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ORIGINAL ARTICLE**Observational Study**

- 1 Brachial arteries sympathetic innervation: A contribution to anatomical knowledge
Ege F, Kazcı O

ABOUT COVER

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Observational Study

Brachial arteries sympathetic innervation: A contribution to anatomical knowledge

Fahrettin Ege, Omer Kazci

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Abstract

BACKGROUND

The sympathetic nervous system makes medium and large peripheral arteries smaller to slow the blood flowing through them.

AIM

To observe brachial artery sympathetic innervation.

METHODS

We developed a neurophysiological autonomous test that measured the effects of peripheral sympathetic fibres on peripheral arteries. Our specific objective was to find the sympathetic innervation of the brachial artery. To accomplish this purpose, the brachial artery baseline diameter and flow rate were measured in the right arm of the patients. Afterwards, electrical stimulus was applied to the medial nerve for 5 s. Through electrical sympathetic activation, the vessel diameter and overall flow rate will decrease. After 7 d, a similar experiment was repeated using the ulnar nerve.

RESULTS

The differences in diameter and flow rate of the brachial artery in response to median and ulnar nerve activation were compared. In the total group, no significant difference in diameter was seen between median and ulnar nerve stimulation ($P = 0.648$). The difference in absolute slowdown of flow rate between median nerve stimulation and ulnar nerve stimulation was not statistically significant for the entire group ($P = 0.733$).

CONCLUSION

As a target organ, the brachial artery receives an equal amount of sympathetic innervation from the median and the ulnar nerves.

Key Words: Median nerve; Ulnar nerve; Brachial artery; Sympathetic nervous system; Functional anatomy

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Core Tip: These observations imply that a peripheral nerve injury causes vasomotor paralyses and higher blood flow in large and medium arteries of extremities. Conversely, physiological activation of a peripheral nerve causes lower blood flow. Our study depended on this pathophysiological background and aimed to investigate the anatomical innervation of the brachial artery by utilizing a neurophysiological experiment. As a target organ, the brachial artery receives an equal amount of sympathetic innervation from the median and ulnar nerves. Expanding similar neurophysiological research to other arteries in the upper and lower limbs will contribute to the advancement of the field of functional neuroanatomy.

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INTRODUCTION

The sympathetic nervous system is primarily responsible for controlling the peripheral arteries[1]. However, there is insufficient information to determine which artery receives more postganglionic sympathetic innervation from which peripheral nerve. To our knowledge, there are only two post-mortem reports that compare the sympathetic fibre intensity of the median and ulnar nerves. The first report by Morgan *et al*[2] was a dark fluid fluorescence microscopic study; according to them, the sympathetic fibre density of the median nerve was higher than the ulnar nerve, particularly at the elbow level. The second report by Balogh *et al*[3] was a immunohistochemistry-assisted investigation; their findings indicated that there was no substantial variation in sympathetic fibre distribution between the median and ulnar nerves. While these two studies examined the density of sympathetic fibres of median and ulnar nerves, they could not make a claim about the effects of these fibres on target organs because such evidence (*e.g.*, specific proof intended for postganglionic innervation of the brachial artery) can only be demonstrated through functional autonomic tests.

The data presented here was composed of a subgroup from a larger unpublished and ongoing study where we are assessing the sensitivity of the brachial artery to sympathetic nervous system activity. It is well known in this field that the sympathetic nervous system narrows the diameter of medium and large peripheral arteries and decreases their blood flow[4]. Based on this knowledge, we developed a model that was analogous to the sympathetic skin response, in which the sympathetic sudomotor response was assessed *via* electrical stimulation of a peripheral nerve[5]. However, unlike the sympathetic skin response, this study did not assess the sudomotor but rather the vasomotor response by utilizing a Doppler ultrasound and focal electrical stimulation of a peripheral nerve.

With the aid of a neurophysiological autonomous test, our primary objective was to determine which peripheral nerve the brachial artery received more intense sympathetic innervation from.

MATERIALS AND METHODS

Subjects

This study conformed to the current version of the Declaration of Helsinki, and the protocols were authorized by the Clinical Research Ethics Committee at Ankara City Hospital No. 2 (Ethics approval No. E2-22-1307). This report followed the guidelines that are described in the "Preliminary Minimum Reporting Requirements for In-Vivo Neural Interface Research: Implantable Neural Interfaces"[6].

Subjects with polyneuropathy, median or ulnar neuropathy, peripheral artery diabetes mellitus, essential hypertension, and cardiac disease were excluded. Individuals experiencing numbness, paraesthesia, or discomfort in their hands were checked for a peripheral nerve injury 24 h prior to the test using a nerve conduction study in the electrophysiology laboratory. Subjects with abnormal values were also excluded. All of the study participants signed an informed consent.

