behavioral control and subjective norms made significant independent contributions to the prediction of intent to treat pediatric obesity scores (Table 5). Although an increase in barriers was correlated with lower intent scores (Table 4), attitudes and barriers did not contribute independently to the prediction of intention to treat (Table 5). Sex, birth country, and years of experience treating pediatric obesity did not contribute independently to the prediction of intent to treat pediatric obesity scores in step 2 of the equation (Table 5). Together in step 2, the demographics of sex, birth country, and years of experience and TPB scores accounted for 56.9% of the variance in intent scores [$F(7,190) = 38.09, P < 0.001$, adjusted $R^2 = 0.569$]. The inclusion of a variable distinguishing surgeons ($n = 38$) vs a group ($n = 160$) including physicians ($n = 149$) and allied health professionals ($n = 11$) did not contribute significantly to the prediction of the intent to treat pediatric obesity at either steps 1 or 2 of the regression equation.

DISCUSSION

The World Health Organization has identified childhood obesity as a public health priority and has called for a collaborative strategy towards tackling the epidemic^[32,33].

Table 4 Pearson inter-correlation matrix between intent to treat pediatric obesity and demographic variables/theory of planned behavior subscales

Variable	Item mean	SD	Correlation coefficients						
			1	2	3	4	5	6	7
Sex	-	-							
Birth country	-	-	-0.1						
Experience	2.6	1.7	-0.05	-0.05					
Attitudes	4.3	0.7	-0.02	0.01	-0.05				
Subjective norms	4	0.5	0.23 ^b	-0.14	0.02	0.27 ^c			
Perceived behavioral control	2.8	0.7	-0.04	-0.01	0.36 ^c	0.02	0.08		
Barriers	3.2	0.6	0.08	-0.1	-0.19 ^b	0.02	0	-0.29 ^c	
Intent	3.1	0.8	0.11	-0.12	0.26 ^c	0.07	0.27 ^c	0.72 ^c	-0.27 ^c

Item mean is based on the average scores per question within each subscale (each question was anchored on a scale of 1 to 5). ^a $P < 0.05$, ^b $P < 0.01$, ^c $P < 0.001$. 1 = Less than 1 year, 2 = 1 to 5 years, 3 = 6 to 10 years, 4 = 11 to 15 years, 5 = 16 to 20 years, 6 = 21 to 25 years, 7 = More than 25 years. SD: Standard deviation.

Table 5 Step two of the hierarchical linear regression analysis for demographic factors and theory of planned behavior subscales on intent to treat ($n = 198$)

Independent variable	B	SE	β	P value
Sex	1.3	0.69	0.09	0.061
Birth country	-1.23	0.69	-0.09	0.077
Years of experience treating pediatric obesity	-0.04	0.21	-0.01	0.86
Attitudes	0.02	0.09	0.01	0.83
Subjective norms	0.38	0.11	0.17	0.001
Perceived behavioral control	0.65	0.05	0.69	< 0.001
Barriers	-0.15	0.09	-0.08	0.097

The P -value is based on the unstandardized regression coefficient. B: Unstandardized regression coefficient; β : Standardized regression coefficient. SE: Standard error.

Pediatric obesity is a multifactorial phenomenon, affected by genetics, family environments, diet and physical activity levels. By engaging in the diagnosis, active management, and prevention of pediatric obesity, clinicians can explore a wide range of treatment interventions with children and their families and subsequently alter the trajectory of a child's health^[34].

This study used the TPB framework to investigate the extent to which attitudes, subjective norms, perceived behavioral control, and barriers predicted Canadian academic tertiary care clinicians' intention to treat pediatric obesity. Coupled with demographic variables, the TPB subscales accounted for 56.9% of the variance in intent scores, a sizeable value strengthening the validity of this model in the context of pediatric obesity treatment^[35]. The study strongly supports the TPB accounting for a significant amount of variance in clinician intentions and is consistent with a previous systematic review, affirming the appropriateness of the TPB in predicting healthcare professional behavior^[23]. The strongest predictors of intent were subjective norms and perceived behavioral control. This suggests that, if one's practice context (*i.e.*, patient and family perspective, experience of colleagues, practice guidelines, and the evidence base) supports specific obesity interventions, and a personal belief in a clinician's own self-efficacy exists, a clinician is more likely to implement or refer a patient for treatment.

The relationship between perceived behavioral control and the intent to manage pediatric obesity was stronger than for any other TPB subscale. Over half of respondents reported lacking skills to provide psychosocial treatment and to manage obesity with medication. This finding is consistent with previous literature highlighting the self-perceived lack of proficiency in childhood obesity management, and reinforces the need for increasing training^[36]. Strengthened training programs for future healthcare professionals and enhanced continuing educational programs for existing professionals will augment their beliefs in their own abilities to implement obesity treatment, as suggested by the guidelines on how to promote evidence-based medicine^[37].

In addition to one's perceived confidence in their clinical abilities, subjective norms was likewise a significant predictor of the intent to treat pediatric obesity, with 72% of clinicians encouraged to manage or treat pediatric obesity if colleagues found treatment successful. This was supported by previous research affirming that subjective norms were strong predictors for physicians' use of clinical and organizational guidelines^[38-40]. Using different methods, our larger conjoint-based study likewise identified that social factors exerted a strong influence on obesity treatment decisions^[30]. We recommend that healthcare institutions support the management of pediatric obesity to enhance uptake of practice guidelines

and promote active management. This may include having local prominent clinical leaders mobilize their colleagues to engage in action. Physicians depend on their peers not only for knowledge exchange, but also for informal consultation to help guide their practice and develop clinical standards^[37]. Knowledge sharing amongst peers within institutions will thus have the potential to accelerate the adoption of clinical best practices and to promote increased treatment behavior in clinicians. The Knowledge-to-Action Cycle recognizes the importance of professional networks and suggests that opinion leaders and change agents be involved in the transfer of information to elicit change in the individual decision-making process^[36]. If the views of even a few colleagues become more proactive towards management, it is suggested by our data that surrounding clinicians will be influenced to act in a similar fashion.

Although attitude scores were high, with the majority of respondents agreeing that management of obesity likely results in reduced health consequences, the absence of a relationship between attitudes and the intent to treat pediatric obesity suggests that simply disseminating information regarding the effectiveness of evidence-based weight management strategies will not adequately influence the clinicians' intent to treat. Fostering skills that enhance perceived behavioral control and creating an enabling environment for obesity management is needed. Continuing professional education that focuses on knowledge translation is not likely to result in a sustained shift in the management of obesity, a finding echoed in past studies stating that the problem with childhood obesity treatment lies not in the elaboration of guidelines but rather in the lack of support systems for primary care practitioners to implement them, including inadequate training and resources^[16].

Our regression model concluded that although years of experience was correlated with perceived behavioral control, demographic variables overall did not account significantly for variance in clinicians' intention to treat childhood obesity. This result is supported by the literature, which demonstrates that attitudes exert a stronger influence on service preferences than demographic characteristics^[41,42]. This finding suggests that the diverse backgrounds of health professionals are not likely to present a major barrier to transforming the attitudes and actions of future clinicians treating pediatric obesity. Additionally, 60% of respondents reported having 0 to 5 years of experience treating pediatric obesity, suggesting that our findings reflect the intent characteristics of the newer generation of clinicians in academic centers who will go on to serve the pediatric population in the forthcoming years.

This study was not without limitations. The survey administered relied on clinicians' self-reports, which are prone to social desirability biases which might inflate the relationship between TPB subscales and intent to treat pediatric obesity^[43,44]. The Likert format on which the TPB scale was based has additional limitations (*e.g.*, ordinal

measurement, halo effects, and end aversion biases). Our sample was unbalanced amongst subspecialties, which may have led to a response bias in our results not reflecting all subspecialty populations. Since this study focused on clinicians within academic tertiary centers, the results may not be fully representative of health professionals' behaviors in community settings. The length of the survey, when coupled with the simultaneously administered discrete choice experiment, may have influenced the completion rate, however our sample size was adequate to power the analysis. Although participants who did not complete the entire survey were excluded from the analysis, given the inherent randomness amongst these participants, we do not believe this significantly affected our sample.

There were also several strengths to this study. The validity of the scale is reflected in the consistency of the study findings with our predictions and hypotheses. Another major strength of the study was its multiple stakeholder involvement. The heterogeneity of the sample makes our study findings generalizable to assorted health professionals and relevant to addressing pediatric obesity management across the spectrum of health professionals in light of the broad validity and applicability of the TPB^[25]. Although our sample contained an unequal proportion of subspecialties from various geographic regions, the diversity of our sample reflected the composition of the health teams responsible for pediatric care (physicians, surgeons, and allied health professions) and allowed for a broad understanding of academic clinicians' needs and preferences.

In conclusion, the TPB has been recognized as a validated model for predicting the behavior of healthcare professionals; however it had yet to be applied to the clinical management of pediatric obesity^[23,24]. This study demonstrates that the TPB can be valuable in understanding the factors that predict clinicians' treatment of the child with obesity. Academic clinicians' intention to treat childhood obesity is, to a large extent, influenced by their personal beliefs regarding their own ability to implement treatment and their practice context, which includes the views of patient and families, practice guidelines, evidence, and the experience of colleagues.

A knowledge and skill translation framework should be developed to improve childhood obesity treatment by increasing clinician self-efficacy and collegial support. Initiatives aimed at fostering clinical skill development and support for health professionals treating pediatric obesity may result in improved diagnosis, management and health outcomes of children with obesity. The TPB should be further investigated to affirm the relationship between subscale modifications and treatment behaviors of clinicians.

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design of the study, and acquisition of data, in addition to Ms. Stephanie Mielko who contributed to the acquisition and analysis of data. We would also like to thank Dr. David Streiner for his review of the statistical methods of this project.

COMMENTS

Background

Pediatric obesity is of significant public health concern globally. There is an urgent need for interventional strategies to curtail the significant physical, psychological, and social burden impacting children who are overweight and obese and their families alike. Around the world, clinicians hold the very integral role of diagnosing and managing pediatric obesity. The actual intent of clinicians to treat obesity amongst children, however, is a complex phenomenon.

Research frontiers

Though past literature has examined the reported attitudes and competency levels of physicians towards obesity treatment, there has been no evidence addressing what factors play a significant role in influencing clinicians' intent to treat obesity within the pediatric population. There has been a call for research exploring the extent to which physician attitudes and health system factors are associated with clinical practice patterns of obesity care.

Innovations and breakthroughs

Perceived behavioral control and subjective norms made significant independent contributions to the prediction of intent to treat pediatric obesity, while attitudes and barriers did not contribute independently to the prediction of intention to treat. Together, the demographics of sex, birth country, and years of experience and TPB scores accounted for 56.9% of the variance in intent scores.

Applications

Enhancing clinicians' skillsets to treat pediatric obesity and improving support from colleagues appear to be important to increasing a clinician's intent to treat pediatric obesity. Therefore, base training and continuing educational programs for health professionals should consider integrating improved instruction of practical treatment skills, and health center institutions should foster a clinical environment supportive of the management of pediatric obesity.

Terminology

The theory of planned behavior is a model used extensively to predict intent and, in turn, behavior. It is a cumulative function of four subscales: (1) attitudes toward the behavior; (2) subjective norms; (3) perceived behavioral control; and (4) barriers. Attitudes are defined as expectations about an intervention's benefits and effectiveness, subjective norms are considered to be the views of one's surroundings with regards to a certain behavior and one's motivations to act in synchrony with these views, perceived behavior control refers to personal beliefs about one's own abilities, and barriers are an individual's estimation of the costs of an action. Intent itself is defined as a proxy of an individual's readiness to engage in a particular behavior.

Peer-review

This paper is well-written and provides valuable findings regarding this field.

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Prospective Study

Video recording of neonatal resuscitation: A feasibility study to inform widespread adoption

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Abstract**AIM**

To determine the feasibility of introducing video recording (VR) of neonatal resuscitation (NR) in a perinatal centre.

METHODS

This was a prospective cohort quality improvement study on preterm infants and their caregivers. Based on evidence and experience of other centers using VR intervention, a contextually relevant implementation and evaluation strategy was designed in the planning phase. The components of intervention were pre-resuscitation team huddle, VR of NR and video debriefing (VD), all occurring

on the same day. Various domains of feasibility and sustainability as well as feasibility criteria were predefined. Data for analysis was collected using quantitative and qualitative methods.

RESULTS

Seventy-one caregivers participated in VD of 14 NRs facilitated by six trained instructors. Ninety-one percent of caregivers perceived enhanced learning and patient safety and, 48 issues were identified related to policy, caregiver roles, and latent safety threats. Ninety percent of caregivers expressed their willingness to participate in VD activity and supported the idea of integrating it into a resuscitation team routine. Eighty-three percent and 50% of instructors expressed satisfaction with video review software and quality of audio VR. No issues about maintenance of infant or caregivers' confidentiality and erasure of videos were reported. Criteria for feasibility were met (refusal rate of < 10%, VR performed on > 50% of occasions, and < 20% caregivers' perceiving a negative impact on team performance). Necessary adaptations to enhance sustainability were identified.

CONCLUSION

VR of NR as a standard of care quality assurance activity to enhance caregivers' learning and create opportunities that improve patient safety is feasible. Despite its complexity with inherent challenges in implementation, the intervention was acceptable, implementable, and potentially sustainable with adaptations.

Key words: Video recording; Neonatal resuscitation; Delivery room; Feasibility; Perinatal centre

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Core tip: Despite proven benefits video recording (VR) of neonatal resuscitation (NR) is not adopted by all perinatal centres. Major reasons include challenges in operationalization and sustainability. Understanding the enablers and mitigation strategies is crucial on making a decision on widespread adoption of VR of NR by hospitals. We conducted a feasibility analysis of introducing VR of NR in the delivery room. It was introduced as a standard of care quality assurance activity to enhance caregiver learning and address system issues that compromise patient safety. Our study results indicate that VR of NR was effective, acceptable, implementable, and potentially sustainable with adaptations.

Shivananda S, Twiss J, el-Gouhary E, el-Helou S, Williams C, Murthy P, Suresh G. Video recording of neonatal resuscitation: A feasibility study to inform widespread adoption. *World J Clin Pediatr* 2017; 6(1): 69-80 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/69.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.69>

INTRODUCTION

About 10% of newborns require assistance to begin

breathing, and about 1% is critically ill and may need life-saving therapies such as ventilation, chest compression, and medications to support heart rate^[1]. In perinatal centres, the goals of neonatal resuscitation (NR) program are to have a system in place to deliver effective, efficient and safe care during the neonatal transition or resuscitation at birth, and later while responding to cardiorespiratory events^[2]. Relevant elements of care include policies that govern the provision of resuscitation services, availability of equipment and staff who are trained and competent to deliver consistent and reliable high-quality care^[2]. Gaps in the delivery of high-quality care may arise out of team performance, adherence to best practices and presence of latent safety threats^[3-5]. Poor or inconsistent team performance, in-turn could be secondary to the inevitability of having multiple teams with variable composition and lack of structured team training and reflective deliberate practice^[6]. In this context, video debriefing (VD) of actual NR is believed to facilitate the acquisition, retention, and application of skills resulting in optimal team performance and outcomes^[7]. Advantages of video recording (VR) include noninterference with resuscitation and collection of unalterable objective data^[8]. Moreover, VR and VD of NR has been shown to facilitate individual learning, identify and address system issues leading to better team performance and patient safety^[8-11]. Despite benefits and apparent feasibility, VR of actual NR is not adopted widely in all perinatal centres because it is a complex intervention^[12] and its operationalization is challenging^[9,13]. To date, there have been no reports of implementing VR of NR as a quality assurance standard of practice activity from a Canadian perinatal centre. We believed that testing the feasibility of this intervention on a small scale in the real world setting with contextual constraints would inform decisions on widespread adoption.

Objective

Conduct a feasibility analysis of introducing VR of NR in the delivery room, as a standard of care quality assurance activity to enhance caregiver learning and create opportunities that improve patient safety.

MATERIALS AND METHODS

This was a prospective cohort quality improvement (QI) study. All inborn preterm infants delivered at less than 33 wk of gestation from November 2013 to January 2014, as well as resuscitation team members, were included.

Setting

Approximately 225 infants of less than 33 wk gestation are born every year at McMaster University Medical Centre hospital. The L and D suite has eight delivery rooms (DR), two operating rooms (OR-A and OR-B) and three obstetric ICU beds. A 47-bedded level 3 regional NICU is located adjacent to L and D suite. All infants are delivered and resuscitated in the same room. Following resuscitation, all babies were transferred to

a dedicated stabilization room adjacent to the delivery suite, before finally being transferred to NICU. A fellow, nurse, respiratory therapist and a nurse practitioner attended all births. A neonatologist participated in the resuscitation and stabilization of infants born at less than 26 wk. of gestation or when indicated for higher gestational age.

Planning of the intervention

In 2010, a large QI project aimed at improving practices during resuscitation in preterm infants was introduced in our center. Video recording of actual neonatal resuscitation as a quality assurance activity (NRQAA) was a project nested within the larger project. The QI team composed of two physicians, nurse practitioner and a nurse was formed to oversee the implementation of this project. We implemented NRQAA program in four phases.

Phase I (January 2010-July 2012): The QI sub-team initially did a literature review to understand the requirements (equipment, personnel, standard procedures), critical success factors and challenges in the implementation of VR of NR^[4,7-11,13-15]. We obtained input from leads of two other centers with experience in the VR of NR. Following that, we developed the first draft of the NRQAA program and presented to nurses, physicians, respiratory therapists, nurse practitioners and managers on separate occasions. Concerns about workload, workflow and seeking approvals from multiple stakeholders were gathered. Concurrently, we reviewed policies, procedures, and guidelines, at the department, hospital, provincial (state) and national level before seeking approvals from all stakeholders. We contacted representatives of above organizations/authorities as necessary to facilitate approvals. A standardized operating manual providing complete details of the intended program, necessary approvals, and implementation process was prepared. Finally, we obtained approval of hospital's quality of care and patient safety committee, represented by all stakeholders. Following approval, installation of camera, web server and necessary hardware and software happened in consultation with engineering, information and communication technology, infection control and obstetric teams. Finally testing and fine-tuning of audio VR, review of software, storage and erasure of videos were completed (Table 1).

Phase II (August 2013-October 2013): Six out of 11 neonatal attending volunteered to participate in NRQAA as instructors and joined the QI sub-team (NRQAA committee). All of them were NRP trainers and two of them had training and certification in debriefing. They were requested to sign up for a one-week block of facilitation and evaluation of NRQAA activity. The NRQAA committee met on two occasions to finalize the NRQAA interventions, facilitator roles, and instruments. All instructors received 2 h of training on: (1) facilitating pre-resuscitation briefing, reviewing VR and debriefing

videos; (2) accessing and using video review software on the web server; (3) maintaining privacy and confidentiality; and (4) use of instruments by using a simulated VR of NR. All instructors received a manual comprising of terms of reference, instruments and tools to facilitate the interventions and perform evaluations.

Phase III (November 2013-January 2014): Physicians assisted and completed all VR and VD assessments and facilitations.

Phase IV (February 2014-July 2014): We conducted a survey of all resuscitation team members and instructors. The instructors also participated in a focus group to discuss the preliminary results and to identify factors critical for sustainability of the program.

Planning the study of intervention

We used the accepted frameworks to assess the effectiveness of NRQAA program and standard criteria for reporting feasibility^[16-18].

Interventions

We introduced three interventions as part of NRQAA program: (1) facilitated pre-resuscitation briefing; (2) VR and review; and (3) facilitated VD (Figure 1).

Facilitated pre-resuscitation briefing: Optimal team performance during NR depends on gathering pertinent perinatal history, understanding team member roles and case specific preparation^[10]. The list of potential high-risk deliveries and the scheduled resuscitation team members for a particular day were almost always known at the beginning of the day. Thus a structured daily pre-resuscitation briefing at 930 was introduced in our center in September 2011. It was mandatory for all resuscitation team members and was led by a neonatal fellow. The neonatal fellow gathered all relevant history and identified case specific preparation before the briefing. During the huddle, member roles were assigned, case specific care plans were discussed, and contingency planning for worst-case scenario was done.

During phase III, a neonatologist instructor observed the briefing process, facilitated case specific preparation and care planning, provided feedback to fellow and documented any system issues identified. The instructor also prompted members to turn on VR during resuscitation of an infant less than 33 wk of gestation.

VR and review: All resuscitation team members were requested to activate the VR when they attended a resuscitation of less than 33-wk gestation infant in OR-B, ISR-1 and room 8. The VR button was supposed to be turned on, just before receiving the baby on the resuscitaire and turned off after 10 min of resuscitation. All members received orientation on NRQAA activity in their respective monthly meetings in October 2013. All members were reminded to press the VR button during

Table 1 Overview of video recording of actual neonatal resuscitation as a quality assurance activity program and contextual details

Overarching goal	Enhance the likelihood of caregivers' delivering effective, safe and high quality NR care
Specific goal	Feasibility of introducing NRQAA program as a standard of care activity in a tertiary perinatal centre
Method of implementation	Quality assurance activity. Not introduced as a research study or a teaching activity
Assessment of readiness	Although NRP certification of all caregivers, <i>in-situ</i> unadvertised mock code (2008), high fidelity simulation using SimnewB (2010) were occurring in the unit, training in team behaviors, crisis resource management and error prevention had not happened
Training in team behaviors and exposure to VR	Interprofessional workshop in team behaviors, crisis resource management and error prevention (October 2011-January 2012), orientation of all new resuscitation team members and learners to team behaviors (January 2011 onwards), use of VD during mock resuscitations and training sessions (July 2011 onwards) were introduced. Pre resuscitation briefing of all anticipated high risk deliveries were introduced as a routine (September 2011). Team composition, configuration during resuscitation, member roles, anticipation of worst-case scenario and care planning were to be discussed by the neonatal fellow in briefing meetings. An expectation to complete the resuscitation and stabilization within 60 min of life was communicated to all members. T piece resuscitator for CPAP and PPV, Oxygen administration based on pulse oximetry reading and targeting saturation value appropriate for minute of life, and prophylactic CPAP for all < 33 wk s gestation infants were introduced as a part of larger QI initiative (January-July 2011)
Training instructors in debriefing	Only two out of 6 instructors had formal training in simulation and debriefing. These two instructors in-turn trained other instructors
Technology	Fixed IP video cameras with audio and video capturing capability and mounted on the roof/walls of the delivery rooms were used. They were wired to a web server placed in a room adjacent to NICU. VR was supposed to be turned on by the resuscitation team members (primarily by RTs) and stopped at the end of resuscitation. This video was automatically stored on the webserver and could be accessed or retrieved by instructors till its erasure
Securing resources	Funding for installation of video camera, web server and storage were obtained from the hospital KT grant. All personnel in QI subcommittee contributed their non clinical time for the program
Consent from family and staff	Obtained waiver of consent as the project was introduced as a Quality assurance standard of care practice and not as a research study. Consent was required for use of video for non quality assurance activity such as teaching providers and learners beyond the NICU team members and for research
Medical record <i>vs</i> quality assurance record	Information about NRQAA was to be provided for all care providers and parents Video was considered, as quality of care documents as videos would offer any health benefit to patient would not be used for care and treatment of individual patient and those other records of resuscitation apart from video would be preserved in medical records
Data ownership, management and disclosure of error	NRQAA committee was to oversee the NRQAA documents. No personal identifiers were collected. Any error was to be disclosed to the family as per the hospital policies
Video storage and security	Videos were directly stored on hospital web servers. They were accessible from a single computer located in a room adjacent to NICU. All VD was supposed to happen in the same room. The room was locked at all times and had swipe access. Access to VR was limited to instructors. All instructors had to sign a confidentiality and security statement after receiving training in accessing and reviewing videos. Any use of videos by instructors apart from quality assurance activity as well as sharing of access information and delegation was prohibited
Medico legal concerns	Following video review the videos were erased from the server manually NRQAA was not organized through QCIPA, as viewing of video by all team members or occasionally by parent would not have been possible. Thus an opportunity for collaborative learning and reflecting on one's own performance would have been lost Care providers were to understand that a video was subpoenaable and parents had to consult hospital legal counsel and NRQAA committee before the release of the video
Risk of spoliation or intentional destruction of evidence allegation.	Video destruction policy was defined with a caveat that any patients for whom there has been a report to hospital health care liability insurance provider, a request for records, or involvement of a coroner, a professional college or any notice of any legal proceeding whatsoever involving the patient, that those videos be maintained as until any proceeding is finalized. We opted to delete the videos when videos are reviewed and debriefed or within 14 d of recording, whichever come first. We also informed care givers and parents that the videos will not be made available for any other reasons apart from those described above
Video erasure policy	The video cameras were focused on the on the infant and not on caregivers. Caregivers' hands were captured inadvertently during the process. All audio including caregivers' conversation was captured during the VR. As per the Personal Health Information protection Act, 2004 (PHIPA) NRQAA was to institute measures to ensure personal information is not inadvertently disclosed or accessed by inappropriate person through out the program course.
Privacy of patient and staff	All learners while attending the VD activity were to sign a confidentiality agreement form. All NICU care providers were to abide with existing hospital confidentiality policy, which clearly prohibited the use of personal names or discussion performance issues outside the quality forums
Privacy office recommendations	Management of access and transfer if any to be done by a person approved by NRQAA. The program lead is responsible for oversight of the process Retention time to not exceed 14 d Transfer and destruction log along with the signature of individual conducting transaction should be noted Use encrypted USB key approved by hospital ICT team for any data transfer between NICU and hospital server Ensure erasure process meets security requirements
Refusal from staff/ family	Risk of refusal was proactively addressed by communicating the rationale for VR and attempting to minimize misconceptions among caregivers. An adequate lead-time and multiple forums to discuss concerns arising out of VR were provided. Similarly supervisors were encouraged to address concerns related to their respective professions and to support their colleagues during NRQAA VR was supposed to be initiated by resuscitation team by turning on the switch as opposed to motion sensing/auto recording All video reviews and VDs were supposed to be done by physicians during the feasibility period

Institutional support	All stakeholders were informed and their support was obtained before launching the project, <i>e.g.</i> , Quality of care and patient safety team, Information technology, Privacy, Obstetrics, Engineering, Infection control, Executives, legal council, risk management, REB and senior executives of the hospital
Support from professional bodies	Support was obtained from Canadian Medical Protection Agency, Nursing association, heads of professional practice of nurses and respiratory therapy, nursing unions
Project management	Project timelines, committee members roles, training and evaluation were all defined by the program lead
Resource limitations	In order to minimize cost of installation, instructors time and workload the following limitations were accepted apriori before the launch of the program Video cameras were installed in three out of possible 13 delivery rooms. These three rooms had contributed to 60%-70% of all high-risk deliveries in 2007-2009. Obstetric staffs were informed to preferentially triage all less than 33 wk gestation laboring mothers to above three rooms Video review was limited to first 10 min of life and scheduled VD to day deliveries on weekdays. Superimposition of heart rate, SpO ₂ , pressure and flow from pulse oximeter and ventilator onto VR s were not done Instructors did not have access to review the videos remotely Resources for all instructors to take certification courses in debriefing was limited

NRQAA: Neonatal resuscitation as a quality assurance activity; VR: Video recording; NR: Neonatal resuscitation; VD: Video debriefing.

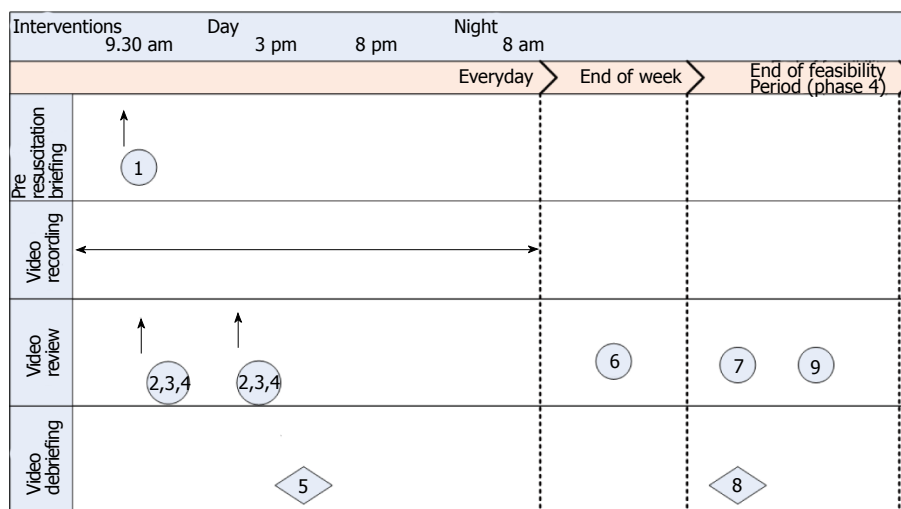


Figure 1 Interventions and tools for assessment. 1: Assessment of nontechnical skills (23); 2: Assessment of team behaviors (3); 3: Assessment of crisis resource management (19); 4: Debriefing template (20); 5: Caregiver feedback form; 6: Instructor weekly report; 7: Instructor survey (22); 8: Caregiver survey; 9: Focus group (21). Circle: Completed/attended by instructors; Diamond: Completed by caregivers.

the pre-resuscitation briefing at the beginning of the day.

We reviewed every VR. The focus of evaluation was team behaviors^[3], leader's crisis resource management skills^[19] and documentation of debriefing points^[20] and system issues^[5]. The instructor contacted the parents of infants whose resuscitation was recorded and provided an information sheet on NRQAA. Resuscitation team members were contacted when necessary to provide feedback on their performance. The most responsible physician in NICU was informed of any system issues identified during the review of videos.

Facilitated VD: Facilitated VD happened every afternoon at 3 pm in a room adjacent to NICU. All videos were accessed and projected during the discussion. The instructors were supposed to review the videos and identify the debrief points before the debriefing. The goal of VD was to create a collaborative learning environment that allows the caregivers to reflect their performance, share their thoughts and emotions without fear, learn how to recognize and improve their deficiencies. VD

session was limited to resuscitation team members who participated in the NR, wherever was done. Other caregivers were allowed to attend the meeting if there was no objection from the participants. The VD session was structured. At the outset, the trainers clarified the purpose of the debriefing, participants and facilitator's role, confidentiality measures and the need for filling the evaluation form. Then the video was presented without interruption for 5-10 min. We used the "observation, advocacy and inquiry" format to initiate debriefing^[20]. Debriefing points were usually kept to a maximum of three to ensure in-depth discussions. Selected parts of a video could be replayed as necessary. Finally, the debriefing session was summarized to distil the lessons learned for future use. All VR done after 4 pm and during night shift or weekends were reviewed but without a VD. On days when there was no VR, a VD session was adjourned. The instructor facilitated VD and documented any system issues identified during resuscitation.

Outcomes

The focus of feasibility analysis was to measure acce-

Table 2 Detailed matrix of outcomes and data collection

	Video review	Video debrief feedback evaluation	End of pilot period caregiver survey	End of pilot period instructor survey	End of pilot period focus group
Limited efficacy testing		X	X	X	X
Caregivers' perception on learning and enhancing patient safety					
Impact on desired organizational outcome					
Create learning environment					
Enhance patient safety					
Acceptability and demand ¹		X	X	X	X
Management ²					
Caregivers					
Parents					
Instructors					
Usability analysis to assess team behaviors, debrief and identify system issues	X	X		X	X
VR and video review software technology ²					
Instruments					
Resource needs ³					X
Initial					
Maintenance					
Unintended adverse or beneficial effects ³	X	X	X	X	X
Sustainability				X	X
Feasibility criteria					
Adaptations before widespread adoption					

¹Assessed by participation rates; ²Assessed in phases II and III; ³Assessed by observations from instructors logbook, team meeting minutes and comments in surveys. VR: Video recording.

ptability, demand, the usability of technology and instruments, adaptations, resource needs, unintended effects and limited efficacy^[17,18] (Table 2). Limited efficacy was assessed using: (1) caregivers' perception of VD on one's learning and a likelihood of enhancing patient safety; and (2) ability of the program to create learning opportunities, identify latent safety threats and elicit solutions from caregivers during VD. Resource needs in initiation and maintenance of VD program were noted during the piloting. We surveyed instructors to determine the resource requirements for facilitating VD activity and its governance. Feasibility was defined apriori as less than 20% caregivers refusing to participate, the conduct VR and debriefing on more than 50% occasions, when resuscitated in delivery rooms with recording facilities, and perceived negative impact on team performance in fewer than 20% of caregivers. A decision on widespread adoption with confidence was based on likelihood of sustainability^[21].

Methods of evaluation

We used the mixed method to assess the effectiveness of implementation and outcomes. Necessary data was collected using participation rates, surveys, feedback forms, focus group, participant observation and by analyzing the comments on feedback forms and surveys.

Instruments to facilitate interventions

Four validated instruments were used to measure team behaviors and system issues^[3,5,19,20,22,23]. These tools were chosen to standardize the facilitation process and evaluation of performance by multiple instructors. We

used caregiver feedback forms to assess the effectiveness of VD and a survey of caregivers and instructors at the end of feasibility period to determine the overall effectiveness of implementation of the intervention and the impact of interventions. Ease and satisfaction of using the instruments were measured by incorporating the USE Questionnaire tool in the instructor survey. We used the weekly reports completed by the instructors to document the frequency of all NRQAA interventions, identify the system issues and individuals who need moderate to significant improvement in crisis management skills. A combination of the focus group, comments in the survey form and logbook notes of program lead were used to identify the challenges, necessary adaptations to enhance sustainability. Finally, NHS sustainability model and guide was used to determine the likelihood of sustainability^[21].

Surveys were designed indigenously to gather caregivers' experience, perceived impact, intentions to continue and their preferences for modifying the program. Instructors' survey had categories on assessing the instruments and workload in addition to above categories. Readability and its appropriateness in measuring the desired outcomes were evaluated by piloting the survey on five caregivers and two instructors. Based on their suggestions, a final draft of the survey was created. Caregivers' and instructors' survey had 15 and 32 questions respectively, required grading the response on a Likert scale, and took 10 and 20 min to complete respectively. At the end of each category, a section for "comments and suggestion" was provided. No personal identifiers were collected.

A focus group discussion was planned to gather

input from instructors, managers, and leaders to assess feasibility, the likelihood of sustainability and to identify necessary adaptations in intervention^[21]. The focus group was of one-hour duration and was moderated by the program lead. The moderator took the field notes and summarized the impressions of the team at the end of the session to confirm participants' agreement with the records.

Sample size: A 3-mo time frame was based on convenience and availability of instructors to participate in this study.

Statistical analysis

Data collected from multiple sources were tabulated and presented as a percentage. Responses to surveys on a five-point Likert scale were condensed into three categories for simplicity and expressed as percentages. The program lead performed a content analysis of field notes, survey responses and minutes of the focus group. The themes and patterns emerging from the triangulation of results were recorded by the program lead and independently confirmed by another instructor.

This project was approved by the hospital's quality of care and patient safety committee as a standard of care quality assurance activity. Since we intended to publish the study and create information sheets for parents and caregivers, a research ethics board approval was also obtained. For any use of VR outside the NRQAA activity, consent forms were created and REB approval was obtained.

RESULTS

Out of 50 high-risk NRs, 30 were performed in delivery rooms with VR facilities. VR and VD occurred in 18 (60%) and 14 (47%) instances. Seventy-one caregivers (31% physicians, 23% nurses, 24% respiratory therapists, 11% nurse practitioners and 11% others) and six instructors participated in VD. The median (range) gestational age and birth weight of neonates were 31 (24-32) wk and 1195 (570-2070) grams respectively. Procedural interventions captured during VR included CPAP (17), Mask PPV (10), intubation and positive pressure ventilation (4) chest compression (2), umbilical venous catheterization (2), epinephrine (2) and normal saline bolus (2). Team behavior event rates observed per resuscitation, median (range) included information sharing 3 (2-8), inquiry 2 (0-4), assertion 3 (0-6), teaching 2 (0-4), evaluation of plans 2 (0-4) and an overall rate of 12 (3-21). The median (range) events of crisis resource management skills observed on leader included Leadership 5 (1-7), problem-solving 5 (1-6), situational awareness 5 (1-7), resource utilization 5 (1-7), communication 4 (1-6) and an overall rate of 4 (1-6). Thirty-nine out of 60 caregivers' (65%) responded to the end of study survey. Four instructors, nursing director, medical director, and nurse manager took part in the focus group.

Limited efficacy

Ninty-one percent of caregivers reported increased ability to reflect individual's performance and learning team behaviors. Similarly, 91% of caregivers perceived VD activity to enhance patient safety. Despite VR happening on 18 occasions, 48 issues related to resuscitation policy and procedures, team member roles and latent safety threats were identified during the study (Tables 3-6). Solutions to above issues were elicited or provided by caregivers or instructors in 21 (43%) issues. Instructors identified ten caregivers as requiring moderate to significant improvement in CRM skills and suggested further training. On eight occasions, caregivers' recognized a deficiency in communication and sought instructors' suggestions on learning those skills. Also, structured opportunities for creating team situational awareness, role clarification and infant specific contingency planning occurred during the pre-resuscitation huddle.

Acceptability and demand

None of the caregivers refused to participate in a video-recording activity. Instructors did not report any untoward instances during their interaction with family, after VD event. Unit leaders and managers supported visible support in promoting caregiver participation and reviewing caregivers' suggestions. Most caregivers (90%) and instructors (100%) expressed their willingness to participate in VD activity and supported the idea of integrating it into a resuscitation team routine. Apart from 78% of caregivers' liking the debriefing experience, they appreciated the opportunity to discuss and provide suggestions on concerns (78%). Only 10% reported that VR made them over conscious, and it may have had a "negative impact" on their performance. Fifty-nine percent of caregivers said that VD on selected NRs, once every two weeks, as opposed to all NRs, was acceptable. Similarly, 53% felt that making the VD activity open to all NICU caregivers, as opposed to those who were involved in a particular resuscitation was acceptable.

Usability

The instructors expressed satisfaction with video-recording and video review software technology (83%). Apart from being easy to learn and use, they reported that the technology helped them to be more effective in supporting analysis and conduct of VD. However, only 50% of instructors expressed satisfaction with the quality of audio VR, as significant challenges in understanding the scenario, assessing team behaviors and quality of procedures and interpretation of response to resuscitation based on audible pulse tone and alarm sounds. All instructors expressed satisfaction with orientation, maintenance of confidentiality and templates used for a pre-resuscitation huddle, VR review, and VD.

Resource needs

Resource needs for facilitation; documentation and support of VD activity are provided in Table 7. The focus

Table 3 Policy, caregiver roles and latent safety threat issues noted during: Pre-resuscitation briefing

Issues	Solution
When do I call an attending for help during resuscitation?	Whenever chest compression is initiated
Can I transfer the first twin from resuscitaire to a basinet and then receive the next twin on the same resuscitaire?	No! Two separate resuscitaire should be kept ready
Why should I know the indication for a laboring mother receiving meropenam and opioids?	To decide on appropriateness of using Naloxone, neonatal isolation and performing a septic work up
Where is the main surgical OR where a C-section is happening on a mother with placenta increta?	To ensure resuscitation team members reach the OR in time
What special preparation is necessary?	Higher room temperature, familiarization with the new environment and all necessary equipment should be ensured
What are the indications for admitting a newborn with fetal arrhythmia to NICU?	Arrhythmia noted on connecting to a multi-channel monitor in stabilization room
How do I create beds for four less than 28 wk, anticipated high-risk deliveries?	Efficient problem solving and triaging
What worst case scenario should I anticipate while attending a delivery in a mother with Spinal Muscular Atrophy, unexplained IUGR and non-reassuring fetal heart rate	Hypoplastic lung with difficulty in resuscitation
What is the role of learners (clerks, residents, others) during resuscitation?	Team leader should assign roles on a case by case basis during the team huddle
Who is responsible for gathering all information on an anticipated high-risk delivery and case specific preparation?	The expectation is that the neonatal fellow covering the Labor and Delivery unit is responsible for gathering information and case specific care planning. The dedicated resuscitation nurse is responsible for calling a team huddle before attending a high risk delivery
How should the family's preference for resuscitating a 23 or 24-wk infant be documented in antenatal consults and handed over?	Family's preference for resuscitation should be documented in written and handed over at every shift. If family's preferences change, the revised plans should be documented in written

group identified that the following elements are crucial for the sustainability of the program. These include: (1) instructors' team should be interdisciplinary with a representative from MD, RN, and RRT group; (2) Instructors should be enthusiastic, non-judgmental and possess background training in simulation, debriefing and QI; and (3) one of the instructors should take on additional role of governance.

Feasibility

The study results showed, no caregiver refusal to participate in VR; VR performed on 60% of occasions and less than 10% caregivers' perceiving a negative impact on team performance. Thus criteria for the feasibility of VR and VD of NR in the delivery room intervention were met.

Sustainability

On completing the NHS sustainability and model guide during the focus group, a score of 32 was obtained for implementing the intervention in the current form. A score of less than 45 indicates the need for adaptations. Further discussions about changes in the intervention to ensure sustainability and continued accrual of benefits generated a list of adaptations (Table 8).

Unintended adverse and beneficial effects

VR and review was helpful in assessing adoption of gentle resuscitation practices, adequacy of team preparation and documentation of facts on charts. Self-reflection of behaviors allowed caregivers to focus on improving their deficiencies and reinforcing their good practices.

Thirty percent of caregivers reported that VR had a positive impact on their performance. No issues about maintenance of infant or caregivers' confidentiality and erasure of videos were found. We did not receive any request for VR by parents and we did not take consent from parents for using VR for purposes other than NRQAA. Challenges observed during piloting are provided in Table 9.

DISCUSSION

Our study has shown that it is feasible to adopt VR and VD of NR in DR as a standard of care quality assurance activity to enhance caregivers' learning and create opportunities that improve patient safety. Despite its complexity and implementation challenges, the intervention was acceptable, implementable, and potentially sustainable with adaptations in a real world setting. To date, no such feasibility study has been reported.

Strengths of this study include methodology and potential for generalizability. Feasibility objectives and criteria, setting and constraints, intervention and implementation strategy were well defined. Validated instruments for evaluation and frameworks for design and implementation were used. Detailed results including lessons learned and mitigation strategies for challenges were found. We believe that such a comprehensive and rigorous approach may allow other centers in making informed decisions on the type of technology, scale of implementation that achieves objectives with limited resources, and adopting strategies that facilitate the application of intervention. Jo Rycroft-Malone has

Table 4 Policy, caregiver roles and latent safety threat issues noted during: Issues noted during video reviewing

	Potential problems/negative impact
Communication	
Not-verbalizing the reasons for initiating an intervention. <i>e.g.</i> , intubation, chest compression, <i>etc.</i>	Lack of understanding the reasons behind an intervention, limits team members' ability to provide suggestions
Chest compression and PPV rhythm not verbalized "one and two and three and breathe"	Lack of synchronization delays neonate's response to resuscitation
Heart rate is not verbalized after auscultating	Delay in making a decision on initiation/non initiation of chest compression
Excessive reliance on non-verbal communication, <i>e.g.</i> , asking for a suction catheter by "stretching hands" after inserting the laryngoscope orally, as opposed to a "verbal request"	Delay in receiving suction catheter causes frustration in the intubator and delays the resuscitation efforts
Silencing alarms and not communicating the alarm to the team leader	Lack of awareness impedes accurate decision making and timely initiation of interventions
Team members not communicating assertively, <i>e.g.</i> , Considering a higher peak inspiratory pressure in a non-responding infant	Delay in trouble shooting leading to ineffective resuscitation
Not sharing of relevant obstetric information with NR team during resuscitation of a depressed infant, <i>e.g.</i> , MSL, abruption, Morphine	Delay in considering appropriate interventions, <i>e.g.</i> , ET suction, fluid bolus and Naloxone respectively
Leadership	
Leader was totally passive	Leads to momentary assumption of role by another member. Often results in delayed decision making, team losing focus, excessive indulgence in unnecessary interventions, <i>e.g.</i> , suctioning, and lack of assessment of response to interventions
Fixation error, <i>e.g.</i> , Making decisions of intubation and chest compression in a nonresponsive infant without ensuring good seal during mask ventilation	Unnecessary invasive interventions with a potential for adverse events
Lack of evaluation of plans during resuscitation	Prevents team members ability to provide suggestions
Team members positioning/configuration	
Hands free team leader standing at the head end and RRTs who are on one side of the infant	Leader impedes effective delivery of mask ventilation
Initiating chest compression with the side walls up	Impedes effective performance of chest compression
Technical	
Ineffective seal around the mask during mask ventilation	Delay in responding to resuscitation
Attempting nasal intubation while resuscitating an unresponsive infant with severe bradycardia	Potential delay in intubation
Not venting stomach after a prolonged mask PPV	Secondary deterioration in SpO ₂ and heart rate
Not vigilant about FiO ₂ during resuscitation. Started 100% FiO ₂ only after 90 s of chest compression	Delay in response to resuscitation
Extubation while securing the ET tube as ET tube is not held firmly against the hard palate during taping	Potential for secondary deterioration or delay in resuscitation

NR: Neonatal resuscitation.

Table 5 Policy, caregiver roles and latent safety threat issues noted during: System issues noted during video debriefing

	Suggestions/solutions
No response from NICU front desk when called for additional help by resuscitation team in infant stabilization room	Avoid unmanned NICU front desk all the time
Preterm infant on CPAP transferred directly to NICU as opposed to stabilization in infant stabilization room and then to NICU	Transfer through stabilization room ensures that a ventilator and incubator is always ready for stabilization
Person attending resuscitation is different from the one who participated in team huddle	Case specific preparation and management plans discussed during team huddle becomes redundant
Difficulty in paging the resuscitation team members as the composition of resuscitation team changed during a shift	Dedicated resuscitation pagers to be carried by resuscitation team members as opposed to individual personal pagers
Infant stabilization room stocking was exhausted when 3 deliveries happened during a shift. Health care aides were replenishing stocks once a shift	Health care aides will be called to replenish stocks when necessary
Delay in sending the blood samples from infant stabilization room to lab	Tube system restored
Needle stick injury to a resuscitation team member while setting up the resuscitaire	Educate all caregivers to remove sharps after the procedures
Fall and injury to foot while running to attend a pink code in labor and delivery unit	Educate caregivers on taking precautions to avoid injury
Undue delay in starting a PIV in infant stabilization room due to non-availability of personnel	Educate RN team members about creating a backup support to establish PIV in time
Who is the first responder (MD/NP) to attend labor and delivery calls during handover? (8-9 am and 5-6 pm)	The day resuscitation team (MD/NP) members
Pending high-risk deliveries and family's preference for resuscitation was not passed on to day team. Thus the day team was unclear about their roles when called to attend delivery	Should be an essential part of handover

Table 6 Policy, caregiver roles and latent safety threat issues noted during: Skills related questions posed by care givers during video debriefing

How do I communicate assertively?
How do I develop leadership skills?
What do I do when a RRT/TT member/Resident asks for intubation when the fellow is almost about to intubate?
How do I provide constructive feedback to team members during resuscitation?
When should I be “hands-on” and “hands-off” during resuscitation?
How can I ensure that I get others input during a difficult resuscitation?
It is very difficult to maintain a global perspective during resuscitation. How do I maintain it?
How do I deal with a member passing sarcastic comments/gestures during resuscitation? “Wish you all the best”

Table 7 Resource needs for facilitating video-debriefing activity and ongoing maintenance of the program

	Time
Facilitation of team activities ¹	
Facilitating a pre-resuscitation briefing	15 min
Reviewing a resuscitation video	30-60 min
Facilitating a VD	60-90 min
Documentation of team activities-good practice ¹	
Completing pre-resuscitation briefing template	5 min
Completing a video review template	5 min
Completing a video debrief template	5 min
Completing a weekly reporting template	5 min
Informing parents about VD activity	15 min
Ongoing maintenance	
Training instructors-once	2 h
Training instructors to ensure reliable review and debriefing-once	2 h
Scheduling instructors and booking rooms	1-2 h/mo
Trouble shooting equipment, deleting videos and ensuring confidentiality of patients and caregivers	1-2 h/mo
Reporting system issues to quality councils and ensuring appropriate training for candidates lacking skills	1-2 h/mo
Addressing system issues and implementing solutions	Variable

¹Usual time taken for facilitating a single video-debriefing activity, unless otherwise stated. VD: Video debriefing.

Table 8 Issues affecting sustainability and suggested adaptations

Themes	Issue affecting sustainability	Suggested adaptations
Resources	Same day video-debriefing is resource intensive Transfer of ownership from project lead to unit leadership helps in buy-in	Conduct video-debriefing once every 2 wk on selected resuscitation recordings. Make the debriefing sessions open to all caregivers Provide resources for scheduling instructors, maintaining technology, and compensate for instructors time and effort Consider VR all deliveries and team members to seek video-debriefing on selected cases by attending on service/call
Low rate of VR	Hesitation to voluntarily record and participate in VR	Change from caregiver activated recording to motion sensor activated VR Link to certification/competence assessment (caregivers/learners)
System to remedy identified latent safety threats in real time	Identified but unaddressed issues result in caregiver disengagement	Set timelines for action Support caregivers to take ownership on addressing issues Communicate actions arising out of identified issues Establish connections with Quality and Education committees for systematic training on frequently identified issues
Inability to assess impact of team actions during resuscitation	Lack of vitals (heart rate, SpO ₂) data on VR	Consider superimposing vitals data on video-recording
Inconsistency in demonstrating team behaviors by caregivers	Lack of focused training in team behaviors and error prevention Team behavior evaluation not mandatory for maintenance of professional accreditation or trainee certification	Sustain video-debriefing activity for creating learning and self evaluation Integrate demonstration of team behaviors during resuscitation into professional accreditation and certification requirements

VR: Video recording.

described that “sustained implementation of evidence into practice is a planned facilitated process involving interplay

Table 9 Challenges identified during video recording and debriefing program

Challenges
Reminding care providers about team huddle, debriefing or turn-on the VR
Conflict with my other work (e.g., NICU service, etc.)
Reviewing videos in time
Engaging care providers during debriefing
Reviewing videos recorded in night
Providing feedback to caregivers who could not attend debriefing
Completing team huddle, video review and debrief templates in time
Completing the weekly report template
Interpreting the audio to assess team communication
Identifying debrief issues arising from videos for debriefing
Time for VD (60 min)
Informing parents about VD in a timely manner, once the VR has happened
Delay in implementing project on time
Reinforcing expectations, providing opportunities for learning especially with rapid turnover of caregivers and trainees in a tertiary centre

VR: Video recording; VD: Video debriefing.

between individuals, evidence, and context to promote evidence-informed practice^[24]. A careful consideration of all above elements was considered in designing and implementing the intervention in our centre. Finally, clarity on the role of organization (enabling and empowering) and project leads (facilitate caregivers' performing discrete practical tasks during NR) in facilitating implementation played a major role in successful implementation^[17].

Based on apriori agreed upon criteria for feasibility, VR of NR in DR is feasible in a tertiary perinatal centre. Caregivers' perceived enhanced learning and organization's ability to create opportunities for learning and identify latent safety threats, observed in this study is consistent with other reports. We speculate that VR and VD of NR in DR creates opportunities that facilitate caregiver learning, promotes the interprofessional collaborative practice and creates a mechanism to address latent safety threats affecting patient safety. Integration of this intervention as a resuscitation team routine is likely to enhance caregivers' delivery of effective, safe and high-quality NR.

Key factors that helped in operationalization of the project in our centre included management support, implementation as a standard of care QA activity as opposed to the research study and ensuring caregivers' readiness through multiple educational sessions, team behavior workshops and acquaintance with VR.

Our study had limitations. Assessment of impact of VR and VD of NR in DR intervention on patient outcomes, cost effectiveness, and actual team performance were beyond the scope of the study. The results may not be generalizable where centers are planning on adopting a technology or implementation strategy different from ours. Sample size was low and duration of study was short to determine any impact on clinical outcomes. A multivariate regression model to identify major barriers and enablers of adoption of VR in NR could not be performed due to small sample size^[25].

A pragmatic cluster randomized trial evaluating the impact of VR of NR on patient and organizational outcomes is warranted. In future, feedback to initiate

immediate corrective actions during a NR is desirable^[2,26]. Similarly, a provision for printing an objective performance report directly from the monitor that shows response to various actions during NR may eliminate the need for a debriefing instructor^[2,26].

It is feasible to adopt VR and VD of NR in delivery room as a standard of care quality assurance activity to enhance caregivers' learning and create opportunities that improve patient safety. Despite its complexity with inherent challenges in implementation, the intervention was acceptable, implementable, and potentially sustainable. The comprehensive approach and detailed results from our study may allow other centers in making informed decisions on the type of technology, scale of implementation that achieves objectives with limited resources, and adopting strategies that facilitate the application of VR of NR.

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COMMENTS

Background

Despite proven benefits video recording (VR) of neonatal resuscitation (NR) is not adopted by all perinatal centres. Major reasons include challenges in operationalization and sustainability. Understanding the enablers and mitigation strategies is crucial on making a decision on widespread adoption of VR of NR by hospitals. The authors conducted a feasibility analysis of introducing VR of NR in the delivery room.

Research frontiers

VR of NR and debriefing has been shown to be an effective tool in enhancing

resuscitation team learning and addressing latent safety threats that compromise the quality of resuscitation. In this study, there is a suggestion that a systematic approach to operationalization of this technology helps in widespread adoption in a perinatal centre.

Innovations and breakthroughs

There is evidence of benefits of VR of NR in improving the quality and safety of resuscitation. However there is a gap in literature in understanding and addressing challenges associated with operationalization. Despite its complexity with inherent challenges in implementation, VR of NR was acceptable, implementable, and potentially sustainable with adaptations in real world setting.

Applications

The current study provides a framework for implementation and sustainability for centres considering adopting VR of NR.

Peer-review

This is a well-written article investigating an interesting issue in the neonatal care.

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Using quality improvement methods to increase use of pain prevention strategies for childhood vaccination

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Abstract

AIM

To increase evidence-based pain prevention strategy use during routine vaccinations in a pediatric primary care clinic using quality improvement methodology.

METHODS

Specific intervention strategies (*i.e.*, comfort positioning, nonnutritive sucking and sucrose analgesia, distraction) were identified, selected and introduced in three waves, using a Plan-Do-Study-Act framework. System-wide change was measured from baseline to post-intervention by: (1) percent of vaccination visits during which an evidence-based pain prevention strategy was reported as being used; and (2) caregiver satisfaction ratings following the visit. Additionally, self-reported staff and caregiver attitudes and beliefs about pain prevention were measured at baseline and 1-year post-intervention to assess for possible long-term cultural shifts.

RESULTS

Significant improvements were noted post-intervention. Use of at least one pain prevention strategy was documented at 99% of patient visits and 94% of caregivers were satisfied or very satisfied with the pain prevention care received. Parents/caregivers reported greater satisfaction with the specific pain prevention strategy used [$t(143) = 2.50, P \leq 0.05$], as well as greater agreement that the pain prevention strategies used helped their children's pain [$t(180) = 2.17, P \leq 0.05$] and that they would be willing to use the same strategy again in the future [$t(179) = 3.26, P \leq 0.001$] as compared to baseline. Staff and caregivers also demonstrated a shift in attitudes from baseline to 1-year post-intervention. Specifically, staff reported greater agreement that the pain felt from vaccinations can result in harmful effects [2.47 *vs* 3.10; $t(70) = -2.11, P \leq 0.05$], less agreement that pain from vaccinations is "just part of the process" [3.94 *vs* 3.23; $t(70) = 2.61, P \leq 0.05$], and less agreement that parents expect their children to experience pain during vaccinations [4.81 *vs* 4.38; $t(69) = 2.24, P \leq 0.05$]. Parents/caregivers reported more favorable attitudes about pain prevention strategies for vaccinations across a variety of areas, including safety, cost, time, and effectiveness, as well as less concern about the pain their children experience with vaccination [4.08 *vs* 3.26; $t(557) = 6.38, P \leq 0.001$], less need for additional pain prevention strategies [3.33 *vs* 2.81; $t(476) = 4.51, P \leq 0.001$], and greater agreement that their doctors' office currently offers pain prevention for vaccinations [3.40 *vs* 3.75; $t(433) = -2.39, P \leq 0.05$].

CONCLUSION

Quality improvement methodology can be used to help close the gap in implementing pain prevention strategies during routine vaccination procedures for children.

Key words: Pediatrics; Quality improvement; Distraction; Pain management; Immunization; Vaccination; Sucrose analgesia; Pain prevention; Non-nutritive sucking; Comfort positioning; Primary care

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Core tip: Application of quality improvement methodology can help close the gap in implementing evidence-based pain prevention strategies during routine medical procedures, such as childhood vaccination. A key element to the adoption and maintenance of practice change appears to be building a meaningful partnership with key staff (*e.g.*, nurses who routinely deliver vaccinations) within the target clinic to elicit their expertise and input, as well as facilitate their ownership of the process. Development of project "champions" among key staff can help reduce barriers to implementation, increase uptake of practice change, and shift culture to support long-term maintenance of gains.

D, Connelly M, Anson L, Mroczka K. Using quality improvement methods to increase use of pain prevention strategies for childhood vaccination. *World J Clin Pediatr* 2017; 6(1): 81-88 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/81.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.81>

INTRODUCTION

Pain is a common adverse effect experienced by children undergoing routine medical procedures^[1]. Vaccinations are the most frequent painful medical procedure in childhood, with current recommended vaccination schedules including at least 17 injections by a child's 5th birthday^[2]. Failure to treat a child's pain from even "minor" medical procedures, such as injections, potentially results in greater sensitivity to future pain and other enduring negative effects *via* the rewiring of a child's pain transmission pathways and the encoding of pain memories^[3-5]. Further, procedural anxiety that develops secondary to pain may contribute to nonadherence to vaccination schedules, needle fear or phobia, and healthcare avoidance into adulthood^[6]. A recently published clinical practice guideline provides a comprehensive review of the wide range of evidence-based approaches to the reduction of pain during vaccination^[7]. Several policy statements also exist to provide the rationale and evidence-based guidance to translate pain interventions into practice^[8-11]. Nevertheless, pain from routine medical procedures often remains undertreated or ignored^[8,12,13].

Recognition of this practice gap has led to a surge of attention and effort, nationally and internationally, aimed at bringing routine medical practice in line with current science. Some of these efforts have focused on raising parents' awareness about children's pain and increasing parent uptake of evidence-based knowledge in this area (*e.g.*, work by Taddio *et al.*^[14] and the "It Doesn't Have to Hurt" social media campaign; for more information see <http://itdoesnthavetohurt.ca/>). Other efforts have focused on increasing awareness within the medical community itself^[10]. In the current project, we used quality improvement (QI) methodology to address the underuse of evidence-based pain prevention during needlestick procedures within a large primary care practice. Our primary project aim was to increase, in a sustainable way, the use of pain prevention techniques for children vaccinated in our ambulatory primary care clinic to greater than 80% and thus close the observed practice gap. Of note, we were not interested in evaluating the effectiveness of strategy use, as this has been well documented and led to development of the above noted clinical practice guidelines. Instead, we were interested in changes in health care provider behavior to reflect uptake of evidence-based pain prevention strategies. Through improved pain prevention processes, we believed that parent/caregiver perception of his/her child's vaccination experience also would improve stakeholder engagement and increase willingness on the

patient side to use pain prevention strategies again in the future. Satisfaction with pain prevention is recommended as a key outcome variable for pain intervention trials as it is also a significant predictor of return vaccination visits^[8,15]. Thus, a secondary aim was to achieve a parent/caregiver pain management satisfaction score of satisfied to very satisfied for greater than 80% of applicable patient visits. Finally, we wanted to assess shifts in staff and parent/caregiver attitudes and beliefs from baseline to 1 year following transition of project control to primary care clinic staff. It was believed that changing the “culture” surrounding pain prevention would be necessary to support sustainability of change in pain prevention procedures for vaccination over the long term.

MATERIALS AND METHODS

Setting

This project was conducted at a large, urban, academic pediatric medical center. The affiliated Pediatric Care Clinic (PCC) offers a medical home to an ethnically and culturally diverse group of patients who are underserved, uninsured or receiving Medicaid benefits, as well as those who require complex care. The PCC team includes board-certified pediatricians and nurse practitioners, as well as pediatric residents and other medical trainees. The PCC’s 41 physicians and 18 nurse practitioners, with the assistance of approximately 45 nurses, conduct more than 45000 patient visits annually.

Planning the intervention

We assembled a multidisciplinary team that included pediatric psychologists with expertise in pain, a certified Pain Management nurse, a PCC nursing administrator, a PCC physician, and a QI specialist. A “superuser” group comprised of PCC nurses was formed to couple the evidence base for pain prevention delivery with the culture and function of the vaccination process within the PCC. Nurses invited to participate in the superuser group were strategically selected to vary on years in practice, current use of pain prevention strategies, and anticipated response to change in practice; this ensured that a wide variety of perspectives were represented. The superuser group met a total of three times in a Kaizen-style format over the course of this QI project. In keeping with the spirit of a Kaizen event, these meetings brought together QI team members and the actual “owners” of the process (*i.e.*, nursing staff who actually provide the vaccinations) to identify and make improvements actually within the scope of process participants (*vs* those needing greater administrative approval and/or financial support). Three interventions targeting the use of pain prevention strategies with routine immunization of children 0-5 years of age were selected from among the wide array of current evidence-based options based on superuser feedback regarding the perceived effectiveness of the technique and relative ease with which that group believed

strategies could be incorporated into current practice and clinic flow. Allowing superusers to have a “voice” in the selection process was intended to enhance buy in and likelihood of short-/long-term uptake, while ensuring that interventions remained evidence based. Given intent to disseminate our findings more broadly, the project was reviewed and approved by the Institutional Review Board of the participating hospital.

Study of the improvement

Given that this project was designed within a QI framework, outcomes were designed to be easily tracked in an ongoing fashion, or at least in “bursts,” that would require little staff time/effort or disruption to clinic flow. First, PCC staff members were asked to complete surveys constructed by the QI project team regarding their current attitudes, beliefs, and experiences with pain prevention for childhood immunization *via* the institution’s internal electronic survey software system. Parents/caregivers also were asked to complete paper-and-pencil surveys covering these topics at the time of a PCC visit that were later entered into a database for analysis (see publication by Connelly *et al.*^[16] for more details regarding the parent/caregiver survey). All surveys were anonymous. Survey data were collected from staff and parents/caregivers at two time points: (1) at baseline, to inform the development of a key driver diagram; and (2) approximately one year after implementation of the interventions in clinic, to assess shifts in attitudes and beliefs that may reflect and/or support sustainability of change in pain prevention procedures for vaccination over time.

Periodic time-based sampling also was employed to collect information on pain management strategy use at baseline and post-intervention. During each of these data collection bursts, QI project team members identified a convenience sample of approximately 100 vaccination visits occurring for patients within our target age range over a 4-wk period ($n = 85$ at baseline, $n = 101$ at post-intervention). Observation and coding of pain behaviors was deemed too burdensome as a long-term data collection/monitoring strategy, particularly as a secondary outcome. Instead, a team member waited outside the exam room door during these visits, and immediately following the vaccinations asked nurses to complete a checklist on what pain prevention strategies were used. The team member then asked each parent a set of standardized questions about his/her child’s vaccination experience and the pain management strategies used. These approaches were believed to be more amenable to automation in the future.

Measures

The primary process measure was the proportion of vaccination visits (for children 0-5 years) during which any evidence-based pain prevention strategy was documented as being offered *via* nursing self-report on a checklist immediately following the vaccination visit.

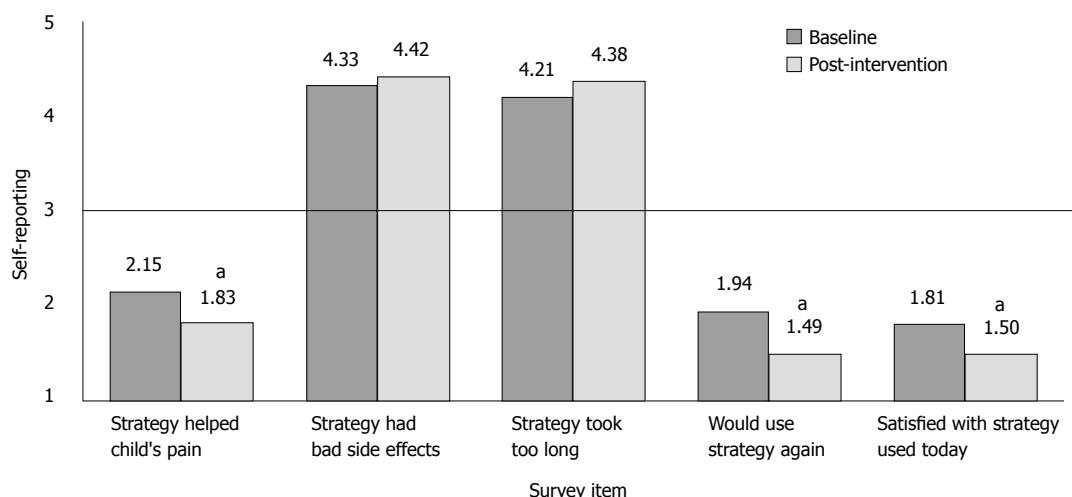


Figure 1 Comparison of parent/caregiver self-reported satisfaction with pain prevention strategies used at visit at baseline ($n = 85$) and at post-intervention follow up ($n = 101$) via parent/caregiver survey. A value of 3 indicates the neutral point; scores above 3 indicate more concern/negative response about this area, while a value below 3 indicates less concern/more positive response. ^a $P < 0.05$ vs Baseline.

The primary outcome measure was consumer (parent/caregiver) pain prevention satisfaction ratings obtained following the visit. A subset of 3 items was adapted by the QI project team from the Pain Treatment Satisfaction Scale^[17], which uses a 5-point scale ("very satisfied" to "very dissatisfied" or "strongly agree" to "strongly disagree") to assess satisfaction with and perceived benefit of pain interventions with lower scores indicating more favorable attitudes. Two balancing items also were included. These items, asking about time spent and other potential side effects of using pain prevention strategies during the vaccination visit, were included to detect if improvements in pain control were associated with increases in negative consequences for the child or caregiver that might ameliorate any benefit and/or indicate barriers to be addressed in future Plan-Do-Study-Act (PDSA) cycles (see Figure 1 for items).

Current state

At baseline, nurses self-reported offering at least one pain prevention strategy 97% of the time ($M = 2.16$ strategies per target visit). However, the validity of this rate was questionable given informal observation by QI project team members waiting outside the door during target vaccination visits which indicated that nurses were not delivering interventions consistent with evidence-based guidelines. At times, a nurse's behavior actually ran counter to the intent of the strategy she/he endorsed for that visit (e.g., checking "comfort positioning" on the pain management strategy checklist when restraining a child in the supine position on the exam table). These observed quality issues were not recorded systematically given that this observation was incidental, rather than by design, but were deemed important and subsequently factored into intervention planning. Taken together with survey data collected from staff (see Table 1) and parents/caregivers^[16], key drivers deemed important to consider in achieving our project aims included nursing factors (e.g.,

knowledge, preferences, attitudes), patient factors (e.g., emotional, behavioral, situational), parent factors (e.g., competing demands, cultural beliefs, knowledge), and broader system factors (e.g., time demands, resource availability, nurse/provider communication).

Improvement activities

Improvement activities occurred in three phases, as outlined below, using a PDSA model. As noted previously, evidence-based interventions targeting the use of pain prevention strategies with routine vaccination of children 0-5 years of age were selected and prioritized based on superuser feedback regarding the perceived effectiveness and relative ease with which that group believed strategies could be incorporated into current clinic practice (i.e., high impact/low difficulty). All interventions were developed consistent with clinical practice guidelines, including sensitivity to developmental considerations in their use.

Intervention 1: The first intervention focused on the correct use of comfort positioning for vaccinations. The QI project team made an educational video featuring members of our superuser group to increase personal identification with the project and enhance willingness to change behavior related to comfort positioning. Every staff nurse was required to watch this video and then use realistic infant and toddler dolls to demonstrate competent use of comfort positioning with children of varying ages to a QI team member. QI project team members answered questions and provided corrective feedback, as needed, during this simulation experience to ensure that skills were understood and applied correctly. As nurses passed this demonstration task, they received a pin to display on their hospital badge or nursing uniform which identified them as a "Comfort Champion" to others.

Intervention 2: The second intervention focused on

Table 1 Primary care clinic culture related to pain prevention: Familiarity, beliefs, and barriers to use at baseline (Faculty MD, *n* = 28; Resident MD, *n* = 98; APN, *n* = 12; Nursing staff, *n* = 28)

Level of cultural familiarity	Pain prevention strategy	Percent endorsement by group	
		APNs/Nurses	Physicians
Most well known	Distraction		
	Topical anesthetic creams		
	Nonnutritive sucking		
Most commonly trained	Swaddling		
	Topical anesthetic creams		
	Distraction		
Most typically used in practice	Nonnutritive sucking		
	Distraction		
	Pre-medication		
Specific belief	Nonnutritive sucking		
	It is important for me, personally, to prevent pain during vaccinations	64%	56%
	There are effective ways to prevent vaccination pain	57%	61%
Pain from vaccinations results in harmful and lasting effects	Pain during vaccinations is "just part of the process"	14%	11%
	Learning to cope with pain (from vaccinations) benefits children	43%	17%
	50%	17%	
Most Salient Reported Barriers to Pain Prevention Use	Lack of accessibility of pain prevention materials or tools in the clinic		
	Not having enough time		
	Lack of education among staff		

the correct use of sucrose analgesia and non-nutritive sucking for vaccinations. A PowerPoint slide show was created to review the rationale and logistics for use of sugar-water mixtures (e.g., Sweet Ease) for the younger end of the age spectrum (≤ 2 years of age). Breastfeeding, as a related intervention, was folded into this presentation. Every staff nurse was required to watch this video and provide attestation to that effect. The QI project team ensured that an appropriate sugar-water mixture was stocked in each medication room and developed/implemented a process to maintain availability over the long-term.

Intervention 3: The third intervention focused on the correct use of *distraction* for vaccinations. The QI project team made a second educational video showing appropriate distraction techniques modeled by PCC nursing staff, including - but not limited to - members of the superuser group. Each staff nurse was required to watch this video and provide attestation to that effect. The QI project team ensured that a variety of age-appropriate distraction items (including toys, games, and iPads) were available in the clinic, with separate bins for "clean" and "dirty" items. A process also was devised/implemented for ensuring daily cleaning of the items used.

As a final step, the educational modules described above were added to the training requirements for new nursing hires and for biannual nursing education updates with the hope that any culture shift initiated by this project would be continued and strengthened over time through these efforts. A "Process Owner," a nurse manager in the PCC, was identified to oversee and monitor the system to ensure early detection of

instability or deterioration of the changes once control and responsibility for continued success of the project was transferred to the PCC staff.

RESULTS

Aim 1: Overall rate of pain prevention strategy use

Unfortunately, the issues with validity of self-report at baseline precluded us from analyzing for pre- to post-change on the rate of evidence-based pain prevention strategies being offered in tandem with vaccination visits. Although this was unfortunate, it was fortuitous that observation uncovered quality issues that might have gone undiscovered and unaddressed within a different design. During the post-intervention period, consistent with our primary aim, nurses self-reported a rate of offering at least one pain prevention strategy 99% of the time. Perhaps most importantly, however, observation by QI project team members waiting outside the door during target vaccination visits yielded no concerns with regard to the validity of these reports and/or to the quality of implementation for strategies used during post-intervention data collection.

With regard to the rate of specific strategy use, nurses self-reported using comfort positioning and distraction approximately half of the time (57% and 54%, respectively) at post-intervention. Nurses self-reported using non-nutritive sucking and sucrose analgesia approximately a quarter of the time (25%) and breastfeeding very rarely (1%). Although not targeted directly by our intervention efforts, nurses self-reported giving the most painful vaccination last nearly three-quarters of the time (73%) at post-intervention, and were observed to encourage parents to dress their children

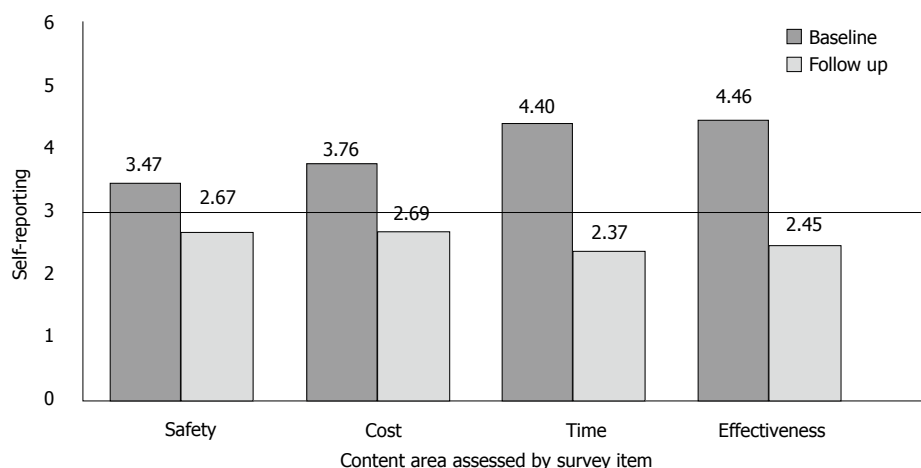


Figure 2 Comparison of parent/caregiver self-reported attitudes about pain prevention strategies for vaccination at baseline ($n = 259$) and at 1 year post-intervention follow up ($n = 336$) via parent/caregiver survey. A value of 3 indicates the neutral point; scores above 3 indicate more concern about this area, while a value below 3 indicates less concern. All comparisons were significant at $P < 0.05$.

prior to the vaccination(s) to allow parents to more quickly comfort their child and leave the area following the procedure.

Aim 2: Parent/caregiver satisfaction with pain prevention strategy use

Overall parent-/caregiver-reported satisfaction with the vaccination visit as a whole remained high and stable from baseline to post-intervention (94% endorsing a 1 or 2 on a 5-point scale with lower values indicating greater satisfaction). Compared to baseline, however, parents/caregivers reported greater satisfaction with the specific pain prevention strategy used [$t(143) = 2.50, P \leq 0.05$], as well as greater agreement that the pain prevention strategies used helped their children's pain [$t(180) = 2.17, P \leq 0.05$] and that they would be willing to use the same strategy again in the future [$t(179) = 3.26, P \leq 0.001$; see Figure 1 for details]. Of note, no differences were observed from baseline to post-intervention on items measuring balancing variables (e.g., whether the strategies used took too long or had other bad side effects) that might serve as barriers to uptake (see Figure 2 for baseline values; post-intervention values not depicted).

Aim 3: Shift in attitudes and beliefs

Approximately 1 year following transition of control and responsibility to PCC staff under the leadership of the Process Owner, staff demonstrated some important shifts in their own attitudes and their perceptions of parents/caregiver attitudes within the context of pain prevention. Specifically, staff reported greater agreement that the pain felt from vaccinations can result in harmful effects [2.47 vs 3.10; $t(70) = -2.11, P \leq 0.05$], less agreement that pain from vaccinations is "just part of the process" [3.94 vs 3.23; $t(70) = 2.61, P \leq 0.05$], and less agreement that parents expect their children to experience pain during vaccinations [4.81 vs 4.38; $t(69) = 2.24, P \leq 0.05$]. Time remained the most commonly reported barrier to use of evidence-based pain prevention

strategies at both time periods.

Parents/caregivers also reported more favorable attitudes about pain prevention strategies for vaccinations across a variety of areas, including safety, cost, time, and effectiveness (see Figure 2). In addition, they reported less concern about the pain their children experience with vaccination [4.08 vs 3.26; $t(557) = 6.38, P \leq 0.001$], less need for additional pain prevention strategies [3.33 vs 2.81; $t(476) = 4.51, P \leq 0.001$], and greater agreement that their doctors' office currently offers pain prevention for vaccinations [3.40 vs 3.75; $t(433) = -2.39, P \leq 0.05$]. Finally, parents/caregivers reported greater agreement that they lack sufficient knowledge about the array of pain prevention strategies that can be used for childhood vaccinations [2.95 vs 3.76; $t(399) = -4.54, P \leq 0.001$].

DISCUSSION

Although problems with validity of nursing self-report at baseline challenged our ability to analyze practice change for the number of pain prevention strategies used, we can confidently assert that we met our goal of one (or more) evidence-based pain prevention option being offered during at least 80% of applicable patient visits following the intervention period. In fact, nurses self-reported a rate of 99% of patient visits meeting this criterion. Further, informal observation of clinic visits at post-intervention found none of the discordance between self-report and actual behavior that was noted during the baseline period, lending greater confidence as to the validity of this post-intervention report. Parent data also suggest a qualitative shift occurred over the intervention period in the appropriate use of pain prevention strategies. Specifically, parents/caregivers reported greater agreement that the pain prevention strategies used helped their child's pain, satisfaction with the strategy used, and willingness to use the strategy again following the intervention phase. This is notable in that parents were generally positive in their satisfaction

ratings initially, and yet we were able to demonstrate a positive shift regardless of this potential ceiling effect.

As previously noted, a substantial shift in staff definition of specific pain prevention strategies was required as part of the intervention phase to ensure both that evidence-based techniques were being used and that self-report of health care provider behavior was valid. Currently, pain management is not generally included in nursing curriculums. Findings from this project suggest that, despite the evidence stressing the importance of incorporating evidence-based strategies to manage the pain a patient experiences in the clinical setting, many nurses do not possess the skills and knowledge to incorporate these practices effectively in their daily patient care. Those nurses who do utilize pain management techniques in their patient care delivery models have done so as a result of actual training they have received while on the job and from peers, which may or may not be consistent with evidence-based guidelines. Because of the role nursing plays in many procedures, including - but not limited to - vaccinations, it would have a much greater impact on reducing the pain associated with procedures that patients experience if nurses were educated not just on the importance of pain prevention techniques, but also on the pragmatics of how to utilize and apply these skills in an evidence-based manner to the care that nurses routinely provide, beginning during school to help build a culture supportive of pain mitigation efforts as a part of standard clinical practice.

Fortunately, results from our project suggest that both individual-level and cultural change are possible even in existing systems, under the right conditions. Many clinical/translational projects fail because they try to impose an "ideal" solution on an existing, complex system. In this case, perfect can be the enemy of good. We believe a key component of our success was the application of QI principles to build a partnership with the nurses and providers in the clinic, eliciting their expertise and input, and working to facilitate their ownership of the process. We were able to do this despite some significant deficits in training/experience with pain prevention among the PCC staff, and a culture that did not understand or promote evidence-based pain prevention. Through this process, some of our initial naysayers became the staunchest champions of pain prevention for vaccinations and, in turn, took the lead in modifying the nursing curriculum for new hires to include both the education modules described here and also to create a nursing preceptor position to support and encourage new hires to use evidence-based pain prevention routinely in their vaccination care. Encouraging to us was the fact that, at post-intervention, nurses self-reported generalization beyond the specific pain prevention strategies targeted for intervention (e.g., giving the most painful shot last, encouraging parents/caregivers to dress children before the vaccination is given). Taken together with survey data from the 1-year post-intervention follow up, this

suggests an overall increased acceptance by nursing staff that some type of pain prevention is important to offer with every vaccination. By engaging the intended system in solving the problem, we were able to meet our final, long-term aim of shifting staff and parent/caregiver attitudes and beliefs in a sustainable way.

Several other areas for continued iterative improvement remain. The fact that several families were offered comfort positioning and declined in the post-intervention period (7% of those offered the technique) suggests that barriers also remain to the successful use of comfort positioning (e.g., acceptability to parents, application to a more active/distressed child; see Connelly *et al.*^[16] for further discussion of this topic). Further, the array of evidence-based pain prevention strategies is wide and we opted to start small with implementing the three that had the greatest support as high impact/low difficulty from our superuser group of PCC nurses. However, combining these more idiographic "nurse-driven" interventions with broadly applied "system-driven" interventions, such as the use of topical anesthetic, has the potential to be even more effective if the logistic (e.g., cost, flow) issues can be resolved at the institutional level. Both of these issues, among others, may provide appropriate targets for intervention in future PDSA cycles. Finally, identifying/implementing an automated method of collecting data on the use of evidence-based pain prevention techniques through the electronic medical record (EMR) would be helpful in both measuring intervention impact over new PDSA cycles while minimizing manpower, as well as for alerting the Process Owner when some type of variation (e.g., outlying points, downward trend in use) occur so that system issues can be addressed in real-time. Setting up the system for sustainability in monitoring can be equally important as setting up the intervention for sustainability in the beginning.

Our current solution may not be the most perfect, but it is a step forward that the system was willing to take on and able to maintain, thus improving the immediate care of our patients and serving as a foundation for future improvement efforts. With our experience, we encourage others to similarly apply QI methods to create "champions" within their own system and promote meaningful, lasting change that narrows the gap between what we know and what we do in providing routine vaccination care to our youngest and most vulnerable patients.

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COMMENTS

Background

Despite strong evidence for the protective and mitigating effects of pain prevention for painful procedures, application to pediatric medical care remains limited. Novel methods to increase the use of evidence-based pain prevention

strategies during routine medical procedures, such as pediatric vaccination visits in patients aged 0-5 years, must be explored. Quality improvement (QI) methodology may be a useful approach given that it is designed to engage the intended system and produce sustainable practice change whether in industry or health care.

Research frontiers

No evaluation has specifically examined the impact of using QI methods on uptake of pain prevention strategies for routine medical procedures (e.g., vaccination) in pediatric primary care. The objective of this study was to increase the use of evidence-based pain prevention strategies during routine pediatric vaccination visits for patients aged 0-5 years in a single primary care clinic (PCC) using QI methodology.

Innovations and breakthroughs

Self-reported use of evidence-based pain prevention strategies increased from baseline to post-treatment, as did parent/caregiver satisfaction with the strategies used with their child during the vaccination procedure. Most importantly, attitude shifts were noted in both staff and parents/caregivers at 1 year post-intervention which provides support to the sustainability of practice change using QI methods.

Applications

Identifying and partnering with "champions" within the target clinic was critical to the adoption and maintenance of evidence-based pain prevention strategies. QI methodology can help close the gap in implementing pain prevention strategies during routine medical procedures for children.

Terminology

Quality improvement (QI) is an approach to the analysis of performance within a system, whether industry or healthcare, and an associated set of methods designed to support efforts to improve performance at the level of the system.

Peer-review

The authors conducted the evidence-based pain prevention strategies during routine pediatric vaccination visits for patients aged 0-5 years in a single primary care clinic using QI methodology and reported that significant improvements were noted post-intervention. The paper is well-written and provides valuable information regarding this field.

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Early infant male circumcision: Systematic review, risk-benefit analysis, and progress in policy

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Abstract

AIM

To determine whether recent evidence-based United States policies on male circumcision (MC) apply to comparable Anglophone countries, Australia and New Zealand.

METHODS

Articles in 2005 through 2015 were retrieved from PubMed using the keyword "circumcision" together with 36 relevant subtopics. A further PubMed search was performed for articles published in 2016. Searches of the EMBASE and Cochrane databases did not yield additional citable articles. Articles were assessed for quality and those rated 2+ and above according to the Scottish Intercollegiate Grading System were studied further. The most relevant and

representative of the topic were included. Bibliographies were examined to retrieve further key references. Randomized controlled trials, recent high quality systematic reviews or meta-analyses (level 1++ or 1+ evidence) were prioritized for inclusion. A risk-benefit analysis of articles rated for quality was performed. For efficiency and reliability, recent randomized controlled trials, meta-analyses, high quality systematic reviews and large well-designed studies were used if available. Internet searches were conducted for other relevant information, including policies and Australian data on claims under Medicare for MC.

RESULTS

Evidence-based policy statements by the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) support infant and later age male circumcision (MC) as a desirable public health measure. Our systematic review of relevant literature over the past decade yielded 140 journal articles that met our inclusion criteria. Together, these showed that early infant MC confers immediate and lifelong benefits by protecting against urinary tract infections having potential adverse long-term renal effects, phimosis that causes difficult and painful erections and "ballooning" during urination, inflammatory skin conditions, inferior penile hygiene, candidiasis, various sexually transmissible infections in both sexes, genital ulcers, and penile, prostate and cervical cancer. Our risk-benefit analysis showed that benefits exceeded procedural risks, which are predominantly minor, by up to 200 to 1. We estimated that more than 1 in 2 uncircumcised males will experience an adverse foreskin-related medical condition over their lifetime. Wide-ranging evidence from surveys, physiological measurements, and the anatomical location of penile sensory receptors responsible for sexual sensation strongly and consistently suggested that MC has no detrimental effect on sexual function, sensitivity or pleasure. United States studies showed that early infant MC is cost saving. The evidence supporting early infant MC has further strengthened since the positive AAP and CDC reviews.

CONCLUSION

Affirmative MC policies are needed in Australia and New Zealand. Routine provision of accurate, unbiased education, and access in public hospitals, will maximize health and financial benefits.

Key words: Male circumcision; Evidence-based policy; Infants; Adults; Urinary tract infections; Adverse events; Sexually transmitted infections; Genital cancers; Risk-benefit analysis; Cost-benefit

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Core tip: Australia and New Zealand should follow the lead of the American Academy of Pediatrics and the United States Centers for Disease Control and Prevention in facilitating education, provider training, patient access and

affordability of circumcision of male infants and boys. Our systematic review of the current scientific evidence finds the protection afforded by early infant male circumcision against infections and other adverse medical conditions exceed risks by 200 to 1 and that over their lifetime over 1 in 2 uncircumcised males will suffer an adverse medical condition caused by their foreskin. Strong evidence shows no adverse effect on penile function, sexual sensitivity or pleasure. Circumcision is a desirable public health intervention. It is moreover cost-saving.

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(1): 89-102 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/89.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.89>

INTRODUCTION

Early infant male circumcision (MC) is a simple, safe procedure that was performed in Anglophone countries for much of the 20th century. A substantial downturn in prevalence occurred after 1950 in the United Kingdom and in the 1970s in Australia and Canada. In the United States, however, only recently has there been a slight downturn^[1]. Paradoxically such declines were accompanied by an increase in the quantity and quality of medical scientific findings attesting to numerous health and medical benefits. A decade ago the American Academy of Pediatrics (AAP) began an extensive review of the accumulated evidence to 2010. This led to the formulation and release of a new affirmative early infant MC policy statement in 2012 which concluded that, based on the evidence: (1) the benefits of early infant MC exceed risks; (2) parents should be given factually correct, nonbiased information on MC before conception or early in a pregnancy; (3) access to MC should be provided routinely for those families who choose it; (4) education and training should be provided to practitioners to enhance their competency; (5) the procedure should be performed by trained competent practitioners using sterile techniques and effective pain management; and (6) the preventive and public health benefits warrant third-party reimbursement^[2]. The American College of Obstetricians and Gynecologists endorsed these recommendations. The American Urological Association has on its website a brief statement that presents benefits and risks of infant MC^[3].

In 2014, after extensive deliberations stemming from a consultation in 2007 in Atlanta with stakeholders^[4], the Centers for Disease Control and Prevention (CDC) released its draft recommendations on MC^[5]. These endorsed the AAP's policy but went further by recommending MC of adolescents and men, especially those in populations in the United States in which prevalence of HIV and other sexually transmitted infections (STIs) is high. In 2015, the Canadian Paediatric Society (CPS) released a policy

statement on newborn MC that recommended MC only for boys in “high risk populations” or “circumstances”^[6]. The basis for its deviation from the AAP and CDC policies was a faulty risk-benefit analysis that failed to include all common conditions that MC protects against and that inflated risk data^[7].

What then has been the response of authorities in other countries outside of North America, especially those with Anglophone populations having socio-cultural roots and current practices similar to the United States? In this regard, perhaps the most comparable countries are Australia and New Zealand. Australia is the only non-United States country in which an evidence-based policy statement has been produced (by the Circumcision Academy of Australia; CAA)^[8]. The authors of the policy included fellows of the Royal Australasian College of Physicians (RACP), as well as fellows of other Colleges and medical bodies. The conclusions reached were similar to those of the AAP and CDC.

Historically, the most influential policy statements for Australia and New Zealand have been ones emanating from the RACP’s Division of Paediatrics and Child Health. The most recent of these was placed on the RACP’s website in 2010^[9]. This was evaluated in detail by authors of the CAA policy, who identified numerous flaws that led them to conclude the RACP’s policy opposing “routine” early infant MC was not evidence-based^[10]. By failing to adequately evaluate all of the evidence, and selectively citing small low-quality studies, the RACP policy falsely concluded that risks exceed benefits. This has led to a general perception that the RACP is opposed to infant MC. It may explain the subsequent withdrawal of parent-approved early infant MC and elective MC by men as allowable procedures in Australian public hospitals, as well as a proposal currently being considered by the Australian federal government to abolish the Medicare rebate for MC. The RACP policy nevertheless stated that, “it is reasonable for parents to weigh the benefits and risks of circumcision and to make the decision whether or not to circumcise their sons”. The policy recommended that, “when parents request a circumcision for their child the medical attendant is obliged to provide accurate unbiased and up to date information on the risks and benefits of the procedure”. It also stated that “parental choice should be respected” and that, the operation, “should be undertaken in a safe, child-friendly environment by an appropriately trained competent practitioner, capable of dealing with the complications, and using appropriate analgesia”.

Other countries do not have evidence-based policy statements. A brief statement placed on the Internet by the Royal Colleges covering surgeons, nurses, paediatricians and anaesthetists in the United Kingdom in 2000^[11] did not claim to be evidence-based and only mentions MC for treatment of phimosis, balanoposthitis and “some rare conditions”. The policy of the Royal Dutch Medical Association in 2010 states that, “non-therapeutic circumcision of male minors is a violation of children’s

rights to autonomy and physical integrity”, refers only to “complications” of the procedure, and urges, “a strong policy of deterrence”^[12]. The recent policy statements by the AAP, CDC, CAA and even the CPS have raised the bar, meaning statements by other bodies should now be expected to similarly consider the evidence rather than rely on opinions.

Here we: (1) systematically evaluate the current evidence on MC, including findings subsequent to reviews by the AAP and CDC; (2) perform a risk-benefit analysis of early infant MC; and (3) determine whether other countries, in particular the comparable countries Australia and New Zealand, should follow the lead of the United States in translating MC science into policy and practice.

MATERIALS AND METHODS

Literature search

Articles dating from January 1 2005 until January 1 2016 were retrieved from PubMed using the keyword “circumcision” together with one of 36 other relevant subtopics (see Supplementary material). This yielded 10609 publications. To ensure no relevant publications were missed as of the date of submission a further search was performed using “circumcision 2016”. This yielded 133 more publications. Any pertaining to “circumcision” of women were excluded. The publications were assessed for quality and those rated 2+ and above by conventional criteria^[13] were studied further; the most relevant and representative of the topic were then cited. Bibliographies were examined to retrieve further key references. In instances in which a MC-related topic had been the subject of recent high quality systematic reviews or meta-analyses (level 1++ or 1+ evidence), these were cited for efficiency instead of all the individual studies on that topic. Internet searches were conducted for other relevant information, including policies and, in Australia, data on claims under Medicare for MC.

Risk-benefit analysis

Data from RCTs, meta-analyses, large observational studies in the United States and United Kingdom in particular and high quality systematic reviews were compiled and risk reduction conferred by MC was calculated in order to determine individual benefit of the various conditions that MC protects against. In the case of sexually transmitted infections and genital cancers, the prevalence of these in Australia was taken into account in order to determine risk reduction in the population. If data for Australia was not available data for the United States, United Kingdom, Canada or European countries was used. Findings for each condition were then summated to determine the overall benefit. The percentage of individuals who experience an adverse events arising from infant MC was determined from high quality studies and from this an overall prevalence of these was calculated.

RESULTS

Articles retrieved and included

We identified 115 journal articles that met our inclusion criteria, including 6 in 2016. Another 25 journal articles were identified from the bibliographies of these. The latter also revealed 9 relevant online documents, mostly by authoritative paediatric or medical bodies. A further 4 were articles "in press".

Prevalence of MC

The global prevalence of MC is approximately 38%^[14]. In the United States, estimates by the CDC indicate 81% of males aged 14 to 59 years are circumcised, the prevalence having increased in the decade to 2010 to 91% in white, 76% in black and 44% in Hispanic males aged 14-59 years^[15]. Figures for early infant MC are difficult to determine, although, after correction for under-reporting, the percentage appears to have declined from 83% in the 1960s to 77% by 2010^[1]. Hospital discharge data, which under-estimate the true prevalence, indicated a decline from 61% in 2000 to 57% in 2010^[16]. Despite MC prevalence having risen in Hispanic males, the greater rise in the Hispanic population as a proportion of the total American population may account in part for a likely fall, overall, in MC prevalence in the United States^[1]. Another reason contributing to a decline in MC in the United States is the withdrawal of Medicaid coverage for elective or parent-approved MC by 18 United States states during the past decade^[16]. Medicaid de-funding poses a barrier to access by poor families, a situation criticized by the CDC^[15] and others^[17]. This resembles the withdrawal of access to elective MC in Australian public hospitals starting in 2006.

In Australia large surveys found 66%-70% of males aged 50-59 years in 2001-2002^[18] and in 2005^[19] were circumcised, whereas prevalence in males aged 16-19 years was 32% in 2001-2002^[18] and 27% in 2005^[19]. Since most circumcisions in Australia occur early in infancy, these data suggest an early infant MC prevalence of 66%-70% in the 1960s but a fall to 27% by 1990^[19]. The decline in infant MC is likely to have been accelerated, at least in part, by the negative RACP paediatric policy statements from the 1970s onwards.

Australian Medicare claims provide a lower bound for prevalence of MC. Claims data do not capture all religious MCs, nor MCs for which a claim is not made. Given the substantial rise in cost of infant and later MC in private practice in Australia to A\$500-1000 (10-20 times the scheduled fee), some parents may forego making a claim for the Medicare rebate, which is less than A\$40. In the most populous state, New South Wales, 14.3% of boys aged under 6 mo attracted a Medicare rebate in 2000, rising to 18.5% in 2007^[20]. Nationwide, claims have stabilized over the past decade at 16433-19981^[21]. This represents 12% of boys aged under 6 mo. For boys aged 0.5-10 years there were 893 claims in 2005 and 834 in 2014, while for males aged 10 years or more

claims for specialist MC rose 54%, from 1906 in 2005 to 2941 in 2014^[21]. Medicare only covers MC for treatment of medical conditions, so after adding MCs for parental preference, cosmetic or religious reasons the actual number of procedures will be higher than Medicare figures. Another large survey similar to those above^[18,19] would help provide information on current MC prevalence in males older than 16 years of age. Publicity about health benefits in recent years and the increase in the number of Muslim families might have contributed to a rise in MC. On the other hand, as in the United States^[16], reduced access and affordability has likely contributed to a decline, especially amongst the poor.