Experimental Design

Nicotine, caffeine, alcohol, and exercise were restricted for 6 h prior to the test. The study was conducted at room temperature (22 °C-24 °C). For 5 min, participants rested in a seated position with

their forearms supinated. Afterwards, blood pressure, heart rate, and body temperature were measured; subjects who had abnormal values were excluded at this stage, including 1 male subject with high blood pressure ($> 135/85$ mmHg). A radiologist with 6 years of expertise in the field of Doppler imaging measured the right brachial artery baseline diameter and flow rate 2 cm above the antecubital fossa using a 9 Hz linear probe from a General Electric LOQIC P2 USG Doppler equipment (Figure 1A). The position of the probe was not changed, and images were continually obtained. Then, for 5 s, a 1 Hz electrical stimulus with an intensity of 10 mA was applied to the median nerve at the wrist level in the direction of the sensory fibres (orthodromic way) using the bipolar stimulus electrode from the Nihon Kohden MEB-9400A EMG/EP system (Figure 1B). On the fifth second of the electrical current, the diameter and flow rate of the brachial artery were measured once again. Through electrical sympathetic activation, the vessel diameter and overall flow rate decreased. We recorded the baseline and post-stimulus data from the brachial artery. After 7 d, the baseline diameter and flow rate measurements were repeated on the right arm with the same intensity of electrical current supplied to the ulnar nerve (Figure 1C). On the fifth second, images from the brachial artery were recorded once more. The differences in the diameter and flow rate of the brachial artery in response to median and ulnar nerve activation were compared.

Statistical Analyses

Frequency distributions for categorical variables and medians (min-max) for the numerical variables were presented. The Mann-Whitney *U* test was used to compare numerical variables between independent groups. For two of the dependent groups, numerical comparisons were made using the Wilcoxon test.

A *P* value of less than 0.05 was considered a statistically significant result. A statistical analysis was performed using the Statistical Package for Social Sciences for Windows software version 20.0. developed in Armonk, NY.

RESULTS

Females accounted for 46.7% of participants. All participants were between the ages of 20-years-old and 51-years-old, with a median age of 29-years-old.

The median flow rate of the brachial artery before the median nerve stimulus for the entire group was 79.80 (32.90-201.10) mL/min, whereas the post-stimulus flow rate was 44.00 (10.90-103.00) mL/min. This flow rate reduction was statistically significant ($P = 0.001$) (Table 1). The absolute decrease in the flow rate following the stimulus was 39.40 (19.90-124.50) mL/min on average. When the flow rate before the stimulus was compared to the flow rate after the stimulus, a median drop of 50.25% (28.97-71.84) was recorded.

For the entire group, the median diameter of the brachial artery before median nerve stimulus was 0.35 (0.26-0.50) cm, whereas the post-stimulus diameter was 0.31 (0.16-0.45) cm. The difference in diameter prior to and following the stimulus was determined to be statistically significant ($P = 0.001$) (Table 2). With stimulation, the absolute change in diameter was 0.05 (0.01-0.14) cm, and the percentage change in comparison to the original diameter was 14.63% (2.86-4.67).

For the entire group, the median flow rate of the brachial artery before ulnar nerve stimulus was 56.40 (28.10-214.00) mL/min, whereas the post-stimulus flow rate was 30.00 (15.00-78.00) mL/min. The difference between the two was statistically significant ($P = 0.001$) (Table 3). After ulnar nerve stimulation, the absolute decrease in flow rate was determined to be 25.10 (7.90-170.10) mL/min, whereas the percentage decrease was 48.08% (20.84-79.67).

The median diameter of the artery prior to ulnar nerve stimulation was 0.36 (0.23-0.50) cm, whereas the median diameter following the stimulus was 0.28 (0.19-0.48) cm. The difference in diameters prior to and following the stimulus was determined to be statistically significant ($P = 0.001$) (Table 4). With stimulation, the median absolute decrease in diameter was 0.04 (0.00-0.14) cm, and the median percentage decrease in diameter relative to the initial diameter was 17.14% (0.00-38.89) for the total cohort. Table 4 shows the diameter of the brachial artery (cm) before and after ulnar nerve stimulation for the entire group.

The difference in absolute decrease of flow rate between median nerve stimulation and ulnar nerve stimulation was not statistically significant for the entire group ($P = 0.733$). There were no statistically significant variations observed when the same assessment was stratified by female and male. Males and females were found to have $P = 0.237$ and 0.327 , respectively (Table 5).

For the total group, no significant difference in diameter change was seen between medial and ulnar nerve stimulation ($P = 0.648$) for either sex ($P = 0.610$ for males and $P = 0.833$ for females) (Table 6).