Benefits of male circumcision

Urinary tract infection (UTI): A UTI is an infection that affects part of the urinary tract. Of any year of life, UTI in males is most common in the first year, affecting 1%-2% of uncircumcised boys compared to 0.1%-0.2% of boys who are circumcised^[22,23]. Risk reduction continues, however, beyond infancy. The most recent meta-analysis (in 2013) noted that over the lifetime 1 in 12 circumcised males experience a UTI compared with 1 in 3 uncircumcised males^[22]. Recurrent UTI in particular may lead to renal parenchymal disease^[24,25]. While treatment by oral antibiotics can be used for older children and men, an infant with a UTI presents with fever, often leading to blood collection, lumbar puncture, and if UTI is diagnosed, hospitalization to enable intravenous antibiotic administration^[26]. Emergence of resistance to most or all antibiotics, including methicillin, will make treatment of UTI more challenging^[27-29], including in Australia^[30]. Swabs taken under the foreskin of boys aged 7 d to 11 years identified 50 bacterial isolates, most of which were multi-drug-resistant strains^[31]. Maternal antibiotic use during pregnancy also increases the risk of resistant pathogens causing early infant UTI^[32].

Phimosis: Phimosis is a penile condition where the foreskin cannot be fully retracted over the glans penis. Phimosis affects approximately 10% of uncircumcised adolescent and adult males^[33-47]. Even though regular application of steroid creams, which may cause undesirable systemic absorption of glucocorticoids, can be used to alleviate this condition, the definitive treatment is MC. Paraphimosis (a condition in which the foreskin cannot be returned after retraction) is less common, but when it occurs represents a medical emergency because of haemostasis and risk of gangrene^[48].

Inflammation: Inflammation of the glans (balanitis) or the foreskin and/or the underlying glans (balanoposthitis) is also common in uncircumcised males and can contribute to secondary phimosis^[49-53]. A meta-analysis found circumcised males are at reduced risk of balanitis [odds ratio (OR) = 0.32; 95%CI: 0.20-0.52]^[54]. A form of penile inflammation, lichen sclerosis, is diagnosed in up to 40% of foreskins removed for phimosis and

peaks at around 10 years of age^[51,52]. Early infant MC virtually eliminates the risk of lichen sclerosis^[53,55]. MC is, moreover, the definitive cure.

Hygiene: Hygiene is less easily attained for an uncircumcised penis^[56]. In the more highly populated east coast states of Australia, MC prevalence increases from south to north^[20], correlating with the greater frequency of inflammatory conditions and skin irritation in an uncircumcised penis in hotter more humid climates. Candidiasis (thrush) is 60% lower in circumcised Australian men^[19].

STIs in men: Several STIs are more prevalent in uncircumcised males^[57,58]. These include oncogenic types of human papillomavirus (HPV)^[59-65], that are the most common STIs in Australia and New Zealand, just as in the United States, and HSV-2^[62,66-69] that is also common. There is a disproportionate burden of these STIs among adolescents and young adults^[66].

Randomized controlled trials (RCTs) showed MC reduced infection of men by high-risk HPV by approximately 40%^[61-63,70-72]. A meta-analysis in 2012 of 21 observational studies and 2 RCTs of MC found risk reductions in high-risk HPV of 43% and 33%, respectively^[73]. A similar result was obtained in an earlier meta-analysis^[65]. In one RCT circumcision of heterosexual men was found to reduce flat penile lesions, which typify oncogenic HPV, by 98%^[63], and in another RCT viral load was reduced by 95%^[72]. In those Australian homosexual men who predominantly practice insertive anal intercourse, protection afforded by MC against the major oncogenic type, HPV16, was 57%^[74].

In the case of HSV-2, RCTs have shown MC reduces infection by approximately 30%^[68,69,75,76] and a meta-analysis of older observational studies found infection to be 15% lower in circumcised men^[67].

Other STIs against which MC affords protection include *Trichomonas vaginalis*^[77], *Mycoplasma genitalium*^[78], syphilis^[67,79,80], chancroid^[67], genital ulcer disease^[81,82] and HIV^[83-90]. Coital injuries, which increase risk of HIV infection, are higher in uncircumcised men^[91]. In comparable developed countries in which HIV prevalence is low, the prevalence of heterosexually acquired HIV in those with low MC prevalence (the Netherlands and France) was 6 times higher in men and 10 times higher in women compared with Israel, a country having a very high MC prevalence^[92].

National HIV statistics for Australia show that after excluding cases from a high prevalence country, the number of cases whose exposure to HIV was attributed to heterosexual contact has increased by 28% over the past decade. In 2013 there were 1236 new diagnoses, 313 (25%) of these being attributed to heterosexual contact (29% of the latter involving individuals born in Australia)^[93].

HIV prevalence is high amongst Australian men who have sex with men, but a Sydney study found those adopting an exclusively insertive role during anal intercourse exhibit 89% protection if circumcised^[94,95].

In the United States the latest data show approximately 10% of new HIV cases were in men infected heterosexually, with one estimate suggesting that universal infant MC could prevent 2500 HIV infections annually^[96]. The increase in HIV infections in African Americans, however, has been faster than in all other groups in the United States^[97]. The CDC has recommended MC for HIV prevention in such groups^[90]. Such findings indicate an important public health role for early infant MC in developed countries, including Australia and New Zealand^[98,99].

It is anticipated that a steep increase in multiple morbidities and drug interactions in aging HIV-infected patients on combination antiretroviral therapy is looming and will lead to a major medical burden^[100], suggesting a flow-on of benefits resulting from the ability of MC to reduce HIV cases.

STIs in women: Circumcision of males also partially protects their female sexual partners from oncogenic types of HPV^[59,60,101], HSV-2^[102], *Trichomonas vaginalis*^[103], bacterial vaginosis^[103], *Chlamydia trachomatis*^[104] and syphilis^[79]. MC, by reducing HIV prevalence in heterosexual men, will help reduce HIV prevalence in women^[105] and children^[106]. Other STIs that MC protects against include ones that exacerbate HIV risk^[107-110].

The impact of condoms on STIs: Condoms are 80% protective against HIV infection, but must be used consistently and correctly^[111,112]. A Cochrane systematic review and meta-analysis of RCTs of condom use (two in the United States, one in England and four in Africa) found, however, "little clinical evidence of effectiveness" and no "favorable results" for HIV prevention^[113]. This study did, however, find condoms exhibited 42% effectiveness against syphilis^[113]. Unlike condoms, MC is a one-off procedure that does not require future voluntary compliance each time a man has sexual intercourse. In this respect MC can thus be compared with vaccination. However, the only vaccines currently in widespread use for STIs are those that protect against certain types of HPV (discussed below). Nevertheless both MC and condom use should be advocated^[98].

Genital cancers: Penile cancer affects approximately 1 in 1000 uncircumcised men over the lifetime, thus making it uncommon, but not rare^[2,114,115]. Infant MC reduces penile cancer later in life by 95%-99%^[116-118]. Prevalence was 22-fold higher in uncircumcised men in a United States study^[116]. MC appeared to afford lesser protection in a meta-analysis^[119], although the inclusion of men circumcised as part of their treatment for penile cancer meant the level of protection was underestimated. Oncogenic HPV is found in one-quarter to one-half of penile cancers^[73,114,120], prevalence varying with type of penile lesion^[121]. Based on meta-analyses of risk factors, phimosis increases risk of penile cancer 12.1-fold (95%CI: 5.57-26.2), balanitis increases risk 3.82-fold (95%CI: 1.61-9.06) and smegma is associated with a 3.04-fold (95%CI: 1.29-7.16) increase in risk^[114]. Each of

these conditions is much more common in uncircumcised males. Vaccination of boys against HPV16 and HPV18 may, under the most optimistic of scenarios, reduce penile cancer by 35%^[115]. Vaccination, MC, consistent condom use and monogamy should all be advocated to achieve maximum protection.

For prostate cancer, MC prior to sexual debut reduces prevalence by 15%-50%^[115,122-124]. The significant protective effect was confirmed in a recent meta-analysis^[125]. In countries globally in which MC prevalence is greater than 80%, prostate cancer-related mortality, corrected for potential confounding factors, is half that of countries with a low or intermediate MC prevalence^[126].

Cervical cancer is 10 times more common than penile cancer. This malignancy is up to 5 times more prevalent in women whose male partner is uncircumcised^[59,60]. Since virtually all cases of cervical cancer are caused by oncogenic types of HPV, the ability of MC to reduce transmission of high-risk HPV to women^[59,60,101] accounts for its protective effect against this commonly fatal and difficult to treat cancer. While prophylactic HPV vaccination of 12-13 years old girls can attenuate, but not eliminate, their future risk, vaccine uptake has not been universal. Current vaccines do not protect against all oncogenic HPV types, but only types HPV16 and HPV18 seen in approximately 70% of cervical cancers. Vaccination has a smaller effect against vulval epithelial neoplasia^[127], oncogenic HPV types being present in only half of cases. There is uncertainty about the long-term durability of the benefits of vaccination. Although introduction of a nonavalent HPV vaccine, which will protect against additional high-risk types 31, 33, 45, 52 and 58 (meaning approximately 90% coverage), should further reduce cervical cancer prevalence, concerns about breadth of protection, adherence and long-term immunity will remain.

Therefore a benefit from MC remains, both for males and for their female sexual partners, in partial protection against genital cancers. In Australia, universal MC would prevent 2800-8400 cancers, comprising 2400-8000 of the prostate, 67 of the penis and 350 of the cervix annually^[115].

Prevalence of adverse events of MC

The literature review by the AAP^[2] and a large detailed study by CDC researchers of 1.4 million MCs from 2001-2010 (93% in newborns)^[128] have determined that adverse events from MC occur in less than 0.5% of newborn infants and are almost all minor and immediately treatable, with complete resolution. In the CDC study, serious adverse events arising from early infant MC were extremely rare (one penile stricture, 4 penile replantations, 16 cases of artery suture and 3 partial, but no complete, penile amputations). In uncircumcised males incidence of infections, surgical procedures, pneumothorax, penile disorders and gangrene were each significantly higher than in circumcised males^[128]. In older boys and men, prevalence of adverse events was, however, 10-20

times higher than in newborn males^[128]. Meatal stenosis has been reported in 0.01%-1% of males during post-circumcision follow-up^[128-131]. The CDC study was not able to identify any deaths from early infant medical MC in recent times, as also documented in a large series of 100157 MCs in United States hospitals from 1980-1985^[132], that the CDC cited. That study noted that amongst 35929 uncircumcised boys 88 developed a UTI in the first month of life, resulting in 32 cases of bacteremia, 3 cases of meningitis related to the same organism that caused the UTI, 2 cases of renal failure and 2 deaths^[132].

MC, sexual function, sensitivity and pleasure

Medical MC does not adversely affect sexual function, sensitivity or pleasure, as shown by a detailed systematic review of all studies (totalling 40473 men) rated by quality^[133] and by a meta-analysis of common forms of sexual dysfunction^[134]. The conclusions were confirmed in a recent United Kingdom study of 6293 men and 8869 women^[135] and a systematic review by Danish researchers^[136].

A systematic literature review of histological correlates of sexual sensation showed that the sensory receptors responsible (genital corpuscles) reside in the glans, not the foreskin, meaning loss of the foreskin by MC should not diminish sexual pleasure^[137]. In fact, by exposing the glans, MC should increase sexual pleasure^[137]. The foreskin, just as other skin on the body, contains sensory receptors that respond to touch, temperature and pain. Since the density of Meissner's corpuscles (touch receptors) in the prepuce diminishes at puberty when male sexual activity is increasing these are unlikely to be involved in sexual sensation^[137]. Moreover, free nerve endings (that also respond to touch) show no correlation with sexual response. Sensitivity of the glans to touch decreases with sexual arousal so further ruling out touch receptors in sexual sensation^[138]. Sensitivity of the penis to vibration, which is able to elicit arousal and ejaculation, is not related to MC status^[137].

Risk-benefit

Table 1 lists the conditions that early infant MC protects against and the adverse events that can occur as a result of the procedure. Also shown are the degree of protection against each condition and the frequency of procedural risk of each adverse event. When the frequency of each were summated, we found that over their lifetime up to 80% of uncircumcised males may be affected by a medical condition related to the presence of their foreskin, whereas only 0.4% of early infant circumcisions are associated with an adverse event, most of these being minor, easily and immediately treatable with complete resolution (Table 1). Comparing benefits to risk we calculated that lifetime benefit exceeded procedural risk by 200:1. Moreover, in contrast to the sum of virtually all risks of an adverse event during infant MC, conditions resulting from lack of MC can be serious, and in the case of genital cancers, syphilis and HIV infection potentially fatal. A recent risk-benefit analysis

Table 1 Risk-benefit analysis for newborn male circumcision

Condition	Decrease in risk ¹	Percent affected ²	Study type and ref	Quality score ³
A: Conditions avoided and risk reduction				
Pyelonephritis (infants)	–	0.6	OS ^[24,25]	2+
With concurrent bacteremia	–	0.1		
Hypertension in early adulthood	–	0.1		
End-stage renal disease in early adult	–	0.06		
Urinary tract infections: Age 0-1 yr	90%	1.3	Meta ^[22]	1+
Urinary tract infections: Age 1-16 yr	85%	2.7	Meta ^[22]	1+
Urinary tract infections: Age > 16 yr	70%	28	Meta ^[22]	1+
Urinary tract infections: lifetime	72%	27	Meta ^[22]	1+
Phimosis ⁴	> 90%	10	OS ^[33-45,47]	2+
Balanitis	68%	10	Meta ^[54]	1+
Candidiasis (thrush)	60%	10	OS ^[19]	2+
High-risk HPV infection	56%	10	Meta ^[73]	1++
	53%-65%	4	Meta ^[65]	1++
	40%	6-10	RCT ^[61-63,70-72]	1++
HIV (acquired heterosexually)	60%	0.2	OS ^[90]	2+
	70%	0.1	Meta ^[87]	1++
Genital ulcer disease	50%	1	OS ^[81,82,161]	2+
Syphilis	47%	1	Meta ^[67]	1+
	40%-55%	1	OS ^[79,80]	2+
<i>Trichomonas vaginalis</i>	50%	1	RCT ^[77]	1+
<i>Mycoplasma genitalium</i>	40%	0.5	RCT ^[78]	1+
Herpes simplex virus type 2	30%	4	RCT ^[68,69,75,76]	1++
	15%	4	Meta ^[67]	1++
Chancroid	50%	< 1	Meta ^[67]	1+
Penile cancer (lifetime)	67%	0.07	Meta ^[119]	1+
	95% ⁵	0.1	OS ^[116]	2+
	95% ⁶	0.11	OS ^[117]	2+
	99% ⁷	0.07	OS ^[118]	2+
Prostate cancer: Population-based	17%	2.1	Meta ^[125]	1+
Black race	42%	17	Meta ^[125]	1+
Total percentage of uncircumcised males affected = approximately 80%				
B: Risks of infant MC				
Excessive minor bleeding	0.1-0.2		OS ^[128,132]	2++
Infection, local	0.06		OS ^[128,132]	2++
Infection, systemic	0.03		OS ^[128]	2++
Need for repeat surgery	0.08		OS ^[128]	2++
Meatal stenosis	< 0.1		OS ^[128-131]	2++
Partial loss of penis	0.0002		OS ^[128]	2++
Death	< 0.000001		OS ^[132]	2++
Reduced penile function, sensitivity, sexual pleasure	0		SR ^[133,134,137]	2++
Reduced penile function	0		Meta ^[134]	1+
Total percentage of adverse events from infant circumcision: About 0.4%				
Risk: Benefit				
Thus, over the lifetime, the risk to an uncircumcised male of developing a foreskin-related condition requiring medical attention may be up to 80%.				
In comparison the procedural risk during infant MC of experiencing an easily treatable condition is approximately 1 in 250. The risk of a moderate or serious complication is approximately 1 in 3000. Thus benefit to risk = 1:200.				
C: Risks reduced by female partners				
Cervical cancer ⁶	58% ^{7,8}		OS ^[59,60]	2++
	28% ⁷		RCT ^[101]	1++
Herpes simplex virus type 2 ⁶	55% ⁷		OS ^[102]	2+
Genital ulceration ⁶	22% ⁷		RCT ^[103]	1+
<i>Trichomonas vaginalis</i> ⁶	48% ⁷		RCT ^[103]	1+
Syphilis ⁶	75% ⁷		OS ^[29]	2++
Bacterial vaginosis ⁶	40% ⁷		RCT ^[103]	1+
<i>Chlamydia trachomatis</i> ⁶	82% ^{7,9}		OS ^[104]	1++

¹Based on data for circumcised vs uncircumcised males; ²The percentage of males who will be affected as a result of the single risk factor of retention of the foreskin. Data for STIs were estimated after taking into account the external factor of heterosexual exposure, which is dependent on population prevalence of each STI in North America and risk reduction conferred by circumcision; ³Quality rating was based on an international grading system^[13]. Rating was 1++ or 1+ for well-conducted meta-analysis and RCTs, was 2++ for well-conducted systematic reviews, and was 2++ or 2+ for the original studies cited; ⁴Phimosis (tight foreskin) is confined almost exclusively to uncircumcised males; ⁵Penile cancer was 22 times more frequent in uncircumcised males in the Californian study cited^[116]; ⁶The last two entries for penile cancer are the references cited by the AAP^[2] and CDC^[5] in their respective circumcision policy statements; ⁷For women with circumcised *vs* women with uncircumcised sexual partners; ⁸For monogamous women whose male sexual partner has had ≥ 6 other female sexual partners; ⁹*Chlamydia trachomatis* was 5.6 times more frequent in female partners of uncircumcised males in a large multinational study^[104]. Shown are the reference(s) and type of study. The meta-analyses provide comprehensive lists of references to individual studies relevant to the topic. Meta: Meta-analysis; OS: Original study; RCT: Randomized controlled trial; SR: Systematic review; HPV: Human papillomavirus; HIV: Human immunodeficiency virus.

by the Canadian Paediatrics Society under-estimated benefits by failing to include several common conditions that MC protects against, confused annual incidence figures for penile cancer with lifetime prevalence and, by citing data from small out-dated studies of meatal stenosis rather than data from the large recent study of adverse events by CDC researchers^[128], greatly overestimated procedural risk of MC in early infancy^[6].

Cost-effectiveness

A Johns Hopkins study that considered just UTIs during infancy and STIs later in life found that if infant MC prevalence in the United States was to decrease from the current prevalence of 80%^[15] to the levels of 10% typically seen in Europe (and Australia and New Zealand), the additional direct medical costs in infancy and later for treatment of these among 10 annual birth cohorts would exceed \$4.4 billion, after accounting for the cost of the procedure (average \$291; range \$146-437) and treatment of complications [at an average cost of \$185 each (range \$130-235); prevalence 0.4% (range 0.2-0.6%)]^[139]. Each forgone infant MC was estimated to lead to an average of \$407 in increased direct medical expenses per male and \$43 per female^[139]. The Johns Hopkins researchers stated that their, "cost increase outcomes (were) highly conservative". Just for HIV in the United States, the "associated indirect costs may be more than 4 times the total direct medical expenses"^[140]. The study further estimated that if early infant MC decreased to 10%, lifetime prevalence of infant UTIs would increase by "211.8%", high- and low-risk human HPV by "29.1%", HSV-2 by "19.8%" and HIV by "12.2%". Among females, lifetime prevalence of bacterial vaginosis would increase by "51.2%", trichomoniasis by "51.2%", high-risk HPV by "18.3%" and low-risk HPV by "12.9%". Clearly, if other conditions such as genital cancers as well as the indirect costs were to be considered, the true cost would be considerably higher. For prostate cancer in the United States in the absence of MC there would be 24%-40% more cases and \$0.8-1.1 billion extra in costs for treatment and terminal care per year^[141]. The CDC found MC in the United States was cost-saving for HIV prevention in black and Hispanic males in whom HIV prevalence is highest^[90]. Another analysis - of just genital cancer prevention in Australia - found that, after taking into account the Medicare rebate totalling A\$9M, if early infant MC were universal, this would save the Australian Federal Government \$80-160 million annually, not adjusted for inflation^[115].

In the United States Medicaid coverage for the poor has parallels with the availability until recent years of parent-approved infant MC in public hospitals in Australia. A study of a Medicaid birth cohort consisting of 29316 males found that for every year of decreased infant MC due to Medicaid defunding there would be over 100 additional HIV cases in the United States and \$30000000 in net medical costs as a result of these^[142]. The cost to circumcise males in this birth cohort was \$4856000, *i.e.*, 6% of the cost of treating only HIV. Modelling studies

have, moreover, found cost savings initially generated by non-coverage of elective infant MC by Medicaid in Louisiana^[143] and Florida^[144] were mitigated by increases in rate and expense of medically indicated MC. The Louisiana study only considered the costs of later MC for boys aged 0-5 years. Lifetime costs would therefore represent a far greater financial impost on healthcare systems. The Florida study, of males aged 1-17 years undergoing MC from 2003-2008, found Medicaid defunding led to a 6-fold rise in publicly funded MCs (cost = \$111.8 million)^[144]. As a result of the findings, Medicaid coverage for parent approved MC was restored by the government of Florida. These findings have implications for costs to the Australian and New Zealand health care systems and research is needed to determine the exact figures.

Thus, as in the United States, barriers to availability of infant MC in Australia and New Zealand based on immediate cost-savings to the health system are, "penny-wise and pound-foolish"^[17]. Costs for later MC for medical need and for treatment of foreskin-related conditions, infections and genital cancers add to the net cost burden for governments, insurers and individuals.

Parental responsibility

Because most parents and guardians value the wellbeing of their children they endeavour to do what is best for them. The AAP recommends unbiased educational material, as well as the routine discussion of early infant MC by medical practitioners with parents prior to conception or early in a pregnancy, to assist in their decision to circumcise a newborn son. When fully informed, evidence suggests that parents are likely to choose to have their baby boy circumcised^[145]. Those parents who are opposed to infant MC, even after being fully informed of the benefits and low risks, would seem to place greater value on preserving the foreskin than in protecting their boy and his future sexual partners against the harms posed by the uncircumcised state^[146]. Parental opposition could include respect for a cultural or religious tradition, or a philosophical ideology that is opposed to anything other than the natural state. Nevertheless, early infant MC and other interventions in childhood (such as vaccination) are not "routine", but require parental approval. MC is therefore a decision for the parent or guardian.

While the RACP also advocates information for parents, its current information brochure is not evidence-based, but rather is biased towards discouraging the procedure^[147]. In contrast, the CAA provides evidence-based brochures on its website: <http://www.circumcisionaustralia.org>. Its guide for parents was recommended as a resource in the recent CPS position statement on newborn MC^[6].

The ideal time for MC

The timing of MC is crucial. Medical and practical considerations point to the neonatal period as the ideal time^[54]. A neonate is less mobile, is amenable to any intervention, surgical risk is minimal and the health benefits conferred begin immediately^[2,54]. The CDC pointed to a study that

found the first week post-partum to be the best time for MC because pain using local anesthesia is negligible^[148], possibly because this period precedes the foreskin growth, thickening and increased vascularization starting in week 4 and ending at 4 mo of age^[149]. Failure to circumcise early in infancy means loss of the benefit of protection against UTIs that result in considerable pain and can cause kidney damage^[22]. It is not correct to suggest that MC is comparable at any age^[146]. Later circumcision is a more substantial, more expensive operation, carries a higher risk of complications, entails risk from general anesthesia (as is often used for older boys and men), healing time in longer and cosmetic outcome is diminished by use of sutures^[2,54]. If the adolescent or adult male normally engages in sexual activity temporary sexual abstinence for 6 wk is required, which some males and their sexual partners find challenging. Education or employment is interrupted, and there is a delay in protection against STIs if the male is sexually active^[2,54]. Such barriers in older males reduce the likelihood that MC will occur. Furthermore, an adult cannot consent in retrospect to his own MC as an infant^[146].

Opposition to circumcision of boys

Arguments by opponents start with the premise that MC has no benefits, only harms, or that the benefits only apply later in life when the male can make the decision to get circumcised^[150-152]. In reality, not only are the benefits considerable, they start in early childhood and extend over the lifetime^[1,2,5,8]. As described above, MC later in life poses significant barriers to adolescent boys and men that usually mean it will not happen except for a medical reason^[54]. Another claim is that MC diminishes sexual function, sensitivity and pleasure^[150,152,153]. But the detailed systematic reviews^[133,136,137] and meta-analysis^[134] referred to above strongly suggest otherwise. If anything sexual pleasure improves after MC, as found in a RCT^[154]. Those findings are supported by data on location of sensory receptors^[137]. Legal and human rights and other arguments used by MC opponents in criticizing the policy statements of the AAP and CDC have been shown to be flawed^[155-159].

Why is it that those who condemn parent-approved MC of boys are not as quick to condemn other procedures that provide no medical benefit to children^[146]? For example, cosmetic orthodontia, correction of harelip, surgery for tongue-tie, treatment of dwarfism by growth hormone injections and surgery for removal of supernumerary digits^[146]. All of these interventions, MC included, should be regarded by parents and physicians as being beneficial to the child. As one commentator remarked, it seems odd that infant MC is regarded by some as controversial^[146]. In European countries rising anti-Semitic and anti-Islamic bias as well as anti-American sentiments appear to parallel the opposition to circumcision of boys.

Implications for public health

Based on the evidence, the fall in early infant MC prevalence in Australia and New Zealand poses a

significant threat to public health and individual wellbeing. Despite the current RACP policy in 2010^[9] being out-dated and not evidence-based^[10], it continues to be cited in Australia as the national medical position on MC. The flow-on effect has been complacency or indifference by other Australian medical bodies. Failure to rigorously assess the evidence so as to arrive at the kind of recommendations made by the AAP, CDC and CAA has given license to state departments of health to remove prophylactic MC as allowable in public hospitals. Although doing so might reduce government expenditure in the short term, United States studies show that in the long-term costs will be substantially higher because of the need for later, more expensive, medically indicated MC^[90,139,142-144], which carries a 10-20 fold higher risk of an adverse event^[128], and for treatment of a wide array of conditions that early infant MC protects against^[117,90,115,139,142-144,160]. An absence of elective MC in teaching hospitals in Australia is an impediment to training in the procedure. Lack of familiarity amongst younger medical graduates may lead to reticence in recommending it.

Early infant MC should no longer be regarded as a controversial procedure. The value placed on evidence-based medicine in clinical practice requires a dispassionate consideration of early infant MC as a desirable intervention in Australia and New Zealand. Past prejudice should be set aside in order that evidence-based recommendations similar to those of the AAP and CDC be adopted in Australia and New Zealand, as well as in other countries. Doing so will improve public health by reducing prevalence, suffering and deaths from highly prevalent foreskin-related conditions and diseases, and at the same time provide cost savings to governments and families.

COMMENTS

Background

There has been a significant shift in male circumcision (MC) policy in the United States over recent years. The American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC) each reviewed the scientific evidence and concluded that benefits exceed risks. The United States has a high rate of MC. In the light of the recent recommendations for the United States, should other wealthy countries follow suit and recommend MC as a desirable public health intervention?

Research frontiers

Since males who are uncircumcised are at increased risk of various infections from infancy through old age, as well as physical problems, penile inflammatory disorders, candidiasis, inferior hygiene and genital cancers, MC would appear to represent a worthwhile intervention. The best time to circumcise has been debated. The authors therefore performed a systematic evaluation of the scientific literature over the past 10 years. The authors then assessed this to see whether the evidence is applicable to the comparable Anglophone countries of Australia and New Zealand. As part of this (unlike the AAP and CDC), the authors performed a risk-benefit analysis using the strongest relevant data.

Innovations and breakthroughs

Similar to the AAP and CDC, the authors identified a wide array of medical conditions that MC protects against, but the evidence has become even stronger as a result of new studies and analyses that have been published since those United States policy reviews on MC appeared. The present study

revealed a high benefit-to-risk ratio and that over their lifetime a large proportion of males will be protected against adverse medical conditions and diseases caused by foreskin retention if they are circumcised soon after birth.

Applications

The dichotomy between the scientific evidence and pediatric MC policy in Australia and New Zealand, as well as various other wealthy countries, is striking. Clearly, Australia and New Zealand should follow the recent AAP and CDC policies by replacing outmoded non evidence-based pediatric recommendations opposing early infant MC with strong evidence-based affirmative policy recommendations in favor. Given the low risks and enormous lifetime benefits, doing so should improve public health considerably and be cost saving to the health system.

Terminology

MC is a simple procedure that involves the surgical removal of the foreskin. Early infancy is the ideal time for the procedure.

Peer-review

The reviewer commented that some of the terms used should be defined and provided a list of minor corrections. All of these suggestions were implemented.

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Vein of Galen malformation in a neonate: A case report and review of endovascular management

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Abstract

Vein of Galen malformation (VOGM) is a rare congenital vascular malformation caused by the maldevelopment of its embryonic precursor, the median prosencephalic vein of Markowski. VOGM results in neonatal morbidity and mortality, and premature delivery does not improve the outcome. We report a term female neonate in whom a vein of Galen malformation was diagnosed prenatally at 37 wk of gestation during a growth ultrasound and confirmed by fetal magnetic resonance imaging. Signs of cardiac decompensation were evident in the fetus. Multiple interventional radiology embolizations of the feeding vessels were performed successfully on days 7, 10, 12, 14 and 19. A review of the literature on the endovascular management of neonates with these malformations is presented herein.

Key words: Vein of Galen malformation; Endovascular therapy; Congenital anomaly; Neonate

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Core tip: Vein of Galen malformation (VOGM) is a rare vascular anomaly that may present in the fetus or newborn, and may cause congestive heart failure. Historically, the management of VOGMs was neurosurgical, but outcomes were uniformly poor. Since the introduction of endovascular interventional techniques, the likelihood of a successful treatment is much greater and a cure is

potentially achievable. We report herein a term female neonate with a VOGM that was successfully treated with multiple endovascular embolizations, and also present a review of the literature on the endovascular management of neonates.

Puvabanditsin S, Mehta R, Palomares K, Gengel N, Da Silva CF, Roychowdhury S, Gupta G, Kashyap A, Sorrentino D. Vein of Galen malformation in a neonate: A case report and review of endovascular management. *World J Clin Pediatr* 2017; 6(1): 103-109 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i1/103.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i1.103>

INTRODUCTION

Vein of Galen malformations (VOGMs) are complex arteriovenous (AV) fistulas that occur infrequently. Their incidence is about one in 3 million population^[1-3], and they represent less than 1% of the cerebral AV malformation. The majority of VOGMs are diagnosed in the neonatal period, and the remainder during early childhood. VOGMs was first reported in 1895 by Steinheil (cited by Dandy^[4] in 1928). The reported lesion was, in fact, an arteriovenous malformation (AVM) of the diencephalon connected to a dilated vein of Galen. The majority of Vein of Galen Aneurysmal malformations (VGAMs) become symptomatic in the neonatal period and if left untreated have an almost 100% morbidity and mortality^[5]. The first attempt to treat a VOGM was at the beginning of the last century, wherein bilateral internal carotid artery ligations were performed on an infant who had presented with intracranial hypertension^[6]. At present, endovascular embolization is preferred for treating VOGMs^[7,8]. The endovascular technique was developed in the early 1980s. Since then, more than 262 neonates with VOGMs have been treated using this method^[7,8]. Because of the rarity of VOGMs, most publications are in the form of case reports. Our experience with a VOGM in a term infant with congestive heart failure is reported herein with a review the literature on endovascular embolization treatment in neonates.

CASE REPORT

A 42-year-old G2P1001 presented for a routine growth ultrasound at 36 wk 5 d. The fetus was found to have a vein of Galen malformation, which had not been identified during the 20-wk anatomy scan (Figure 1A). A review of her medical history was significant for a prior uncomplicated full-term vaginal delivery. Her living child is alive and well, meeting all appropriate milestones. The patient denied any significant family history for congenital anomalies or social history for toxic environmental or occupational exposures. Prenatal care was otherwise uneventful. Fetal MRI confirmed the diagnosis of VOGM, demonstrating a persistent median prosencephalic vein, which measured up to 22 mm in the

transverse dimension and 74 mm in length (Figure 1B and C). There was a network of feeding vessels (greater on the right as compared to the left) in the region of the medial temporal lobe, midbrain, and thalami, which likely represented feeder vessels emanating from the posterior cerebral arteries. Torcula and bilateral transverse sinuses were also enlarged. The lateral ventricles and cortical sulci were appropriate for the patient's gestational age. The infratentorial brain appeared normal, with no mass effect or midline shift.

A fetal echocardiogram showed cardiomegaly with preserved biventricular systolic function. The superior vena cava (SVC) was moderately dilated. The right atrium was severely dilated whereas the left atrium was only mildly dilated and there was an aneurysmal patent foramen ovale (PFO) with right to left shunting. The right ventricle (RV) was moderately dilated with qualitatively good RV systolic function. There was marked reversal of flow in the distal aortic arch, apparently draining predominantly to the brachiocephalic artery.

Over the next 2 d, repeat sonographic evaluation demonstrated new polyhydramnios and abnormal Doppler studies. The fetus developed an abnormal fetal heart rate tracing with areas of minimal variability and non-reactivity. At this point, because of the massive VOGM causing a steal phenomenon, evidence of heart failure, worsening doppler studies, and fetal monitoring showing fetal compromise, the decision was made to proceed with delivery and to achieve optimization of management in the neonate. An elective uncomplicated primary cesarean section was performed because of fetal cardiac failure and breech presentation. The neonate had Apgar scores of 4 at 1 min and 8 at 5 min. Cord blood gas studies showed a pH of 7.30 and base deficit of -2.2.

Physical examination revealed a weight of 2675 g (25th centile), length 47 cm (30th centile), head circumference 33 cm (40th centile). No visible anomalies were noted at birth. The pertinent physical findings were cranial bruit and a grade 2/6 soft systolic heart murmur at the left sternal border.

Chest radiography immediately after birth showed cardiomegaly. An echocardiogram performed at 1 h of life showed pulmonary hypertension, patent foramen ovale, dilated superior vena cava and reversal of flow in the descending aorta. Neurosonogram showed a large midline venous structure. MRI and magnetic resonance (MR) angiography showed VGOM and the vessels feeding the aneurysm (Figures 2 and 3). The feeding arteries are from bilateral middle cerebral arteries, bilateral anterior cerebral arteries and posterior cerebral arteries.

Over the first few days, the infant gradually became tachypneic and had a hyperdynamic precordium. Medical treatment of cardiac failure (furosemide, digoxin, and milrinone) was begun on the second day of life. Since the patient showed signs of cardiac decompensation despite the cardiac failure therapy, embolization with N-butyl cyanoacrylate (NBCA) was performed *via* the umbilical artery catheter at 7 d of age. The patient was intubated and placed on a conventional ventilator at 10 d of age.

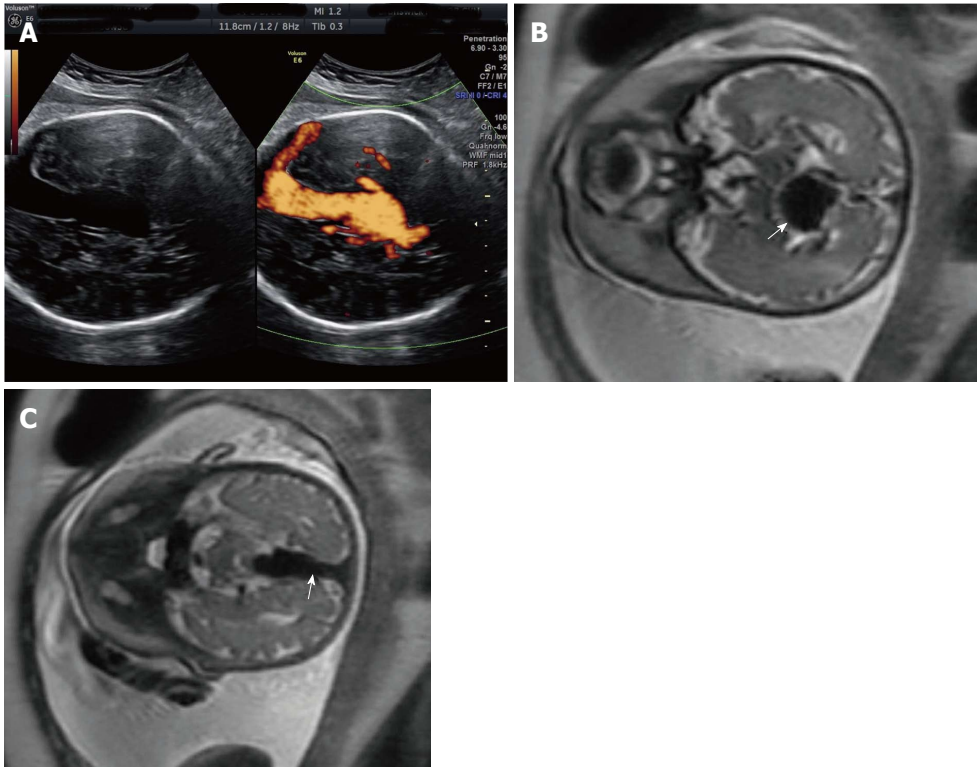


Figure 1 A 42-year-old G2P1001 presented for a routine growth ultrasound at 36 wk 5 d. A: Prenatal ultrasonography shows vein of Galen aneurysm and color flow examination reveals a turbulence flow in the lesion and in the connected strait sinus; B: Prenatal T1-weighted magnetic resonance images show the markedly enlarged median procerebral vein of Markowski, characteristic of vein of Galen aneurysmal malformation (arrow); C: Persistence of the falcine draining sinus (arrow).

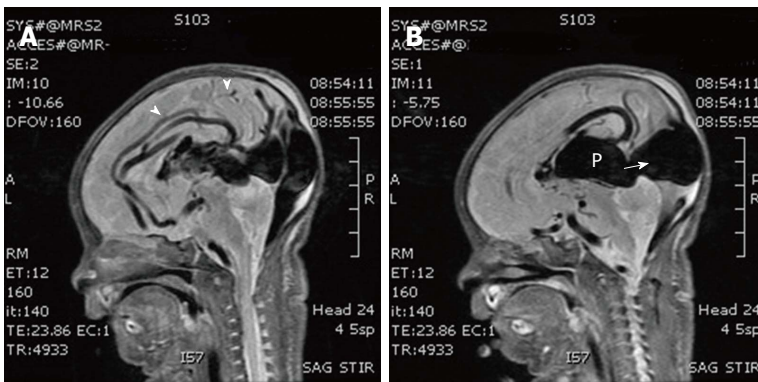


Figure 2 Sagittal T1-weighted magnetic resonance images show a choroidal type. Vein of Galen aneurysmal malformation with feeders (arrow heads, A) to arteriovenous fistulas, dilated prosencephalic vein of Markowski and persistence of the falcine draining sinus (white arrow, B).

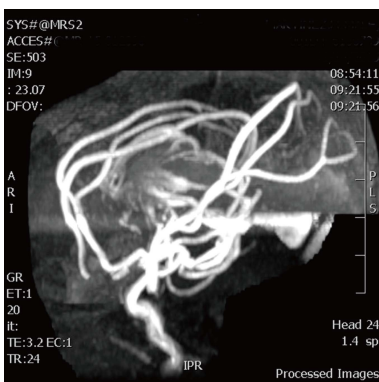


Figure 3 Magnetic resonance angiographic images show multiple enlarged arterial branches from the anterior and posterior cerebral arteries coalescing on the lateral margins of the dilated recipient vein.

Trans-femoral embolizations were performed on the 10th, 12th and 14th day of life, and finally trans-axillary artery embolization was performed at 19 d of age. A repeat neurosonogram done on the 19th day of life showed intraventricular hemorrhage and mild post hemorrhagic hydrocephalus, which however, did not require any intervention. The patient was extubated on the 20th day of life, MRI and MR angiography performed on the following day showed that the dilatation of the Vein of Galen had decreased markedly (Figure 4). The infant was discharged at 53 d of age. When seen at 6 mo of age in the follow-up clinic, the patient was developing normally.

DISCUSSION

The vein of Galen is located under the cerebral hemisp-

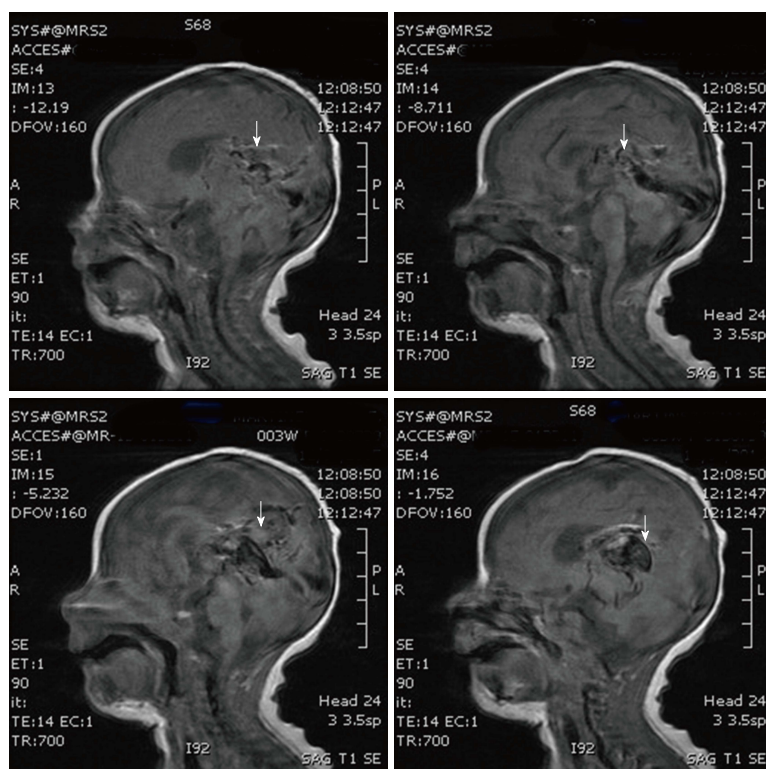


Figure 4 T1-weighted sagittal magnetic resonance images at 41 d of age after 5 embolizations show thrombosis and shrinkage of the median vein of procencephalon and embryonic falcine sinus (arrows).

heres and drains the anterior and central regions of the brain into the sinuses of the posterior cerebral fossa. The median prosencephalic vein of Markowski usually regresses during the 11th week of gestation, and by 3 mo of gestation, its posterior part joins the internal cerebral veins and basal veins to form the vein of Galen. The term “vein of Galen malformation” is a misnomer because the dilated vein seen in the location of the vein of Galen is the prosencephalic vein. An arteriovenous (AV) shunt between this vein and the arteries supplying the brain induces hemodynamic changes because of excess blood flow from these arteries into the VOGM, and the heart having to work harder^[9]. Hydrocephalus is the most common finding associated with a diagnosis of VOGM^[7,10,11].

VGAMs are AVFs supplied by a variety of feeder vessels that drain into the aberrantly persistent fetal median prosencephalic vein of Markowsky^[10], an embryonic precursor of the vein of Galen. The development of a VGAM may be an acquired event between the 6th and 11th week of gestation^[10]. VGAMs have been classified in various ways, based on their complexity, type of supplying arteries, location of fistula, or degree of venous ectasia (Table 1)^[1,6,10]. Lasjaunias classified VGAMs into two types, namely the choroidal and mural type^[10,12]. In the choroidal type, multiple fistulas communicate with the median vein of the prosencephalon *via* an arterial network in the choroid fissure. The feeder vessels generally come from the anterior and posterior choroidal, and anterior cerebral, and at times, also the quadrigeminal and thalamoperforating arteries. The choroidal type is the most severe form of VGAM, which frequently presents with high-output cardiac failure, macrocephaly with loud bruits,

and dilated orbital veins due to multiple high-flow fistulas with less restriction of outflow^[10,13]. In the mural type of VGAM, single or multiple fistulas are present in the wall of the dilated median vein of the prosencephalon, generally at its inferolateral margin. The feeder vessels arise from the quadrigeminal or posterior choroidal arteries or both, and could be either unilateral or bilateral. The mural type has less fistulas and more restriction of outflow, which leads to greater dilation of the median vein of the prosencephalon but protects the heart from high-output failure. It manifests in late infancy as macrocephaly, hydrocephalus, seizures, subarachnoid hemorrhage, developmental delay, and failure to thrive^[10,11]. Vein of Galen aneurysmal malformations (VGAMs) and vein of Galen aneurysmal dilations (VGADs) are the most frequently seen arteriovenous malformations in infants and fetuses. VGAD is an enlargement of the true vein of Galen and not its embryonic precursor.

The mortality rates of the patients (all ages) who were embolized during the 1980s were 17%, and in the 1990s and 2000s they were 12%. The complication rates during the 1980s were 45%, and in the 1990s and 2000s they were approximately 35%^[7]. Post-embolization complications included cerebral hemorrhage/hematoma (37%), cerebral ischemia (6%), macrocephaly or hydrocephalus, leg ischemia (3%), vessel perforation (3%), pulmonary embolism, and non-target embolization. Over the 1980s, 1990s, and 2000s, good clinical outcome rates of the patients that were embolized were 49%, 70% and 70%, respectively^[7].

A systemic review (1987-2014) of endovascular embolization was performed for VOGMs that included 667 subjects^[7], of which 44% were neonates at the time

Table 1 Classification of vein of galen aneurysmal malformations

Classification system	
Litvak	
Category A	Aneurysms of the great vein of Galen
Category B	Racemose conglomeration of blood vessels in the cerebral structures
Category C	Transitional types of midline AV shunts
Lasjaunias	
Type I	Choroidal type
Type II	Mural type
Yasargil	
Type I	Pure AVF between leptomeningeal arteries and feeders from P3, segments of posterior cerebral arteries and vein of Galen
Type II	Feeders from the thalamo-perforating vessels and from P1 and P2 segments of the posterior cerebral arteries
Type III	Mixture of type I and II
Type IV	
IV A	Aneurysmal dilation of the vein of Galen resulting from shunting from an adjacent thalamic AVM
IV B	Similar to type IV A with the AVM being mesencephalic instead of thalamic
IV C	Thalamomesencephalic or mesodiencephalic plexiform malformation along with an adjacent and separate cisternal AVF to the vein of Galen
Secondary enlargement of vein of Galen	
Vein of Galen dilation	Malformations that drain pial or dural shunts into the true vein of Galen or its tributary associated with the dilation of the vein of Galen
Vein of Galen varix	Dilation of the vein of Galen in the absence of AV shunt

of treatment. In the cases with a neonatal diagnosis, the most common presenting symptoms (94%) were cardiovascular and respiratory distress due to the high-flow AV shunts of VOGMs^[7,14]. Our case supports the findings. A study showed that 23%-70% of the children with VOGMs who received endovascular embolizations were neurologically normal at short-term follow-up^[15,16]. A recent review of outcomes of neonatal cases published over the past 15 years revealed poor prognosis for neonates who did not receive interventional embolization for severe cardiac failure secondary to VGAM^[16,17].

Transarterial embolization is the preferred route in most specialized centers. However, it best controls heart failure when there are only a small number of arterial feeders. When there are many small arterial pedicles, it often is impossible to occlude more than a few at a time in the unstable neonate. In such cases, transvenous embolization may help achieve some control of the heart failure. A combination of the transvenous and transarterial embolization (kissing microcatheter technique) is another feasible endovascular option with a differing success rate^[18]. The outcome of neonates with VGAM has improved tremendously due to advances in endovascular treatment. Table 2 summarizes the clinical details and outcomes of 47 neonates who were treated with endovascular embolization since the beginning of the 21st century^[5,16-23].

Due to the natural history of disease progression, prenatal diagnosis of VGAM is often not made until the third trimester when imaging studies (including a fetal MRI) are done. Progressive fetal cardiac dysfunction implies that the high flow lesion may not respond to treatment^[24]. Melting brain syndrome is the term used to describe an advanced stage of a hydrodynamic disorder where cerebral blood flow is reduced because of the venous hypertension, and the brain parenchyma (mainly white matter) is progressively destroyed. It has been associated with all types of AV fistulas (including VOGMs),

and can occur in fetuses, neonates and infants^[13,25,26], but it has not been observed in adults.

Fetal MRI is now the preferred modality for diagnosing fetal central nervous system (CNS) abnormalities because of its advantages over ultrasonography^[2,27,28]. Prenatal MRI and MR angiography can identify the prognostic factors (cardiac failure, polyhydramnios, pericardial and pleural effusion, ascites, fetal hydrops, and brain injury) that affect prenatal counseling and aid in delineating the blood supply to the lesion for planning postnatal management^[2,27-29]. Yuval *et al*^[15], while enumerating the prognostic features for VGAMs have suggested that neonates with cardiomegaly, dilated vena cava or jugular vein, retrograde aortic flow and multiple feeder arteries may have a better prognosis if there is immediate intervention. However, others have a more gloomy view based on the factors associated with a poorer outcome^[20,24,30]. Fetal MRI may play an important role by identifying additional findings that are unrelated to the primary pathology but may be important for planning the type of delivery, *e.g.*, placenta previa, umbilical cord wrapped around the neck, and uterine fibroids. Evidence of progressive fetal cardiac dysfunction is a grave sign and may suggest that the high flow lesion may not respond to therapy^[24]. Prenatal diagnosis, fetal MRI, and fetal echocardiography provide an opportunity to plan the delivery of the fetus at a tertiary care center where immediate and definitive care can be provided by a multidisciplinary team.

In summary, we report herein the case of a term neonate with a prenatally diagnosed VOGM, dilated SVC and right atrium, cardiomegaly, reversal of flow in the descending aorta, and polyhydramnios. Our case had extensive feeders arising from the anterior, middle, and posterior cerebral arteries. Additionally, we have provided a review of the literature regarding endovascular intervention during the neonatal period,

Table 2 Clinical details and outcome of 47 neonatal embolizations

Diagnosed	Gestational age (wk)	Birth weight (g)	Symptoms	Total sessions	Outcome	Ref.
Antenatal (31 wk)	N/A	N/A	CCF	Multiple	Normal	Mitchell <i>et al</i> ^[19] 2001
Postnatal	N/A	N/A	CCF	Multiple	Normal	
Postnatal	N/A	N/A	CCF	1	Death (2 d)	
Postnatal	N/A	N/A	CCF	Multiple	Normal	Frawley <i>et al</i> ^[17] 2002
Antenatal (36 wk)	Full term	N/A	CCF	3	Death (24 d)	
Postnatal	Full term	N/A	CCF	3	Normal	
Postnatal	Full term	N/A	CCF	1	Death (2 d)	
Postnatal	Full term	N/A	CCF	4	Psychomotor delay	
Postnatal	Full term	N/A	CCF	4	Normal	
Postnatal	Full term	N/A	CCF	1	Normal	
Antenatal (38 wk)	Full term	N/A	CCF	3	Normal	Jones <i>et al</i> ^[20] 2002
Antenatal (32 wk)	Full term	N/A	CCF	4	Death (39 d)	
Postnatal	36	N/A	CCF	1	Death (24 h)	
Postnatal	Full term	N/A	CCF	Multiple	Normal	
Antenatal (28 wk)	N/A	N/A	CCF	1	Death (29 h)	
Postnatal	Full term	3400	CCF	1	Death (7d)	Maheshwari <i>et al</i> ^[23] 2003
N/A	Full term	N/A	CCF	2	Normal	Mathew <i>et al</i> ^[21] 2013
N/A	Full term	N/A	CCF	1	Normal	McSweeney <i>et al</i> ^[22] 2010
N/A	Full term	N/A	CCF	1	Normal	
N/A	Full term	N/A	CCF	4	Psychomotor delay	
N/A	Full term	N/A	CCF	3	Psychomotor delay	
N/A	Full term	N/A	CCF	5	Psychomotor delay	
N/A	Full term	N/A	CCF	1	Death	
N/A	Full term	N/A	CCF	1	Death	
Antenatal (35 wk)	Full term	3290	CCF	1	Normal	Karadeniz <i>et al</i> ^[16] 2011
Postnatal	N/A	N/A	CCF	2	Normal	Meila <i>et al</i> ^[18] 2012
Antenatal	N/A	N/A	CCF	4	Normal	
Postnatal	N/A	N/A	CCF	6	Death (2 yr)	
Postnatal	N/A	N/A	CCF	2	Psychomotor delay	
Postnatal	N/A	N/A	CCF	6	Psychomotor delay	
Antenatal	N/A	N/A	CCF	3	Normal	
Postnatal	N/A	N/A	CCF	4	Normal	
Antenatal	N/A	N/A	CCF	3	Psychomotor delay	Berenstein <i>et al</i> ^[5] 2012
Postnatal	36	2897	CCF	5	Normal	
Postnatal	34	1810	CCF	1	Death	
Antenatal	Full term	4165	CCF	2	Normal	
Antenatal	36	3409	CCF	4	Normal	
Postnatal	Full term	3400	CCF	6	Normal	
Postnatal	Full term	2930	CCF	6	Hemiparesis	
Antenatal	Full term	2386	CCF	2	Normal	
Antenatal	Full term	4204	CCF	6	Psychomotor delay	
Antenatal	36	2825	CCF	3	Psychomotor delay	
Antenatal (36 wk)	Full term	2675	CCF	5	Normal	

and outcomes.

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COMMENTS

Case characteristics

A 2675-g term female neonate was diagnosed prenatally as vein of Galen malformation.

Clinical diagnosis

The infant developed congestive heart failure with signs of decompensation despite medical intervention.

Imaging diagnosis

MRI and MR angiography showed vein of Galen malformation. Chest radiography showed cardiomegaly.

Treatment

Five endovascular embolizations with N-butyl cyanoacrylate (NBCA) was performed via the umbilical artery, femoral artery and axillary artery.

Related reports

The development of the endovascular technique began in the early 1980s. Since then, more than 262 neonates with vein of Galen malformation have been reported using this method.

Term explanation

Endovascular treatment has transformed this previous bleak outlook of the infants with vein of Galen malformation and a cure is now potentially possible.

Experiences and lessons

This entity is rare intracranial arteriovenous malformation and can be fatal in neonates. Endovascular treatment has had a significant impact in outcome.

Peer-review

The authors presented their experience in a rare case of cerebral arteriovenous malformation that cause cardiovascular instability in a newborn infant. Generally, the manuscript is well prepared and interesting.

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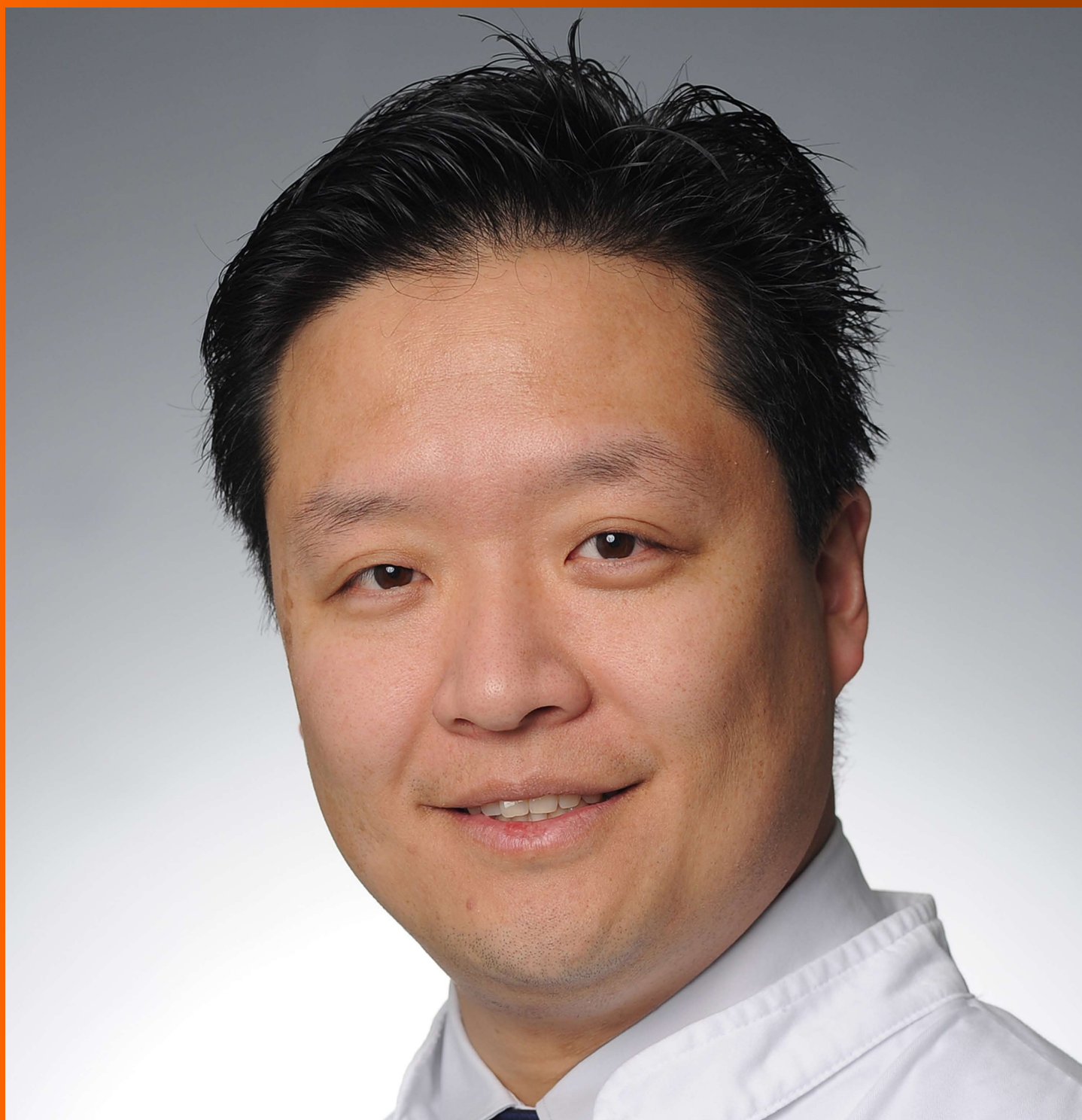
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Retrospective Study

Conversion from prolonged intravenous fentanyl infusion to enteral methadone in critically ill children

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Abstract

AIM

To describe our institutional experience with conversion from intravenous (IV) fentanyl infusion directly to enteral methadone and occurrence of withdrawal in critically ill mechanically ventilated children exposed to prolonged sedation and analgesia.

METHODS

With Institutional Review Board approval, we retrospectively studied consecutively admitted invasively mechanically ventilated children (0-18 years) sedated with IV fentanyl infusion > 5 d and subsequently converted directly to enteral methadone. Data were obtained on

subject demographics, illness severity, daily IV fentanyl and enteral methadone dosing, time to complete conversion, withdrawal scores (WAT-1), pain scores, and need for rescue opioids. Patients were classified as rapid conversion group (RCG) if completely converted ≤ 48 h and slow conversion group (SCG) if completely converted in > 48 h. Primary outcome was difference in WAT-1 scores at 7 d. Secondary outcomes included differences in overall pain scores, and differences in daily rescue opioids.

RESULTS

Compared to SCG ($n = 21$), RCG ($n = 21$) had lower median WAT-1 scores at 7 d (2.5 *vs* 5, $P = 0.027$). Additionally, RCG had lower overall median pain scores (3 *vs* 6, $P = 0.007$), and required less median daily rescue opioids (3 *vs* 12, $P = 0.003$) than SCG. The starting daily median methadone dose was 2.3 times the daily median fentanyl dose in the RCG, compared to 1.1 times in the SCG ($P = 0.049$).

CONCLUSION

We observed wide variation in conversion from IV fentanyl infusion directly to enteral methadone and variability in withdrawal in critically ill mechanically ventilated children exposed to prolonged sedation. In those children who converted successfully from IV fentanyl infusion to enteral methadone within a period of 48 h, a methadone:fentanyl dose conversion ratio of approximately 2.5:1 was associated with less withdrawal and reduced need for rescue opioids.

Key words: Methadone; Withdrawal; Children; Intensive care; Prolonged opioid infusion

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Core tip: Critically ill children exposed to prolonged opioid infusions for sedation and analgesia frequently experience withdrawal symptoms when these infusions are discontinued. Conversion to intermittent opioids such as methadone may reduce such withdrawal symptoms, but published studies and guidelines vary widely in terms of dosing and timeframes for such conversions. In this pragmatic analysis of current practice in our institution, we observed wide variation in dosing conversion and timeframes. We observed that it is feasible to convert from intravenous fentanyl infusion directly to enteral methadone within a timeframe of 48 h using a methadone:fentanyl dose conversion ratio of approximately 2.5:1 to minimize withdrawal and reduce need for rescue opioids.

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INTRODUCTION

Children admitted to the pediatric intensive care unit (PICU) are often administered opioids in the form of intravenous (IV) infusions to provide consistent sedation and analgesia titrated to effect^[1,2]. Tolerance and physical dependence frequently develop with prolonged opioid use resulting in an increased likelihood of developing a withdrawal syndrome when the IV opioid infusion is abruptly discontinued^[3]. Withdrawal is frequently associated with neurologic, autonomic and gastrointestinal abnormalities, which can result in considerable morbidity with prolongation of PICU and hospital length of stay^[4]. The risk of withdrawal increases depending on the cumulative dose exposure as well as the duration of infusion^[3,4]. For example, a cumulative IV fentanyl dose of at least 1.5 milligrams per kilogram (mg/kg) or 5 d of IV infusion has been associated with a 50% risk of developing withdrawal symptoms when the IV fentanyl infusion was rapidly weaned over 2 d^[4]. This risk increases to 100% when the patient has received a cumulative dose of at least 2.5 mg/kg or 9 d of continuous IV fentanyl infusion^[4]. Withdrawal may be avoided or attenuated during recovery either by slowly tapering the IV infusion, or by conveniently substituting the IV opioid infusion with IV or enteral opioids that are then tapered slowly over a period of time.

Methadone is a commonly used synthetic opioid for weaning critically ill children off IV opioid infusions due to its long half-life, good oral bioavailability and low cost^[5-9]. Methadone is available for administration in both IV and enteral forms. However, concerns with use of methadone include lack of pharmacokinetic data in children, significant interactions with other drugs, and increased risk of electrocardiographic abnormalities such as QTc prolongation^[10-12]. Importantly, there is a lack of consensus on an optimal dosing guideline for conversion from IV fentanyl infusions directly to enteral methadone (or *via* IV methadone as an intermediate step). A variety of studies have documented varying methadone:fentanyl conversion ratios (ranging from 1:1 to 4:1) and time frames (ranging from 24-48 h or longer) during conversion from IV fentanyl infusion to enteral methadone^[6-9,13-16]. We undertook this study to describe our institutional experience with conversion from IV fentanyl infusion directly to enteral methadone and occurrence of withdrawal in critically ill children exposed to prolonged IV fentanyl infusion for sedation and analgesia. A secondary objective of our study was to derive an optimal dose conversion ratio of methadone:fentanyl associated with minimal withdrawal when converting from IV fentanyl infusion completely and directly to enteral methadone within a 48-h timeframe.

MATERIALS AND METHODS

Study design

With Institutional Review Board approval and waiver

of informed consent, we retrospectively reviewed the medical records of consecutive children admitted to our PICU between November 2004 and February 2008. Patients were included if they were between 0-18 years of age, invasively mechanically ventilated *via* endotracheal tube or tracheostomy, on IV fentanyl infusion for more than 5 d and started on scheduled enteral methadone with the intention to wean off the IV fentanyl infusion completely. Patients with "Do not attempt resuscitation" status, burns, malignancy, chronic pain syndromes, or prior opioid use for more than 7 d in the 3 mo preceding admission to the PICU were excluded. Children undergoing cardiac surgery and neonates are cared for in other intensive care units separate from the PICU at our institution and were not eligible for this study. The pharmacy computer system database and the hospital electronic health record systems were screened for eligible subjects. Data collected included demographic information on age, weight, gender and diagnoses, severity of illness expressed as pediatric risk of mortality (PRISM III) scores^[17], daily IV fentanyl and enteral methadone dosing, duration and adjustments of IV fentanyl infusion, time to conversion from IV fentanyl infusion to enteral methadone, administration of opioid rescues, and use of concomitant sedative and analgesic medications (benzodiazepines, barbiturates, clonidine, acetaminophen, non-steroidal anti-inflammatory drugs, and neuromuscular blockers).

All patients were monitored for opioid withdrawal symptoms using the Withdrawal Assessment Tool-Version 1 (WAT-1)^[18]. The WAT-1 scale ranges from 0 to 12, with higher scores indicating more withdrawal symptoms. All patients were also monitored for pain during this period using pain scales depending on patient age and verbal/cognitive capacity: We used the Face, Legs, Activity, Cry, and Consolability scale in nonverbal children 0 to 6 years of age; the Individualized Numeric Rating Scale in nonverbal cognitively impaired children aged 6 years or older; and the Wong-Baker Faces Pain Scale in verbal children aged 3 years or older^[19-21]. All pain scales range from 0 to 10, with higher scores indicating more pain. Data on WAT-1 scores were abstracted at 12, 24, 48, 72, 96 h and 7 d from the time of enteral methadone initiation. Data on overall pain scores were abstracted during the 7 d from initial enteral methadone initiation.

Institutional practice during study period

During the study period, critically ill children requiring invasive mechanical ventilation in our PICU were typically provided sedation and analgesia with IV fentanyl infusions in combination with other agents. Patients who were administered IV fentanyl infusions for prolonged periods (typically greater than 5 d) were usually switched to enteral methadone administered every 12 h during recovery to manage dependence and prevent symptoms of withdrawal. The initial dose conversion from IV fentanyl infusion to enteral methadone was determined by the clinical team based on clinical judgment and in

discussion with the Clinical Pharmacist. The suggested time frame for conversion from IV fentanyl infusion to enteral methadone was usually 48 h, but was not standardized and left to attending physician discretion. After the second dose of enteral methadone, the IV fentanyl infusion was decreased by 50%. After the third dose of enteral methadone, the IV fentanyl infusion was decreased by a further 50%. After the fourth dose of enteral methadone, the IV fentanyl infusion was typically discontinued. Thereafter, the dosing of enteral methadone was adjusted by the attending physician to prevent both withdrawal symptoms as well as over-sedation.

Definitions and outcomes

Patients were classified into the rapid conversion group (RCG) if they were completely converted from IV fentanyl infusion to enteral methadone in 48 h or less, or the slow conversion group (SCG) if they were completely converted from IV fentanyl infusion to enteral methadone in more than 48 h. The primary outcome measure was difference in WAT-1 scores between the RCG and the SCG at 7 d from the time of enteral methadone initiation. Secondary outcome measures were differences in WAT-1 scores at 12, 24, 48, 72 and 96 h from the time of enteral methadone initiation, as well as overall WAT-1 and overall pain scores during the 7 d from enteral methadone initiation. Additional secondary outcomes included differences in ventilator free days at 28 d (VFD), PICU length of stay (LOS), and use of daily rescue opioids and concomitant medications.

Statistical analysis

Statistical analysis was performed using Stata 12.0 software (StataCorp, College Station, TX). Standard descriptive summaries were reported for baseline demographic data. The data were presented as mean $\pm$ SD if normally distributed, or median with inter-quartile range (IQR) if not normally distributed. Differences between the RCG and the SCG were compared using the *t*-test (in the case of continuous variables that were normally distributed) or the Mann-Whitney *U* test (in the case of continuous variables that were not normally distributed). Differences in categorical variables were compared using the χ^2 test or Fisher's exact test. Differences at respective paired time points for WAT-1 and pain scores between the RCG and the SCG were compared using the Mann-Whitney *U* test (as these were rank ordered). A *P*-value of less than 0.05 was considered statistically significant. Statistical methods and analysis were completed by Srinivasan V (first author of the study and trained in analytical methods *via* University of Pennsylvania biostatistics certificate courses).

RESULTS

A total of forty-two children were included in the study: 21 (50%) in the RCG and 21 (50%) in the SCG. The

Table 1 Baseline characteristics of rapid and slow conversion groups

	Rapid conversion group ^a (<i>n</i> = 21)	Slow conversion group ^b (<i>n</i> = 21)	<i>P</i> value
Age, yr (median, IQR)	1 (0.3-3.5)	2 (0.8-4)	0.95
Gender, male (%)	14 (67%)	9 (43%)	0.21
Weight, kg (median, IQR)	10 (5.5-14.3)	9.6 (6.8-15.9)	0.88
PRISM III (mean $\pm$ SD)	11.4 $\pm$ 9	16.1 $\pm$ 9.9	0.13
Admitting diagnosis, <i>n</i> (%)			1
ARDS/acute lung injury	14 (67)	14 (67)	
Other (sepsis, seizures)	7 (33)	7 (33)	
Pre-existing tracheostomy, <i>n</i> (%)	6 (29)	6 (29)	1
Duration of IV fentanyl infusion prior to initiation of enteral methadone, d (median, IQR)	9 (8-14)	10 (8-21)	0.48
Maximum dose of IV fentanyl infusion, μ g/kg per hour (median, IQR)	6 (4-7)	6.75 (4-9.25)	0.41
Cumulative dose of IV fentanyl infusion at time of initiation of enteral methadone, mg/kg (median, IQR)	1.48 (1.11-1.92)	1.64 (1.03-1.98)	0.49
Concomitant sedative and analgesic infusions			0.61
Benzodiazepine, <i>n</i> (%)	18 (86)	20 (95)	
Ketamine, <i>n</i> (%)	0 (0)	0 (0)	
Dexmedetomidine, <i>n</i> (%)	0 (0)	0 (0)	

^aRapid conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in 48 h or less; ^bSlow conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in more than 48 h. IQR: Inter-quartile range; SD: Standard deviation; PRISM III: Pediatric risk of mortality; ARDS: Acute respiratory distress syndrome; IV: Intravenous.

median time to complete conversion from IV fentanyl infusion to enteral methadone in the RCG was 25 h (IQR 19-34 h), while the median time to complete conversion in the SCG was 109 h (IQR 77-240 h, $P < 0.05$). Both groups were comparable with regard to baseline characteristics, including severity of illness and admitting diagnosis (Table 1). There were no significant differences in initial fentanyl infusion dose, duration of fentanyl infusion, maximum dose of fentanyl infusion or cumulative dose of fentanyl prior to conversion between the two groups. Table 2 compares the two groups during conversion from IV fentanyl infusion to enteral methadone. Compared with the SCG, the RCG required fewer rescue opioids in the first 96 h of transition per patient and fewer increases in the scheduled dose of enteral methadone. There were no significant differences between the use of concomitant sedative and analgesic medications across the groups.

The initial daily median enteral methadone dose was 2.3 times the daily median IV fentanyl dose in the RCG, compared to 1.1 times in the SCG ($P < 0.05$). Both groups had similar daily doses of enteral methadone at initiation (0.064 mg/kg in the RCG vs 0.06 mg/kg in the SCG, $P = 0.62$) and at 48 h (0.064 mg/kg in the RCG vs 0.076 mg/kg in the SCG, $P = 0.9$). However, at 7 d, the RCG had a significantly lower daily dose of enteral methadone compared to the SCG (0.03 mg/kg vs 0.189 mg/kg, $P = 0.02$) (Figure 1A). While the RCG experienced a consistent reduction in the IV fentanyl infusion dropping to zero by 48 h, the SCG experienced an increase in the IV fentanyl infusion over the first 48 h followed by a consistent reduction thereafter (Figure 1B).

For the primary outcome measure of withdrawal at 7 d, the RCG had lower median WAT-1 scores at 7 d (2.5 vs 5, $P = 0.03$) (Figure 2). Secondary outcome measures

differed between RCG and SCG for: Lower median WAT-1 scores at 48 h (5.5 vs 9, $P = 0.04$), lower overall median WAT-1 scores (5 vs 6, $P = 0.03$) and lower overall median pain scores (3 vs 6, $P < 0.05$). There were no significant differences between RCG and SCG for median WAT-1 scores at 12, 24, 72 and 96 h. Additionally, the RCG had significantly more VFD and shorter PICU LOS than the SCG (Table 3).

DISCUSSION

Critically ill children are at high risk of dependence and withdrawal after prolonged IV opioid infusion use for sedation and analgesia^[3]. A significant withdrawal syndrome may occur if IV opioid infusions are abruptly discontinued resulting in considerable morbidity with prolongation of intensive care dependency. Such withdrawal may be minimized, or prevented by a variety of methods including gradually reducing the IV opioid infusion, conversion of the IV opioid infusion to intermittent IV dosing, and conversion of IV opioid infusions to enteral opioids followed by a gradual taper. In this paper, we report the results of our institutional experience with the conversion of IV fentanyl infusion directly to enteral methadone and occurrence of subsequent withdrawal in critically ill mechanically ventilated children receiving prolonged sedation. We observed wide variability in conversion from IV fentanyl infusion directly to enteral methadone and variability in withdrawal in critically ill mechanically ventilated children exposed to prolonged sedation. We also observed that in the subset of children who converted completely from IV fentanyl infusion directly to enteral methadone within a period of 48 h, a methadone:fentanyl dose conversion ratio of approximately 2.5:1 was associated with less withdrawal

Table 2 Conversion from intravenous fentanyl infusion to enteral methadone in rapid and slow conversion groups

	Rapid conversion group ^a (n = 21)	Slow conversion group ^b (n = 21)	P value
Dose of IV fentanyl infusion at initiation of enteral methadone, µg/kg per hour (median, IQR)	4 (3-4)	4.5 (3.6-7)	0.23
Adjustments in scheduled enteral methadone dose			< 0.05
Increase in dose	15	33	
Decrease in dose	17	3	
Opioid rescues in first 96 h of transition per patient (median, IQR)	3 (1-7)	12 (4-17)	< 0.05
0-24 h	0 (0-2)	3 (0-4)	< 0.05
24-48 h	1 (0-2)	2 (1-6)	0.02
48-72 h	0 (0-1)	1 (1-6)	0.01
72-96 h	0 (0-2)	2 (0-4)	0.12
Opioid rescues in first 96 h of transition by agent			< 0.05
Morphine	44	51	
Fentanyl	51	210	
Concomitant medications administered in first 96 h of transition (number of administrations)			0.6
Benzodiazepines	32	40	
Clonidine	5	3	
Barbiturates	2	8	
NSAIDS	2	2	
Neuromuscular blockers	4	6	
Acetaminophen	9	10	

^aRapid conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in 48 h or less; ^bSlow conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in more than 48 h. IV: Intravenous; IQR: Inter-quartile range; NSAIDS: Non-steroidal anti-inflammatory drugs.

Table 3 Clinical outcomes in rapid and slow conversion groups

	Rapid conversion group ^a (n = 21)	Slow conversion group ^b (n = 21)	P value
Ventilator free days at 28 d, d (median, IQR)	18 (13.3-18.8)	8 (1.5-10.8)	< 0.05
Total PICU length of stay, d (median, IQR)	17 (12-24)	38.5 (24.8-68.5)	0.05

^aRapid conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in 48 h or less; ^bSlow conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in more than 48 h. IQR: Inter-quartile range; PICU: Pediatric intensive care unit.

and reduced need for rescue opioids.

Guidelines and studies describing the conversion of IV opioid infusions such as fentanyl to enteral opioids such as methadone often differ with respect to optimal conversion dose, frequency and duration of therapy^[6,9,13-16]. One such published guideline recommends a 1:1 dose conversion of IV fentanyl directly to enteral methadone over a period of 48 h to prevent withdrawal from dependence^[13]. Another institutional policy recommends a 2.5:1 conversion ratio from IV fentanyl to IV methadone initially and subsequently to enteral methadone once patients tolerate oral intake^[14]. These differences in formulation and dosing of methadone at the time of conversion in these studies and guidelines serve to highlight the paucity of knowledge and likely reflect differences in patient profiles, individual pharmacokinetic variation, and prescriber characteristics.

Previous studies have largely focused on transitioning from IV opioid infusions to IV methadone as an intermediate step before transitioning over to enteral methadone^[6,7,9]. In contrast, the findings from our study establish that it is feasible to convert from IV fentanyl infusion

directly to enteral methadone within a 48 h time period. Table 4 provides an example using data from our study to illustrate dose conversion using a methadone:fentanyl ratio of 2.5:1. Lugo *et al*^[8] also studied such a direct conversion to enteral methadone, but employed a fixed methadone dose of 0.1 mg/kg administered enterally every 6 h for conversion regardless of IV fentanyl infusion dose at the time of conversion. A direct conversion has the advantage of reducing the need for continued IV access with the potential to decrease IV catheter infiltrates (in the case of peripheral IV catheters) and catheter-associated complications such as infections and thrombosis (in the case of central IV catheters). Additionally, such a strategy can favorably influence hospital admission costs by reducing the overall duration of PICU and hospital LOS as further weaning of enteral medications can take place either on the general floor or even at home^[22].

In the present study, we included critically ill children with a high likelihood of opioid dependence from exposure to IV fentanyl infusion for greater than 5 d who were converted directly to enteral methadone. Methadone is

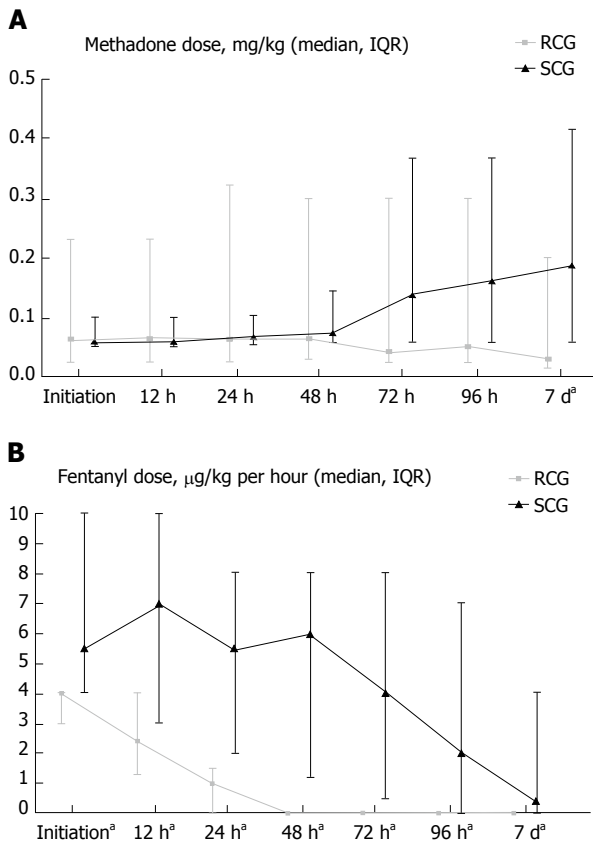


Figure 1 Comparison of enteral methadone and intravenous fentanyl titration across groups in the study. A: Paired comparison of median enteral methadone doses (mg/kg) between rapid conversion group and slow conversion group at serial time points following initiation of enteral methadone ($^aP < 0.05$); B: Paired comparison of median intravenous fentanyl infusion doses (µg/kg per hour) between rapid conversion group and slow conversion group at serial time points following initiation of enteral methadone ($^aP < 0.05$). RCG: Rapid conversion group consisted of patients who were completely converted from fentanyl infusion directly to enteral methadone in 48 h or less; SCG: Slow conversion group consisted of patients who were completely converted from fentanyl infusion directly to enteral methadone in more than 48 h.

a commonly used synthetic enteral opioid to prevent opioid withdrawal in our unit due to its long mean elimination half-life in children (19 ± 14 h, range 4-62 h), good oral bioavailability (70% to 100%), low cost and ease of tapering^[5-9]. Even though the suggested time frame for conversion was 48 h, we observed that only half the patients (RCG) were converted within this time period (in the absence of a unit specific protocol). This variation may have been due to patient factors such as intercurrent illness or perception of pain that may have influenced the conversion. Additionally, prescribing providers might have been anxious about possible withdrawal symptoms due to the perceived rapid time frame for conversion. Consequently, it is possible that in the RCG patients, providers preferentially used a higher dose of enteral methadone during conversion from IV fentanyl infusions to alleviate such concerns. In the other half of patients (SCG), the approximately 1:1 dose conversion required a longer time frame for conversion (median time of 109 h) raising the possibility that the dose of methadone was inadequate to prevent

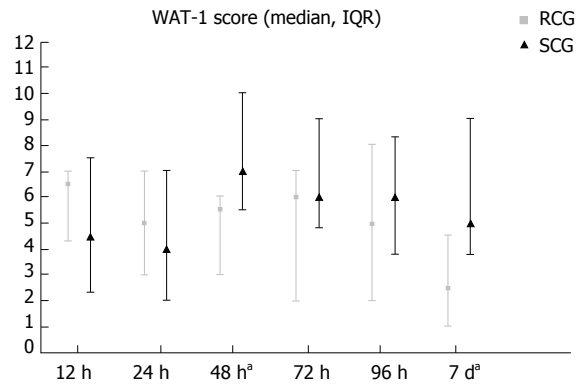


Figure 2 Paired comparison of median withdrawal (Withdrawal Assessment Tool-Version 1) scores between rapid conversion group and slow conversion group at serial time points following initiation of enteral methadone ($^aP < 0.05$). RCG: Rapid conversion group consisted of patients who were completely converted from fentanyl infusion directly to enteral methadone in 48 h or less; SCG: Slow conversion group consisted of patients who were completely converted from fentanyl infusion directly to enteral methadone in more than 48 h. WAT-1: Withdrawal Assessment Tool-Version 1.

withdrawal. However, several confounding factors could have delayed the conversion in this group, including comorbidities and intercurrent procedures that we were unable to adjust for in our analyses due to the small sample size. The SCG group was also observed to have an increase in the IV fentanyl infusion within the first 48 h of conversion, and ultimately ended up with a higher daily median methadone dose compared with the RCG (0.189 mg/kg vs 0.03 mg/kg, $P = 0.02$) which could possibly reflect an attempt to “catch-up” with withdrawal and pain symptoms.

Importantly, when compared to the SCG patients, the RCG patients were observed to have more ventilator free days and shorter PICU length of stay. While association does not imply causation, it is possible that the “higher” initial dose conversion in the RCG minimized withdrawal during conversion and allowed for subsequent progressive weaning of the enteral methadone. In contrast, the SCG which started out with a “lower” initial dose conversion ended up with higher doses of enteral methadone later on that might have resulted in over sedation and prolonged needs for intensive care dependency. However, this observation requires further prospective study in future trials.

The current study has several limitations. This was a retrospective review of patients admitted to the PICU and therefore subject to bias from incorrect or missing documentation in the patient charts. We attempted to overcome this limitation with rigorous definitions and integrity of data abstraction that we established a priori. Though it is possible that patients in the RCG happened to experience less withdrawal symptoms and were easier to wean compared to those in the SCG, both groups were well balanced with regard to age, illness severity, diagnoses, and extent of exposure to IV fentanyl infusion (Table 1). The small sample size precluded us from adjusting for confounding factors between the groups to study the independent association of methadone

Table 4 Example of dose conversion from intravenous fentanyl infusion directly to enteral methadone

A 10-kg child is receiving IV fentanyl infusion of 5 mcg/kg per hour. The total daily fentanyl dose is 5 µg/kg per hour × 24 h = 1.2 mg/d
Dose conversion ratio - methadone:fentanyl = 2.5 (rounded up from 2.3 observed in rapid conversion group in the present study that converted from IV fentanyl infusion directly to enteral methadone within 48 h) based on potency, half-life and enteral bioavailability
Total daily dose of enteral methadone = 2.5 × 1.2 mg/d = 3 mg/d administered in 2 divided doses, <i>i.e.</i> , 1.5 mg dosed every 12 h
Following the second dose of enteral methadone, the IV fentanyl infusion is decreased by 50% to 2.5 mcg/kg per hour
Following the third dose of enteral methadone, the IV fentanyl infusion is decreased again by 50% to 1.25 mcg/kg per hour
Following the fourth dose of enteral methadone, the IV fentanyl infusion is discontinued

IV: Intravenous.

dosing in relation to other clinically relevant outcomes such as ventilator free days and PICU length of stay. The findings from this study cannot be extrapolated to conversions other than from IV fentanyl infusion to enteral methadone. The dosing of enteral methadone was subject to the discretion of the attending physician and the time frame for conversion from the IV infusion, though intended to be 48 h, was variable. This study did not take into account withdrawal symptoms from discontinuation of other medications such as benzodiazepines and barbiturates. Though sedative and analgesic regimens with ketamine and dexmedetomidine could theoretically lower the risk for withdrawal^[23,24], none of our patients received either of these medications. The findings of this single center study may not be generalizable to other institutions. Incomplete cross-tolerance could have also complicated assessment of our findings. This phenomenon, in which exposure to one opioid could result in some degree of tolerance with exposure to another opioid, can be partial or complete^[25].

Though methadone is commonly prescribed to facilitate conversion from prolonged IV opioid infusion use and minimize opioid withdrawal in the PICU, concerns exist that methadone may be more potent than suggested when using equianalgesic dose conversion ratios from opioids such as morphine^[26]. This is particularly notable as a function of prior opioid dose and tends to increase with higher doses with consequent risk for oversedation and toxicities. A recent systematic review by Johnson *et al.*^[27] did not find differences between weight-based and formula-based approaches to initial methadone dosing in critically ill children. However, this review did note that children receiving a formula-based approach to dosing tended to experience more instances of oversedation. The authors concluded that the most prudent course is to start with the lowest possible dose and titrate based on clinical response to avoid complications^[27].

In recent years, efforts to develop pathways and protocols have emerged as rational approaches to reduce intensive care dependency and rein in healthcare costs by decreasing variations in treatment styles. Our results are similar to the findings of the quality improvement study by Abdouni *et al.*^[14] who observed that employing a standardized treatment protocol to convert from IV fentanyl infusion to intermittent methadone dosing using a dose conversion ratio of 2.5:1 reduced the length of opioid exposure and minimized withdrawal symptoms. By observing the feasibility of a direct conversion from

IV fentanyl infusion to intermittent enteral methadone, our study provides additional support to further refine such clinical pathways and ultimately improve clinical outcomes for critically ill children.

In our institutional experience, we observed wide variation in clinician practice during conversion from IV fentanyl infusion to enteral methadone and variability in withdrawal in critically ill mechanically ventilated children exposed to prolonged sedation. In those children who converted successfully from IV fentanyl infusion to enteral methadone within a period of 48 h, a methadone:fentanyl dose conversion ratio of approximately 2.5:1 appeared to minimize withdrawal with less need for rescue opioids. Further prospective studies are needed to examine the optimum methadone:fentanyl dosing conversion to reduce withdrawal and improve clinical, economic and patient satisfaction outcomes.

COMMENTS

Background

Critically ill children are at high risk of dependence and withdrawal after prolonged intravenous (IV) opioid infusion use for sedation and analgesia which can result in considerable morbidity with prolongation of intensive care dependency. The optimal strategy to minimize such withdrawal remains controversial.

Research frontiers

Direct rapid conversion of IV opioid infusions to enteral medications are ideal to minimize withdrawal as well as enhance patient satisfaction. An additional benefit of such a strategy is to facilitate rapid transition from intensive care to home with decrease in healthcare costs.

Innovations and breakthroughs

In contrast to most previous studies that examined conversion from IV opioid infusions to IV methadone, this study demonstrates the feasibility of a direct conversion from IV fentanyl infusion to enteral methadone within a 48-h time frame with minimal withdrawal in critically ill children.

Applications

In practical terms, a direct conversion from IV fentanyl infusion to enteral methadone over a 48-h timeframe appears to be feasible in a ratio of methadone:fentanyl of 2.5:1 with minimal withdrawal and less need for rescue opioids.

Terminology

FLACC: Face, Legs, Activity, Cry and Consolability; IQR: Inter-quartile range; IV: Intravenous; LOS: Length of stay; PICU: Pediatric intensive care unit; PRISM: Pediatric Risk of Mortality; RCG: Rapid conversion group; SCG: Slow conversion group; WAT-1: Withdrawal Assessment Tool-version 1.

Peer-review

The findings are very valuable and should be shared with the scientific community. The corrections are shown as green highlight in the manuscript.

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Retrospective Study

Significance of platelet count in children admitted with bronchiolitis

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Informed consent statement: As this was a retrospective review of case notes where all the clinical data was anonymized, patients were not required to give informed consent to the study.

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Abstract

AIM

To determine the true prevalence of thrombocytosis in children less than 2 years of age with bronchiolitis, its association with risk factors, disease severity and thromboembolic complications.

METHODS

A retrospective observational medical chart review of 305 infants aged two years or less hospitalized for bronchiolitis. Clinical outcomes included disease severity, duration of hospital stay, admission to pediatric intensive care unit, or death. They also included complications of thrombocytosis, including thromboembolic complications such as cerebrovascular accident, acute coronary syndrome, deep venous thrombosis, pulmonary embolus, mesenteric thrombosis and arterial thrombosis and also hemorrhagic complications such as bleeding (spontaneous hemorrhage in the skin, mucous membranes, gastrointestinal, respiratory, or genitourinary tracts).

RESULTS

The median age was 4.7 mo and 179 were males (59%). Respiratory syncytial virus was isolated in 268 (84%), adenovirus in 23 (7%) and influenza virus A or B in 13 (4%). Thrombocytosis (platelet count $> 500 \times 10^9/L$) occurred in 88 (29%; 95%CI: 24%-34%), more commonly in younger infants with the platelet count declining with age. There was no significant association with the duration of illness, temperature on admission, white blood cell count, serum C-reactive protein concentration, length of hospital stay or admission to the intensive care unit. No death, thrombotic or hemorrhagic events occurred.

CONCLUSION

Thrombocytosis is common in children under two years of age admitted with bronchiolitis. It is not associated with disease severity or thromboembolic complications.

Key words: Hospitalization; Bronchiolitis; Platelet count; Thrombocytosis; Infant; Virus diseases

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Core tip: This is as a retrospective observational study of platelet counts in 305 infants aged two years or less who were hospitalized for bronchiolitis. Thrombocytosis (platelet count $> 500 \times 10^9/L$) was frequent, occurring in 88 (29%; 95%CI: 24%-34%), more commonly in younger infants with the platelet count declining with age. There was no significant association with the duration of illness, temperature on admission, white blood cell count, serum C-reactive protein concentration, length of hospital stay, admission to the intensive care unit, death, thrombotic or hemorrhagic complications.

Al Shibli A, Alkuwaiti N, Hamie M, Abukhater D, Nouredin MB, Amri A, Al Kaabi S, Al Kaabi A, Harbi M, Narchi H. Significance of platelet count in children admitted with bronchiolitis. *World J Clin Pediatr* 2017; 6(2): 118-123 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i2/118.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i2.118>

INTRODUCTION

Bronchiolitis is a common viral infection in young children, usually caused by respiratory syncytial virus (RSV), adenovirus infections or influenza. Thrombocytosis is uncommon and its incidence and etiology are age-dependent^[1]. It is rare in childhood, especially the primary form, which is of hemopoietic nature. More common is the secondary form or reactive thrombocytosis, which is often asymptomatic, transient, occurring during the course of a viral infectious illness, mainly respiratory, and it is often considered to be an acute phase reactant response to cytokines production during the infection. Other causes of reactive thrombocytosis include inflammation, anemia,

hypoxia and some medications^[2-6]. Cytokines [interleukins (IL)-6, IL-8, IL-11] and thrombopoietin have been implicated in its pathogenesis^[7,8].

Thrombocytosis has only occasionally been reported in viral bronchiolitis with a prevalence ranging from as low as 8.4% up to 38.6%, with higher platelet counts observed in RSV positive infections^[9,10]. This has led to the suggestion that RSV infection should strongly be suspected when thrombocytosis occurs in a child with a respiratory infection^[11,12]. Although platelets play an important role in anti-microbial host defense, in the induction of inflammation and tissue repair, the significance of thrombocytosis during an infection is not fully clarified, as it may be caused by both disease aggressiveness and a higher capacity for host defense. For example, in adult patients hospitalized for community-acquired pneumonia, a high platelet count, is associated with a significant increase risk of mortality^[13]. Likewise, in children with human immunodeficiency virus infection, thrombocytosis correlates with severe disease^[14].

Reactive thrombocytosis in children is usually benign and does not cause thromboembolic or hemorrhagic complications, except if it occurs secondary to splenectomy or if there is underlying disease with additional thrombotic risk factors such as thalassemia^[15,16] especially when complicated by cardiomyopathy, diabetes, hepatopathy and portal hypertension^[17]. Neonatal thrombocytosis carries a higher thrombo-embolic risk in the presence of risk factors like maternal diabetes and antiphospholipid syndrome, septicemia, intrauterine growth retardation or in the presence of cyanotic cardiac malformation^[18].

None of the few reports of thrombocytosis in children with bronchiolitis has looked at its association with risk factors, disease severity or thromboembolic complications. We therefore undertook this study to ascertain the prevalence of thrombocytosis in a cohort of children with bronchiolitis admitted to a general pediatric ward and analyze the risk factors associated with it. We also looked for thromboembolic complications and analyzed if elevated platelet count was associated with, and therefore a marker of bronchiolitis severity.

MATERIALS AND METHODS

The study was a retrospective observational medical chart review of all infants aged two years or less who were hospitalized for bronchiolitis in the pediatric departments of Tawam hospital from 1st November 2008 to 30th June 2012. Indications for admission included worsening of the respiratory status, decreased oral intake, requirement for oxygen or parenteral therapy. The diagnosis of bronchiolitis was clinical and was made by the physician on admission based on the presence of an upper respiratory tract infection (either by history or by cough or rhinorrhea on physical examination), tachypnea, hypoxia, cough, subcostal or intercostal retractions, nasal flaring, grunting, with wheezing and/or crackles on auscultation. The management of admitted children was

left to the discretion of the attending physician.

Excluded from the study were children with a bacterial co-infection, chronic disease, immune deficiencies, splenectomy, congenital cyanotic heart disease with polycythemia, presence of intravascular lines, treatment with medications associated with thrombocytosis, or with a personal or family history of thrombophilia.

Data for each infant were extracted through review of emergency department case files and admission notes. Demographic data (gender, age, weight at birth, and gestational age), duration of illness before admission and clinical features at the time of admission including basic observations were recorded. Maximal temperature was defined as the highest rectal temperature recorded in the emergency department or at the time of admission to the pediatric department and fever was defined as a temperature $> 38^{\circ}\text{C}$. Nasopharyngeal aspirates were obtained on admission and sent for enzyme-linked immunoassay rapid antigen detection of RSV (Tru RSV[®], Meridian Bioscience, INC), and adenovirus, influenza A and B, parainfluenza 1, 2 and 3 viruses (LIGHT DIAGNOSTICS[™] SimulFluor[®] Respiratory Screen, EMD Millipore). Platelet count was measured by CELL - DYN Sapphire (Abbot). Thrombocytosis was defined as a platelet count of more than $500 \times 10^9/\text{L}$. Counts of > 500 and $\leq 700 \times 10^9/\text{L}$ were considered mild thrombocytosis, levels of > 700 and $\leq 900 \times 10^9/\text{L}$ as moderate thrombocytosis, and levels of $> 900 \times 10^9/\text{L}$ as severe thrombocytosis^[9]. For the purpose of the study only the first platelet count taken upon admission was used. Serum C-reactive protein (CRP) was measured with the Beckman Coulter DXB-800, with values $< 8 \text{ mg/L}$ defined as normal.

Clinical outcomes included disease severity as judged by duration of hospital stay, admission to pediatric intensive care unit (PICU), or death. They also included complications of thrombocytosis, including thromboembolic complications such as cerebrovascular accident, acute coronary syndrome, deep venous thrombosis, pulmonary embolus, mesenteric thrombosis and arterial thrombosis^[19-21] and also hemorrhagic complications such as bleeding (spontaneous hemorrhage in the skin, mucous membranes, gastrointestinal, respiratory, or genitourinary tracts).