Table 1 Brachial artery flow rate before and after median nerve stimulation in the entire group (mL/min)

	<i>n</i>	Median	Min	Max	<i>P</i> value
Median pre-stimulation flow rate (mL/min)	15	79, 80	32, 9	201, 1	0.001
Median after-stimulation flow rate (mL/min)	15	44	10, 9	103	

Table 2 Brachial artery diameters prior to and following median stimulation (cm)

	<i>n</i>	Median	Min	Max	<i>P</i> value
Median pre-stimulation diameter of the brachial artery (cm)	15	0.35	0.26	0.5	0.001
Median after-stimulation diameter of the brachial artery (cm)	15	0.31	0.16	0.45	

Table 3 Flow rate (ml/min) prior to and following ulnar stimulation

	<i>n</i>	Median	Min	Max	<i>P</i> value
Ulnar pre-stimulation flow rate (mL/min)	15	56, 40	28, 10	214	0.001
Ulnar after-stimulation flow rate (mL/min)	15	30	15	78	

Table 4 shows the diameter of the brachial artery (cm) before and after ulnar stimulation in the entire group

	<i>n</i>	Median	Min	Max	<i>P</i> value
Ulnar pre-stimulation diameter of the brachial artery (cm)	15	36	23	50	0.001
Ulnar after-stimulation diameter of the brachial artery (cm)	15	28	19	48	

Table 5 Absolute change in the brachial artery flow rate following medial and ulnar stimulation (mL/min)

	Absolute change in flow rate with median stimulation (mL/min)		Absolute change in flow rate with ulnar stimulation (mL/min)	
Entire group (<i>n</i> = 15)	Median	3940	2510	
	Min	1990	790	
	Max	12450	17010	
Female (<i>n</i> = 7)	Median	3090	2270	
	Min	2040	790	
	Max	6010	5300	
Male (<i>n</i> = 8)	Median	4130	6865	
	Min	1990	1210	
	Max	12450	17010	

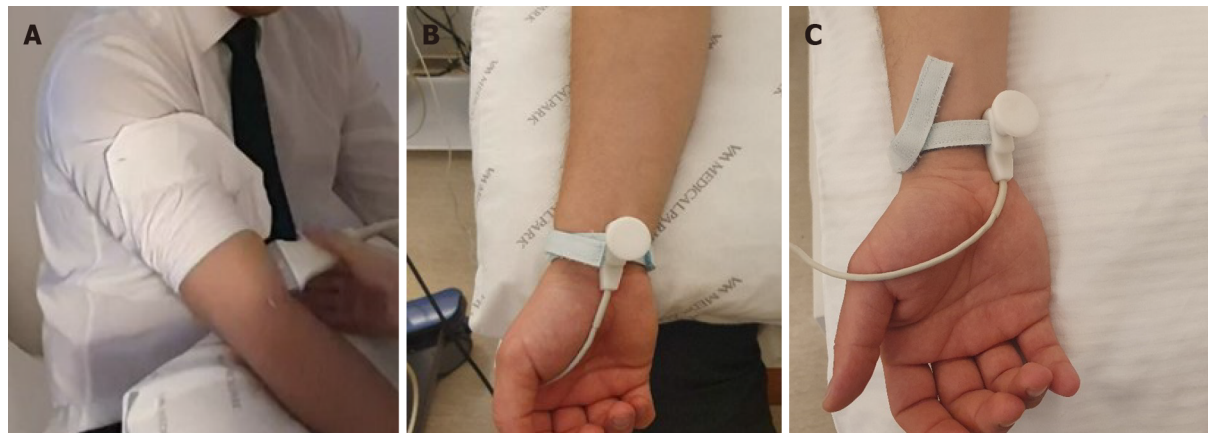
DISCUSSION

It is well established that the sympathetic fibres in the median nerve exert control over the flow parameters of the arteries in the upper extremities. For example, Badal *et al*[7] discovered that medial nerve blockage increased radial artery peak velocity. According to Galea *et al*[8] triggering sympathetic activation induced by coughing, followed by deep inspiration, does not significantly increase the Pulsatile Index of the radialis indicis artery in patients with carpal tunnel syndrome compared to healthy controls. Similarly, Ghasemi-Esfe *et al*[9] showed that people with carpal tunnel syndrome have a Pulsatile Index value for the radialis indicis artery that is much lower than the healthy controls.

These observations imply that a peripheral nerve injury causes vasomotor paralysis and higher blood flow to the large and medium arteries of the extremities; conversely, physiological activation of a peripheral nerve causes lower blood flow. Our study depended on this pathophysiological background

Table 6 Absolute diameter change over time for the entire group

		Change in diameter with a median stimulation (cm)	Change in diameter with an ulnar stimulation (cm)	P value
Entire group (n = 15)	Median	5	4	0.648
	Minimum	1	0	
	Maximum	14	14	
Female (n = 7)	Median	8	6	0.610
	Minimum	2	0	
	Maximum	14	14	
Male (n = 8)	Median	4	4	0.833
	Minimum	1	1	
	Maximum	11	8	



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Figure 1 Experimental procedure. A: Positioning of Doppler probe; B: Positioning of bipolar stimulator on the median nerve; C: Positioning of bipolar stimulator on the ulnar nerve.

and aimed to investigate the anatomical innervation of the brachial artery by utilizing a neuro-physiological experiment.

Campero *et al*[10] reported a study based on invasive approaches that was scientifically similar to our work; according to their findings, the median and ulnar nerves blockage resulted in cutaneous vasodilatation at the respective innervation areas, but a similar result was not observed for radial nerve blockage. On the other hand, the approach we developed was non-invasive and generated local sympathetic discharge through peripheral nerve stimulation, allowing for rapid, practical, and reproducible measurements of vasomotor responses. This advantage has made comparative investigations in neurophysiology and functional anatomy easier. Our findings indicated that stimulating both the median and ulnar nerves produced identical changes in the diameter and flow rate of the brachial artery and corroborated the assumption that the median and ulnar nerves exert equal control and equally innervate the brachial artery. This result may have impact not just on the neurophysiological field but also on vascular surgery investigations in the future. On the other hand, the limitation of this study was the small sample size, and further studies in larger sample sizes are needed.

Our results also suggested that unlike muscles and sensorial skin areas the vasomotor control of some large arteries was supplied by several peripheral nerves. However, when small arteries are considered, target organs are separated once again. This assumption was supported by two reports that demonstrated that the medial nerve was the single supplier of the vasomotor control of the medial and radial hand areas, the ulnar nerve is the single supplier of the ulnar hand area, and the radial nerve does not have a meaningful impact on arterial sympathetic control of the hand[10,11]. However, current research in this field has been limited, and further neurophysiological or interventional studies are needed to determine the neural-vascular liaisons of the extremities in more detail.

CONCLUSION

As a target organ, the brachial artery receives an equal amount of sympathetic innervation from the median and ulnar nerves. Expanding similar neurophysiological research to other arteries in the upper and lower limbs will contribute to advancing the field of functional neuroanatomy.

ARTICLE HIGHLIGHTS

Research background

The sympathetic nervous system is primarily responsible for controlling the peripheral arteries. It decreases the size of medium and large peripheral arteries to slow the blood flow rate.

Research motivation

There is insufficient information to determine which artery receives more postganglionic sympathetic innervation from which peripheral nerve.

Research objectives

To determine if the ulnar and median nerves contribute equally to sympathetic stimulation of the brachial artery.

Research methods

We developed a neurophysiological autonomous test that measured the effects of peripheral sympathetic fibres on peripheral arteries. The brachial artery baseline diameter and flow rate were measured in the right arm of the patients. Afterwards, electrical stimulus was applied to the medial nerve for 5 s. Through electrical sympathetic activation, the vessel diameter and overall flow rate will decrease. After 7 d, a similar experiment was repeated using the ulnar nerve.

Research results

The differences in diameter and flow rate of the brachial artery in response to median and ulnar nerve activation were compared. In the total group, no significant difference in diameter was seen between medial and ulnar nerve stimulation ($P = 0.648$). The difference in absolute slowdown of flow rate between median nerve stimulation and ulnar nerve stimulation was not statistically significant for the entire group ($P = 0.733$).

Research conclusions

The brachial artery serves as a target organ and is equally innervated by the median and ulnar nerves.

Research perspectives

Expanding similar neurophysiological research to other arteries in the upper and lower limbs will contribute to advancing the field of functional neuroanatomy.

FOOTNOTES

Author contributions: Ege F and Kazci Ö both contributed to the preparation of the project, obtained, analysed, and interpreted data of the study, and made a significant contribution to writing of the article.

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CASE REPORT

- 8 Delusional disorder with depression and history of early trauma: A case report

Aranas DR

ABOUT COVER

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WJN mainly publishes articles reporting research results and findings obtained in the field of neurology and covering a wide range of topics including autoimmune diseases of the nervous system, autonomic nervous system diseases, central nervous system diseases, chronobiology disorders, cranial nerve diseases, demyelinating diseases, nervous system malformations, nervous system neoplasms, neurocutaneous syndromes, neurodegenerative diseases, neurologic manifestations, neuromuscular diseases, neurotoxicity syndromes, restless legs syndrome, sleep disorders, and nervous system trauma.

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Delusional disorder with depression and history of early trauma: A case report

Denmarc Romero Aranas

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Abstract

BACKGROUND

The case report supports the recent findings regarding the correlation of posttraumatic stress disorder (PTSD) and schizophrenia. The report accomplished the following objectives: (1) To present a case of an adult female manifesting with somatic type of delusion (foul body odor) and history of PTSD; (2) To discuss the biopsychosocial factors, psychodynamics and management of the patient; and (3) To differentiate delusional disorder from schizophrenia according to recent studies. Schizophrenia and delusional disorder have certain defining features that separate the two. However, at times it may be difficult to actually classify one from the other. A psychiatrist must be able to carefully examine and assess the history of the patient, helping them share early life experiences of past traumatic events. The early past traumatic experiences and life events greatly influence the predisposition of a patient to develop schizophrenia. However, people with schizophrenia were known to underreport their trauma experience.