Statistical analysis

The prevalence of thrombocytosis was calculated with 95% confidence intervals (CI). Proportions were compared with the χ^2 test, or the Fisher exact test if the number of observations was less than 5. The Student *t*-test was used to compare the means of Normally distributed variables between two groups. Analysis of variance was used to compare the means of normally distributed continuous variables amongst more than 2 groups, with Bonferroni adjustment for multiple comparisons. The odds and odds ratio of the association of thrombocytosis with the type and number of isolated viruses were calculated with 95%CI. For all statistical analyses, a 2-tailed *P* value was considered statistically

significant if < 0.05 .

Ethical approval

Approval was granted by the Institutional Review Board (IRB 296/13) and the requirement for consent was waived as it was a retrospective study and patient anonymity was preserved.

RESULTS

Descriptive

During the study period there were 305 children admitted for acute bronchiolitis ($n = 179$ males, 59%). Their median age was 4.7 mo (mean $\pm$ SD 6.5 ± 0.2 mo, range 7 d to 1.9 years) and 49 (18%) were born preterm (< 38 completed weeks of gestation) with a median gestational age 40 of weeks (mean 39, range 23 to 42 wk) and a median birth weight of 3000 g (median 2.9, range 870 to 4600 g). The median duration of symptoms prior to admission was three days (mean $\pm$ SD 2.8 ± 1.2 , range 0 to 6 d) and 203 children (68%) were febrile on presentation. Mild to moderate dehydration was present in 131 children (43%).

Virology studies were performed on all. Infection with a single virus occurred in 291 children (95%). RSV was isolated in 255 children (84%), adenovirus in 23 (7%) and influenza virus A or B in 13 (4%). Co-infection of RSV infection with adenovirus occurred in 8 (3%) and with influenza in six (2%).

The mean $\pm$ SD platelet count was $431 \pm 141 \times 10^9/\text{L}$ (median $421 \times 10^9/\text{L}$ and range 51 to $1000 \times 10^9/\text{L}$). The platelet count was normal in 213 children (70%). Thrombocytosis occurred in 88 children (prevalence 29%; 95%CI 24% to 34%) and it was mild in 78 children (89%), moderate in 9 (10%) and severe in one (1%). The mean $\pm$ SD of blood white cell count were $3.4 \pm 1.0 \times 10^9/\text{L}$ and for serum CRP $1.4 \pm 1.2 \text{ mg/L}$.

Forty children (1.3%) required admission to PICU: 25 (63%) required continuous positive airway pressure, mechanical ventilation was required in nine (22%) and six children (15%) only required additional oxygen administration. No death occurred. The mean $\pm$ SD duration of hospital stay was 4.2 ± 5.2 d (median 3, range 1 to 54 d). No thrombotic or hemorrhagic events were observed and no treatment for thrombocytosis was initiated for any of the affected children.

Analysis

Thrombocytosis occurred significantly more commonly in younger infants (mean age 4.8 mo) (Table 1). The platelet level significantly declined with advancing age (Figure 1) with a slope of -8.9 in a linear regression model ($P < 0.001$) resulting in a decrease of approximately $9 \times 10^9/\text{L}$ in the platelet count for each month of increase in age.

There was no significant difference in platelet count between genders, history of prematurity, duration of illness prior to admission, temperature on admission,

Table 1 Characteristics of 305 children admitted with bronchiolitis

	Platelet count ($\times 10^9/L$) <i>n</i> (%) or mean $\pm$ SD		<i>P</i> value
	> 500	< 500	
Children	217 (71)	88 (29)	
Age (mo)	7.3 $\pm$ 5.8	4.8 $\pm$ 4.1	< 0.001 ¹
Males	132 (74)	47 (26)	0.2 ²
Born < 38 wk gestation	32 (65)	17 (35)	0.3 ²
Duration of illness before admission (d)	2.9 $\pm$ 1.2	2.7 $\pm$ 1.4	0.3 ¹
Fever (> 38 °C) on admission	148 (73)	55 (27)	0.3 ²
Blood white cell count ($\times 10^9/L$)	3.5 $\pm$ 1.1	3.2 $\pm$ 0.5	0.8 ¹
Nasopharyngeal aspirate isolate			
RSV	189 (74)	66 (26)	
Adenovirus	13 (57)	10 (43)	
Influenza	6 (46)	7 (54)	0.09
RSV + Adenovirus	5 (62)	3 (38)	
RSV + Influenza	3 (50)	3 (50)	
Serum CRP (mg/L)	1.4 $\pm$ 1.3	1.5 $\pm$ 1.2	0.5 ¹
Duration of hospitalization (d)	4 $\pm$ 5.5	4.4 $\pm$ 4.2	0.6 ¹
Admitted to intensive care	25 (62)	15 (37)	0.2 ²

¹*t*-test; ² χ^2 test or Fisher exact test if number < 5. *n*: Number of infants; SD: Standard deviation; RSV: Respiratory syncytial virus; CRP: C-reactive protein.

blood white blood cell count or serum CRP concentration (Table 1). No association with dehydration was observed ($P = 0.06$). The severity of thrombocytosis was not significantly associated with disease severity as judged by length of hospital stay or admission to the pediatric intensive care unit (Table 2).

There was no significant difference in platelet count amongst the viruses identified in nasopharyngeal aspirates (Table 1), nor between infection with a single or more viruses (Table 3). Similarly, no significant difference in the prevalence of thrombocytosis ($P = 0.5$) was found between the children with RSV-positive infection (39%) and all those who were RSV-negative (41%).

DISCUSSION

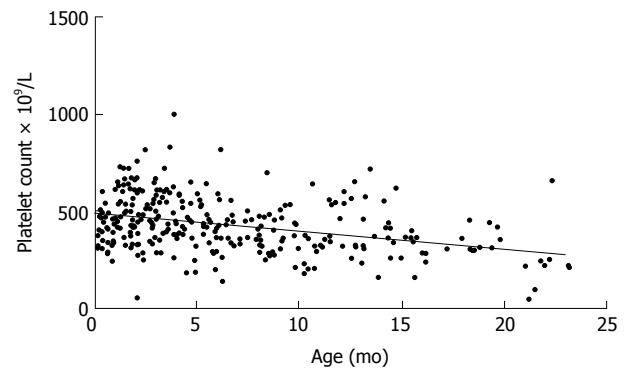
The prevalence of thrombocytosis in children under the age of two years admitted for bronchiolitis was 29% (95%CI: 24%-34%). This contrasts sharply with a reported prevalence of 8% in a previous report^[11]. The reason might be that the previous study included all respiratory infections, including measles infection, and not only bronchiolitis. In addition, as older children (up to nine years) were enrolled in that review, the lower prevalence of thrombocytosis is not surprising because it occurs less commonly in older children^[1,22,23]. Another study reported a much higher prevalence (38%) of thrombocytosis in infants with bronchiolitis, but it enrolled only infants younger than four months where thrombocytosis is more prevalent^[12]. We confirms the findings of previous reports that thrombocytosis in children with bronchiolitis is more common in the very young and declines steadily with age^[22,23].

Although it is known that reactive thrombocytosis

Table 2 Thrombocytosis (platelet count > 500 $\times 10^9/L$) and number of pathogenic viruses identified on nasopharyngeal aspirates of 305 children with bronchiolitis

No. of virus isolated	Total	Thrombocytosis <i>n</i> (%)	Odds	OR (95%CI)	<i>P</i> value
One	291	82 (28)	0.4	1.0 (reference)	0.2
Two	14	6 (43)	0.75	1.9 (0.6-5.7)	

n: Number of infants; OR: Odds ratio; CI: Confidence intervals.

**Figure 1** Platelet count by age in 305 children admitted with bronchiolitis. Linear regression coefficient = -8.9 ($P < 0.001$).

during childhood infections peaks during the second week of the illness^[24], we deliberately chose to examine the platelet count on admission because the great majority of children with bronchiolitis are likely to be asymptomatic or discharged from hospital during the second week of the infection. We found no association of thrombocytosis with the duration of illness prior to admission, perhaps because platelet counts are often higher in patients with long duration of illness prior to admission^[4] and children are usually admitted early in the course of bronchiolitis. We acknowledge, however, that firm conclusions regarding the timing of thrombocytosis in bronchiolitis cannot be drawn because only one platelet value was recorded in each patient and there were no serial measurements. Our findings corroborate previous reports, which showed that the secondary thrombocytosis is common and occurs early in RSV infection^[11].

In our study, thrombocytosis occurred less commonly in RSV infections compared to other viruses. This contrasts with the results of a previous study which found it more common in RSV infections and even suggested that thrombocytosis should be considered as an early laboratory marker of RSV infection in childhood; however it included not only bronchiolitis, but all types of respiratory infections, including measles, and also enrolled much older children, up to 9 years of age^[11,15]. Another report found a higher prevalence of thrombocytosis in RSV positive compared to RSV negative infections; however, the enrolled children were much younger, under four months of age, and no comparison with other viruses was performed^[12]. Another possible explanation for the different results obtained in our study is that, unlike viral

Table 3 Degree of thrombocytosis and outcomes in 305 children with bronchiolitis

	Thrombocytosis, <i>n</i> (%)				<i>P</i> value
	None (<i>n</i> = 217)	Mild (<i>n</i> = 78)	Moderate (<i>n</i> = 9)	Severe (<i>n</i> = 1)	
Mean (SD) duration of hospitalization in days	4.0 (5.5)	4.4 (4)	4.5 (3)	5.0 (0)	0.9 ¹
Admission to ICU	25 (11)	25 (30)	3 (33)	0 (0)	0.2 ²

¹ANOVA with Bonferroni correction for multiple comparisons; ²Fisher exact test. *n*: Number of infants; Thrombocytosis: None if platelet level < 500 × 10⁹/L; mild if 500 to 700 × 10⁹/L; moderate if 700 to ≤ 900 × 10⁹/L and severe if > 900 × 10⁹/L. ICU: Intensive care unit.

culture and polymerase chain reaction, the rapid antigen detection method that we have used does not have high sensitivity for the detection of viruses other than RSV and influenza.

Unlike earlier reports, thrombocytosis on admission was not associated with the severity of inflammation which we defined as the presence of fever, leukocytosis or elevated serum CRP level. It has already been established that, in the first week of acute infections, serum CRP, IL-6 and thrombopoietin levels start to rise while the platelet count is still normal. The platelet count peaks later, in the second and third weeks when CRP and IL-6 levels are decreasing^[8]. This, however, does not explain our findings because all admissions for bronchiolitis occurred within one week of the onset of symptoms, when fever and serum CRP are expected to be still elevated and the platelet count have not yet started to rise. The exact explanation for that discrepancy remains therefore elusive.

We did not find that disease severity, as defined by length of hospital stay or admission to the intensive care unit, was associated with the presence of thrombocytosis nor its severity. This is in contrast with a previous report that found thrombocytosis to predict mortality, but the cause for the difference is likely to be that, unlike our study in children with viral bronchiolitis, it had enrolled elderly adults with community-acquired pneumonia presumably of bacterial origin^[19].

The absence of thromboembolic or hemorrhagic complications observed in our study confirms previous reports of reactive thrombocytosis^[25,26]. In accordance with published guidelines, no treatment for thrombocytosis was initiated for any of the children in this study as none had intravascular lines, or congenital cyanotic heart disease associated with thrombosis, or medications associated with thrombocytosis, or a personal or a family history of thrombophilia^[3,27].

The study has some limitations. The bronchiolitis score was not used as an index of disease severity, nor was the platelet count measured serially throughout the stay in hospital. Similarly, cytokines and thrombopoietin measurements were not performed. These limitations should be addressed in future studies.

In conclusion, secondary thrombocytosis is common in children under two years of age admitted with bronchiolitis, affecting 29% of them. It is not associated with a severe course for bronchiolitis or with thromboembolic complications.

COMMENTS

Background

Bronchiolitis is a common viral infection in young children, usually caused by respiratory syncytial virus (RSV), influenza or adenovirus infections. Secondary or reactive thrombocytosis may occur and is considered to be an acute phase reactant response to thrombopoietin or cytokines production during the infection [interleukins (IL)-6, IL-8, IL-11]. Its prevalence in bronchiolitis may range from 8.4% to 38.6%, with higher platelet counts observed in RSV positive infections. It usually does not result in thromboembolic or hemorrhagic complications.

Research frontiers

None of the few reports of thrombocytosis in children with bronchiolitis has looked at its association with risk factors, disease severity or thromboembolic complications. The authors therefore undertook this study to ascertain the prevalence of thrombocytosis in a cohort of children with bronchiolitis admitted to a general pediatric ward and analyze the risk factors associated with it. They also looked for thromboembolic complications and analyzed if elevated platelet count was associated with, and therefore a marker of bronchiolitis severity.

Innovations and breakthroughs

In this retrospective observational study of platelet counts in 305 infants aged two years or less who were hospitalized for bronchiolitis, thrombocytosis (platelet count > 500 × 10⁹/L) was frequent, occurring in 88 (29%; 95%CI: 24%-34%), more commonly in younger infants with the platelet count declining with age. There was no significant association with the duration of illness, temperature on admission, white blood cell count, serum C-reactive protein concentration, length of hospital stay, admission to the intensive care unit, death, thrombotic or hemorrhagic complications.

Applications

Thrombocytosis is common in children under two years of age admitted with bronchiolitis. It is not associated with disease severity or thromboembolic complications.

Terminology

Thrombocytosis is defined as a platelet count of more than 500 × 10⁹/L. Counts of > 500 and ≤ 700 × 10⁹/L are considered mild thrombocytosis, levels of > 700 and ≤ 900 × 10⁹/L as moderate thrombocytosis, and levels of > 900 × 10⁹/L as severe thrombocytosis.

Peer-review

The article is well written and interesting.

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Observational Study

Decision-making patterns in managing children with suspected biliary dyskinesia

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Abstract**AIM**

To explore and to analyze the patterns in decision-making by pediatric gastroenterologists in managing a child with a suspected diagnosis of functional gallbladder disorder (FGBD).

METHODS

The questionnaire survey included a case history with right upper quadrant pain and was sent to pediatric gastroenterologists worldwide *via* an internet list server called the PEDGI Bulletin Board.

RESULTS

Differences in decision-making among respondents in managing this case were observed at each level of investigations and management. Cholecystokinin-scintigraphy scan (CCK-CS) was the most common investigation followed by an endoscopy. A proton pump inhibitor was most commonly prescribed treating the condition. The majority of respondents considered a referral for a surgical evaluation when CCK-CS showed a decreased gallbladder ejection fraction (GBEF) value with biliary-type pain during CCK injection.

CONCLUSION

CCK infusion rate in CCK-CS and GBEF cut-off limits were inconsistent throughout practices. The criteria for a referral to a surgeon were not uniform from one practitioner to another. A multidisciplinary team approach with pediatric gastroenterologists and surgeons is required guide the decision-making managing a child with suspected FGBD.

Key words: Biliary dyskinesia; Functional gallbladder disorder; Cholecystectomy; Gallbladder ejection fraction

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Core tip: Functional gallbladder disorder (FGBD) is a common motility disorder of the gallbladder that results in abdominal pain and cholecystectomy in children. The guideline for managing children with FGBD is lacking. The questionnaire survey is a pilot study performed by pediatric gastroenterologists worldwide *via* the PEDGI Bulletin Board. Differences in decision-making among respondents in managing this case were observed at each level of investigations and management. Since, a different risk-benefit ratio should be considered in children with suspected FGBD. The authors include an algorithm for the approach in managing children with suspected FGBD based on literature review.

Nakayuenyongsuk W, Choudry H, Yeung KA, Karnsakul W. Decision-making patterns in managing children with suspected biliary dyskinesia. *World J Clin Pediatr* 2017; 6(2): 124-131 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i2/124.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i2.124>

INTRODUCTION

Functional gallbladder disorder (FGBD) is a motility disorder of the gallbladder that results in decreased contractility of the gallbladder and colicky pain in the epigastrium and/or the right upper quadrant of the abdomen (RUQ). FGBD was previously called chronic acalculous cholecystitis, acalculous cholecystitis, or biliary dyskinesia and is a diagnosis of exclusion. Therefore further investigations are routinely performed to exclude other hepatobiliary or gastrointestinal diseases. Experts' consensus developed the Rome III criteria in 2006^[1] to help guide the management of FGBD. A child who is suspected to have FGBD must experience recurrent episodes of the abdominal pain which last longer than 30 min without relief after bowel movements, postural changes or antacids. The child must have normal liver enzymes, conjugated bilirubin, and amylase/lipase. In addition, the gallbladder must be present and other structural diseases must be excluded. Supportive criteria include the presence of nausea and vomiting, classic biliary pain at RUQ that radiates to the back and/or right infra subscapular region, and pain disturbing sleep^[1].

The cholecystokinin-scintigraphy scan (CCK-CS) is generally recommended as a part of the diagnosis for FGBD. The test reports a cut-off value of a gallbladder ejection fraction (GBEF) The cut-off limits that are < 40% suggest the diagnosis of FGBD. FGBD is frequently diagnosed in children with an increase in the number of cholecystectomies performed over the past two decades^[2-8]. Several children with a diagnosis of FGBD, however, did not improve their pain symptoms after cholecystectomy^[2-8]. The study involves a questionnaire based survey delivered to pediatric gastroenterologist members *via* the PEDGI Bulletin Board, the internet list server. The objective of the study was to explore and

to analyze the patterns in decision-making by pediatric gastroenterologists in managing a child with a suspected diagnosis of FGBD.

MATERIALS AND METHODS

This is a questionnaire-based survey distributed to the PEDGI Bulletin Board accessible by hundreds of pediatric gastroenterologists worldwide. The PEDGI Bulletin Board is the internet list server that encourages pediatric gastroenterologists and hepatologists worldwide to communicate with one another electronically. This study was approved by the Institutional Review Board of Johns Hopkins School of Medicine. At the beginning of the questionnaire introduced to the GI bulletin board, only practicing pediatric gastroenterologists (not trainees) were requested and consented themselves to perform the questionnaire. The survey data were collected from the participating PEDGI Bulletin Board users who used the network from January 2011 to April 2011. The survey was completed and analyzed using an Internet-based questionnaire (SurveyMonkey.com, Portland, Oregon, United States). The questionnaire was designed to have participants complete within 10 min.

The survey includes a case history with right upper quadrant pain in Figure 1. The questionnaire consists of 7 questions (Q1-7) in order to observe the patterns of decision-making in managing the case (Figure 1). Q1 gives a direction at the initial step whether the patient should have a test or a medical or surgical treatment performed first. Q2-3 is specifically addressed to the types and the duration of such medical treatments. Q4 is related to the decision-making patterns in investigations. Q5-7 is for their criteria for the CCK-CS and GBEF cut-off limits in diagnosing FGBD and the surgical treatment of FGBD.

RESULTS

The questionnaire survey consisted of 7 questions. One hundred pediatric gastroenterologists participated in the questionnaire study. Of these 100 respondents, 99 completed all questions in the survey, and 71 informed the location of their practices (60 in the United States and 11 from non-United States countries). For Q1 and 2, 19 respondents (19%) decided to treat the abdominal pain with the medical treatment first. Of these 19 respondents, 13 (68.4%) selected proton pump inhibitors (PPI), 8 (42.1%) for antispasmodics, 1 (5.3%) for acetaminophen, 2 for histamine 2 receptor antagonists, 1 for probiotic, 1 for ciproheptadine as their choices of the treatment. In Q3, 17 respondents answered the duration of such a medical treatment. Interestingly, 2 respondents in Q1 referred the patient to a surgeon without further investigations or a treatment trial.

Figure 2 demonstrated the patterns in decision-making of the ordered investigations (Q4). CCK-CS (67.7%) and an upper endoscopy (52.9%) were the most

A 10-year-old girl with recurrent abdominal pain at right upper quadrant for 3 mo is referred to your office by a pediatrician. The pain is described as severe during the episodes, not relieved by bowel movement, postural changes, antacids, typically follows a meal, often lasts 30 min or longer, and radiates to the shoulder and under the tip of the right scapula. Physical exam in general is within normal limits, negative tenderness and negative for Murphy's sign. She has normal CBC with differential count, comprehensive metabolic panel, and stool guaiac is negative from rectal exam. Abdominal ultrasound is completely negative by all systems.

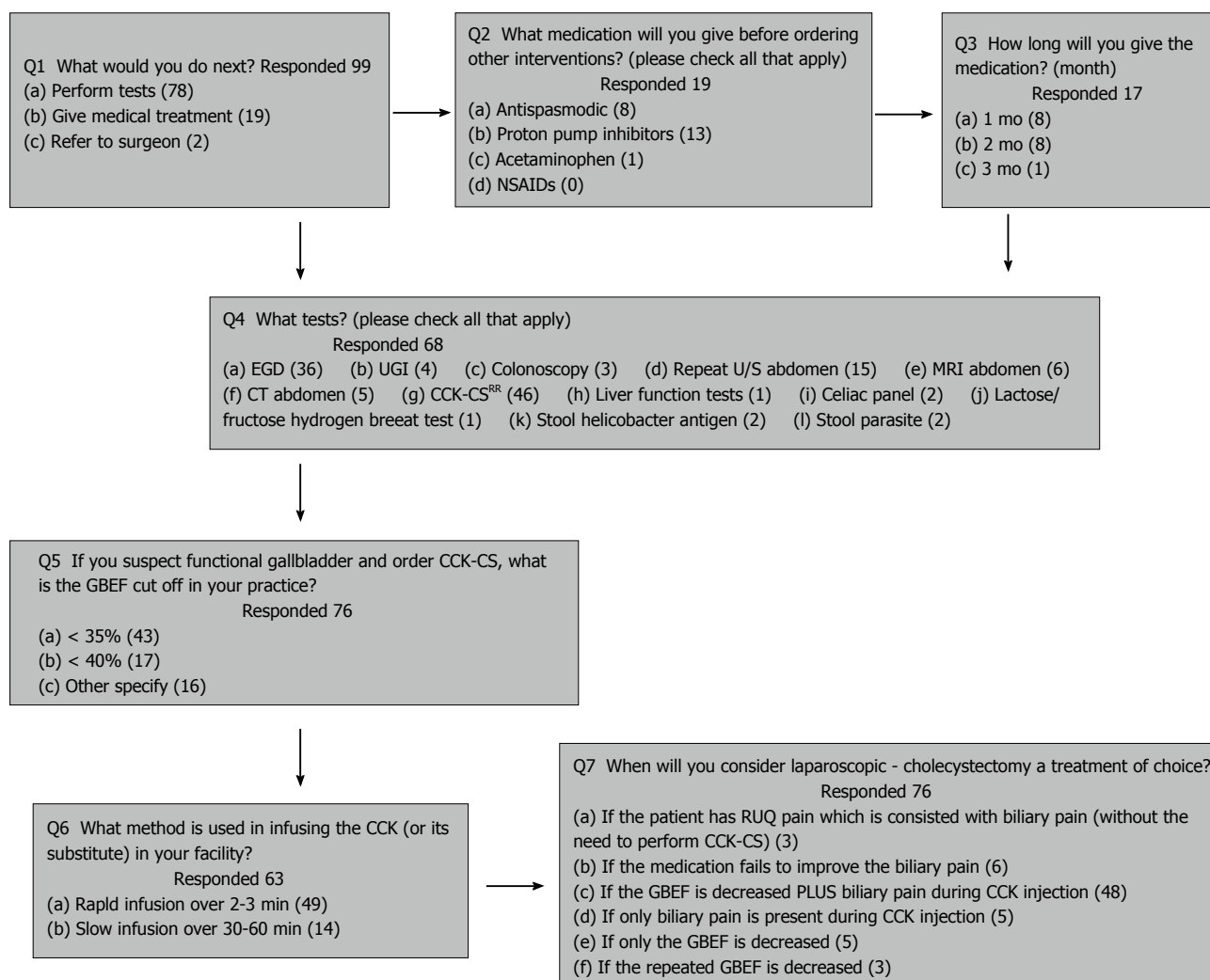


Figure 1 Questionnaire for pediatric gastroenterologists to assess a case with chronic right upper quadrant pain. EGD: Esophagogastroduodenoscopy; UGI: Upper gastrointestinal; U/S: Ultrasonography; MRI: Magnetic resonance imaging; CCK-CS: Cholecystokininscintigraphy scan; GBEF: Gallbladder rejection fraction; RUQ: Right upper quadrant; NSAIDs: Nonsteroidal anti-inflammatory drugs.

commonly ordered tests. Q5-7 indicated the techniques used for CCK-CS and the criteria of GBEF cut-off limits used to diagnose FGBD and to refer to a surgeon for an evaluation for cholecystectomy at their institutions. Seventy-six respondents responded to Q6 and different GBEF cutoff limits were used, < 35% in 43 respondents (56.6%), < 40% in 17 respondents (22.4%), < 30% in 3 respondents, < 25% in 3 respondents, < 20% in one respondent, and < 15% in one respondent (Table 1). Four respondents did not know the GBEF cutoff limits at their institutions. Three respondents decided not to order or to avoid ordering the test, and one respondent did not have the test available at the institution.

Sixty-three respondents responded to Q6. While 49 respondents (77.8%) selected CCK-CS with the rapid infusion of CCK over 2-3 min as the technique used

at their institutions, 14 (22.2%) chose the CCK-CS technique with the slow infusion over 30-60 min. For Q7, the majority of respondents (64%) responded by referring the patient to a surgeon with the criteria when both the GBEF value was abnormal and similar types of abdominal pain was reproduced during the infusion of CCK (Figure 3).

DISCUSSION

Several GI diseases and biliary disorders share a similar type of abdominal pain. The presentation of this clinical vignette described in the questionnaire is consistent with FGBD defined by the ROME III criteria when all known causes of epigastric and/or RUQ pain are excluded^[1]. The patterns in decision-making in managing the case

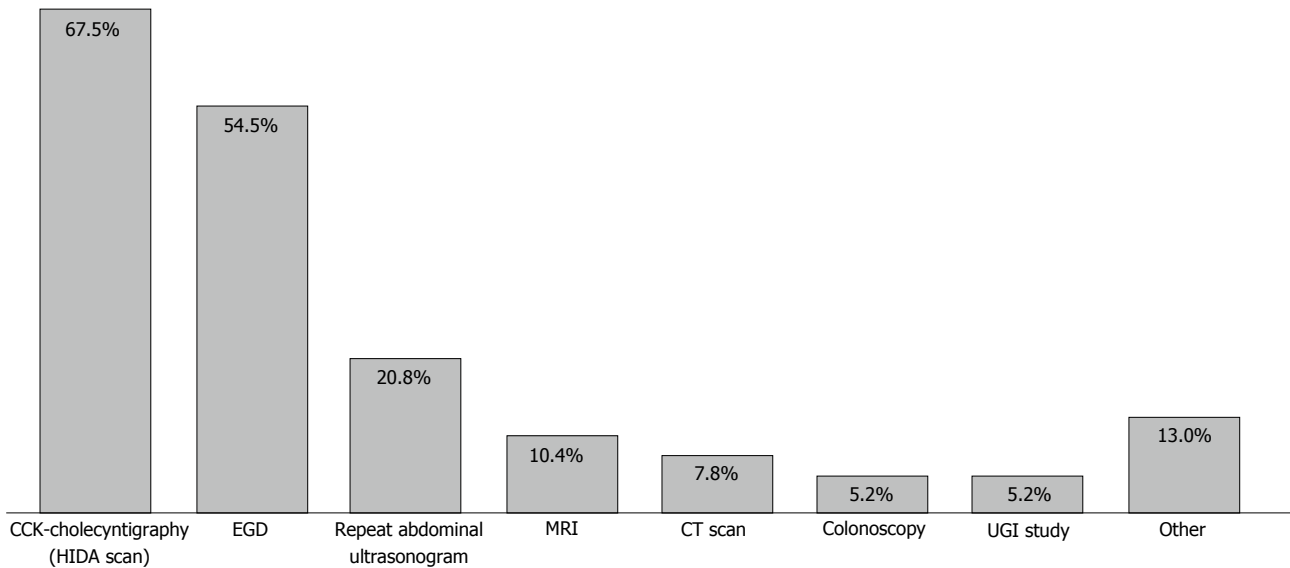


Figure 2 Investigations for chronic right upper quadrant pain in children. CCK: Cholecystokinin; EGD: Esophagogastroduodenoscopy; MRI: Magnetic resonance imaging; CT: Computed tomography; UGI: Upper gastrointestinal; HIDA: Hepatobiliary iminodiacetic acid.

- If GBEF is decreased + biliary pain during CCK injection
- If only GBEF is decreased
- If medication fail to improve the biliary pain
- If only biliary pain is present during CCK injection
- If the patient has RUQ pain which is consistent with biliary pain without the need to perform CCK-CS
- If the repeated GBEF is decreased

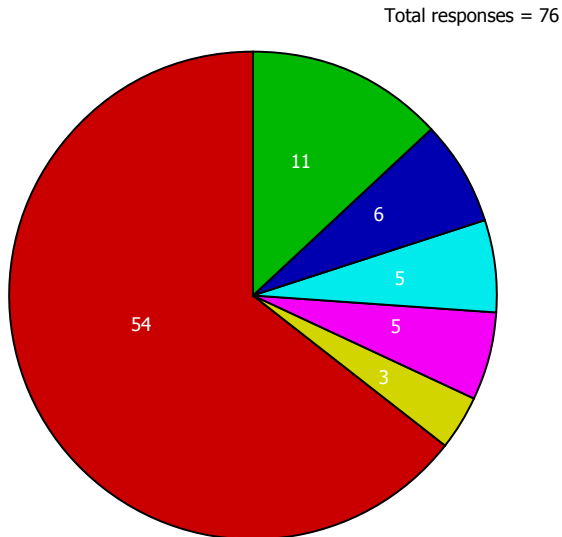


Figure 3 Criteria for referral for a surgical evaluation. GBEF: Gallbladder ejection fraction; CCK: Cholecystokinin; RUQ: Right upper quadrant; CCK-CS: Cholecystokinin scintigraphy scan.

throughout the questionnaire were quite heterogeneous. Interestingly, 2 respondents in Q1 referred the patient to a surgeon without investigations or any treatment trial. Our questionnaire survey demonstrated that only 19% of respondents prescribed PPI or histamine 2 antagonists as the first-line management before performing the tests. This is contrary to other studies which have documented that it is a common practice to empirically treat gastro-

Table 1 Cut-off limits of gallbladder ejection fraction used for criteria to diagnose abnormal gallbladder function

% GBEF used as cut-off	Responses ¹
< 40%	17 (20)
< 35%	47 (55)
< 30%	3 (3.5)
< 25%	4 (4.7)
< 16%	2 (2.4)
< 15%	2 (2.4)

¹Number of responses for each gallbladder ejection fraction cutoff.

esophageal reflux disease (GERD) and acid peptic disease prior to extensive investigations in such a case when FGBD is suspected^[1,9]. Few case reports described children with the diagnosis of FGBD who had a complete relief from the abdominal pain when a PPI was used^[10,11].

Further investigations were preferred in the majority of the respondents. It is generally recommended that hepatic function panel (AST, ALT, serum total and direct bilirubin, alkaline phosphatase) amylase/lipase, and an abdominal ultrasound be performed first to exclude hepatobiliary and pancreatic disorders^[12,13]. Since these tests were already ordered and reported as normal in the clinical vignette, CCK-CS and an upper endoscopy were observed to be the most common tests chosen by respondents. Biopsies of the proximal GI tract are generally considered even in the absence of gross endoscopic findings as microscopic endoscopic findings may reveal features of eosinophilic gastritis, GERD, *Helicobacter pylori* (*H. pylori*) infection, Crohn's disease, and villus atrophy in those who were also diagnosed with FGBD^[10,14,15] to look for mucosal disease that might explain symptoms or improve symptoms when treated. For example, Tutel'ian *et al*^[16] reported chronic atrophic gastritis from *H. pylori* infection in patients who were

diagnosed with FGBD prior to the endoscopy. A series of children with FGBD were later diagnosed with Crohn's disease, hiatal hernia, and cyclic vomiting^[16], and with esophagitis, *H. pylori* infection and duodenitis after cholecystectomy^[17]. Children with functional constipation had a significant impairment of the gallbladder motility^[18]. Colonoscopy is usually not required in the absence of lower abdominal pain, chronic diarrhea, or hematochezia^[14,15]. As such, an upper endoscopy is recommended to exclude any possible GI diseases which can cause epigastric and/or RUQ pain before a referral to a surgeon for cholecystectomy.

Currently there is no definite guideline in the pediatric practice regarding the appropriate technique performed for the CCK infusion rate and the GBEF cut-off limit in performing a CCK-CS study. The diversity of the techniques used for CCK-CS was observed not only from the questionnaire responses, but experts' consensus such as ROME III committee and the Gastrointestinal Council of the Society of Nuclear Medicine. This 3-min rapid CCK infusion and the GBEF cut off limit of < 35% were most common choices in Q5 and Q6, respectively. This rapid infusion technique in theory can cause a severe degree of abdominal pain and nausea in even a healthy subject. This is explained by the fact that CCK slows down the gastric emptying^[19,20]. According to the ROME III criteria a continuous intravenous CCK infusion over a 30-min period is preferred^[1]. On the contrary, the new guidelines from the Gastrointestinal Council of the Society of Nuclear Medicine recommend the slow infusion rate of the CCK over 60 min as the standard test in adults since this technique generates a physiologic response for contraction of the gallbladder and discourage the evidence of the reproducible pain after the CCK injection during CCK-CS^[19,21].

Table 1 demonstrates the difference in the GBEF cut-off limits used as the criteria to guide the management for the questionnaire respondents. The GBEF cut-off limits vary from 15%-40% in the reported literature depending on the CCK-CS techniques^[22]. When GBEF cut-off limit < 35% was used as an indication for the surgery, the resolution of symptoms was more frequently observed after cholecystectomy in several studies^[23]. The cut-off limit of < 15%, however, was a better predictor for a successful outcome after cholecystectomy with negative predictive value of 85%^[8]. A CCK provocation test is even a better predictor for the resolution of symptoms than using GBEF cut-off limits alone after cholecystectomy^[24]. Reproducible symptoms during the CCK stimulation predicted a symptom relief after cholecystectomy^[25,26]. Lyons *et al*^[27] reported that 44 children with a stringent GBEF cut-off limit at < 11% had the resolution of symptoms after cholecystectomy. However, there was no observed correlation between with GBEF and the presence of gallbladder pathology such as cholecystitis, cholelithiasis, or cholesterosis^[28]. Interestingly Mahida *et al*^[29]

reported symptom improvement by 82% of 153 children with FGBD undergoing cholecystectomy regardless of their GBEF values. The number of children undergoing cholecystectomy has increased in the past decade^[30]. Despite the safety of laparoscopic cholecystectomy in children, a different risk-benefit ratio should be considered in children with suspected FGBD^[31]. Figure 4 demonstrates the algorithm for the best practice management approach in children with suspected FGBD based on our literature review.

There are several limitations in the present study. The sample size was small. Since the survey was voluntary, the respondents were able to withdraw the participation of the questionnaire at any time. Although almost all respondents (99%) responded to Q1, the ambiguity of the question may attribute to the lower response rates in the subsequent questions. FGBD may not be the condition that respondents regularly treat and, therefore, up to one-third of respondents skipped questions without explanations or comments. For Q5-6, the information on the techniques and the cut-off limits of the CCK-CS used at their institutions may not have been available at the time they performed the questionnaire survey.

In our opinion, none of these diagnostic modalities are absolute for the diagnosis of FGBD. Ultimately the decision making for cholecystectomy should be individualized as some patients suffer from severe abdominal pain despite aggressive pain management (Figure 4). As many children who are diagnosed with FGBD may experience recurrent symptoms even after cholecystectomy, they often follow-up with pediatric gastroenterologists or pediatricians and do not have a follow-up with the surgeons who operate them. Therefore, we recommend them to continue to follow-up with both pediatric gastroenterologists and surgeons as a team approach that if no recurrent symptoms are observed within a year after cholecystectomy, the diagnosis of FDGB is confirmed.

The diversity in decision-making among pediatric gastroenterologist respondents in managing the child in this clinical vignette was observed at each step in the questionnaire. A decision for the referral for cholecystectomy should be carefully considered on an individual case basis. The consensus for the guideline in managing children with FGBD may require a team effort among pediatric gastroenterologists, nuclear medicine radiologists, and pediatric surgeons. A multicenter clinical trial study may be necessary to collect longitudinal data in children diagnosed with FGBD. This collaboration will likely shed light on the natural history and the outcome of FGBD in children.

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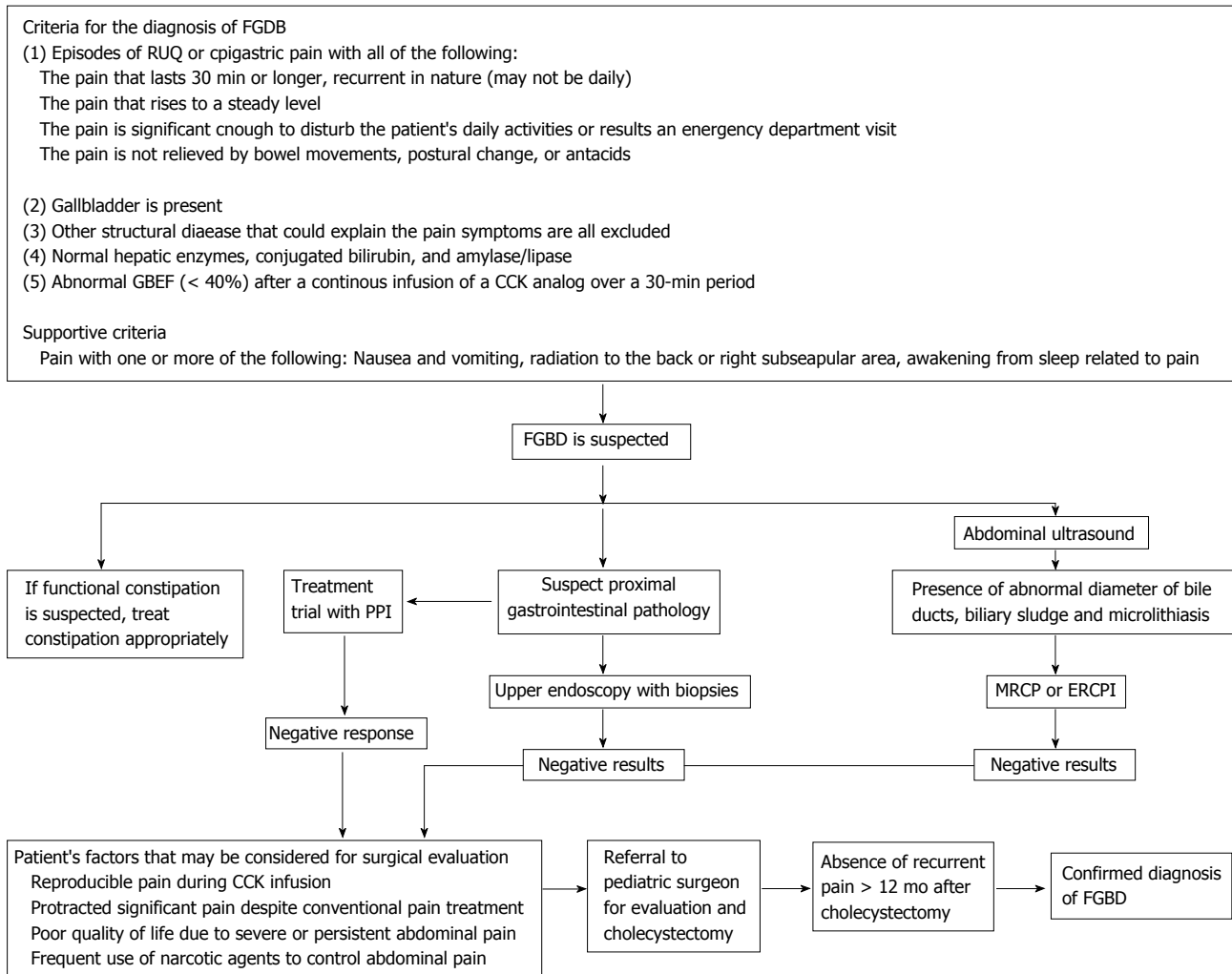


Figure 4 Algorithm for the best practice management approach in children with suspected functional gallbladder disorder (Ref. [1]). FGBD: Functional gallbladder disorder; RUQ: Right upper quadrant; GBEF: Gall bladder ejection fraction; CCK: Cholecystokinin; GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

COMMENTS

Background

The rates of cholecystectomy are rising in children with biliary dyskinesia or functional gallbladder disorder (FGBD). FGBD may be a cause of chronic abdominal pain in children and is a diagnosis of exclusion. Not all symptoms of FGBD disappeared after cholecystectomy. The cut-off limits of a gallbladder ejection fraction of the cholecystokinin-scintigraphy scan (CCK-CS) are the key to the diagnosis and the treatment of FGBD. This raises the issue of the accurate interpretation of the test and a thorough investigation to exclude other diseases which have symptoms like FGBD. The study was to explore discrepancy of decision making in managing a case, a scenario of which is consistent with FGBD.

Research frontiers

FGBD is one of the challenging fields in pediatrics. Symptoms overlap with other gastrointestinal disorders such as functional dyspepsia. Limited knowledge in this field of FGBD in children is currently observed in the current medical literature for interpretation of safety and efficacy of the investigations and treatment. There is a need for consensus on symptoms defining and a test diagnosing FGBD. Children with suspected FGBD requires a team approach with primary care physicians, pediatric gastroenterologists and pediatric surgeons. A multicenter randomized controlled trial study comparing medical vs surgical management will shed more light to understand the natural history of FGBD. There are several limitations in the present study. The sample size

was small. Since the survey was voluntary, the respondents were able to withdraw the participation of the questionnaire at any time. Although almost all respondents (99%) responded to Q1, the ambiguity of the question may attribute to the lower response rates in the subsequent questions. FGBD may not be the condition that respondents regularly treat and, therefore, up to one-third of respondents skipped questions without explanations or comments. For Q5-6, the information on the techniques and the cut-off limits of the CCK-CS used at their institutions may not have been available at the time they performed the questionnaire survey.

Innovations and breakthroughs

This is a pilot study using questionnaire-based survey distributed to the PEDGI Bulletin Board accessible by hundreds of pediatric gastroenterologists worldwide. The PEDGI Bulletin Board is the internet list server that encourages pediatric gastroenterologists and hepatologists worldwide to communicate with one another electronically. FGBD is a rare disease in children. A multicenter randomized controlled trial study comparing medical vs surgical management is possible and feasible through the collaborations of a broader network among primary care physicians, pediatric gastroenterologists and pediatric surgeons.

Applications

Based on the result from this study, there was diversity in decision-making among pediatric gastroenterologist respondents in managing the child in this clinical vignette was observed at each step in the questionnaire. A decision for the referral for cholecystectomy should be carefully considered on an individual

case basis.

Terminology

Other terminologies that may be used to describe FGBD include biliary dyskinesia or acalculous cholecystitis.

Peer-review

The authors have nicely summarized the problems clinicians face with the diagnosis and treatment of Functional Gallbladder Disorder. They have also proposed a guideline to help clinicians manage this condition. The publication will aid clinicians in their practice and hence should proceed. It does require minor revisions as it needs to be highlighted that cholecystectomy is ultimately a decision that needs to be made after thorough counseling of the family by the pediatric surgeon.

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Role of vitamin D in cystic fibrosis and non-cystic fibrosis bronchiectasis

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(CF) related or CF unrelated (non-CF); the latter is not considered an orphan disease any more, even in developed countries. Irrespective of the underlying etiology, bronchiectasis is the result of interaction between host, pathogens, and environment. Vitamin D is known to be involved in a wide spectrum of significant immunomodulatory effects such as down-regulation of pro-inflammatory cytokines and chemokines. Respiratory epithelial cells constitutively express 1α -hydroxylase leading to the local transformation of the inactive 25(OH)-vitamin D to the active $1,25(\text{OH})_2$ -vitamin D. The latter through its autocrine and paracrine functions up-regulates vitamin D dependent genes with important consequences in the local immunity of lungs. Despite the scarcity of direct evidence on the involvement of vitamin D deficiency states in the development of bronchiectasis in either CF or non-CF patients, it is reasonable to postulate that vitamin D may play some role in the pathogenesis of lung diseases and especially bronchiectasis. The potential contribution of vitamin D deficiency in the process of bronchiectasis is of particular clinical importance, taking into consideration the increasing prevalence of vitamin D deficiency worldwide and the significant morbidity of bronchiectasis. Given the well-established association of vitamin D deficiency with increased inflammation, and the indicative evidence for harmful consequences in lungs, it is intriguing to speculate that the administration of vitamin D supplementation could be a reasonable and cost effective supplementary therapeutic approach for children with non-CF bronchiectasis. Regarding CF patients, maybe in the future as more data become available, we have to re-evaluate our policy on the most appropriate dosage scheme for vitamin D.

Key words: Vitamin D; Bronchiectasis; Cystic fibrosis; Vitamin D supplementation

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Core tip: Vitamin D deficiency seems to be associated with respiratory health. Herein, we present the experimental and epidemiological data that imply a role of vitamin D

Abstract

Bronchiectasis is usually classified as cystic fibrosis

deficiency in the development of cystic fibrosis (CF) and non-CF bronchiectasis. Numerous experimental data provide insight to the mechanism by which vitamin D modulates immunity, and therefore its deficiency may enhance the susceptibility to infectious diseases and affect the control of inflammation process. Epidemiological data provide evidence for the association of vitamin D deficiency and bronchiectasis, either directly or indirectly, through its relation with the risk for respiratory tract infections. This knowledge is of interest for the pediatrician as vitamin D supplementation may be a future candidate therapeutic option for bronchiectasis.

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INTRODUCTION

In 1922, vitamin D was identified as a nutrient, derived from cod, shark and burbot liver oil, which promoted calcium deposition in the bones of rachitic rats^[1]. In 1925, it was found that vitamin D is mainly synthesized in the skin by the transformation of 7-dehydrocholesterol upon exposure to sunlight^[2,3]. Nowadays, it is well known that the main source of vitamin D is the skin through the transformation of its precursor, 7-dehydrocholesterol by ultraviolet B radiation. Only tiny amounts are ingested from the usual diet, with the exception of fish oil and dairy products fortified with vitamin D.

Vitamin D is hydroxylated in the liver by mitochondrial 25-hydroxylase enzyme to 25(OH) vitamin D [25(OH)D, calcidiol], and then an amount of this compound undergoes a further conversion to 1,25(OH)₂ vitamin D [1,25(OH)₂D, calcitriol] by the kidney enzyme 25-hydroxyvitamin D-1- α hydroxylase (1 α -hydroxylase). The latter is encoded by the gene *CYP27B1*^[4]. Additionally, the mitochondrial enzyme 25-hydroxyvitamin D-24 hydroxylase produces the inactive forms 24,25(OH)₂D and 1,24,25(OH)₃D using as substrates the 25(OH)D and 1,25(OH)₂D, respectively^[5,6].

1,25(OH)₂D and 25(OH)D are the most biologically active and the major circulating forms of vitamin D, respectively^[7,8]. The relatively stable metabolite 25(OH)D and, to some extent, 1,25(OH)₂D are bound to the vitamin D binding protein (VDBP)^[9]. In total, 99% of circulating vitamin D compounds are bound either to the VDBP or, to a lesser degree, to albumin and lipoproteins^[10].

The serum levels of the 25(OH)D reflect the vitamin's body stores are used to determine its status^[11]. Calcitriol is not an adequate status indicator as it has short half life and its synthesis depends mainly on homeostatic regulation mechanisms and not on 25(OH)D levels^[12,13]. The deficiency and insufficiency status of vitamin D are

generally defined by 25(OH)D serum levels < 20 ng/mL and 20-30 ng/mL, respectively^[14]. Using these definitions it has been estimated that about 1 billion people worldwide have either vitamin D deficiency or insufficiency, with children and adolescents being at high risk for vitamin D deficiency^[15]. However, the definition of the different states of vitamin D status is not unambiguous and it remains a matter of debate among scientists.

To date, calcitriol is considered a hormone with endocrine actions that are not limited to calcium and phosphorus homeostasis and bone turnover, as it was initially thought. For the exertion of most of its biological actions calcitriol, interacts with the nuclear vitamin D receptor (VDR) which belongs to the superfamily of nuclear receptors for steroid hormones^[10]. As early as 1979, it was shown in a rat model that receptors of calcitriol exist in target tissues that were not known to participate in vitamin D metabolism until then^[16]. The first time the extra-skeletal effects of vitamin D were observed was in early 80's, with the reports of differentiation-inducing effect of 1,25(OH)₂D₃ in mouse leukemia and human myeloid leukemia cells^[17,18]. Thus far, it is recognized that VDRs are present in several (but not in all) tissues throughout the body such as skin, placenta, pancreas, breast, prostate, and immunity cells^[7,19]. Additionally, it was shown that 1,25(OH)₂D can also be produced extrarenally as 1 α -hydroxylase has been isolated in different tissues and cells such as prostate, breast, colon, lung, skin, pancreatic β cells, immune cells (including alveolar macrophages, dendritic cells and lymphocytes), and airway epithelia^[10,20]. Extrarenally produced 1,25(OH)₂D has autocrine and paracrine functions inhibiting cell proliferation, promoting cell differentiation, regulating apoptosis and modulating immune responses^[10].

Since the discovery that VDRs, and 1 α -hydroxylase are present in several tissues and in different types of cells, several research efforts, either experimental or epidemiological, have been performed aiming to understand the biological significance of these findings. There is now a growing body of evidence suggesting that vitamin D may have a role in the evolvement of different diseases such as malignant, autoimmune, infectious, cardiovascular, and lung disorders^[21]. More specifically, it seems that vitamin D through the modulation of immune and inflammatory responses may be involved in the pathophysiology of several respiratory disorders such as asthma, cystic fibrosis (CF), chronic obstructive lung diseases, cancer, respiratory infections, interstitial lung diseases and bronchiectasis^[12,22-26]. Respiratory epithelial cells constitutively express 1 α -hydroxylase leading to the local transformation of the inactive 25(OH)D to the active 1,25(OH)₂D^[27]. This active form of vitamin D exerts its autocrine/paracrine function upregulating vitamin D dependent genes with important consequences in the local immunity of lungs^[27]. It is reasonable therefore to postulate that vitamin D may play some role in the pathogenesis of lung diseases and especially bronchiectasis.

The aim of the current review is to present the existing scientific information on the possible association of vitamin D with bronchiectasis, related or not to CF. The potential contribution of vitamin D deficiency in the process of bronchiectasis is of particular clinical importance, taking into consideration the increasing prevalence of vitamin D deficiency worldwide and the significant morbidity of bronchiectasis, especially among children of socially disadvantaged populations^[28].

BRONCHIECTASIS

Non-CF bronchiectasis

Bronchiectasis is a word of Greek origin and means dilated bronchi. This condition was first described in pathological specimens in 1819 by Rene Laennec, who also invented the stethoscope^[29]. The term was used to describe dilated and inflamed bronchi according to the pathological findings^[30].

Thirty years ago, bronchiectasis in children was considered an orphan disease^[31]. Since then, and especially after bronchography was superseded by high resolution computed tomographic scanning (HRCT) as the most commonly used technique for diagnosis, it has been recognized that the burden of bronchiectasis in childhood is low but not negligible^[31]. However, the etiology is now different from that noted in the 50's when symptoms of bronchiectasis usually started after pertussis or measles^[32]. Bronchiectasis nowadays is classified as either related or unrelated to CF, with the latter defined as non-CF bronchiectasis. The etiology of non-CF pediatric bronchiectasis is only remotely associated with vaccine preventable diseases such as measles or pertussis. There are several original studies and reviews in the literature that discuss the etiology of pediatric non-CF bronchiectasis. A recent systematic review of 989 affected subjects from twelve relevant studies summarized the available information of cases diagnosed by chest computed tomography. Infectious diseases, such as pneumonia, measles, tuberculosis, varicella, accounted for 19% of non-CF pediatric bronchiectasis followed by primary immunodeficiency (17%), aspiration/foreign body (10%), and primary ciliary dyskinesia (7%). No causal association was identified in about a third of cases^[33].

In the guidelines published by the Thoracic Society of Australia and New Zealand, the prerequisites for clinical suspicion of the syndrome in children is: (1) persistent wet cough not responding to four weeks of antibiotics; (2) more than three episodes of wet cough per year responding to antibiotics and lasting more than four weeks; or (3) a persisting for more than six weeks chest radiograph abnormality despite the appropriate treatment^[34].

As it has already been mentioned, HRCT is now the gold standard for the diagnosis of bronchiectasis^[33,34]. As it was shown by Grenier *et al*^[35] in an adult population, using as diagnostic standard the bronchographic findings, HRCTs with 1.5 mm section thickness at 10

mm intersection spacing, attained a sensitivity of 96% and specificity of 93% regarding the detection of bronchiectasis. Eastham *et al*^[36] studied retrospectively 93 children with HRCT confirmed bronchiectasis and found that they constituted 9.6% of all new referrals to their tertiary pediatric respiratory center; this number represented a 10-fold higher rate of the respective diagnosis prior to the introduction of HRCT scanning^[37]. It is therefore plausible to assume that the introduction of HRCT scanning has contributed significantly to the recognition of the true burden of bronchiectasis in childhood. Furthermore, Eastham *et al*^[36] showed that HRCT diagnosed bronchiectasis in children is not always irreversible; it may progress to established bronchiectasis, but it may also return to a pre-bronchiectatic stage, or even resolve entirely. It is therefore conceivable that the early recognition of bronchiectasis and the prompt initiation of the appropriate treatment are of great importance in order to prevent the establishment of irreversible lesions.

CF bronchiectasis

Cystic fibrosis is the most common lethal, autosomal recessive disorder, among Caucasians. It is due to mutations in a gene called cystic fibrosis transmembrane conductance regulator (CFTR) that encodes chloride channels called CFTR proteins; bronchial epithelial cells, express CFTR proteins in their apical membranes^[38]. Pathologic CFTR mutations impair the production of the corresponding protein and therefore, there is dysregulation of ion movement in the bronchial surface, excessive absorption of airway surface liquid, and dehydration and hyperviscosity of airway secretions. The latter remain stagnant, form mucus plugs and obstruct bronchial lumen. The ensuing defective mucociliary clearance favours the intraluminal survival and proliferation of bacteria, and leads in chronic endobronchial infection^[39-41]. Chronic infection induces a persistent and intense inflammatory response in the airways characterized by abundance of neutrophils. The main proinflammatory mediators involved in the recruitment of neutrophils are interleukin (IL)-1 β , tumour necrosis factor α , leukotriene β 4, and especially some cytokines of the CXC chemokine family, particularly CXCL8 (also known as IL-8)^[42]. Neutrophils generate cytokines, oxidants and proteases, such as neutrophilic elastase. The produced proteases are so abundant that overpower the antiprotease protection of the lung^[40,43,44]. However, despite extensive mobilization of the lung's defensive mechanisms, infection cannot be eradicated from the airways. On the contrary, it persists and deteriorates progressively, leading to worsening of chronic inflammation, further impairment of mucociliary clearance, and permanent presence of bacteria growing in biofilm structures. Collectively, these events represent a vicious cycle that results in progressive destruction of the airways and will eventually lead to bronchiectasis and respiratory failure. In addition to the above described sequence of detrimental events there is also evidence

suggesting that mutations of the *CFTR* gene, can have a direct deleterious impact on airway immunity, through dysregulation of inflammatory mediators production, ineffective airway inflammation, and modification of responses to pathogens^[40,45].

Common features between CF and non-CF bronchiectasis and a possible role for vitamin D in disease pathogenesis

Irrespective of its underlying etiology, bronchiectasis is the result of the interaction between host, pathogens and environment^[31]. Dysregulated host immune responses, airway inflammation and the presence of pathogens contribute to the pathophysiology of bronchiectasis. The current concept on the pathogenesis of bronchiectasis in children is the "vicious circle hypothesis". The vicious circle may begin with any event that impairs mucociliary clearance and permits the establishment of bacterial "colonisation" in the lower airways, and hence predisposes to biofilm formation^[46]. What it follows is a period of persistent bacterial bronchitis, which acts as the driving force for the chronic inflammation, and finally creates sufficient bronchial damage to appear as bronchiectasis on a CT scan. The initial impairment to mucociliary clearance may be due to various reasons, such as a viral lower respiratory tract infection that destroys cilia which may take many weeks before fully recover^[47], airway inflammation and mucus plugging as in asthma; dehydration of the peri-ciliary liquid and mucus as in CF; structural obstruction as in tracheomalacia and foreign body aspiration; microaspirations and impaired cough in children with serious neurological impairments; or is in itself secondary to bacterial infections in patients with significant immunodeficiencies^[48].

Vitamin D, as it was aforementioned, may have anti-infective and anti-inflammatory properties and therefore may play some role in the pathogenesis of the disease. For this reason, the host immune and inflammatory responses in CF and non-CF bronchiectasis in relation to vitamin D status, as well as its potential link with respiratory tract infections, will be presented in the following sections.

VITAMIN D AND IMMUNITY

Innate immunity

The presence of VDR in cells of the innate immune system, such as dendritic cells, peripheral blood mononuclear cells, activated T lymphocytes, and even quiescent CD4 T cells^[49,50] along with the presence in macrophages and dendritic cells of the enzymes responsible for activation and degradation of vitamin D (1 α -hydroxylase, and 25-hydroxyvitamin D-24-hydroxylase, respectively)^[51], implies that vitamin D has an active part in innate immunity. Indeed, several studies have shown that vitamin D possesses a modulatory function exerted in a number of ways, some of which will be discussed below. Antimicrobial activity of innate immunity is influenced by vitamin D through the

induction in monocytes, skin, and lung, of cathelicidin^[52,53] which is an antimicrobial peptide having a central role in host defense against bacterial infections^[54,55]. It is most likely that vitamin D inhibits the growth of bacteria in the airways through cathelicidin. It is known that the ability of CF airway epithelia to kill bacteria is impaired^[56]. The antibacterial activity of CF bronchial cells against *Pseudomonas aeruginosa* can be partially restored through cathelicidin induction after treatment with 1,25(OH) $_2$ D^[57,58]. Besides, cathelicidin expression in the airways is associated with local - but not serum - levels of vitamin D^[59,60], and bronchial cells with mutated *CFTR* have a decreased ability to activate vitamin D^[61]. Collectively, the above results may suggest that vitamin D up-regulates activity of cathelicidin, and perhaps of other innate immunity components, in response to bronchial bacterial infections. This up-regulation seems to be impaired in CF airways due to inadequate local activation of vitamin D.

The immune stimulus per se can affect local 25(OH) D metabolism as it is suggested by the increase in 1 α -hydroxylase mRNA expression and 1,25(OH) $_2$ D synthesis of respiratory epithelial cells, after stimulation of Toll-like receptor-3 by viral RNA^[27]. The above evidence strongly supports the hypothesis that a local pro-inflammatory microenvironment can influence vitamin's D metabolism. This fascinating phenomenon has been described in patients suffering from Crohn's disease^[62]; however, up to now, there are no studies examining the effects of chronic endobronchial infection on the local metabolism of vitamin D.

Dendritic cells have a critical role in innate immunity and can promote the differentiation of naive CD4⁺ T cells to either effector or regulatory T-cells (Treg). vitamin D can affect the stimulatory characteristics of DCs and change the balance towards the induction of CD4⁺CD25⁺Foxp3⁺ Treg. It can also enhance recruitment of Treg cells at inflammatory sites^[63]. This suppressive, anti-inflammatory function of vitamin D may contribute to the limitation of chronic bronchial inflammation and have a beneficial effect in the control of the disease.

Adaptive immunity

Vitamin D also plays a role in modifying adaptive immunity while it is not yet clear if it moves the balance towards Th1 or Th2 response. The literature has provided us with a surge of evidence, though sometimes the results are conflicting. Thus, it was demonstrated that the administration of vitamin D decreased Th1 cytokine secretion and inhibited T-cell proliferation^[64,65]. Vitamin D was also shown to either inhibit or enhance Th2 cell differentiation and production of Th2 cytokines^[66]. In another study on human cord naive CD4 and CD8 T cells it was demonstrated that vitamin D exhibits an inhibitory effect on IFN- γ production through IL-12, and it can also suppress IL-4, and IL-13 expression induced by IL-4^[67]. Matheu *et al*^[68] found that the administration of vitamin D in rodents could induce IL-4, IL-5, and IL-13. However, Jorde *et al*^[69] study on the effects of vitamin

D administration in obese humans did not corroborate the previous result. Vitamin D supplementation did not induce Th2 responses *in vivo* whereas, on the other hand, proinflammatory TH17 responses were blocked by administration of vitamin D in mice and humans^[70-72]. Regarding B cells, it is known that treatment with 1,25(OH)₂D hinders proliferation and differentiation to IgG secreting plasma cells^[73]. Although there are enough data to recognize the impact of vitamin D in adaptive immunity, the picture becomes less clear when considering the direct consequences in CF and non-CF bronchiectasis. There are only some sparse data indirectly relating the immunological effects of vitamin D with bronchiectasis. Vitamin D reduces the expression in Th17 cells of IL-17, which is a cytokine found elevated in the sputum and the lungs of CF patients^[74,75]. *Aspergillus fumigatus*, has been implicated as a common cause of both CF and non-CF bronchiectasis^[76]. Recently, it was shown that CF patients with allergic bronchopulmonary aspergillosis (ABPA) had increased Th2 reactivity, and this was associated with lower serum vitamin D levels. When 1,25(OH)₂D was added to CD4⁺ T cells isolated from these patients, the induction of IL-5 and IL-13 by *Aspergillus* decreased and Th2 responses of CD4⁺ T cells were reduced^[71]. *Aspergillus*-induced lung inflammation in CF was further studied by Coughlan *et al.*^[77] who demonstrated that *Aspergillus* bronchial colonization can increase Th2 cytokine production, through down-regulation of VDR expression. This down-regulation could be reversed with itraconazole treatment of *Aspergillus*^[77]. The authors suggested that supplementation of vitamin D could probably have a useful therapeutic effect in preventing ABPA on condition that there would be concurrent elimination of *Aspergillus* to permit VDR expression.

INDIRECT EVIDENCE IMPLYING A ROLE OF VITAMIN D IN THE PATHOGENESIS OF BRONCHIECTASIS

Relation between vitamin D and lung disease:

Experimental and epidemiological data

Despite the knowledge gained over the years on the role of vitamin D in musculoskeletal system, the existing evidence over its effects in the pathogenesis and outcome of CF and non-CF bronchiectasis is sparse. There are some interesting data however implying a pathogenetic role of vitamin D insufficiency in the induction of damage in lung tissue.

The main reasoning behind this hypothesis is that lung is deprived of the vitamin's anti-inflammatory capacity. Vitamin D down-regulates cytokines and chemokines that promote tissue destruction, and are found in abundance in CF and non-CF bronchiectatic lungs^[22,78]. It was shown that CF respiratory epithelial cells and macrophages incubated with 1,25(OH)₂D displayed a significant down-regulation in the neutrophil-attracting chemokine, IL-8^[79,80], and that high doses of

cholecalciferol (250000 IU) in adults hospitalized with pulmonary exacerbation of CF resulted in a reduction in the serum levels of IL-6 and TNF- α ^[81].

The anti-inflammatory activity of vitamin D may originate from the promotion of anti-inflammatory/regulatory cytokines secretion, such as IL-10^[82]. However, the mechanisms involved in up-regulation of anti-inflammatory and down-regulation of pro-inflammatory cytokines may not be simply due to the 1,25(OH)₂D binding to vitamin D Response Elements (VDRE), which are specific upstream sequences in gene promoters that activate gene transcription. They may also occur through other indirect modulatory routes acting through signaling proteins that control the expression of anti- and pro-inflammatory cytokines^[78].

MAPK phosphatase 1 (MKP-1), is such an example; the enzyme is an inhibitor of pro-inflammatory signaling and contains VDRE within its gene promoter. It is known to be up-regulated by either 25(OH)D or 1,25(OH)₂D, in a dose-dependent manner. 1,25(OH)₂D induces the expression of MKP-1 in human monocytes^[83]. In blood mononuclear cells isolated from asthmatic patients, baseline MKP-1 mRNA was associated with serum 25(OH)D levels. Also, in patients not treated with inhaled steroids, dexamethasone-induced MKP-1 expression increased with higher 25(OH)D levels. These results imply that local 1,25(OH)₂D production may increase MKP-1 expression^[78,84].

Other likely mechanisms implicated in cytokine suppression may include VDRE-independent inhibition of a major pro-inflammatory factor, namely nuclear-factor kappa B (NF- κ B). 1,25(OH)₂D has been associated with a significant decline in translocation of NF- κ B into the nucleus, possibly through the stimulation of I κ B- α (the inhibitor of NF- κ B) by 1,25(OH)₂D^[19,85]. 1,25(OH)₂D has been shown to modulate I κ B- α through either transcriptional or transcription-independent mechanisms, resulting in an increase of mRNA expression of I κ B- α and stabilization of I κ B- α protein^[86,87]. The above data are summarized in Table 1.

In two retrospective studies vitamin D insufficiency was found to be correlated with the severity of lung disease in CF children. Simoneau *et al.*^[88] observed that vitamin D insufficiency was associated with *Pseudomonas* bronchial infection, and McCauley *et al.* observed that 25(OH)D levels were negatively associated with the rate of pulmonary exacerbations in children, and positively with FEV1 in adolescents. The results from some studies in CF patients indicate towards an association between low 25(OH)D levels and declining lung function. However, this finding was not universal, and has not been confirmed in children^[81,89-93]. The effects of vitamin D in the lung function of adults, but not pediatric, CF patients may suggest that vitamin D deficiency exerts greater influence on CF lungs as the disease progresses^[78]. A reduction in the strength of respiratory muscles has been proposed as a likely mechanism, though there is no evidence to prove it. Furthermore, the relation might not be causal since the severity of lung disease may result

Table 1 Potential immunological functions of vitamin D involved in the pathogenesis of lung disease

Function	Affected immune responses
Direct down-regulation of pro-inflammatory cytokines	IL-8, IL-6, and TNF- α
Direct up-regulation of regulatory cytokines	IL-10
Up-regulation of MKP-1	Inhibition of MAPKs pathways (critical for the mounting of innate immune responses)
Increase production and stabilization of I κ B- α	Inhibition of NF- κ B (regulates the expression of numerous inflammatory components)

MAPK: Mitogen-activated protein kinases; IL: Interleukin; TNF: Tumor necrosis factor; MKP-1: MAPK phosphatase-1; NF- κ B: Nuclear-factor kappa B; I κ B- α : Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (the inhibitor of NF- κ B).

in the sequence of reduced physical activity, less sun exposure, and decrease in serum 25(OH)D levels.

Vitamin D and respiratory tract infection: Epidemiological studies

Bacterial bronchial infection constitutes an integral part in the pathogenesis of bronchiectasis, although it has also been suggested that resident microbiota as well as viral and other infections (mycobacteria) are among the pathogens of the vicious cycle of bronchiectasis pathophysiology^[31]. It has been well known since 1959 that the majority of children with bronchiectasis grew some pathogen in their sputum cultures. Recent bronchoalveolar lavage studies have shown that the most commonly isolated pathogens in children with non-CF bronchiectasis are non typeable *Haemophilus influenza*, *Streptococcus pneumonia*, *Moraxella catarrhalis*, and to a lesser extent *Staphylococcus aureus* and *Pseudomonas aeruginosa*^[31,36,94].

Vitamin D deficiency is related with the risk of lung infections^[95] and may be implicated in the bronchiectasis development and progression through this pathway. The first example of a possible association between vitamin D deficiency and an infectious disease was tuberculosis. It was in 1848, prior to the discovery of vitamin D, when in a study held in a London hospital, 1000 patients with tuberculosis were given either the usual care for the disease, or care plus cod liver oil three times a day. About a third of patients in the control group deteriorated or died compared to only a fifth of those on cod-liver oil^[96]. Since 1980, many studies investigated a possible association of tuberculosis and vitamin D deficiency. A meta-analysis conducted in 2008 by Nnoaham *et al.*^[97] showed that low serum vitamin D levels were associated with increased risk for active tuberculosis. Although this meta-analysis included studies with only adult subjects, it was also shown in two later studies that serum vitamin D levels were lower in children with latent or active tuberculosis compared to the non-infected controls^[98,99].

Similarly, it has been demonstrated that vitamin D deficiency is related with the risk for acute respiratory tract infection. It was in 1975 when Salimpour^[100] found that 43% of 200 rachitic children suffered from bronchopneumonia, a finding that he characterized as unexpected. Later, it was corroborated by other investigators that children with rickets were at increased

risk for developing respiratory infectious disease^[101,102]. Muher *et al.* found that, after correcting for confounders, there was a 13-fold increased incidence of rickets among Ethiopian children hospitalized with pneumonia compared to controls^[101]. The results of another study from Jordan pointed to the same direction^[102]. More specifically, 85% of the rachitic infants were admitted due to lower respiratory tract infections compared to only 30% of the control non-rachitic group. In two other studies from the Indian subcontinent it was found that serum vitamin D levels in non-rachitic children with lower respiratory tract infection were significantly lower compared to healthy controls^[103,104]. This finding, however, was not confirmed by other investigators^[105]. It is of interest however, that McNally *et al.*^[106] who found no association between 25(OH) vitamin D levels and risk of hospitalization for acute lower tract infection (bronchiolitis or pneumonia), observed that vitamin D deficiency influenced disease severity. More specifically, the children with acute lower tract infection who were eventually admitted to the pediatric intensive care unit, had significantly lower serum vitamin D levels compared to either the rest of the group with milder respiratory infection or the control group with no respiratory infection.

A systematic review of observational studies that was conducted by Jolliffe *et al.*^[95] showed that there was a significant association between low vitamin D status and the risk for acute respiratory tract infections in subjects of all ages (children and adults). On the other hand, they found that the randomized controlled clinical trials, which investigated the protective role of vitamin D supplementation from respiratory tract infections, did not point to the same direction. They attributed this inconsistency to the heterogeneity of the included trials regarding both the dose of vitamin D supplementation and the baseline levels of vitamin D prior to the intervention. Bergman *et al.*^[107] conducted a similar meta-analysis and found that vitamin D supplementation had a protective effect against acute respiratory infection in subjects of all ages (6 mo-75 years). However, they recognized as limitations of their meta-analysis the heterogeneity of included studies and the high likelihood of publication bias. Another systematic review^[108] that included only randomized controlled pediatric trials failed to show a significant association between vitamin D supplementation and

risk for acute respiratory infection. The researchers emphasized that their results should be interpreted with caution due to the small number and heterogeneity of included studies. It seems therefore that although many studies have revealed an association between vitamin D deficiency and risk for acute respiratory infection the data are not sufficient enough to support supplementation with vitamin D as a preventive measure to lower this risk.

As calcitriol exerts most of its biological actions *via* binding to the VDR, the possibility that VDR polymorphisms were associated with the risk of respiratory infections was also explored by a number of investigators^[109-111]. The majority of studies were performed in children with RSV bronchiolitis and it was suggested that there was a positive association between the FokI minor allele (ff) and susceptibility to RSV bronchiolitis^[112]. This association seems to be biologically plausible since f allele encodes a less active VDR that may affect the final activity of calcitriol^[110]. More recently, a VDR polymorphism was found to be associated with the susceptibility to community acquired pneumonia as well as with the disease severity in Chinese children^[113].

VITAMIN D AND BRONCHIECTASIS: CLINICAL STUDIES AND CHALLENGES

To the best of our knowledge, there are no clinical studies directly exploring the presumed link between vitamin D deficiency and CF or non-CF bronchiectasis, in children. However, there is a case control study in adults with non-CF bronchiectasis. More specifically, Chalmers *et al.*^[114] showed that 50% of patients with bronchiectasis were vitamin D deficient and 43% insufficient, and these percentages were significantly higher in comparison with the control group. They also found that vitamin D deficient patients were more commonly colonized with bacteria. Vitamin D deficient patients had lower FEV1, more frequent pulmonary exacerbations, higher sputum levels of inflammatory markers (myeloperoxidase, neutrophil elastase, IL-8) and demonstrated a more rapid decline in lung function over 3 years follow-up. However, the assessment of LL-37 levels in airways, and neutrophil phagocytosis either revealed a significant difference to the opposite direction of the initial hypothesis, or they failed to show any difference. Therefore, the authors were not able to provide an explanation on the hypothesized mechanism, namely, the implication of vitamin D deficiency in bronchiectasis severity.

Another small study in patients with primary cilia dyskinesia (PCD) showed that 79% of patients with bronchiectasis had vitamin D deficiency or insufficiency. However, 72% of the total population had also vitamin D deficiency or insufficiency, and there was no difference between PCD patients with and without bronchiectasis in vitamin D levels^[115]. The study may have failed to provide clear results because of its small sample size.

The paucity of studies prevents firm conclusions on the association between vitamin D deficiency and CF or non-CF bronchiectasis. And what is more, some authors have even expressed doubts on the anti-inflammatory of vitamin D. Among other things, it has been argued that vitamin D is primarily synthesized in the skin through the exposure to UV radiation and therefore it may simply be a surrogate of sunlight exposure^[116]. As it is well known, UV radiation has immunomodulatory properties in itself, irrespective of the UV-synthesized vitamin D^[117]. It has also been speculated that the observed low vitamin D levels could be a direct consequence of reduced outdoor physical activity of patients with chronic lung diseases such as bronchiectasis^[114,116]. This very important issue, to the best of our knowledge, has not been examined as a confounder in any of the relevant studies. Another issue that has been discussed in the literature is whether 25(OH)D could be a negative acute phase reactant and therefore its values may not be a reliable indicator of vitamin D status in inflammatory conditions^[118,119].

VITAMIN D AS A THERAPEUTIC POTENTIAL IN BRONCHIECTATIC LUNG DISEASE

Given the well-established association of vitamin D deficiency with increased inflammation, and the indicative evidence for harmful consequences in lungs, it is intriguing to speculate that the administration of vitamin D supplementation could be a reasonable and cost effective supplementary therapeutic approach for children with non-CF bronchiectasis. Vitamin D (as well as the rest of lipid-soluble vitamins), in doses sufficient to achieve serum levels > 30 ng/mL, has been part of the standard treatment for CF since many decades ago.

Vitamin D desirable serum levels reflect our current knowledge on preserving bone health. However, the issue of dose will become much more complex if we consider administering vitamin D for lung diseases, since we have to take into account the - yet unknown - levels required for its extra-skeletal functions. To make matters more complicated, a given dose of vitamin D will not necessarily attain the same increase of 25(OH)D serum levels in all patients. The required daily doses to reach optimal levels for bone health, vary greatly in patients ranging from 400 to 5000 IU daily^[120]. The dose needed in order to attain the vitamin's maximum immune-modulatory function is probably higher than the dose required for optimal bone health. Based on currently available data, 1,25(OH)₂D exerts its immune-modulatory functions at concentrations ranging from 10-100 nmol/L^[78], which are much higher than the usually observed serum levels of 100 to 135 pmol/L^[121]. This apparent paradox is due to the fact that vitamin D function in tissues is exerted mainly by the locally-produced 1,25(OH)₂D^[122]. Indeed, lung epithelial cells express high levels of 1 α -hydroxylase and are able of producing locally high levels of 1,25(OH)₂D. When these

cells were supplemented with 1 mmol/L of 25(OH)D, they produced 600 pmol/L of 1,25(OH)₂D^[27].

The above highlight briefly how complex still remains the tempting prospect of including vitamin D supplements to the armamentarium of remedies for non-CF bronchiectasis. Among the many issues that have to be sufficiently addressed before any recommendations can be made, is to show that vitamin D supplementation is associated with measurable disease outcomes, define which patients would be benefited by this treatment, the serum levels that have to be attained, and the optimal doses. Physicians' clinical decisions could be only assisted through carefully designed randomized controlled trials that will provide substantiated answers to above questions.

CONCLUSION

Vitamin D deficiency is associated with the risk for respiratory infectious diseases as it has been shown in epidemiological studies; additionally, vitamin D has a variety of immune-modulatory properties. Given the above, it is plausible to assume that there is an association between vitamin D deficiency and bronchiectasis. However, this association has been corroborated only in a single epidemiological study in adult population with non-CF bronchiectasis, and so it is premature to conclude causality. Nevertheless, the clarification of this issue is of great clinical importance. Maybe, in the light of new data, we have to reconsider the most appropriate doses and serum levels of vitamin D in CF. As for non-CF bronchiectasis, vitamin D supplementation could be an effective and safe option in the management of the disease, especially so because of the paucity of really effective treatment regimens.

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Cardiometabolic risk factors in children with celiac disease on a gluten-free diet

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Abstract

Celiac disease (CD) is an immune-mediated systemic condition evoked by gluten and related prolamines in geneti-

cally predisposed subjects. It is characterised by a variable combination of gluten-dependent clinical symptoms, CD-specific antibodies, HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy. The only therapy of CD consists of a life-long gluten free diet (GFD). Strict GFD adherence results in full clinical, serological and histological remission, avoiding long-term complications in CD patients. However, this diet is not without problems. Gluten free products have high levels of lipids, sugar and salt to improve food palatability and consistency, and subjects with CD show an excessive consumption of hypercaloric and hyperlipidic foods to compensate dietetic restriction. GFD may therefore have a negative impact on cardiometabolic risk factors such as obesity, serum lipid levels, insulin resistance, metabolic syndrome, and atherosclerosis. In adults, some studies have suggested that GFD have a beneficial effect on cardiovascular profile, whereas others have shown an atherogenic effect of GFD. In children, very few studies are available on the issue. Thus, the aim of the present narrative review was to analyze the current clinical evidence on the impact of GFD on cardiometabolic risk factors in children with CD.

Key words: Celiac disease; Children; Gluten free diet; Cardiometabolic risk; Atherosclerosis

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Core tip: Recent epidemiological studies suggest that gluten free diet (GFD) may have adverse effects on body weight, serum lipid levels and insulin resistance in youths with celiac disease (CD). Screening for cardiometabolic risk factors in celiac children is to be recommended not only at diagnosis but also during follow-up since an early intervention may prevent cardiovascular morbidity. Dietary guidance over time, targeting obesity and other components of metabolic syndrome besides monitoring adherence to GFD may be warranted in CD youths.

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INTRODUCTION

Celiac disease (CD) is an autoimmune systemic condition elicited by ingestion of food containing gluten and related prolamines in genetically predisposed subjects. It is characterized by heterogeneous clinical symptoms and signs, specific antibodies including anti-transglutaminase antibodies (tTGA), HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy. Genetic, immunological and environmental factors therefore appear to be responsible for the disease. In 90% to 95% of patients with CD is present HLA-DQ2, whereas 5% carry the HLA-DQ8 haplotype, and the remaining 5% at least one of the two DQ2 alleles^[1,2]. CD affects up to 1% of the population in the western world, and has been related to several complications^[3,4].

Nowadays the only accepted treatment is gluten free diet (GFD). It consists in life-long elimination from the diet of gliadin and glutamin proteins, fractions contained in wheat, rye, and barley and hybrids like kamut and triticale. Strict GFD adherence leads to full clinical, serological and histological remission and avoids long-term complications in CD patients^[1,2]. However, this diet is not without problems. Some available reports show that GFD may result in macro- and micronutrient deficiencies; in particular, the dietary intake of patients on GFD is characterized by low levels of fiber, vitamin B, folate, vitamin D, calcium, iron, zinc and magnesium^[5-7]. GFD may also have other important consequences. Overweight and obesity have been added to the list of possible nutritional consequences while on GFD, being partially related to hypercaloric content of commercially available gluten-free foods. Indeed, there is clinical evidence indicating an increased caloric intake as well as higher consumption of fats, saturated fats, simple carbohydrates and food with elevated glycemic index^[8-10] with such diets. Gluten free products have high levels of lipids, sugar and salt to improve food palatability and consistency, and subjects with CD show an excessive consumption of hypercaloric and hyperlipidic foods to compensate dietetic restriction. GFD may therefore have a negative impact on cardiometabolic risk factors such as obesity, serum lipid concentrations, insulin resistance, metabolic syndrome, and atherosclerosis.

Whether GFD affects the cardiovascular risk profile in patients with CD remains under discussion. In adults, some studies have suggested that GFD have a beneficial effect on cardiovascular profile consequently to its anti-atherosclerotic effects^[11,12], whereas others have shown atherogenic effects of GFD^[13,14]. In children, very few studies are available on this topic. Thus, the purpose of the present narrative review was to analyze the current clinical evidence on the impact of GFD on cardiometabolic risk factors in children with CD.

OBESITY

Obesity nowadays is more frequent in CD than in the past. Numerous reports in adults and youths with CD have shown that overweight and obesity is not unusual at diagnosis. The proportion of CD children affected by overweight and obesity at diagnosis is between 8.8% and 20.8% and between 0% and 6%, respectively^[13,15,16]. Also, there is some evidence that GFD may predispose to development of overweight and obesity^[15-18] for several reasons. First, GFD improves intestinal absorption; second, GFD is an unbalanced diet rich in lipids and proteins^[9]; third, CD patients prefer food with elevated caloric fat and protein contents to contrast the GFD unpalatability. The development of increased weight in CD patients may be also linked to the global trend toward overweight and obesity in the pediatric age^[19].

There are multiple reports on the association of GFD and obesity in youths with CD, with conflicting results^[9,13,15-18,20-27]. Mariani *et al.*^[9] first reported a higher rate of overweight and obesity in CD adolescents on GFD in comparison with CD subjects on gluten-containing diet and healthy controls (72% vs 51% and 47%). Valletta *et al.*^[15] found that the prevalences of overweight and obesity were 11% and 3%, respectively, at diagnosis in 149 youths with CD. After at least 12 mo of GFD, there was a significant increase in the body mass index (BMI) z-score, and the percentage of overweight children almost doubled (11% vs 21%, $P = 0.03$). The proportion of obese patients remained the same (3% vs 4%). In a recent cross-sectional multicenter study, Norsa *et al.*^[13] evaluated 114 CD children with negative CD serology after at least 1 year of GFD. They found that 9.6% of youths were underweight, 76.3% had normal weight, and 8.8% were overweight, whereas 5.3% were obese. Both prevalences of overweight and obesity rose up to 11.4% and 8%, respectively, after GFD introduction.

Opposite results were reported by Venkatasubramani *et al.*^[26], Brambilla *et al.*^[16], Reilly *et al.*^[18] and Nenna *et al.*^[27]. In a retrospective study including 143 CD subjects diagnosed between 1986 and 2003, Venkatasubramani *et al.*^[26] identified 7 (5%) patients with a BMI > 95th percentile. After 1-year GFD, BMI increased in 2 (25%), but decreased in 4 (50%). They, therefore, concluded that GFD in obese CD children may reduce BMI. Brambilla *et al.*^[16] compared 150 CD children on GFD (median time, 4.4 years) with 288 age- and sex-matched healthy subjects. They evaluated retrospectively BMI changes since CD diagnosis to the latest clinical assessment, and found that the frequencies of overweight and obesity in CD children at diagnosis and during GFD were significantly lower than those reported in healthy controls. The study by Reilly *et al.*^[18] involving 142 pediatric CD patients showed that 19% of subjects at diagnosis presented an elevated BMI (12.6% were overweight and 6% were obese), while 74.5% had a normal BMI. Seventy-five percent of children with high BMI at diagnosis had a

significant decrease in their BMI z-scores on a strict GFD. In particular, 44% of them normalized their BMI z scores. The authors concluded that GFD may have a favorable effect upon the BMI of overweight and obese youths with CD. Finally, in a retrospective study evaluating the prevalence of CD in a large cohort of overweight/obese children and adolescents, Nenna *et al.*^[27] observed that the prevalence of CD (1.11%) was similar to that found in general population. Moreover, they demonstrated that these subjects may benefit from a balanced GFD diet.

SERUM LIPIDS

The consequences of GFD on lipid profile in childhood have been analyzed in several studies. Rosenthal *et al.*^[28] compared plasma lipids and lipoprotein pattern between 12 untreated CD children and 10 control subjects. They found an altered lipid profile characterized by decreased serum triglycerides levels, very low density lipoprotein (VLDL) and apolipoprotein-A-I (apo-A-I), and increased low density lipoprotein cholesterol (LDL-C) in CD children, because of fat malabsorption. On GFD the lipid profile reverted to normal as consequence of improvement of mucosal damage caused by gluten withdraw. Ciampolini *et al.*^[29] investigated the plasma lipid levels in CD children (45 under and 49 over 3 years of age, at diagnosis) on GFD, and in comparison with children affected by irritable bowel syndrome (IBS) matched for body size, gender, and age. They found that untreated CD children had significantly lower total and high density lipoprotein cholesterol (HDL-C) levels and significantly higher triglyceride concentrations than IBS controls in both age groups. A period of GFD increased HDL-C in both age groups, while total cholesterol, LDL-C, and triglyceride levels decreased only in the younger age group. Pillan *et al.*^[30] compared serum lipids and lipoprotein (a) concentration in 17 adult and pediatric CD patients at diagnosis and after 3 mo of GFD. They found that mean total cholesterol and LDL-C did not significantly change, while mean HDL-C significantly rose and mean triglyceride levels significantly decreased after the diet, suggesting that GFD may positively influence lipid profile. Recently, in a cross-sectional prospective study, Forchielli *et al.*^[31] analyzed the impact of GFD on serum lipid concentrations in children with CD compared with the general pediatric population. They studied 235 CD children and adolescents: In 205 patients the lipid profile was available only after diagnosis (group 1), whereas in 30 patients it was available both before and after GFD (group 2). The Authors found that in group 1, total cholesterol, triglyceride, and HDL-C concentrations were significantly elevated in girls in comparison with boys. Furthermore, compared with the general pediatric population, group 1 girls had higher total cholesterol, triglycerides, HDL-C and LDL-C, while group 1 boys had lower total cholesterol, triglycerides and LDL-C, and higher HDL-C. In group 2, total cholesterol did not change over time, triglycerides diminished, and

HDL-C increased. They therefore suggested that GFD, being appropriate in terms of fibers and unsaturated fats^[31], may have a positive influence on lipid profiles, determining higher HDL-C in CD children than in the reference population.

Against this background, Médiène *et al.*^[32], who compared 46 CD adult and pediatric patients and 155 control subjects, found that untreated CD patients had decreased cholesterol, phospholipid and apo-A-I levels and elevated triglycerides. However, they did not find a return towards normal lipid profile following GFD.

INSULIN RESISTANCE

There are only few studies on insulin resistance in both CD adults and youths on GFD. In a retrospective study evaluating the effects of 1-5 years of GFD on markers of cardiovascular risk in a large cohort of adult patients, Zanini *et al.*^[12] found that insulin resistance remained constant from baseline to follow-up. Of note, absolute levels of serum glucose rose from 87.9 mg/dL at baseline to 89.7 mg/dL during GFD ($P = 0.0001$), reaching statistically significance only in females. In a sample of Italian and Israeli CD patients on GFD, Norsa *et al.*^[13] found that 3.5% of 114 children on GFD had insulin resistance. Because of lack of data on insulin values before CD diagnosis, the authors were not able to determine whether insulin resistance could be, indeed, attributed to the start of GFD.

METABOLIC SYNDROME

Data regarding the prevalence of metabolic syndrome (MetS) in patients with CD on free diet or on GFD are still scarce and limited to adults with CD. In an observational prospective study involving 98 adult CD patients, Tortora *et al.*^[33] found that 2% of them fulfilled the diagnostic criteria for MetS at diagnosis while 29.5% after one year of GFD. Among the MetS components, there was a significant increase in BMI, waist circumference, blood pressure and blood glucose levels, whereas no significant difference was detected in the lipid profile from baseline to 12 mo after the introduction of GFD. They concluded that patients with CD on GFD are at risk of developing MetS. In contrast, Kabbani *et al.*^[34] comparing 26 CD adults with 81 controls, reported that MetS is less frequent in CD than in controls (3.5% vs 12.7%, $P < 0.0001$).

Nonalcoholic fatty liver disease (NAFLD), considered as the hepatic component of MetS, is the most frequent cause of chronic liver disease in youths worldwide. Potential triggers for NAFLD including metabolic risk factors (*i.e.*, abdominal adiposity and insulin resistance) as well as altered intestinal permeability may be present in CD patients. However, there are very few reports of NAFLD in subjects with CD. Recently, Reilly *et al.*^[35] compared the risk of NAFLD diagnosed between 1997 and 2009 in 26816 pediatric and adult CD patients with that in 130051 age-, gender-, calendar year-, and

county-matched subjects. They observed a 4.2-fold increased risk of NAFLD in the first five years after diagnosis of CD. This increased risk was mainly due to NAFLD diagnosed in the first year after diagnosis of CD, but was still significantly high 15 years after the diagnosis of CD.

SUBCLINICAL ATHEROSCLEROSIS

Several studies have shown that atherosclerosis begins in childhood and protracts into adulthood^[36,37]. Early detection of arterial damage is fundamental to prevent future vascular risk since subclinical atherosclerosis can be reversible if detected earlier and intervention is provided. Subjects at high risk for cardiovascular disease (CVD) may be identified by determination of arterial thickness and distensibility, endothelial function and proinflammatory and protrombotic state alone or in combination^[38-40]. Altered flow-mediated vasodilatation, as well as increased carotid-artery intimal medial thickness (cIMT) can be assessed by ultrasonography allowing an early diagnosis of preclinical atherosclerosis^[41]. Arterial stiffness can be assessed by pulse wave velocity (PWV) measurement^[42], the main index for estimating arterial elasticity.

Endothelial dysfunction and increased arterial stiffness have been reported in adult patients with CD^[43,44]. To the best of our knowledge, only Demir *et al.*^[45] investigated markers of preclinical atherosclerosis in children with CD. In a cross-sectional study, the authors studied arterial stiffness and thickness using PWV and cIMT in 37 pediatric patients with CD compared to 36 age- and sex-matched healthy controls. A strict adherence to GFD, evaluated by determination of tTGA levels, was detected in 59.4% of 37 CD patients. There was no significant difference between tTGA positive and tTGA negative children in terms of PWV and cIMT. Nonetheless, cIMT was significantly lower in CD subjects adherent to GFD in comparison with healthy controls. Moreover, cIMT was positively associated with tTGA levels in patients with CD, suggesting that lack of dietary compliance in such patients might pave the road to arterial thickness^[43]. These results suggest that GFD is likely to be anti-atherogenic, and that long-term gluten withdrawal might prevent premature atherosclerosis.

CV RISK PROFILE

Several studies have reported an increased risk of CVD as well as an increased risk of death for CVD in CD patients, especially those with untreated CD, in comparison with the general population^[46-50]. In a systematic review and meta-analysis, Emilsson *et al.*^[48] reported that CD was associated with a 10% increased risk of CVD, but some studies did not confirm these data^[49,50]. Of note, it has been suggested that transglutaminases can modulate several cardiovascular risk factors, mainly hypertension, atherosclerosis, vascular permeability and

angiogenesis^[51].

To our knowledge, only two studies have explored the cardiovascular risk profile in children with CD^[13,52]. In a cross-sectional multicenter study involving 114 CD children on GFD, Norsa *et al.*^[13] reported the profile of CVD risk factors including obesity, abdominal obesity, high LDL-C, high triglycerides, hypertension, and insulin resistance. The main prevalent CVD risk factors were elevated triglycerides (34.8%), hypertension (29.4%), and elevated serum levels of LDL-C (24.1%). The Authors found 3 or more coexistent risk factors for CVD in 14% of the entire cohort, whereas absence of risk factors was found in only 30.7% of the cohort. Moreover, significant increments in both total cholesterol and HDL-C were found in CD children on GFD. This is in line with some authors arguing that alteration of intestinal absorption, chylomicron production and lipoprotein metabolism may underlie the presence of lower concentrations of total cholesterol and HDL-C in CD subjects at diagnosis, which can return to normal levels after GFD^[28,52]. They therefore highlight the critical role of screening for cardiovascular risk factors in CD youths at diagnosis as well as at follow-up. Very recently, in a retrospective study Assa *et al.*^[53] found that at the age of 17 years the prevalence of certain CVD risk factors such as hypercoagulability, hyperlipidemia, and type 2 diabetes was higher in adolescents with CD compared to the general population. In contrast, the prevalence of traditional cardiovascular risk factors such as high blood pressure and overweight/obesity was similar between the two groups. However, these findings should be cautiously interpreted since information on age at diagnosis as well as on GFD adherence was not available.

Early cardiac involvement in youths with CD and the impact of GFD on this issue have also been evaluated. Lionetti *et al.*^[54] compared cardiac structure and function before and after 1 year of GFD in 60 children with CD and in a control group of 45 healthy children. There were significantly lower contractility indices, and higher left ventricular dimensions in untreated CD. Notably, these parameters reverted to normal after GFD. Interestingly, GFD, along with immunosuppression, can be effective in CD-associated autoimmune myocarditis^[55].

CONCLUSION

The available literature shows conflicting data on the effects of GFD on cardiometabolic risk factors in children and adolescents with CD. The majority of the studies indicate changes in markers associated with cardiovascular risk. These variations, in any case, do not constantly point at a better or worse cardiovascular risk profile. Limitations of most studies comprise the relatively small sample size, the cross-sectional design that does not permit comparison between pre- and post-GFD values of the evaluated parameters, and the absence of knowledge of familial history for CVD risk factors. Therefore, additional longitudinal, well-

designed studies involving a large number of children with long-term follow-up are necessary to clarify whether prolonged exposure to GFD might result in an increased cardiometabolic risk. At this time, GFD remains the milestone of CD treatment. Nonetheless, an in-depth assessment of nutritional status along with cardiometabolic screening in CD children at diagnosis and during GFD have to be recommended because an early intervention may prevent cardiovascular morbidity. Dietary guidance over time, targeting obesity and other components of MetS besides monitoring adherence to GFD may be warranted in youths with CD.

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Basic Study

Confirming longline position in neonates - Survey of practice in England and Wales

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Abstract

AIM

To establish how neonatal units in England and Wales currently confirm longline tip position, immediately after insertion of a longline.

METHODS

We conducted a telephone survey of 170 neonatal units (37 special care baby units, 81 local neonatal units and 52 neonatal intensive care units) across England and Wales over the period from January to May 2016. Data was collected on specifically designed proformas. We gathered information on the following: Unit Level designation; whether the unit used longlines and specific type used? Modality used to confirm longline tip position? Whether guide wires were routinely removed and contrast injected to determine longline position? The responders were primarily senior nurses.

RESULTS

We had 100% response rate. Out of the total neonatal units surveyed (170) in England and Wales, 141 units (83%) used longlines. Fifty-five out of 81 local neonatal units (68%) using longlines, used ones that came with guide wires; a similar percentage of neonatal intensive care units, *i.e.*, 31 out of 52 units (60%) did the same. All of those units used radiography, plain X-rays, to establish longline tip position. Out of 55 local neonatal units using

longlines with guide wires, 42 (76%) were not removing wire to use contrast while this figure was 58% (18 out of 31 units) for neonatal intensive care units. Overall, only 49 out of 141 units (35%) of the units using longlines were using contrast. However it was interesting to note that use of contrast increased as one moved from special care baby units (25%, 2 out of 8 units) to local neonatal units (28%, 23 out of 81 units) and neonatal intensive care units level (46%, 24 out of 52 units) designation.