CASE SUMMARY

This is a case of a young adult female diagnosed with delusional disorder with a history of PTSD and associated depression. The patient manifested with somatic type of delusion with a fixed false belief that a foul body odor was coming from her underarms.

CONCLUSION

Developing a therapeutic alliance is vital in achieving therapy goals through empathy, support and warmth between the patient and physician. History of PTSD predisposes patients with schizophrenia to develop depressive disorders as a comorbidity.

Key Words: Delusional disorder; Depression; Posttraumatic stress disorder; Biopsychosocial formulation; Somatic delusion; Case report

Core Tip: Schizophrenia and delusional disorder have certain defining features that separate the two. However, at times it may be difficult to actually classify one from the other. One must be able to carefully examine and assess the history of the patient to help them share early life experiences of past traumatic events. Developing a therapeutic alliance is vital in achieving this goal through empathy, support and warmth between the patient and physician. History of posttraumatic stress disorder actually predisposes patients with schizophrenia to develop depressive disorders. This case report supports the recent studies associating the two disorders.

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INTRODUCTION

This manuscript discusses an individual with delusional disorder with a history of posttraumatic stress disorder with associated depression. This report accomplished the following objectives: (1) To present a case of an adult female manifesting with somatic type of delusion (foul body odor) and history of posttraumatic stress disorder; (2) To discuss the biopsychosocial factors, psychodynamics and management of the patient; and (3) To differentiate delusional disorder from schizophrenia according to recent studies.

A recent study by González-Rodríguez *et al*[1] differentiated schizophrenia from delusional disorder according to the latest studies available. A summary of the comparisons between the two is presented in Table 1. Schizophrenia typically manifests with delusion. However, a pertinent feature is its characteristic of being bizarre. Unlike in delusional disorder (DD) in which the delusion is more understandable. The most common type of delusion for schizophrenia is persecutory in nature. For DD, it is jealous type followed by somatic delusion and then erotomanic type. Aside from that, schizophrenia has other prominent traits such as more persistent hallucinations and negative and cognitive symptoms. On the other hand, DD is more associated with a comorbidity of depressive disorders (21.0%-55.8%). Impairment in various areas of functioning is more notable with schizophrenia, while patients with DD have superior functional ability.

The lifetime prevalence of schizophrenia is 0.48%-1.00%, while DD is much rarer with only 0.2% prevalence. Furthermore, the age of onset for schizophrenia is during late teens and early adulthood, while DD is much later occurring at around middle age and above.

According to a recent observational registry-based cohort study completed in Sweden, the effective dose of haloperidol is 12.7 mg/d and 4.7 mg/d for schizophrenia and DD, respectively, and the average duration of treatment is 104 d for schizophrenia and 65 d for DD[2]. It shows that for DD it takes a much lower dose and fewer days of treatment. However, a systematic study was recommended for further studies to better support these findings. The recommended pharmacologic treatments for both are clozapine, olanzapine and long acting injectable drugs. Also, both disorders can be given adjunct treatment of antidepressants to help address symptoms of the patient. Lastly, the best recommended psychotherapy for both disorders is cognitive behavioral therapy.

Schizophrenia is one of the psychotic disorders defined by abnormalities in one or more of the following five domains: Delusions; hallucinations; disorganized speech; grossly disorganized or abnormal motor behavior; and negative symptoms[3,4]. A recent meta-analysis study has shown that compared to the general population, those who are diagnosed with schizophrenia are more likely to experience trauma over the course of their lifetime either before or following the onset of their illness [5]. The most common consequence of trauma exposure is posttraumatic stress disorder (PTSD) with same prevalence among the general population and people with schizophrenia. However, people with schizophrenia or other severe mental disorders were known to underreport their trauma experience[6]. Recent studies have shown that trauma exposure and PTSD among people with schizophrenia are actually not related with more severe cognitive impairments but associated with more severe depression[6,7].

Table 1 Differentiation of schizophrenia and delusional disorder

	Schizophrenia	Delusional disorder
Clinical features	Delusional content: Bizarre; Most common: Persecutory type of delusion associated with prominent hallucinations, negative and cognitive symptoms; Functional ability: Severe dysfunction	Delusional content: More understandable; Most common: Jealous followed by somatic and erotomanic delusion; Comorbid: Depression (21.0%-55.8%); Functional ability: Superior
Epidemiological	Lifetime prevalence: 0.48%-1.00%; Age of onset: Late teens and early adulthood	Lifetime prevalence: 0.2%; Age of onset: Middle age and above
Treatment response: Observational registry-based cohort study (Swedish population)	Effective dose of haloperidol 12.7 mg/d; Duration: 104 d; Pharmacologic: Clozapine, olanzapine, lai; Adjunct treatment: Antidepressants; Psychotherapy: Cognitive behavioral therapy	Effective dose of haloperidol 4.7 mg/d; Duration: 65 d; Pharmacologic: Clozapine, olanzapine, lai; Adjunct treatment: Antidepressants; Psychotherapy: Cognitive behavioral therapy

lai: Long acting injectable.