CONCLUSION

Neonatal units in England and Wales are overwhelmingly relying on plain radiographs to assess longline tip position immediately after insertion. Despite evidence of its usefulness, and in the absence of perhaps more accurate methods of assessing longline tip position in a reliable and consistent way, *i.e.*, ultrasonography, contrast is only used in a third of units.

Key words: Central venous catheters; Newborn; Contrast media; Line placement; Premature infants

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Core tip: Accurate placement of longlines is important as malposition can lead to serious complications. A number of different techniques and specialised modalities have been described in the literature. A readily available adjunct to plain radiography, shown to help avoid catheter malposition, is the use of contrast. Our survey shows that the majority of neonatal units in England and Wales are overwhelmingly reliant on plain radiographs for confirmation of longline position. Despite evidence of its usefulness and in the absence of perhaps more accurate methods of assessing longline tip position in a reliable and consistent way, *e.g.*, ultrasonography, contrast is only used in a third of units to confirm longline position immediately after insertion of a longline.

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INTRODUCTION

Percutaneous central venous lines (longlines) are commonly used in neonatal practice. A longline is a fine plastic (silastic) tube 10 to 30 cm long that is threaded into one of the newborn's veins, usually in the upper or lower limbs, to reach a point where the vein becomes much larger, usually just outside the heart. It can be used to deliver parenteral nutrition and for the safe and uninterrupted administration of clinically essential or locally toxic solutions. The higher blood flow in the larger veins leads to a decrease in the risk of complications

from the plastic itself and also the infused solutions. A longline can stay in place for several weeks, which reduces the number of times a newborn baby needs to have a drip inserted. Correct placement is important to avoid complications such as extravasation of fluids into pleural, peritoneal, pericardial and subcutaneous compartments^[1].

Different methods are used to assess longline tip position. The most common, plain radiography is plagued with concerns about poor intra- and inter-observer reliability^[2]. Other modalities, *e.g.*, echocardiography^[3] and CT^[4] might be more reliable but are not readily available in most units. Use of contrast, an injectable solution that can be used to improve radio-opacity of the longline by injecting into the longline in sufficient volume to fill the connecting device and catheter, can help with recognition of unusual patterns of contrast medium dispersal and lead to easier identification of catheter malposition when combined with radiographs^[5,6]. Although it is recognized that even with use of contrast precise localization of longline tips can be difficult, its use improves the likelihood that observers can see the tip more reliably and reduces inter-observer variability as regards to the anatomical placement of the tip^[7].

MATERIALS AND METHODS

Discussions with relevant departments in our Institution, led to the conclusion that this study was a review of practice and hence no ethical approval was necessary. After registration with the audit department of our Institution, we conducted a telephone survey of all neonatal units in England and Wales. The aim was to establish the current practice for confirming longline position immediately after insertion of a longline. All responses were collected on specifically designed proformas. We gathered information on Unit Level designation, whether the unit used longlines and specific type(s) used, the modality used to confirm longline tip position, and whether guide wires were routinely removed and contrast injected to determine longline position. A guidewire is a thin wire that comes already inserted into a longline to increase rigidity which helps with line insertion and also helps with better line visualization with plain radiography as it is radio-opaque.

RESULTS

We identified 177 neonatal units in England and Wales in Feb-May 2016. Out of those, 7 units had either closed or merged, leaving 170 individual units; 37 special care baby units (SCBUs), 81 local neonatal units (LNUs) and 52 neonatal intensive care units (NICUs). Responses were collected on specifically designed proformas. The responders were primarily nursing shift leaders. One hundred and forty-one units used long-lines and all units used plain radiography (single view) to establish

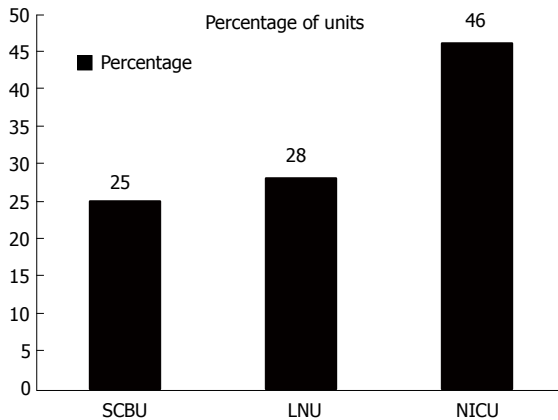


Figure 1 Contrast use by unit level. SCBU: Special care baby unit; LNU: Local neonatal unit; NICU: Neonatal intensive care unit.

longline tip position. We had 100% response rate. Out of the total neonatal units surveyed (170) in England and Wales, 141 units (83%) used longlines.

Fifty-five out of 81 LNUs (68%) using longlines, used ones that came with guide wires; a similar percentage of NICUs 60% (31 out of 52 units) did the same.

Focusing on those units using longlines with guide wires, 76% (42 out of 55 units) of LNUs were not removing wire to use contrast; this figure was 58% (18 out of 31 units) for NICUs.

It was interesting to note that use of contrast increased as one moved from SCBUs (25%, 2 out of 8 units) to LNUs (28%, 23 out of 81 units) and NICUs level (46%, 24 out of 52 units) designation.

Overall, only 49 out of 141 units (35%) of the units using longlines were using contrast, with the proportion increasing with level designation as can be seen in Figure 1 and as mentioned above.

DISCUSSION

Percutaneous central venous lines are commonly used in neonatal practice. The position of these lines is important because incorrect placement may be associated with complications. It is therefore essential that the paediatricians/radiologists are able to recognize sub-optimally positioned catheters in their radiographic assessment to avoid such complications. Serious complications include extravasation of fluids into pleural, peritoneal, pericardial and subcutaneous compartments.

There are a number of case reports where longline migration has caused pericardial effusion and tamponade. The fluid aspirated was confirmed to be consistent with parenteral nutrition which was delivered by longline^[8-10]. Even death has been reported in neonates due to complications such as myocardial perforation and cardiac tamponade related to percutaneously placed longlines^[11,12].

A case series done over a 5 year period in neonates identified an incidence rate of 1.1% of extravasation in the study (pericardial and pleural effusion). The reported mortality for pericardial effusions in this study

was 67%^[13].

In a case report of an intra-abdominal extravasation of parenteral nutrition, the authors suggest that complication could have been prevented by optimal placement of catheter tip^[14]. De *et al*^[15] presented the case of a preterm infant in whom a longline had inadvertently been placed into the left ascending lumbar vein. When such catheters enter the spinal canal, paraplegia and even death can ensue^[16]. In view of the above known infrequent but serious complications, it is vital that all line placements should be confirmed as accurately as possible. As stated above, there are studies showing poor intra- and inter-observer reliability when radiographs are used to assess longline tips and the major determinant of line repositioning was the perceived location. There are many studies where different modalities have been used to suggest confirmation of line tip as accurately as possible. Examples are two-view radiographs^[17], use of echocardiography, CT radiography, intracavity ECG^[18], transthoracic ultrasonography^[19], horizontal beam technique^[20], and use of lateral radiographs^[21]. Use of ultrasound can be very helpful but it is user dependant. Longline tip position is the important factor in determining the correct position of the catheter; however one can be misled or misguided if the plain supine X-ray is solely relied upon^[22]. This is because X-rays are viewed in a two dimensional form and unless contrast is given it will be difficult to perceive the exact localisation of tip position.

Some studies as listed above suggest that contrast should be used routinely in the assessment of longline position in the neonate, because it helps in easier identification of catheter malposition by recognizing unusual contrast medium dispersal. One should acknowledge the existence of reports where use of contrast failed to identify abnormal positioning of the catheter tip in the abdomen leading to harm in the neonate^[23]. Having said that, the specific methodology of contrast injection was not described in this case report and some of the largest case series published on the subject support use of contrast during radiographic exposure and back it up with reduced complication rates^[24]. Although it is recognized that even with the use of contrast precise localization of longline tips can be difficult, its use has been shown to reduce inter-observer variability.

Conclusion

Our study had 100% response rate and it therefore gives a full and accurate picture of current reality in English and Welsh Neonatal Units. Accurate placement of longlines is important as malposition can lead to serious complications. A number of different techniques and specialized modalities have been described in the literature. Despite evidence showing poor intra- and inter-observer reliability, our review suggests that we are still overwhelmingly relying on plain radiographs to identify longline tip position. Contrast has been

proposed to be superior to plain radiographs in the confirmation of the line tip position; however, our study shows that neonatal units in England and Wales do not currently use this as widely as one might have expected. Contrast is used in just over a 1/3 of units though it is interesting to note the trend towards its use with increasing level designation. There might indeed be more accurate modalities in existence but, on the whole, these may need expertise or equipment that might not be available at the point of care in real time. Therefore, use of contrast should be explored further and be the focus of clinical trials exploring its reliability and safety. It might also be useful to look at the rates of adverse longline events in those units that use contrast vs those that do not.

ACKNOWLEDGMENTS

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COMMENTS

Background

Percutaneous central venous lines (longlines) are commonly used in neonatal practice. A longline is a fine plastic (silastic) tube 10 to 30 cm long that is threaded into one of the newborn's veins, usually in the upper or lower limbs, to reach a point where the vein becomes much larger, usually just outside the heart. It can be used to deliver parenteral nutrition and for the safe and uninterrupted administration of clinically essential or locally toxic solutions. The higher blood flow in the larger veins leads to a decrease in the risk of complications from the plastic itself and also the infused solutions. A longline can stay in place for several weeks, which reduces the number of times a newborn baby needs to have a drip inserted. Correct placement is important to avoid complications such as extravasation of fluids into pleural, peritoneal, pericardial and subcutaneous compartments. Different methods are used to assess longline tip position. The most common, plain radiography is plagued with concerns about poor intra- and inter-observer reliability. Other modalities, e.g., echocardiography and CT might be more reliable but are not readily available in most units. Use of contrast can help with recognition of unusual patterns of contrast medium dispersal and lead to easier identification of catheter malposition when combined with radiographs.

Research frontiers

Despite evidence showing poor intra- and inter-observer reliability, the review suggests that clinicians are still overwhelmingly relying on plain radiographs to identify longline tip position. Contrast has been proposed to be superior to plain radiographs in the confirmation of the line tip position; however, the study shows that neonatal units in England and Wales do not currently use this as widely as one might have expected. Contrast is used in just over a 1/3 of units though it is interesting to note the trend towards its use with increasing level designation. There might indeed be more accurate modalities in existence but, on the whole, these may need expertise or equipment that might not be available at the point of care in real time. Therefore, use of contrast should be explored further and be the focus of clinical trials exploring its reliability and safety. It might also be useful to look at the rates of adverse longline events in those units that use contrast vs those that do not.

Innovations and breakthroughs

The study had 100% response rate and it therefore gives a full and accurate picture of current reality in English and Welsh Neonatal Units. Accurate placement of longlines is important as malposition can lead to serious complications. A number of different techniques and specialized modalities have been described in the literature. A readily available adjunct to plain radiography, shown to help avoid catheter malposition, is the use of contrast. The survey shows that the majority of neonatal units in England and Wales are

still, overwhelmingly, relying on plain radiographs to confirm longline position. Despite evidence of its usefulness, contrast is used by about a third of neonatal units to confirm longline position immediately after insertion of a longline.

Applications

Despite evidence showing poor intra- and inter-observer reliability, the review suggests that authors are still overwhelmingly relying on plain radiographs to identify longline tip position. Contrast has been proposed to be superior to plain radiographs in the confirmation of the line tip position; however, the study shows that neonatal units in England and Wales do not currently use this as widely as one might have expected. Contrast is used in just over a 1/3 of units though it is interesting to note the trend towards its use with increasing level designation. There might indeed be more accurate modalities in existence but, on the whole, these may need expertise or equipment that might not be available at the point of care in real time. Therefore, use of contrast should be explored further and be the focus of clinical trials exploring its reliability and safety. It might also be useful to look at the rates of adverse longline events in those units that use contrast vs those that do not.

Terminology

Longline: A fine plastic (silastic) tube, usually 10 cm to 30 cm long, that is threaded into one of the baby's small veins usually in the arm or leg and towards the wider central veins; Guidewire: A thin wire that comes already inserted into a longline to increase rigidity, which helps with line insertion, and also with better line visualization during plain radiography as it is radiopaque; Contrast: A radiopaque substance used to improve visualisation of a structure, in this case the longline, as it is injected into the longline during radiographic exposure in sufficient volume to fill the connecting device and catheter and leave a blush of contrast visible at the catheter tip.

Peer-review

Authors analyzed use of different methods in confirming long line position in newborns. This is a worthy audit of contemporary practice in England and Wales.

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Prospective Study

Screening for asymptomatic chlamydia and gonorrhea in adolescent males in an urban pediatric emergency department

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Author contributions: All authors contributed to this paper.

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Informed consent statement: All participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Abstract

AIM

To determine the prevalence of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhea* (GC) in young men seeking care in the emergency department (ED) for non-sexually transmitted infection (STI) related symptoms.

METHODS

This was a prospective, cross-sectional study in an urban ED. The main outcome was the rate of positive CT and GC on urine nucleic acid amplification testing in males aged 16-21 presenting with non-STI related complaints.

RESULTS

Two hundred and eighty-four patients were enrolled, 271 were included in the final data analysis [age range 16-21, median: 18 (quartiles 16-18, 19-21)]. Overall, 17 (6.3%, 95%CI: 4%-10%) tested positive for CT and 0% (95%CI: 0%-2%) were found to have GC. The proportion of sexually active subjects was 71% (95%CI: 65%-76%) and 2% (95%CI: 0.6%-4%) reported sex with men. Previous STI testing was reported in 46% (95%CI: 43%-54%) and 13% (95%CI: 8%-20%) of those patients previously tested had a history of STI. Of the patients who tested positive for CT in the ED, 88% (95%CI: 64%-98%) were successfully followed up.

CONCLUSION

The prevalence of CT infection found by screening

was 6.3%. Screening and follow-up from the ED was successful. The findings justify routine STI screening in male adolescents presenting to the ED with non-STI related complaints.

Key words: Chlamydia; Gonorrhea; Adolescent; Public health; Emergency department; Pediatric

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Core tip: Chlamydia trachomatis and Neisseria gonorrhea are the most common bacterial sexually transmitted infections (STIs), the sequelae of which are among the most costly of any STI except human immunodeficiency virus infection and acquired immune deficiency syndrome. Disease is often asymptomatic in young males, for whom there is a lack of consensus on screening recommendations and who are screened less often than women. Most studies on emergency department screening focus on young females, or group both asymptomatic and symptomatic patients together. We found 6.3% prevalence of asymptomatic Chlamydia by screening adolescent males who were not seeking screening and would likely not otherwise have been tested.

Maraynes ME, Chao JH, Agoritsas K, Sinert R, Zehtabchi S. Screening for asymptomatic chlamydia and gonorrhea in adolescent males in an urban pediatric emergency department. *World J Clin Pediatr* 2017; 6(3): 154-160 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v6/i3/154.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v6.i3.154>

INTRODUCTION

Chlamydia trachomatis (CT) and *Neisseria gonorrhea* (GC) are the most common bacterial sexually transmitted infections (STIs) among sexually active adolescents^[1]. The sequelae of untreated disease such as ectopic pregnancy and pelvic inflammatory disease are among the most costly of any STI except human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS)^[2,3]. Risk factors for these diseases include age less than 25, low socioeconomic status, lack of health insurance, African American, high-risk behaviors such as multiple partners, older sex partners for females, alcohol use and lack of condom use^[4-7].

Current CDC recommendations do not include screening asymptomatic adolescent males for STIs, focusing instead on sexually active women, men who have sex with men, drug users and prisoners^[8]. Their rationale for not regularly screening asymptomatic males is that there are little to no reproductive consequences for patients with asymptomatic disease and therefore no substantial secondary prevention is gained. However, many

infectious disease specialists argue that by screening young men the burden of disease among young women (and subsequent reproductive and infectious consequences) can be significantly decreased.

Studies on the prevalence of Chlamydia and Gonorrhea among adolescents largely include males and females, with emergency department (ED) screening studies reporting rates from 4%-14%^[1,2,9,10]. Rates are generally reported as higher in females. The lower rate of both Chlamydia and Gonorrhea reported in males is likely due to lower testing rates^[11]. Males are tested less often than women in part because they are less likely to have symptoms and also because until recently, the only available method of testing was a painful and invasive urethral swab. With the advent of urine RNA amplification tests, there now exists a non-invasive, inexpensive, highly sensitive and specific screening method^[12,13]. While many studies focus on screening females and symptomatic patients in the ED setting, and some focus on screening asymptomatic adult males and females, none that we found focused solely on males seeking care for non-genitourinary (GU) complaints^[14,15].

MATERIALS AND METHODS

We performed a prospective, cross-sectional study of adolescent males age 16-21 who presented to either the pediatric ED or the adult fast track area at Kings County Hospital Center, Brooklyn, NY from October 2013 to May of 2015. The State University of New York Downstate institutional review board approved the study protocol.

Enrollment

Only male patients were enrolled by a health care provider or research assistant (to be referred to as "recruiter"). All recruiters were trained in enrollment, informed consent and urine Nucleic Acid Amplification Testing (NAAT) specimen collection.

A recruiter other than the physician primarily responsible for the patient approached subjects during their evaluation and invited them to participate in the study. Patients under 16 or over 21 years of age, those with a chief complaint involving GU symptoms, or Emergency Severity Index score 1-3 (higher acuity) were excluded. While we considered including younger teenagers (age 13 and above) this was not allowed by our institutional review board (IRB) due to concerns that parents of these patients would find the suggestion of sexual activity in this age inappropriate. If a patient agreed to participate, written informed consent was obtained from the subject and their parent or guardian if under 18. In accordance with our IRB's requirements and New York State law, parents were informed of the nature of the study, but not involved in follow up or informed of results. In other words, they consented to allow their son to receive information about test results and follow up for treatment independently. Results were

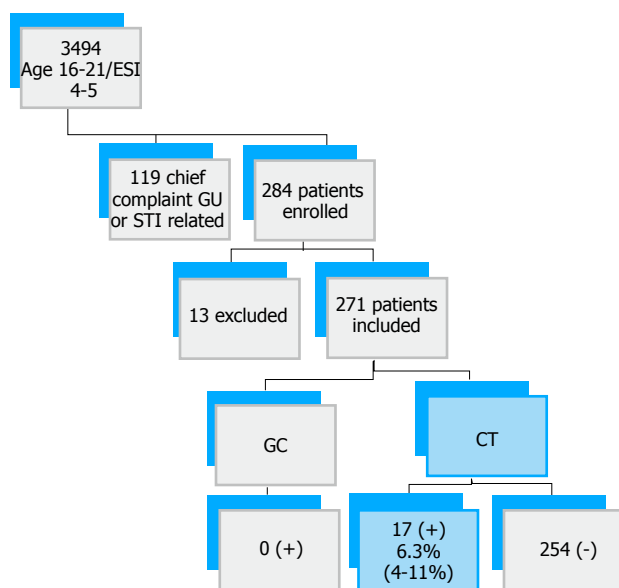


Figure 1 Patient recruitment and results summary. GC: *Neisseria gonorrhea*; CT: *Chlamydia trachomatis*; STI: Sexually transmitted infection; GU: Genitourinary.

part of the permanent medical record, but patients were not billed for the testing.

Data collection

Once enrolled and consented to participate in the study, parents/guardians or others present were asked to leave the room. A verbal survey was administered by the recruiter collecting data on age, race, chief reason for visit, follow up contact information, current GU symptoms, previous sexual activity, previous STI testing results and treatment, and history of primary care visits. All questions were asked in laymen's terms and the answers were recorded in writing by the recruiter. Next, an early stream "dirty catch" specimen was collected and sent for CT and GC testing using urine NAAT testing (gen-probe®). The test is 98.9% sensitive and 97.4% specific for CT in male urine samples. The coefficient of variation is 7.8%^[16].

The ED staff reviewed urine NAAT results as per hospital protocol as soon as results became available (usually within 48-72 h) and patients were contacted at confidential phone numbers provided and treatment arranged if the results were positive. As per hospital protocol, if patients were not contacted successfully by phone after 3 attempts, a telegram was sent to the patient's address, prompting them to contact the ED for test results.

Statistical analysis

Sample size estimate: Based on previous studies and available public health data we anticipated a positive STI rate of 7%. We calculated a sample size goal of 300 to obtain a prevalence of 7% with a 95%CI between 4% and 10%.

Data analysis

The main outcome was the proportion of positive tests

Table 1 Participant characteristics

Characteristic	n (%)
Chief complaint	
Minor trauma	129 (48)
Acute illness	100 (35)
Other	40 (14)
Age	
16-18	208 (73)
19-21	62 (22)
Ethnicity	
Black	230 (81)
Latino	21 (7)
Asian/Indian	5 (2)
White	3 (1)
Other	11 (4)
Sexual activity	202 (71)
Sex with men	5 (2)
Previous STI test	131 (46)
Previous STI	17 (6)
Regular PMD	201 (7)

STI: Sexually transmitted infection.

for either CT or GC. Data are presented as medians with quartiles for continuous variables and as percentages with 95%CI for proportions. Descriptive statistics are used to report additional variables. When applicable, a Fisher exact test was used to report associations. Data analysis was performed using IBM SPSS Statistics for Windows, Version 20.0.

RESULTS

During our study recruitment period a total of 3494 males between age 16 and 21 with ESI levels 4 and 5 presented to the pediatric ED and fast track areas combined. One hundred and nineteen of these patients presented with chief complaints of urinary symptoms, penile discharge, or need for STI testing. We recruited a total of 284 subjects, of whom 13 were not included in the final data analysis due to un-resulted samples (Figure 1). The vast majority of subjects were black (81%), and the majority (73%) were age 16-18 (Table 1 and Figures 2-4). Due to limitations in staffing and inconsistencies with initial data collection, we were unable to collect data on rates of declination for the entire study period of 19 mo. Over a sample period of 5 mo, 61% (95%CI: 51%-69%) of patients approached agreed to participate.

Prevalence

Six point three percent (95%CI: 4%-10%) of patients tested positive for CT and 0% tested positive for GC. Seventy-one percent (95%CI: 65%-76%) of patients reported being sexually active. Forty-six percent (95%CI: 43%-54%) reported previous STI testing and 13% of those reported having had an STI in the past. Of those who tested positive, none denied sexual activity. Of those who tested positive for CT in the ED, 88% (95%CI: 64%-98%) were successfully followed up. As expected, the prevalence of chlamydia was significantly

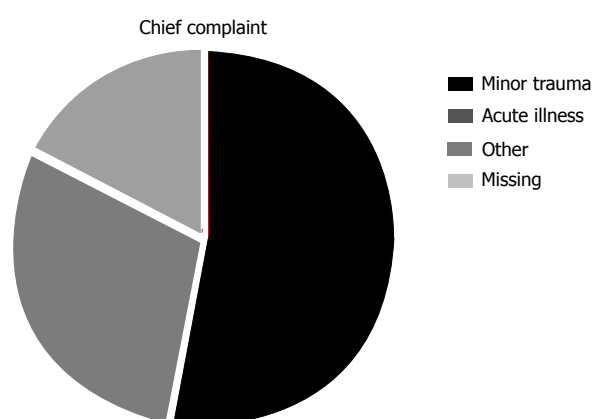


Figure 2 Chief complaint.

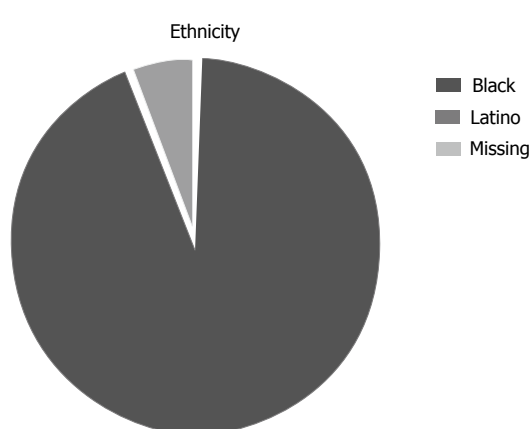


Figure 3 Ethnicity.

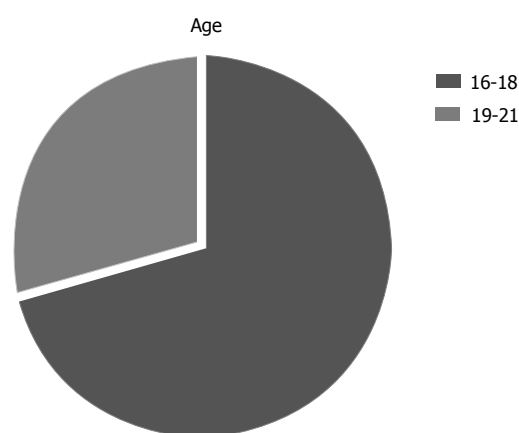


Figure 4 Age.

higher at 9% (95%CI: 5%-14%) in the subgroup of sexually active patients than in the overall group.

The only patient characteristics with statistically significant associations with positive Chlamydia NAAT were sexual activity and lack of regular primary care (Table 2). All of the patients who tested positive were either Black or Latino, therefore other races were not included in the results table. The proportion of sexually active subjects was significantly higher in the 19-21

Table 2 Results and significant associations with patient characteristics

	Chlamydia positive <i>n</i> = 17, <i>n</i> (%)	Chlamydia negative <i>n</i> = 271, <i>n</i> (%)	<i>P</i> values Fisher's exact test
Chief complaint			0.514
Minor trauma	9 (53)	120 (44)	
Acute illness	5 (29)	90 (35)	
Other	3 (15)	37 (14)	
Age			0.346
16-18	12 (71)	208 (77)	
19-21	5 (29)	57 (21)	
Ethnicity			1.00
Black	16 (94)	230 (85)	
Latino	1 (6)	20 (7)	
Sexual activity	17 (100)	172 (68)	0.008+
Sex with men (y)	0 (0)	5 (2)	1.00
Previous STI	11 (65)	114 (42)	0.467
test (y)			
Previous STI (y)	3 (18)	14 (5)	0.099
Regular PMD (y)	9 (53)	192 (70)	0.044+

STI: Sexually transmitted infection.

Table 3 Differences in rates of sexual activity by age

Sexual activity	<i>n</i> (%)
16-18	148 (71)
19-21	54 (87)

Sixteen percent of difference in sexual activity rates between 16-18 and 19-21 years old age groups (95%CI: 10%-25%), *P* = 0.012.

year age group than the 16-18 year age group (Table 3 and Figure 5).

DISCUSSION

We found a 6.3% prevalence of Chlamydia and 0% prevalence of Gonorrhea in male patients 16-21 years presenting to the ED for non-STI related complaints. Our study confirms that the burden of disease among sexually active male adolescents is high when compared with public health department estimates. The New York City (NYC) public health department estimates a CT rate of 1343 cases per 100000 men (1.34%) between age 15-19 and 1847 per 100000 in men (1.85%) between age 20 and 24. Gonorrhea rates are estimated to be lower at 319 per 100000 (0.3%) in the 15-19 age group and 567 per 100000 (0.6%) in the 20-24 age group. These are less than half the rates reported in females^[8,10,17]. The NYC Department of Health and Mental Hygiene (DOHMH) collects data on all positive tests and relies on reported cases. Additionally, they exclude cases where age or gender information is missing - which could account for the relatively low rates in comparison with our findings.

Our numbers are comparable to studies that focus on targeted screening of undifferentiated symptomatic

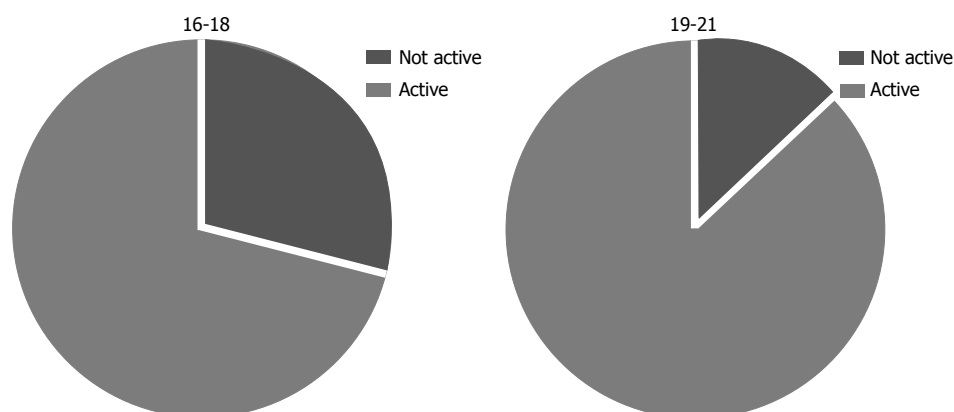


Figure 5 Differences in rates of sexual activity by age.

and asymptomatic male and female ED patients, which cite CT and GC rates in the young adult age group ranging from 4%-14%^[1,2,9,14,18].

These numbers indicate that the prevalence of disease in patients seeking care for reasons entirely unrelated to STI screening is significantly high. A sizeable number of patients with disease are likely being missed by not being screened. None of the patients in our study reported GU symptoms on initial presentation, and likely none would have been screened during their ED visit.

Many adolescents have no centralized primary care^[19]. They commonly seek health care only for non-preventive reasons, often in the ED setting, and males are even less likely to seek regular primary care than females^[20]. The acute care setting is ideal for screening adolescents who do not have regular primary care. Adolescents have been found to be responsive and agreeable to screening for STIs in the ED setting^[2,9,21-25]. However, in the current state there is a lack of consensus on whether the ED should provide routine preventive services^[26].

One of the challenges to stopping spread of CT is that infections are often asymptomatic in both males and females^[8,27,28]. Some studies report as many as 90% of infections in males being asymptomatic^[5,21]. Routine screening of all patients is therefore a crucial step in decreasing the burden of disease. The CDC currently recommends annual screening for all females, and biannual screening if high risk^[17]. Concise recommendations for males focus mostly on those who are incarcerated and those who have sex with men^[17]. We believe these recommendations are insufficient and lead to missed screening opportunities, contributing to spread of an easily treatable disease.

In addition to being feasible, screening efforts in the ED setting have been shown to be cost effective and to decrease the burden of disease^[29,30]. Opt-out screening in the ED setting using non-rapid technology in the setting of HIV has been shown to be feasible and effective^[31]. Given its success, we view opt-out screening as a potential model for how screening for other STIs such as CT and GC may be implemented.

There are several limitations to our study. Firstly, our sample size is relatively small due to lack of around the clock patient recruitment staff and relatively inconsistent recruitment efforts and training. Early in the study, the training of the enrollers was not as rigorous, and this likely lead to incomplete data collection (missing variables on several patients in Tables 1 and 2). We also did not collect comprehensive data on patients who declined. Over a 5 mo period, when data was collected on enrollment, we found that 39% of patients approached declined screening. We can only speculate that the IRB's requirement for parental consent contributed since it is higher than other similar studies on STD screening. We presume that younger patients may have not wanted to participate with their parents' knowledge and likewise some of these declinations could have been due to parental refusal to consent. Conversely, there could have been a selection bias; patients who agreed to participate could have been more likely to engage in risk-taking behavior or had unreported symptoms causing them to choose testing. Our patient population and thus our study sample was largely black and urban, which while consistent with studies of similar microorganisms in similar populations may not be generalizable to rural and more diverse populations in which other STIs we did not test for may be more prevalent^[1,2,9,14,18]. Lastly, the study was not powered to assess demographic and behavioral factors associated with having an STI, nor was it powered to assess feasibility, both of which are important ideas for future studies.

To our knowledge, our study is one of the only to date that focuses on targeting asymptomatic males for screening. Although the general prevalence was 6.3%, if the study were translated into an opt-out model for asymptomatic males, it would likely be closer to the 9% found in sexually active patients.

In conclusion, our results support the need for increased STI screening efforts in the acute care setting, particularly among asymptomatic sexually active young men. Increased screening and effective treatment has been shown to reduce both risk-taking behaviors^[32,33] and sequelae of disease^[2,34]. Young men

are well established as a vulnerable population who are likely to miss screening opportunities^[35]. Further studies should focus on expanded screening efforts including implementation of opt-out policies. Additionally, more comprehensive and demographic data on declination rates could help develop a targeted screening approach to maximize acceptance rates. Future studies should assess disease reduction as a result of new and improved screening interventions.

COMMENTS

Background

Chlamydia and Gonorrhea are the most common bacterial sexually transmitted infections. The sequelae of untreated disease include abscesses, chronic pelvic inflammation and infertility. Testing and treatment is inexpensive and easy. While screening practices in young women are well established, there is a paucity of concise screening recommendations in young men, in whom infection is often asymptomatic. The study investigates the prevalence of disease in asymptomatic young men being seen in the emergency department (ED) who would otherwise not have been screened.

Research frontiers

Adolescents are a generally healthy population and typically do not have regular primary care where most screening occurs. Particularly in poor communities, the ED is often the only place they are seen and evaluated by physicians and thus is an ideal setting for addressing public health issues.

Innovations and breakthroughs

Screening adolescents for sexually transmitted infections (STIs) in the ED setting has been well studied, however to our knowledge this is the only study focusing solely on young men who are both asymptomatic and presenting for low acuity issues, who might not otherwise have been screened.

Applications

Opt-out testing has been shown to be effective at achieving early diagnosis and treatment of HIV in sexually active adolescents and adults. By showing a significant burden of disease in asymptomatic patients who are not regularly screened in any other setting, they support the use of opt-out testing in the context of bacterial STIs as well as human immunodeficiency virus which could potentially significantly reduce spread of disease.

Terminology

The authors use the word screening to describe testing for a disease as a matter of routine rather than in response to symptomatology. The authors use the term adolescent to describe patients aged 16-21.

Peer-review

This is a very interesting paper.

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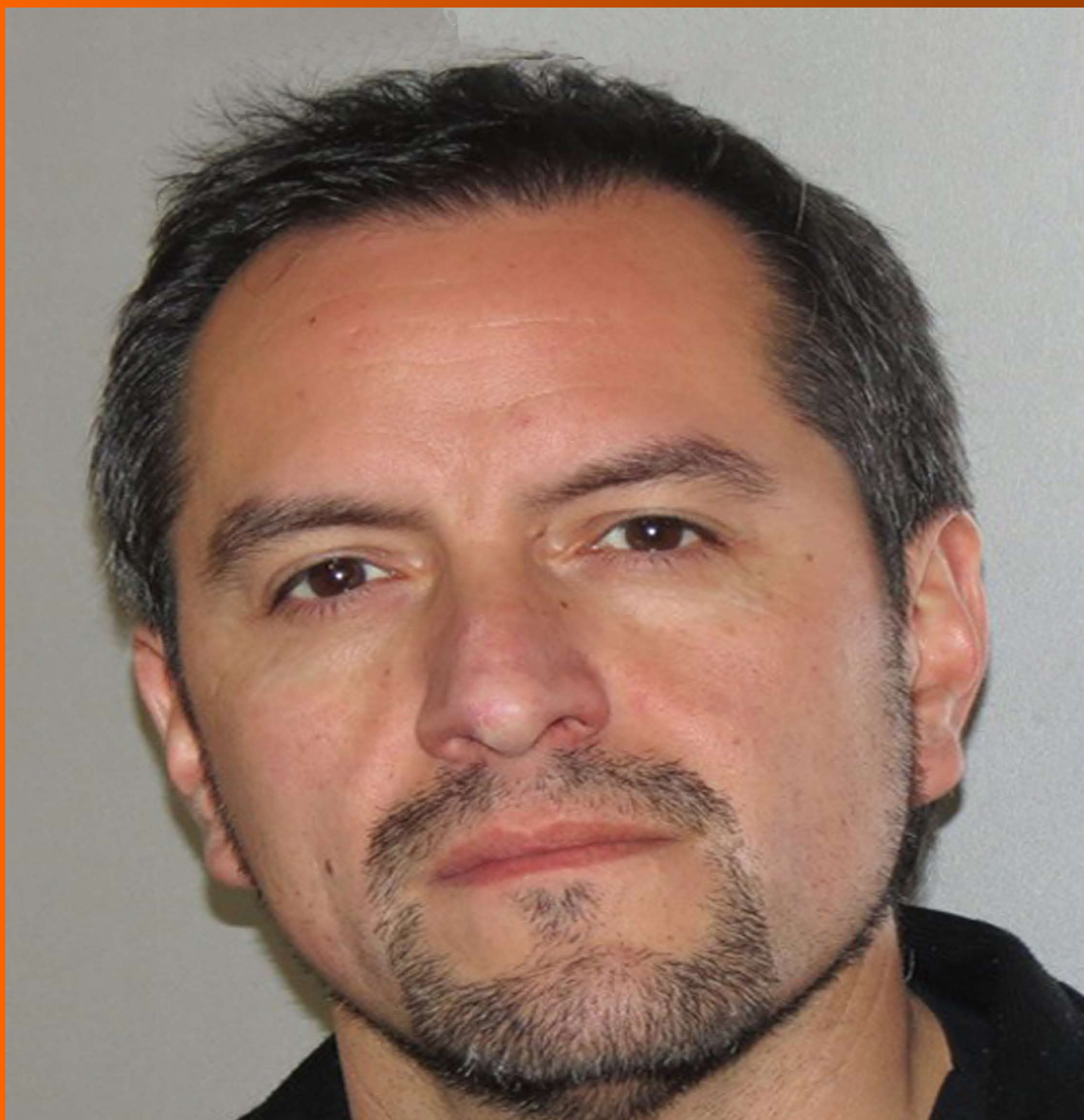


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Retrospective Study

Rhabdomyolysis with different etiologies in childhood

Demet Alaygut, Meral Torun Bayram, Belde Kasap, Alper Soylu, Mehmet Türkmen, Salih Kavukcu

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Abstract**AIM**

To investigate different etiologies and management of the rhabdomyolysis in children.

METHODS

Eight pediatric rhabdomyolysis cases who applied to the Dokuz Eylul University Faculty of Medicine Department of Pediatric Nephrology with different etiologies between January 2004 and January 2012 were evaluated in terms of age, gender, admission symptoms, physical examination findings, factors provoking rhabdomyolysis, number of rhabdomyolysis attacks, laboratory results, family history and the final diagnosis received after the treatment.

RESULTS

Average diagnosis ages of eight cases were 129 (24-192) $\pm$ 75.5 mo and five of them were girls. All of them had applied with the complaint of muscle pain, calf pain, and dark color urination. Infection (pneumonia) and excessive physical activity were the most important provocative factors and excessive licorice consumption was observed in one case. In 5 cases, acute kidney injury was determined and two cases needed hemodialysis. As a result of the further examinations; the cases had received diagnoses of rhabdomyolysis associated with mycoplasma pneumoniae, sepsis associated rhabdomyolysis, licorice-induced hypokalemic rhabdomyolysis, carnitine palmitoyltransferase II deficiency, very long-chain acyl-CoA dehydrogenase deficiency, congenital muscular dystrophy and idiopathic paroxysmal rhabdomyolysis (Meyer-Betz syndrome).

CONCLUSION

It is important to distinguish the sporadic and recurrent

rhabdomyolysis cases from each other. Recurrent rhabdomyolysis cases should follow up more careful and attentive.

Key words: Rhabdomyolysis; Children; Etiology; Acute kidney injury; Treatment; Hemodialysis

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Core tip: This is a retrospective study to evaluate rhabdomyolysis in childhood. Rhabdomyolysis could be caused by a number of reasons, which could be classified as sporadic and hereditary/recurrent. The initial point that is to attract attention in this manuscript is the importance of the rhabdomyolysis type (recurrent/sporadic). Even though rhabdomyolysis is not routinely involved in textbooks concerning neuromuscular diseases, it is an integral part of these diseases. It should be taken into consideration in the first diagnosis and clinical follow-up of patients. It is possible to encounter with a rhabdomyolysis attack in every case. But its treatment is different from that of a primary disease.

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INTRODUCTION

Rhabdomyolysis is a pathological condition that occurs as a result of musculoskeletal damage. Substances such as creatine kinase (CK), myoglobin, aspartate aminotransferase, alanine aminotransferase, and potassium pass from cells into circulation as a result of this damage^[1]. Among them, particularly myoglobin is substantially toxic for kidneys and causes acute kidney injury (AKI)^[2]. The syndrome generally presents with the triad muscle pain, weakness and dark urine^[3]. Nearly half of patients with rhabdomyolysis have these symptoms^[4]. For the clinician, suspicion starts with increase of creatinine kinase level. This suspicion is verified by measuring serum or urine myoglobin level^[4]. Rhabdomyolysis can result from a wide range of disorders. While 80% of the cause of rhabdomyolysis in adults is trauma and drugs, it is infections and congenital disorders in children^[4,5]. If rhabdomyolysis is recurrent, it is recommended to carry out some further examinations (muscle biopsy, metabolic and genetic tests). Early diagnosis is crucial to prevent AKI. Prevention is important in patients with inherited forms^[4]. The purpose of this article is to present eight pediatric cases with rhabdomyolysis diagnosis depending upon different etiologies.

MATERIALS AND METHODS

The study consisted of eight patients with rhabdomyolysis.

Medical files of cases, who were referred to Pediatric Nephrology of Medicine Faculty of Dokuz Eylül University, were retrospectively examined between the years of 2004 and 2012. The following parameters were recorded as age, gender, presenting symptoms, provocative factors, attacks number, positive physical examination findings, background and family history, laboratory results on admission, management, and final diagnosis. All cases were inquired at the admission time in terms of drug usage, infections, excessive physical activity, alcohol usage and herbal treatments. Family history was evaluated in terms of the individuals diagnosed with rhabdomyolysis in his/her family and neuromuscular diseases. In terms of etiology; further examinations were performed other than basic laboratory evaluation especially for the cases with recurrent rhabdomyolysis attacks. These consisted of serologic screening (Hepatitis, TORCH, EBV, Mycoplasma, Trichinella) in terms of infection parameters, bleeding profile and sepsis screenings, toxic screening, thyroid function test, ANA and ENA panels, lactic acid, ammonia, pyruvic acid levels, organic acid profile, acylcarnitine, total and free carnitine levels, metabolic screening (in terms of glucose and fat metabolism defects), electrography and echocardiography, electromyography (EMG), muscle biopsy and genetic studies. SPSS 18.0 - software package program was used to conduct statistical analysis.

RESULTS

Average diagnosis ages of eight cases, five of them being female, in the patient series was 129 (24-192 mo) $\pm$ 75.5. Examining the admission symptoms; all the patients in older age group had specified muscle pain, myalgia, calf pain, fatigue, and dark urination complaints. In two younger cases (case 1 and 7); dark color urination finding was the most remarkable finding. Cases 4 and 5 were also presented with muscle weakness. Additionally, first, second and seventh cases had cough and fever and third case had vomiting complaints. Examining the factors provoking rhabdomyolysis attack; infection (pneumonia) in three cases (case 1, 2, 7), excessive physical activity in three cases (case 4, 5, 8), both infection and excessive physical activity in one case (case 6), and excessive licorice consumption in one case (case 3) were observed. Assessing their physical examination findings on admission; three patients had fever over 38 degrees and bilateral crepitation in their pulmonary examination (case 1, 2, 7). Muscle strength loss was determined in upper and lower extremities in 2 cases (case 4, 5). Findings of volume loss were present in the third case but blood pressure was normal and the physical examinations of sixth and eighth cases were normal except for their muscle sensitivities. In the evaluation of personal backgrounds; case 7 was followed for epilepsy due to microcephaly. In cases 4, 5, 6 and 8, recurrent rhabdomyolysis attack was present. Also hemodialysis (HD) treatment was applied to case 6 at a different center due to a rhabdomyolysis attack 10 mo ago. Parents of cases 4, 5 and 6 were relatives. Cases 4 and 5 were siblings. In 4 of the cases;

Table 1 General characteristics of patients

Case no	Age (mo)	Gender	Presenting symptoms	Provocative factors	Positive physical examination findings	Past/family history	Attacks number
1	24	F	Dark colored urine, fever, cough	Infection	Fever, bilateral crepitations in chest examination	Unremarkable	1
2	84	F	Fever, cough, myalgia, calf pain, fatigue, dark colored urine	Infection	Fever, bilateral crepitations in chest examination	Unremarkable	1
3	192	M	Myalgia, calf pain, fatigue, dark colored urine, vomiting	Excess licorice use	Volume depletion signs, normal blood pressure	Unremarkable	1
4	132	F	Myalgia, calf pain, fatigue, muscle weakness, dark colored urine	Prolonged physical exercise	Muscle strengths 3-4/5 bilateral in upper and lower extremities	Recurrent rhabdomyolysis, parents are consanguineous	7
5	192	M	Myalgia, calf pain, fatigue, muscle weakness, dark colored urine	Prolonged physical exercise	Muscle strengths 3-4/5 bilateral in upper and lower extremities	Recurrent rhabdomyolysis, parents are consanguineous	6
6	192	F	Myalgia, calf pain, fatigue, dark colored urine	Infection, prolonged physical exercise	Muscle pain	Recurrent rhabdomyolysis, hemodialysis treatment 10 mo ago due to attack, parents are consanguineous	6
7	24	M	Dark colored urine, fever, cough	Infection	Fever, bilateral crepitations in chest examination	Epilepsy, microcephalia	1
8	192	F	Myalgia, calf pain, fatigue, dark colored urine	Prolonged physical exercise	Muscle pain	Recurrent rhabdomyolysis	3

M: Male; F: Female.

rhabdomyolysis attack was seen for the first time (case 1, 2, 3, 7), but it was the seventh rhabdomyolysis attack for the fourth case, sixth rhabdomyolysis attack for the fifth and sixth cases and third rhabdomyolysis attack of the eighth case. Table 1 illustrates general characteristics of the patients. In line with rhabdomyolysis; CK values of all the patients was > 1000 U/L, and their blood and urine myoglobin levels were additionally high. In none of the patients; hypoglycemia and cardiac enzyme increase were observed. In five cases, AKI was present (case 1, 2, 3, 4, 7). Table 2 illustrates laboratory results at the time of admission.

Hydration, alkalinization, electrolyte replacement if needed, antibiotics treatment and allopurinol were applied to all the patients. HD was applied to cases three and four. Examining in terms of etiology; the patients were diagnosed with rhabdomyolysis associated with mycoplasma pneumoniae, sepsis associated rhabdomyolysis, licorice-induced hypokalemic rhabdomyolysis, carnitine palmitoyltransferase II deficiency, very long-chain acyl-CoA dehydrogenase deficiency, congenital muscular dystrophy and idiopathic paroxysmal rhabdomyolysis (Meyer-Betz syndrome) (Table 3).

DISCUSSION

Rhabdomyolysis is a clinical result that may appear in numerous situations. In this article, eight cases with developed rhabdomyolysis related to different etiologies were assessed. Rhabdomyolysis is diagnosed when serum CK level exceeds 1000 U/L in case of absence of myocardial infarction^[5].

Some studies accept that serum myoglobin level of

> 300 ng/mL and urine myoglobin level of > 10 ng/mL are diagnostic^[6].

Presence of myoglobin in serum and its infiltration to urine turns the color of urine into red. While heme reaction occurs in urine sticks, it is typical not to observe erythrocyte in microscopy^[7]. Compared to CK, myoglobin is eliminated more quickly and if there is no myoglobinuria at high CK level, the diagnosis of rhabdomyolysis is not excluded^[8]. CK levels of all the patients was > 1000 and their concurrent blood and urine myoglobin levels were over the reference values. All of them had red or brown urine findings and no erythrocyte was observed in microscopy. Common symptoms include myalgia, muscle tenderness, and weakness. While numerous patients experience lower-leg pain, some patients may have nonspecific symptoms such as fever, fatigue, vomiting, and nausea^[8]. All the patients had applied with the above-mentioned common symptoms. Only the diagnosis of the 24-mo-old first and seventh cases was established with the red urine and laboratory values.

AKI is the most significant complication of rhabdomyolysis. It is defined as creatinine level above 97 percentile with respect to age and gender^[5]. Previous studies identified that rhabdomyolysis-related AKI was 17%-35% in adults and 42%-50% in children^[6,7,9]. If AKI is also comorbid in the cases with CK level above 10000 U/L, mortality rates reach up to 80%^[4]. In five of the cases in this series, AKI was determined at the time of admission.

We stated that infections were more critical in etiology of rhabdomyolysis in children compared to adults. Several causes of infection may be associated with rhabdomyolysis. Viral infections are responsible for one

Table 2 Laboratory results of patients on admission

Case No.	Hb g/dL	WBC /mm ³	Plt /mm ³	Glu mg/dL	BUN mg/dL	Creat mg/dL	CPK U/L	AST IU/L	ALT IU/L	LDH U/L	Uric acid mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	Urine myog. mg/dL	Blood myog. mg/dL
1	8.6	17.5	225	86	36	2.3	1158	451	3903	1227	6.1	139	4.2	110	8.6	4.5	193	155
2	12.9	6.5	93	102	65	4.7	12976	788	215	933	6.8	149	4.8	114	7.8	8.3	679	274
3	15.2	20.6	307	95	150	3.7	8379	780	250	1100	10	125	2.2	65	8.2	8.8	1370	3740
4	12.6	3.6	163	90	57	7	42670	998	249	1303	2.6	136	3.9	107	8.7	4.3	1200	1200
5	13.2	10.6	213	75	12	0.5	3012	210	664	1466	3.5	141	4.9	104	9.9	4.3	1200	1200
6	12.4	17.5	127	119	10	0.7	25983	338	87	1797	5	136	3.9	105	9.4	3.5	1200	1200
7	9.3	9.6	146	85	38	1.1	31119	683	235	1853	6.9	144	2.9	115	8.4	3.7	767	800
8	14.2	18.6	332	90	12.5	0.8	51228	1108	341	2381	2.3	135	3.7	107	10.1	3.6	800	1200

Hb: Hemoglobin; WBC: White blood cell; Plt: Platelet; Glu: Glucose in urine; CPK: Creatine phospho kinase; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase.

Table 3 Management and final diagnosis of patients

Case	Management	Renal replacement therapy	Final diagnosis
1	Antibiotic treatment, hydration, alkalinization	No	Rhabdomyolysis associated with Mycoplasma pneumoniae pneumonia
2	Antibiotic treatment, hydration, alkalinization, fresh frozen plasma	No	Sepsis, pneumoniae, rhabdomyolysis
3	Hydration, alkalinization, antiemetic, hemodialysis	Yes, HD	Licorice-induced hypokalemic rhabdomyolysis
4	Hydration, alkalinization, hemodialysis	Yes, HD	Rhabdomyolysis due to congenital palmitoyltransferase II deficiency
5	Hydration, alkalinization	No	Rhabdomyolysis with carnitine palmitoyltransferase II deficiency ?
6	Hydration, alkalinization	No	Rhabdomyolysis with very long-chain acyl-CoA dehydrogenase deficiency
7	Hydration, alkalinization	No	Rhabdomyolysis due to congenital muscular dystrophy
8	Hydration, alkalinization	No	Idiopathic paroxysmal rhabdomyolysis "Meyer- Betz Syndrome

HD: Hemodialysis.

third of the cases^[5,10] (Many infections are associated with rhabdomyolysis. While influenza takes place on the top among viral infection agents, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV) are the other causes^[4]. Although the pathophysiology is not presently clear, bacterial infections have also been associated with rhabdomyolysis. In a review in which 60 cases were reported, *Legionella* spp, *Francisella* spp, *Streptococcus* spp, *Salmonella* spp, and *Staphylococcus aureus* were determined as the most frequent factors^[11]. Rhabdomyolysis was also reported with *Enterococcus* species, *Pseudomonas aeruginosa*^[12], *Neisseria meningitidis*^[13], *Escheria coli*^[14], and *Haemophilus influenzae*^[15], *Mycoplasma pneumoniae*^[16], leptospirosis^[17], and *Coxiella burnetii* (Q fever)^[18]. In this case series; two cases (case 1, 2) had infection-associated rhabdomyolysis. Case 1 had applied with cough and high fever complaints and anemia (Hb 8.6 g/dL) reticulocytosis (8.5%), leukocytosis (17500) and acute renal insufficiency (BUN 36, creatinine 2, 3) were found in the laboratory examinations. Blood gas and urine analysis were normal. Concurrently AST, ALT, LDH, CPK and uric acid values were also found high. Empirical antibiotics treatment (IV clarithromycin), hydration and alkalinization were started to be given. Hemolysis findings were found in the

peripheral smear which was examined due to anemia, and direct combs test was found as + 2 positive. In the tests sent in terms of the infection agents; mycoplasma pneumoniae IgM was positive. The outcome was rapidly favorable, and she did not experience another attack. The family history was negative for the rhabdomyolysis. Mycoplasma pneumonia infection may lead to multiple organ involvement as well as it may be asymptomatic. 25% of the patients develop extrapulmonary complications (cardiovascular, gastrointestinal, hematologic, and central nervous system). These complications may occur before, during, and after the infection. Sometimes, they appear with autoimmune events without pulmonary findings^[19]. Formation of cold agglutinin which is observed in 10% of the patients also occur with this infection agent and is responsible for antibody-induced hemolysis^[20].

It has not been understood exactly yet why rhabdomyolysis develops during mycoplasma infections, however direct invasion of muscles by the organism or muscular damage resulting from immune reactions are considered as responsible^[16]. Although it is rare, rhabdomyolysis-induced AKI or glomerulonephritis, interstitial nephritis and nephrotic syndrome may develop with this infection^[20,21].

Renal biopsy was not administered to patient due

to normal complement levels, absence of nephrotic syndrome, and existence of an AKI that does not require dialysis. Diagnosis of the patient was supported with positive serum mycoplasma IgM titration, antibody-induced hemolysis, and rapid response to anti-mycoplasma antibiotic treatment. Second case was a 84-mo-old girl. While she was being followed up for pneumonia; sepsis chart (thrombocytopenia, hypotension, bradycardia and disseminated intravascular coagulation) was developed. Then, diagnosis of rhabdomyolysis was made due to acute renal insufficiency and high CK, LDH, AST, ALT values. The patient had recovered without the need of appropriate antibiotherapy, hydration and alkalization treatments and renal replacement treatment. Rhabdomyolysis attack of this patient did not repeat, and her family history was also negative. Sepsis-associated rhabdomyolysis was reported in numerous case reports^[22-25]. In this case, we could not show any specific agent in the blood culture that may cause sepsis. Also no causative agent was reported in some studies about sepsis and rhabdomyolysis^[26]. But specific causes such as blood pressure, electrolyte abnormalities, tissue hypoperfusion, hyperthermia, hypoxia, dehydration, and acidosis are known to induce rhabdomyolysis in any patient with a critical condition^[27]. However, sepsis-associated microorganisms were identified in very few original studies. Even though these studies reported that bacterial sepsis-induced rhabdomyolysis can develop with numerous types of microorganisms, Betrosian *et al.*^[11] stated that it may occur mostly with gram positive organisms and Kumar *et al.*^[27] indicated that they may develop mostly with gram negative organisms^[12,28].

Drugs, toxins and foods are other important causative factors for rhabdomyolysis. There are many drugs associated with development of rhabdomyolysis^[8]. Drugs cause rhabdomyolysis due to direct or indirect muscle damage. Toxin poisoning related rhabdomyolysis has been reported by using honeybees^[29], rattlesnakes^[30], and brown recluse spider bites^[31]. Carbon monoxide poisoning is another reason^[32]. All the patients were examined during the anamnesis in terms of drug and toxin exposure and there were no patients with positive findings. Foods may also be a triggering factor. The most remarkable example about this issue is consumption of licorice root which may lead to hyperaldosteronism, hypokalemia, and rhabdomyolysis^[33-35]. Third case was a 16-year-old male patient with chronic heavy cola consumption-associated rhabdomyolysis and AKI that were reported previously by Kasap *et al.*^[32] Due to the laboratory results that are concordant to hypokalemia, metabolic alkalosis, acute kidney insufficiency; diagnosis of hypokalemia associated metabolic alkalosis was made.

It was then learned from the history of patient that he/she was drinking about 1 lt of cola every day for 2-3 years. A substance was suspected causing the aldosterone effect with low serum plasma renin activity, normal aldosterone, and existence of hypokalemia. Licorice root in the cola consumed by the patient daily was emphasized. The patient was diagnosed with

hypokalemic rhabdomyolysis induced by the use of licorice root. HD was applied because of volume load and oliguria developing when the patient was treated with intravenous fluid therapy. Acute tubular damage was determined in the renal biopsy performed in order to exclude the underlying chronic renal disease.

Hereditary diseases, most of which are metabolic diseases, develop another group that cause rhabdomyolysis. It should be especially considered in the cases with positive rhabdomyolysis in the family history and with recurrent rhabdomyolysis attacks^[8]. Some individuals tend to have muscle damages especially after exercise. This low exercise tolerance is tried to be explained by CK-MM gene polymorphism and angiotensin-converting enzyme (ACE) polymorphism. C49T and C3788A genotypes of myosin light chain kinase cause CK level increased in response to exercise^[36]. When 114 asymptomatic patients varying between ages of 3 and 70 and with incidental CK level increase were evaluated; 18% metabolic or neuromuscular diseases were determined.

The most frequent diagnoses were carnitine palmitoyltransferase deficiency and malignant hyperthermia^[37]. Carnitine palmitoyltransferase deficiency was the most frequently observed disease in 36-patient series of idiopathic rhabdomyolysis^[38].

Long chain fatty acids (LCFA) are the major source of energy for muscles in case of prolonged exercise. These fatty acids which cannot passively pass into mitochondria move inside actively *via* carnitine palmitoyltransferase pathway in the outer membrane of mitochondria. This pathway consists of enzymes of carnitine palmitoyltransferase I located in the outer membrane and carnitine palmitoyltransferase II located in the inner membrane.

Autosomal recessive carnitine palmitoyltransferase II deficiency is the most frequent disorder in LCFA metabolism^[39]. Clinic of rhabdomyolysis accompanying this condition is considerably variable. CK levels are normal or slightly high between attacks of rhabdomyolysis induced by this enzyme deficiency, increase between attacks, and muscle pains occurring after exercise start as from the childhood^[40].

Enzyme analysis and mutation scanning should be performed for the diagnosis. Forth case in this article was an 11-year-old girl and we have learnt that she had complaints of not walking for a long distance, generalized muscle weakness from time to time, muscle cramps and dark colored urination problems from her early childhood ages. Her parents were relatives and her two brothers also had similar complaints. One of these brothers was the case five in our patient group. In CPT 2 gene; homozygote mutation was determined for SI13L. Genetic analysis was planned for his brother and possible CPT II deficiency was accepted.

Case six was a 16-year-old female patient who had applied with sixth rhabdomyolysis attack and was within acyl-CoA dehydrogenase (ACAD) family and taken the diagnosis of very long chain acyl-CoA dehydrogenase

(VLCAD) deficiency. Very long chain acyl-CoA dehydrogenase deficiency is an autosomal recessive disorder progressing with inability for beta oxidation of fatty acids in the mitochondria. Its three phenotypes that are associated with different mutations were identified. The first one is the most critical phenotype starting in newborn period and having high mortality progressing with hypertrophic cardiomyopathy and hypoketotic hypoglycemia. The second one is observed during infancy period. There is no cardiomyopathy. Hypoketotic or nonketotic hypoglycemia develops. Rhabdomyolysis occurring in case of hunger or after exercise in preadolescence period, like in our patient, exists in the muscle type with late onset^[41]. In the fibroblast culture of the case; very long chain acyl-CoA dehydrogenase activity was 4.3 nmol/min per milligram protein (controls: 5.1-21.7) ($n = 28$) and heterozygote carrier was found. Case seven was a patient who was followed up due to epilepsy, microcephaly and hypotonia and who had been diagnosed with infection-induced rhabdomyolysis. Myopathic findings were found in the electromyography and dystrophic changes were specified in the muscle biopsy. Visual examination and hearing test of the patient were normal. Congenital muscular dystrophies are a disease group which is clinically and genetically heterogeneous and is evident with early-onset and progressive muscle weakness. It has numerous genetic types that have been defined till now^[42]. Thus, it was decided to conduct a genetic study on the patient in order to determine the sub type.

Despite all the further examinations; it cannot be possible to find the reason of recurrent rhabdomyolysis in some patients and idiopathic recurrent rhabdomyolysis is known as "Meyer Betz Syndrome". In fact, this is an exclusion diagnosis. Case eight was reported by Kasap *et al.*^[43] previously. The patient was applied with rhabdomyolysis finding that was induced by excessive physical activity at the first attack and after two months, he had applied again with a moderate CK increase. Metabolic screening of the patient (blood acylcarnitine analysis, total and free serum carnitine levels, and blood lactic acid level were normal, or tests conducted in terms of fatty acid oxidation defect -) was normal. EMG was normal. Ischemic effort test was applied in order to exclude McArdle's disease. Blood lactate and ammonia levels examined before and after exercise were above the normal. This picture is not expected in McArdle disease. Thus, muscle biopsy was applied to the patient and no glycogen deposit was observed.

If rhabdomyolysis is suspected in terms of the history and laboratory independently from underlying etiology, aggressive fluid treatment should be immediately started with isotonic saline^[8]. Electrolyte abnormalities should be closely monitored and treated^[8]. After urine output was observed, the urine may be alkalized with sodium bicarbonate. Many authors suggest a high hydration value, like 200 mL/h, until CK level decreases below 1000 U/L. Of course, this should be performed in a more

controlled manner in pediatric cases. The indications for HD were severe hyperkalemia and prolonged oligo-anuric renal failure^[41]. Two patients in this series were applied with HD treatment because of prolonged oligoanuric phase and hypertension in case three and high creatinine level and also hypertension in case four.

As a consequence; although the rhabdomyolysis picture is basically presented to us together with the same clinical and laboratory results, clarification of the etiology should be the primary factor. Especially it is very important to distinguish the sporadic and hereditary cases from each other. It should be considered that the primary organ to be rescued in the acute period is the kidney and aggressive fluid therapy, alkalization and when needed, HD should be taken into consideration.

COMMENTS

Background

Rhabdomyolysis could be caused by a number of reasons, which could be classified as sporadic and hereditary/recurrent. All of the diseases causing rhabdomyolysis lead formation of cell membrane damage, hypoxia and lytic enzymes such as phospholipase A2, and decrease of energy source ATP as a result of cell's exposure to mechanical stress. Final outcome is disruption of intracellular ion balance, Ca concentration occurring within cell, hyperactivity in Ca-dependent proteolytic enzymes, and formation of oxidative free radicals. In the next periods, on the other hand, cell death occurs as a result of free radicals and proteases. It was intended to convey clinical and laboratory outcomes of rhabdomyolysis to reader and to identify extreme conditions within the scope of basic information. In this study, the authors evaluated clinical differences and etiologies of rhabdomyolysis in childhood.

Research frontiers

Rhabdomyolysis is an important clinical process in childhood. Clinicians must be keep in mind that sporadic and recurrent cases have different clinical properties.

Innovations and breakthroughs

Rhabdomyolysis is an important clinical situation. Clinician must be investigate it carefully. Unless a convenient treatment is performed, it will result in an acute kidney injury.

Terminology

Although the rhabdomyolysis picture is basically presented to us together with the same clinical and laboratory results, clarification of the etiology should be the primary factor. Especially it is very important to distinguish the sporadic and hereditary cases from each other. To concisely and accurately describe, define or explain the specific, unique terms that are not familiar to majority of the readers, but are essential for the readers to understand the article. AKI: Acute kidney injury; ACAD: Acyl-CoA dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BM: Blood myoglobin levels; BUN: Blood urea nitrogen; Ca: calcium; CPT II: Carnitinepalmitoyltransferase II enzyme; Ch: Chlor; CMV: Cytomegalovirus; Creat: Creatinine; CK: Creatinine kinase; EMG: Electromyography; EBV: Epstein-Barr virus; FDA: Food and Drug Administration; HD: Hemodialysis; Hb: Hemoglobin; HIV: Human immunodeficiency virus; K: Potassium; LDH: Lactate dehydrogenase; LCFA: Long-chain fatty acids; Na: Sodium; P: Phosphorus; PRA: Plasma renin activity; Plt: Platelet; UM: Urine myoglobin levels; VLCAD: Very long chain acyl-coA dehydrogenase; WBC: White blood cell.

Peer-review

The manuscript is a series of 8 case-reports occurring in children. I would thank the authors for these clinical cases that reminds us that rhabdomyolysis also occurs in children and that the etiologies are quite different from adults.

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Observational Study

Transition from early intervention program to primary school in children with autism spectrum disorder

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Abstract

AIM

To evaluate the characteristics that are associated with successful transition to school outcomes in preschool aged children with autism.

METHODS

Twenty-one participants transitioning from an early intervention program were assessed at two time points; at the end of their preschool placement and approximately 5 mo later following their transition to school. Child characteristics were assessed using the Mullen Scales of Early Learning, Vineland Adaptive Behaviour Scales, Social Communication Questionnaire and the Repetitive Behaviour Scale. Transition outcomes were assessed using Teacher Rating Scale of School Adjustment and the Social Skills Improvement System Rating Scales to provide an understanding of each child's school adjustment. The relationship between child characteristics and school outcomes was evaluated.

RESULTS

Cognitive ability and adaptive behaviour were shown to be associated with successful transition to school outcomes including participation in the classroom and being comfortable with the classroom teacher. These factors were also associated with social skills in the classroom including assertiveness and engagement.

CONCLUSION

Supporting children on the spectrum in the domains of adaptive behaviour and cognitive ability, including language skills, is important for a successful transition to school. Providing the appropriate support within structured transition programs will assist children on the spectrum with this important transition, allowing them to maximise their learning and behavioural potential.

Key words: Autism spectrum disorder; School transition; Primary school; Outcomes

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Core tip: Assess, address and communicate children's strengths and difficulties during the transition to school process for better outcome including language skills, cognitive ability and adaptive function.

INTRODUCTION

Children with autism often find change difficult. This makes transitioning between different settings and stages of life particularly challenging^[1]. In this regard, transition to primary school from preschool settings or early intervention programs is particularly significant as this is a major transition point in the child's life. A successful start to school has been defined as consisting of feeling secure and comfortable in the new school environment, increased academic and social skills, increased independence, engagement and motivation to participate in class and school activities^[2]. It is also associated with academic progress, positive relationships with peers and teachers, positive attitudes and feelings about school and learning, and a sense of wellbeing, belonging and inclusion^[2]. There is evidence to suggest that children who have a positive start to school are likely to engage well and experience academic and social success^[3,4]. While there have been some efforts to provide specific programs to support transition to school, this is often targeted broadly for children with a disability and not specific to children on the autism spectrum, who arguably have individualised transition support needs^[3]. Children with autism attend a variety of school settings including mainstream schools, specialised support classes within mainstream settings, specialised schools or centres^[5].

Children with autism have a greater risk of poor school outcomes, including emotional and behavioural problems^[6], bullying^[7], school exclusion^[8] and peer rejection^[9]. It is therefore critical that both the barriers and protective factors for a positive transition for children with autism are well understood. However, there is a lack of empirical research that examines the transition to school for children with autism, and existing research on primary school transition has tended to adopt cross-sectional survey based methodology^[3,4,10,11], rather than longitudinal designs with specific measurement of children's social, emotional, adaptive, cognitive and academic progress. A large number of school transition practices has been identified and endorsed from these survey studies; however, the adequacy of these practices has not been established. There is a need to understand the specific support needs of children on the autism spectrum in order to develop evidence based programs to enhance the school transition process. Additionally, a more systematic monitoring of developmental and behavioural progress, using standardised instruments, is also required in order to understand transition outcomes for children with autism^[12].

This project aimed to evaluate transition to school outcomes for children transitioning from early intervention settings to primary school. It also aimed to

Eapen V, Grove R, Aylward E, Joosten AV, Miller SI, Van Der Watt G, Fordyce K, Dissanayake C, Maya J, Tucker M, DeBlasio A. Transition from early intervention program to primary

determine the individual characteristics associated with successful transition to school in children on the autism spectrum.

MATERIALS AND METHODS

Participants

Data were collected from children with a confirmed diagnosis of autism who were transitioning to school from six early intervention centres [Autism Specific Early Learning and Care Centres (ASELCCs)] across six states in Australia in 2016. The early intervention programs provided at each ASELCC were varied and included manualised programs like the Early Start Denver Model^[13] and the SCERTs program^[14], through to other programs based on evidence based principles that are still to be manualised. This total sample of 21 participants included 3 females (14%) and 18 males (86%). The mean age of the sample at exit from the centres was 5.4 years (SD = 0.4). Children had been attending the centre for a mean duration of 23 mo (SD = 9.9).

Design

Data were collected at two time points; at the end of the preschool placement and approximately 5.4 (SD = 1.8) months later following their transition to school. A number of measures were administered at the end of the early intervention program. These included the Mullen Scales of Early Learning (MSEL)^[15], Vineland Adaptive Behaviour Scales (VABS)^[16], Social Communication Questionnaire (SCQ)^[17,18], and the Repetitive Behaviour Scale (RBS)^[19]. There were a number of outcome measures that were collected following transition to school. Teachers were asked to complete the Teacher Rating Scale of School Adjustment (TRSSA)^[20] and the Social Skills Improvement System Rating Scales (SSIS)^[21]. Parents were also asked to rate their child on the parent form of the SSIS. Parents were also asked questions about their child's school placement.

Measures

MSEL: The MSEL^[15] is a standardised assessment which provides a measure of cognitive and motor development in children from birth to 68 mo. The MSEL consist of four subscales evaluating visual reception, fine motor, and receptive and expressive language skills. Developmental quotients (DQs) were calculated for each subscale of the MSEL by dividing each child's age equivalent score by their chronological age at the time of testing and multiplying by 100^[22] given that a number of children in the sample did not receive MSEL subscale raw scores that were high enough for calculation of a meaningful *t* score (*i.e.*, they were performing at a level < 0.1 percentile).

VABS: The VABS second edition^[16] evaluates parent perceptions of their child's adaptive functioning in a number of domains including communication, daily living skills, socialisation and motor skills. A norm-referenced standardised score with a mean of 100 and SD of 15 is calculated for each domain. This is also calculated for the

overall adaptive behaviour index. VABS scale scores with a mean of 15 and an SD of 3 are calculated for each sub-domain. Higher scores are indicative of better adaptive function.

Social communication questionnaire: The SCQ^[17,18] is a 40 item parent report measure evaluating autism symptoms, with a total score above 15 indicating probable autism^[18].

RBS: The RBS^[19] is a 44 item parent report questionnaire designed to evaluate repetitive behaviour in children with autism. The RBS consists of six subscales including stereotyped, self-injurious, compulsive and ritualistic behaviour, as well as restricted interests. Higher scores indicate a greater presence of repetitive behaviours.

SSIS: The parent and teacher SSIS^[21] were included in the project to collect information on children's social skills development following their transition to school. The SSIS includes subscales evaluating social skills, including communication, cooperation, assertion, responsibility, empathy, engagement and self-control. It also evaluates problem behaviours, including bullying, hyperactivity/inattention, and symptoms of autism. A measure of academic competence is also included on the teacher rating form. Standard scores and percentile ranks are calculated for the social skills and problem behaviours composite scales.

TRSSA: TRSSA^[20] is a 52 item measure that assesses adjustment to the school or classroom setting. It consists of five subscales including independent participation, cooperative participation, teacher's perception of children's school liking, teacher's perception of children's school avoidance, and teacher's perception of children's interest/comfort with the teacher. Higher scores on these subscales indicate a higher frequency of this behaviour.

Semi-structured interview: Parents completed a semi-structured interview following their child's transition to school. This was included in order to provide details regarding their child's school placement setting and experience of starting school.

Statistical analysis

The TRSSA and teacher rated SSIS were assessed as outcome variables of successful school transition. Cognitive ability, adaptive behaviour, autism symptoms and repetitive behaviours at exit from early intervention were entered into correlation analyses to evaluate their relationship with the TRSSA and teacher SSIS at school follow up. In order to account for the multiple comparisons and minimise type I errors alpha was set at $P = 0.01$ across all analyses.

RESULTS

School placement details

A large proportion of the sample (94%) transitioned

Table 1 Correlation between Teacher Rating Scale of School Adjustment and child characteristics at exit (*n* = 21)

	Cooperative participation	Independent participation	Likes School	Avoids School	Comfortable with teacher
Cognitive ability (MSEL)					
Visual reception	0.317	0.442	0.26	0.406	0.574 ^a
Fine motor	0.318	0.486	0.454	0.421	0.622 ^a
Receptive language	0.469	0.488	0.364	0.289	0.598 ^a
Expressive language	0.453	0.603 ^a	0.316	0.284	0.635 ^a
Early learning composite	0.453	0.603 ^a	0.316	0.284	0.635 ^a
Adaptive function (VABS)					
Communication	0.596 ^a	0.588 ^a	0.124	-0.018	0.493
Daily living skills	0.531	0.505	0.051	-0.212	0.355
Socialisation	0.411	0.555 ^a	0.22	0.045	0.519
Motor skills	0.568 ^a	0.721 ^b	0.445	-0.004	0.621 ^a
Adaptive behaviour composite	0.567 ^a	0.727 ^b	0.332	-0.031	0.621 ^a
Autism symptoms (SCQ)					
Total score	0.027	-0.156	-0.286	-0.254	-0.493
Repetitive behaviours (RBS)					
Stereotypic	-0.206	-0.248	0.209	0.129	-0.044
Self-injurious	0.204	0.301	0.353	0.454	-0.025
Compulsive	-0.188	-0.101	0.313	0.09	-0.065
Ritualistic	0.28	0.319	0.343	0.4	0.021
Restricted interests	-0.177	-0.258	0.189	0.49	-0.381

^a*P* < 0.05, ^b*P* < 0.01. MSEL: Mullen Scales of Early Learning; VABS: Vineland Adaptive Behaviour Scales; SCQ: Social Communication Questionnaire; RBS: Repetitive Behaviour Scale.

from the early intervention centres to a full time (5 d a week) school program. Fifty-six percent transitioned to a mainstream setting, with 29% enrolled in a specialised school setting, 10% attending a mixed mainstream and special school, and 5% a special class in a mainstream school setting. Parents reported that the experience of starting school ranged from very good (53%) to fairly good (37%), with a smaller proportion indicating that their experience was just ok (5%) or not very good (5%).

Predictors of transition outcomes at school follow up

Correlations were conducted to evaluate the relationship between the child measures at exit and teacher ratings on the domains of the TRSSA and SSIS following transition to school. Results are presented in Tables 1-3.

TRSSA: Table 1 outlines the relationship between the TRSSA and child characteristics including cognitive ability, adaptive function and autism symptoms. Results indicated a significant positive relationship between scores on the MSEL and the TRSSA, with visual reception, fine motor skills and receptive and expressive language shown to be positively associated with comfort with the teacher. Expressive language skills were also associated with increased independent participation in the classroom.

Communication skills, as measured by the VABS, were also positively associated with both cooperative and independent participation in the classroom. Motor skills and overall adaptive function were also positively related to both forms of classroom participation, as well as comfort level with the teacher. There was no relationship between autism severity or repetitive behaviours and the TRSSA.

SSIS: There were a number of associations between scores on the social skills subscales of the SSIS and child characteristics at exit (Table 2). All subscales of the MSEL were positively associated with the communication, assertion, empathy and engagement subscales of the SSIS. Receptive and expressive language skills were also related to overall teacher rated social skills.

Results indicated a significant positive relationship between all subscales of the VABS and communication and engagement on the teacher rated SSIS. The overall adaptive behaviour composite score was also shown to be associated with communication, assertion, empathy, engagement and social skills.

As noted for the TRSSA, there were no significant relationships between autism symptoms or repetitive behaviours and the social skills subscales of the SSIS. There was no significant relationship between cognitive ability, adaptive function, autism symptoms or repetitive behaviour and the problem behaviour subscales of the SSIS (Table 3).

DISCUSSION

This study evaluated the characteristics associated with transition to school outcomes in children transitioning from early intervention to their first year of school. There were a number of significant relationships between child characteristics at exit and school transition outcomes. Cognitive ability, including visual reception, fine motor skills and receptive and expressive language were positively associated with the level of comfort children showed with their classroom teacher. Expressive language skills and overall scores on the MSEL were also associated with increased independent participation in the classroom. This indicates that cognitive ability, and particularly

Table 2 Correlation between the social skills subscales of the Social Skills Improvement System Rating Scales and child characteristics at exit ($n = 21$)

	Communication	Cooperation	Assertion	Responsibility	Empathy	Engagement	Self-control	Social skills scale
Cognitive ability (MSEL)								
Visual reception	0.590 ^a	-0.065	0.660 ^a	0.114	0.591 ^a	0.697 ^b	0.161	0.468
Fine motor	0.606 ^a	-0.03	0.671 ^a	0.14	0.574 ^a	0.733 ^b	0.182	0.492
Receptive language	0.665 ^a	0.101	0.718 ^b	0.29	0.574 ^a	0.792 ^b	0.326	0.600 ^a
Expressive language	0.784 ^b	0.151	0.793 ^b	0.259	0.651 ^a	0.833 ^b	0.321	0.655 ^a
Early learning composite	0.784 ^b	0.151	0.793 ^b	0.259	0.651 ^a	0.833 ^b	0.321	0.655 ^a
Adaptive function (VABS)								
Communication	0.732 ^b	0.076	0.597 ^a	0.416	0.563 ^a	0.698 ^b	0.319	0.591 ^a
Daily living skills	0.656 ^a	0.145	0.497	0.437	0.479	0.570 ^a	0.372	0.548
Socialisation	0.677 ^a	-0.099	0.695 ^b	0.195	0.443	0.634 ^a	0.096	0.464
Motor skills	0.799 ^b	0.329	0.836 ^b	0.35	0.529	0.717 ^b	0.343	0.680 ^a
Adaptive behaviour composite	0.815 ^b	0.136	0.821 ^b	0.338	0.580 ^a	0.762 ^b	0.261	0.647 ^a
Autism symptoms (SCQ)								
Total score	-0.28	0.482	-0.4	0.218	-0.245	-0.256	0.289	-0.032
Repetitive behaviours (RBS)								
Stereotypic	-0.45	0.09	-0.331	-0.244	-0.358	-0.187	-0.346	-0.294
Self-injurious	0.107	0.29	0.168	0.222	-0.084	0.303	0.239	0.213
Compulsive	-0.291	0.099	-0.095	-0.194	-0.195	-0.03	-0.211	-0.153
Ritualistic	0.176	0.396	0.199	0.322	-0.044	0.319	0.317	0.289
Restricted interests	-0.38	0.035	-0.362	-0.029	-0.405	-0.121	-0.089	-0.201

^a $P < 0.05$, ^b $P < 0.01$. MSEL: Mullen Scales of Early Learning; VABS: Vineland Adaptive Behaviour Scales; SCQ: Social Communication Questionnaire; RBS: Repetitive Behaviour Scale.

Table 3 Correlation between the problem behaviours subscales of the Social Skills Improvement System Rating Scales and child characteristics at exit ($n = 21$)

	Bullying	Hyperactivity/inattention	Externalising	Internalising	Problem behaviours scale	Academic competence scale
Cognitive ability (MSEL)						
Visual reception	0.233	0.005	0.218	-0.145	0.001	0.158
Fine motor	0.232	0.013	0.245	-0.28	0	0.101
Receptive language	0.097	-0.086	0.145	-0.167	-0.066	0.201
Expressive language	0.158	-0.119	0.146	-0.204	-0.08	0.093
Early learning composite	0.158	-0.119	0.146	-0.204	-0.08	0.093
Adaptive function (VABS)						
Communication	-0.083	-0.315	-0.095	-0.476	-0.374	-0.214
Daily living skills	-0.099	-0.374	-0.201	-0.452	-0.415	-0.025
Socialisation	0.243	-0.006	0.245	-0.237	-0.051	0.013
Motor skills	0.166	-0.186	0.113	-0.078	-0.104	0.384
Adaptive behaviour composite	0.149	-0.164	0.125	-0.257	-0.171	0.227
Autism symptoms (SCQ)						
Total score	-0.382	-0.296	-0.443	0.497	-0.138	0.404
Repetitive behaviours (RBS)						
Stereotypic	-0.228	0.023	-0.05	0.088	0.113	0.334
Self-injurious	0.004	-0.112	-0.031	0.255	0.033	0.41
Compulsive	-0.032	0.133	0.136	0.267	0.256	0.314
Ritualistic	-0.147	-0.188	-0.098	0.237	-0.045	0.36
Restricted interests	-0.140	0.075	0.031	0.317	0.17	0.179

MSEL: Mullen Scales of Early Learning; VABS: Vineland Adaptive Behaviour Scales; SCQ: Social Communication Questionnaire; RBS: Repetitive Behaviour Scale.

language skills, play a role in successful transition to school for children with autism. This is consistent with previous research highlighting that children on the spectrum with a higher level of skills, particularly in communication, tend to make more progress over time^[12]. Interestingly, the current research also indicates that these skills are also associated with being comfortable with the teacher in the school environment.

Communication skills, as measured by the VABS, were also positively associated with both cooperative and independent participation in the classroom. Motor skills and overall adaptive function were also positively related to both forms of classroom participation, as well as comfort level with the teacher. Previous research has highlighted that both independent and cooperative participation in the classroom are critical to a child's

achievement and educational progress^[23]. These findings therefore have clinical implications for transition practices.

Interestingly, while there were a number of cognitive and adaptive characteristics that were associated with successful transition to school for children with autism, there was no relationship between autism severity or repetitive behaviours and transition outcomes. This has important clinical implications for transition practices, as it indicates that autism symptoms were not the most important predictors of transition outcomes for children with autism exiting early intervention. This highlights that it is cognitive, language and adaptive functioning that are critical to successful transition to school.

Taken together, these findings indicate the need to assess and address cognitive ability, communication skills and adaptive function for better transition to school outcomes for children on the autism spectrum. Understanding and supporting any communication and cognitive difficulties will be of significant benefit to children with autism transitioning to school.

There were also a number of significant associations between child characteristics at exit and the social skills subscales of the teacher rated SSIS. Cognitive ability, as measured by the MSEL, was positively associated with communication, assertion, empathy and engagement. Receptive and expressive language skills were also positively related to overall social skills. This indicates the importance of cognitive ability and language in the development of social skills, particularly in the classroom environment. This is consistent with previous research outlining the link between language and social skills in autism^[24].

Results indicated a significant positive relationship between all subscales of the VABS and communication and engagement on the teacher rated SSIS, highlighting the importance of adaptive function in relating to others. The overall adaptive behaviour composite was also shown to be associated with communication, assertion, empathy, engagement and social skills. This highlights the importance of adaptive behaviours in the development of social skills and school transition.

As noted for the TRSSA, there were no significant relationships between autism symptoms or repetitive behaviours and the social skills subscales of the SSIS, highlighting that autism symptom severity is not a significant barrier to school transition and less important than the language, cognitive and adaptive skills of the child. There was also no relationship between child characteristics at exit and the problem behaviour subscales of the SSIS, indicating that cognitive ability and adaptive function are more important in the development of participation in the classroom, level of comfort with the teacher and social skills but do not play as much of a role in the number of problem behaviours reported by school teachers.

Limitations

The response rate for this study was low, resulting in a limited sample size. This made it difficult to include

models with a large number of predictors and correlates. Future research is warranted to replicate these findings within a larger sample. The findings from the current study would also benefit from the inclusion of a comparison group of children without a diagnosis of autism, as well as children who may not have transitioned from targeted early intervention settings. Future research incorporating these comparisons would allow for a more fine grained understanding of the unique challenges that are associated with children attending more specialised intervention programs and those receiving support in the community.

The results of the study indicated that child characteristics, including cognitive ability and adaptive function had a significant influence on transition to school outcomes for preschool aged children with autism. It is important to target relevant issues as they emerge across both home and school contexts. Targeting these issues in early intervention programs will assist children on the spectrum with this important transition, allowing them to maximise their learning and behavioural potential.

COMMENTS

Background

Transition from early intervention programs to the school setting can be a challenging time for children with autism. While a number of programs have been implemented to support transition to school, these have not been specifically tailored for children with autism. Children who have a positive start to school are more likely to experience academic and social success. This highlights the importance of effectively supporting children on the spectrum to experience a positive transition from early intervention services to primary school.

Research frontiers

This study aimed to evaluate the characteristics that are associated with successful transition to school outcomes in preschool aged children with autism. This study addresses an area that is currently under researched.

Innovations and breakthroughs

Cognitive ability and adaptive behaviour were shown to be associated with successful transition to school outcomes for children with autism. These factors were also associated with social skills in the classroom including assertiveness and engagement.

Applications

Understanding the factors associated with successful school transition will enable the development of guidelines for service providers and families to assist children on the spectrum to achieve academic and social success.

Terminology

ASELCC: Autism Specific Early Learning and Care Centres; MSEL: Mullen Scales of Early Learning; VABS: Vineland Adaptive Behaviour Scales; SCQ: Social Communication Questionnaire; RBS: Repetitive Behaviour Scale; TRSSA: Teacher Rating Scale of School Adjustment; SSIS: Social Skills Improvement System Rating Scales.

Peer-review

The paper is well-written and has interesting findings.

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Neonatal pyknocytosis in a preterm dizygotic twin

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Abstract

Infantile pyknocytosis (IP) is a rare, self-limited neonatal haemolytic anaemia that may require multiple blood transfusions. Only a little more than 50 cases have been reported in the medical literature, and the great majority of them concerns term infants. The etiology of IP is not well understood; most likely it results from a transient extra-corpuscular factor, whose nature is unknown, transmitted from mother to child or, alternatively, from a deficiency of an anti-oxidative agent. We report the case of two preterm twins, one of which suffered from IP and developed severe anaemia at age 2 wk, while the other was unaffected. Although no specific agent was identified as the cause of anaemia and IP, we speculate that the transmission of an agent from mother to child was unlikely, as only twin one suffered from IP. Smelly greenish diarrhoea occurred just before the presentation of IP, suggesting that the same agent led to both the diarrhoea and the oxidative injury. Because IP may remain underdiagnosed, it should be considered in cases of early unexplained severe hemolytic anemia.

Key words: Infantile pyknocytosis; Glucose-6-phosphate

dehydrogenase deficiency; Anemia; Oxidative stress; Hemolysis

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Core tip: This manuscript describes the first case of infantile pyknocytosis affecting only one of the twins, and contributes to understand the etiology of infantile pyknocytosis.

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INTRODUCTION

Premature neonates commonly experience a fall in haemoglobin concentration. This has been termed “physiologic” anaemia of prematurity, since it is commonly not associated with any abnormalities in the red blood cells (RBCs). Repeated blood sampling and many diseases of prematurity can worsen this “physiologic” anaemia. However, more rare underlying diseases may mimic anaemia of prematurity or increase its severity.

Infantile pyknocytosis (IP) was first described by Tuffy *et al.*^[1] and is characterized by a self-limited neonatal haemolytic anaemia, which may require multiple blood transfusions. The aetiology of IP is unclear. Pyknocytes most likely result from a transient extracorporeal factor, whose nature is unknown^[2]. An exogenous oxidative agent transmitted from mother to child or a deficiency of an anti-oxidative agent has been hypothesized^[3].

We report the case of two Caucasian female preterm twins, one of whom suffered from IP and developed severe anaemia at age 2 wk. We discuss factors possibly associated with IP.

CASE REPORT

A dizygotic twin pregnancy resulted from an *in vitro* fertilization-embryo transfer. There was no familial history of unexplained transient neonatal anaemia.

Preterm labour occurred at 32 wk’ gestation, and an emergency caesarean section was required due to breech presentation.

Twin 1 (first born). The Apgar score was 8 and 9 at the 1st and 5th min respectively, birth weight was 1735 g, length was 39 cm and cranial circumference was 25 cm. At birth, the red blood cell count and haemoglobin levels were normal (Figure 1). On day three the neonate suffered from jaundice and required phototherapy. The clinical course was uneventful until day 10, when

stools became smelly and the baby required further phototherapy. The fecal occult blood test was positive.

On day 17 she was referred to our neonatal intensive care unit because of jaundice, foul-smelling greenish diarrhoea and worsening anaemia, which required a packed RBC transfusion.

The reticulocyte count was 169 per milliliter. Liver and renal function tests were normal. A direct antiglobulin test and search for irregular agglutinins were negative; haemoglobin electrophoresis as well as glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase activity were normal, while lactate dehydrogenase was mildly abnormal (518 U/L). Bacterial cultures were sterile; detailed viral investigations yielded normal results.

A peripheral blood smear demonstrated high rates (> 25%) of irregularly contracted, bite, and densely stained RBCs (Figure 2). The morphological changes in the RBCs accompanied with normal enzyme activity led us to suspect IP.

The jaundice worsened further on day 19, and additional phototherapy was administered. A further packed RBC transfusion was given on day 28. Subsequently the infant recovered spontaneously, and no further transfusions were given.

At age 5 mo both the haemoglobin level and RBC morphology were normal. G6PD test yielded normal result, confirming overall the initial diagnosis of IP. Twin 2 (second born). The Apgar score was 8 and 9 at the 1st and 5th min respectively.

The birth weight was 1760 g, the length 45 cm and cranial circumference 30 cm. The newborn had mild jaundice (maximum bilirubin levels 90.4 mg/L) on day five. Thereafter her clinical course was uneventful and she never suffered from anaemia. The haemoglobin level was 135 g/L on day 25.

DISCUSSION

Pyknocytes are small, irregular, distorted erythrocytes, which are densely stained in a peripheral blood smear. A low percentage of pyknocytes is commonly found in healthy full-term neonates (from 0.3% to 1.9%) and preterm neonates (from 0.3% to 5.6%) during the first weeks of life^[1].

IP is a transient but often severe neonatal haemolytic anaemia associated with an accentuation of the physiologic presence of pyknocytes. Factors that increase oxidative stress may damage erythrocyte membranes, resulting in the formation of pyknocytes^[3]. Since IP was first described, only a little more than 50 cases have been reported in the literature and the great majority of IP cases concern term infants^[4]. The rarity of the disease as well as the lack of awareness about this cause of neonatal anaemia may lead to an underestimation.

IP may account for approximately 10% of cases of unexplained neonatal haemolytic anaemia^[3]. Most cases present during the first days of life, with neonatal

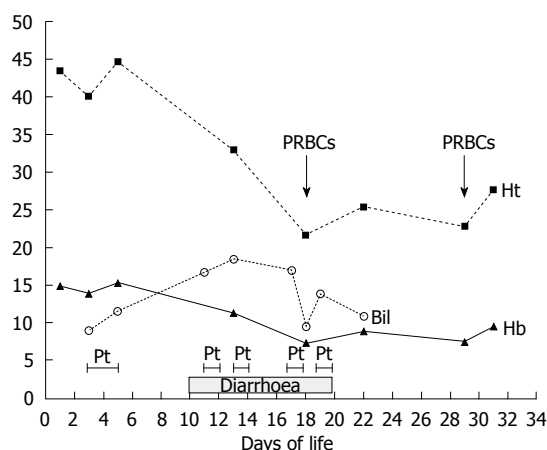


Figure 1 Twin 1 haematocrit, haemoglobin and bilirubin levels during the first month of life. Ht: Haematocrit; Hb: Haemoglobin; Bil: Bilirubin level; Pt: Phototherapy; PRBCs: Packed red blood cell transfusion.

jaundice as the first manifestation; approximately 70% of affected infants develop severe anaemia from the second to the fourth week of life, commonly requiring one or more packed RBC transfusions^[1,3]. Anaemia resolves spontaneously by the age of 4 to 6 mo^[5].

The aetiology of IP is unclear. A transient extra-corporeal factor damaging the erythrocyte membrane, rather than an intrinsic factor, has been implicated in the pathogenesis of the disease. Indeed, flow cytometric analysis has shown that morphological changes do not affect reticulocytes, suggesting that erythropoietin treatment could prevent severe anaemia^[3,6]. Furthermore, among the seven cases of pyknocytosis reported by Ackerman, two showed the same morphologic abnormalities even after exchange transfusion, suggesting that erythrocytes of donor origin may also be affected^[2]. There are only 2 reports of IP in twins; in all reported cases both twins were affected^[7,8].

Pyknocytes most likely result from a transient extra-corporeal factor, whose nature is unknown. Causes such as an exogenous oxidative agent or a deficiency of an anti-oxidative agent have been hypothesized^[3].

In the current case report, only twin one suffered from IP. Therefore the transmission of an oxidative agent from mother to child, as well as a familial susceptibility or a hereditary factor^[8,9] seem unlikely. Even if no specific agent was identified as the cause of the severe anaemia, the occurrence of smelly greenish diarrhoea was just before a decrease in haemoglobin and a rise in bilirubin levels, suggesting that the same cause, most likely an exogenous agent (perhaps infectious), and acquired after birth, led to both the diarrhea and the oxidative injury. Preterm birth possibly contributed to worsening the IP, as premature infants are more susceptible to oxidative stresses^[9].

In conclusion, this is first case of IP affecting only one of the twins. The most likely cause of IP was an exogenous oxidative agent associated with diarrhoea and not transmitted from mother to child.

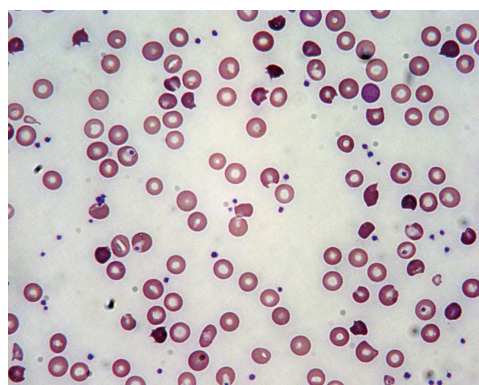


Figure 2 Twin 1 peripheral blood smear during the haemolytic phase of infantile pyknocytosis (magnetogastrogram x 400). Erythrocyte morphological changes: bite cells, irregularly contracted cells (pyknocytes). Changes are comparable to glucose-6-phosphate dehydrogenase deficiency.

COMMENTS

Case characteristics

A preterm female twin presented with recurrent jaundice and severe hemolytic anemia at age 2 wk.

Clinical diagnosis

The diagnosis was based on jaundice and hemolytic anemia.

Differential diagnosis

Common causes of jaundice and hemolytic anemia were excluded.

Laboratory diagnosis

Liver, renal tests, viral and bacterial cultures were normal.

Pathological diagnosis

A peripheral blood smear demonstrated high rates (> 25%) of irregularly contracted, bite, and densely stained red blood cells (supporting the diagnosis of pyknocytosis).

Treatment

The newborn underwent blood transfusions and phototherapy.

Related reports

Infantile pyknocytosis is a transient but often severe neonatal haemolytic anaemia associated with an accentuation of the physiologic presence of pyknocytes.

Term explanation

Infantile pyknocytosis is a rare, self-limited neonatal haemolytic anaemia characterized by high rates of pyknocytes (small, irregular, distorted, densely stained erythrocytes).

Experiences and lessons

Infantile pyknocytosis may remain underdiagnosed; it should be considered in cases of early unexplained severe hemolytic anemia.

Peer-review

The submitted paper by Alberto Berardi *et al.*, titled "Neonatal pyknocytosis in a preterm dizygotic twin", is very interesting, well structured, with clear presentation.

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