CASE PRESENTATION

Chief complaints

The patient's chief complaint was the foul body odor she believed she had.

History of present illness

Seventeen years prior to consultation, the patient was with her elder sister when they were involved in a motor vehicular accident. The patient incurred multiple injuries including hip dislocation and open fracture in her left leg. She was hospitalized for 6 mo, and during her stay the patient had a normal reaction to the stressful situation. Pertinent negatives were no nightmares and flashbacks related to the accident and no other symptoms of PTSD. The patient was discharged fully recovered regaining her sensation and motor movement. PTSD symptoms only appeared upon passing by the site of accident, which persisted for 3 mo. The patient experienced palpitations while having intrusive and distressing memories of the accident when passing by the area of the accident. Since then, the patient avoided riding the bus as she feared that the accident might happen again. Also, the patient takes another route to avoid that area. Recurrent distressing thoughts of the accident occurred once or twice a week with associated poor sleep, palpitations and headache. The patient also noted to have problems in concentrating as she would be easily distracted by intrusive thoughts. The patient used to like visiting the town often. However, she lost interest in doing so as she constantly fears being in another accident. These posttraumatic symptoms persisted for almost 3 mo. The patient did not seek any psychiatric help and instead confided her struggles to her siblings. The patient was always accompanied by her elder sister to help her overcome the fear of going to the area of the accident. The patient would resort to praying and frequently attend bible studies to help her cope with her trauma. The patient noted that because of family support and her religion she was able to overcome her trauma.

Interval history revealed that her symptoms of PTSD did not recur anymore. However, the patient struggled with social interaction and preferred to be isolated as she feared rejection. The patient was able to finish her studies and pass the licensure examination for teachers. She also had a romantic partner who had a different religion than hers. Their relationship was kept as a secret to their families as the patient feared that her family would disapprove. The patient was then shocked by an unplanned pregnancy with her partner.

Two years prior to consultation, at around the 2nd trimester of the patient's pregnancy, she falsely believed that an unpleasant odor, characterized as sour body odor, was coming from her underarms. The patient believed that the scent gradually worsened as her pregnancy progressed, becoming more noticeable by others thinking that the scent would be permanent. During this time, she became insecure about her own odor, making her not want to go out of the house anymore. She would even ask her husband to run simple errands, such as grocery shopping or going to the nearest store, because she was too ashamed to go out. The patient would also spend almost an hour inside the bathroom just to repeatedly wash her underarms. Even after several washes, the patient claimed that the odor persisted causing her to be frustrated. The patient then bought a variety of cleansing soaps and perfume. She would then test each of these products during baths thus spending almost an hour in the shower room. However, all of these failed as she still strongly believed that her foul body odor persisted. She searched online for a variety of deodorants and spent excessive amounts of money for these products. After applying the products bought online the patient was frustrated as it all failed to remove her foul odor.

The patient then sought consultation with a dermatologist where she was told that there was no foul odor coming from her. The patient was then given an unrecalled oral and topical supplement for skin care. After a week of taking the home medications, the patient felt frustrated once again as she believed all of it was ineffective. The patient also refused to believe the assessment done by her first dermatologist. Hence, the patient went to another dermatologist wherein she was only offered cleansers and

given an option of laser underarm treatment. Nothing was confirmed regarding her odor. She used the products given to her but again believed that they were ineffective. She was offered more aggressive options but declined the options as she did not want those to affect her pregnancy. Her worries regarding her odor persisted, making her more and more ashamed about going out. The patient decided to alternately go for follow-up consultations with the two dermatologists. When she asked her husband about her odor, he would always say that he did not smell anything. However, the patient insisted on her fixed false belief that she had a foul body odor. Pertinent negatives were no chronic headache, no seizure, no head trauma and no loss of consciousness noted. No depressive or manic episodes noted at this time.

In the interim, the patient was converted to Iglesia ni Cristo (INC) or Church of Christ in preparation for their wedding. The patient noted that she was actually not willing to change her religion as she was raised as a devout Pentecostal. The patient was also given a negative connotation about people practicing INC. Her aunts and uncles had told her during family meetings that once she would be converted her whole life would be dedicated for the INC religion. Relatives feared that she would no longer be the same as an INC. The patient felt anxious about entering the INC church. The patient was ambivalent about her decision but claimed she had no choice but to do it for the sake of her pregnancy. After converting to INC, the patient thought that her relatives would no longer treat her the same way and felt anxious about it. Soon after converting, the wedding was held in the INC church. During the wedding, the patient falsely believed that she had a foul-smelling underarm. The patient observed that the guests at the wedding, her husband's family and her own family were behaving in a civil manner but in her mind, she thought that the difference of religion caused them to be distant to each other. The patient also claimed that the husband's family was talking behind her back and that they noticed her foul body odor. The patient kept this to herself and decided to avoid interacting much with anyone at the reception. The wedding ended and made the patient feel relieved as she was no longer around many people.

Interval history revealed persistence of delusion of foul body odor. The patient was noted to be asocial and anxious persistently. No increased goal directed activities nor risky behaviors such as impulsive buying or excessive alcohol use nor illicit drug use were noted.

Five months prior to consultation, she requested another leave immediately after having her maternity leave but was only allowed for a short time. Upon returning back to work, she immediately requested another leave due to the fixed false belief of foul body odor.

Interval history revealed symptoms of depressive episode such as depressed mood for most of the week, poor sleep and appetite, feeling fatigue for most of the day, anhedonia in taking care of herself and her family and asociality. The patient had inappropriate guilt of causing trouble to her family and officemates believing she was burdening them about her foul odor. The patient was able to cope with stress by talking to her immediate family and her husband. A month prior to consultation, the patient had thoughts of death with suicidal ideation, as she could not get rid of the unpleasant odor. A week prior to consultation, the patient asked her husband to submit her resignation letter to the school head on her behalf. The school head was alarmed and bothered about this and instead offered her a proposition. Her resignation was not approved and instead was offered a 6 mo leave to seek help about her behavior, leading to our consultation.

History of past illness

Patient had no allergies to food or drugs and no other comorbidities like hypertension, diabetes, cardiac disease or thyroid disease. She had no other previous psychiatric consultation and denies history of self-injurious behavior or suicide attempts and no previous psychiatric medications nor admissions. The patient also denies any substance use.

Personal and family history

No psychiatric diagnosis was present in the family. However, her father had a possible paranoid personality disorder traits and alcohol use disorder. Since infancy to early childhood, the family struggled with domestic violence from the father being inappropriately jealous and suspicious towards her mother. Her father would accuse the mother of having an affair with another man, which was not true. Aside from experiencing domestic violence, the mother also had poor prenatal care while carrying the patient. Her mother underwent significant stress during her pregnancy with the patient. Later on, the patient had an irregularly present mother due to working as a market vendor, and she was left most of the time under the care of her elder sisters. The patient felt neglected and missed her mother during these times. The patient was raised by strict disciplinarian parents. The patient experienced corporal punishments whenever she would fail to meet the standards of cleaning by her father. She felt anxious about the presence of her father and had poor self-esteem as a child. The patient and her sisters were also mandated to practice Pentecostal religion strictly and to avoid having male friends. The patient struggled with social interaction upon entering school as she would prefer to be isolated most of the time as she was anxious of being rejected by her peers.

Physical examination

Patient had an unremarkable physical and neurologic exam.

Laboratory examinations

Laboratory tests requested were all unremarkable as well.

Imaging examinations

Imaging tests requested were all unremarkable as well.

FINAL DIAGNOSIS

Patient had a final diagnosis of international classification of diseases-10 DD, severe depressive episode with psychotic symptoms and PTSD (resolved). The diagnostic and statistical manual of mental disorders diagnosis was DD (somatic type, continuous, severe), major depressive disorder (single episode, severe with mood-congruent psychotic features) and PTSD with delayed expression (resolved).

TREATMENT

For the management, the biological treatment of choice given for the patient was olanzapine. According to studies of Leucht *et al*[8], for second-generation antipsychotics, olanzapine, clozapine and amisulpride were found to be more efficacious than aripiprazole, quetiapine and risperidone. Olanzapine was found out to be the most efficacious, however with the most adverse metabolic effects. The patient was mesomorph in build with a normal body mass index of 21. Patient had no history of diabetes, hypertension or heart diseases. Hence, the benefit outweighed the said risks related with olanzapine. The patient started on the minimum dose to check efficacy and was able to go low and slow in the dosaging of her medications. Olanzapine 10 mg/tab ODHS was started for the patient. The increase in dosage was done after 5-6 wk of administration with refractory response.

Psychological treatment given to the patient was personal therapy that followed the phases as recommended by Gabbard[9]. Initial phase focused on clinical stabilization of symptoms, development of therapeutic alliance and provision of basic psychoeducation.

For the intermediate phase, awareness of the internal affective cues associated with the stressors must be achieved. By this time, social skills training, exercises in relaxation and training to enhance social perception may begin. For the long-term phase, provision for opportunities of introspection will be given. Guidance for principles of conflict resolution and criticism management would also be provided at this phase.

For the social aspect of treatment, psychoeducation is vital in developing the alliance of the family to the therapeutic regimen. Stepwise and gradual encouragement must be done to achieve this. The ultimate goal is to be able to reintegrate the patient to the community. However, the minimum expectation for the patient is to be able to maintain good work and social functioning and prevent relapse to an acute phase.

OUTCOME AND FOLLOW-UP

Patient had persistent delusion upon follow-up consultation. Hence, continued with the treatment plans.

DISCUSSION

The biopsychosocial model in understanding a mental illness is vital to explain the phenomena of how the disorder developed or is maintained. Examining all the relevant biological, psychological and social factors contributing to the condition is required.

First, the biological factors predisposing the patient were as follows. Abdelmalik *et al*[10] stated that certain physical disorders such as effects of head injury may lead to development of schizophrenia, which happened in the patient when she was involved in a car accident. She incurred head trauma and even lost consciousness on top of multiple physical injuries. According to Wahlberg *et al*[11], genetics play a key role in the development of schizophrenia in the offspring, and in this case the father had a possible paranoid personality trait wherein he had a preoccupation that the mother was having an affair with another man. He had certain negative symptoms of asociality from not participating in social activities including church services and had been withdrawn and lacked affection towards family. In

addition, the study of Tienari *et al*[12] showed that there is an interactive effect of genetic risk and the rearing environment. In this case, there is a higher risk of development of schizophrenia as there was exposure to a stressful environment as early as at the stage of mother's pregnancy wherein she had poor maternal/prenatal care, and the mother was exposed to domestic violence while carrying the patient.

Next, the psychological factors predisposing the development of schizophrenia would be the avoidant personality type of the patient grounded on the poor resolution of psychosocial conflict of trust *vs* mistrust in early development. Freud suggested that neurosis of patients with schizophrenia was based on withdrawal of ego boundary cathexis wherein patients had an impaired transference attachment[13]. Patients manifest with anxieties involving contact with others grounded on the fear of fusion with others hence patients would tend to isolate themselves. This was manifested by this patient when she would tend to isolate herself most of the time than interact with others.

Furthermore, the social factors predisposing the patient would be early exposure to a severely dysfunctional family environment, which lead to a higher risk of developing schizophrenia. The exposure of the mother to severe stress during the first trimester of pregnancy was also attributed to a higher risk of developing schizophrenia. Based on the study of Khashan *et al*[14], severe stressors in the environment may interact with combined effects of multiple susceptibility genes to influence neurodevelopment at the fetoplacental-maternal interface. Later on, there was continuous exposure to a stressful family environment wherein the patient experienced domestic violence and high criticism from her father. In addition, the patient experienced a traumatic event (the motor vehicular accident) in her childhood years.

Chronic stress in the life of the patient also contributed to the biological precipitation of her schizophrenia as the study of Spitzer[15] showed continuous exposure to stress can lead to dysregulation of the dopaminergic system. The patient had various stressors in life starting with domestic violence, motor vehicular accident and a rapid cycle of changes from unplanned pregnancy to sudden shifting of her religion.

Based on Freud's ego psychology, the patient experienced intrapsychic conflict from the psychosocial stressors of unplanned pregnancy and being forced to change her religion[13]. The superego of the patient wanted to preserve the internalized expectations of their culture and the demands of her parents while her id wanted to preserve her relationship with her partner under the demands of pleasure principle. Hence, the ego disintegrated due to this unresolved conflict. The patient had feelings of shame as she viewed herself as sinful.

According to McFarlane[16], a high rate of change in life events and disruption of social supports in a short span of time can precipitate development of schizophrenia. Unplanned pregnancy led to an adjustment to a new religion of the patient causing disruption in the family dynamics and the pressure from their community about maintaining her religion were too much to handle for the patient in a short span of time. According to Kalayasiri *et al*[17], the biological factor perpetuating the condition is the continuous disturbed dopaminergic neurotransmission specifically hyperdopaminergic activity that will result in an increased signal-noise difference in the neural network.

Furthermore, according to Fromm-Reichmann[18], patients with schizophrenia are not happy in their withdrawn state. They are fundamentally lonely people who cannot overcome their fear and distrust of others because of adverse experiences early in life. The denial and poor insight lead to feelings of worthlessness. The patient then chose to engage in under stimulating factors that perpetuate negative symptoms and worsen disability. These include factors such as isolating self and restriction of productive work. These factors tend to lead to clinical deterioration such as inactivity, blunted affect, loss of social competence and self-neglect. As in this case, the patient chose to resign from her work and would typically isolate herself from friends and family. Lastly, the presence of co-occurring diagnoses, particularly depression, may be an additional factor that negatively influences the course of the disorder.

On the other hand, a social factor perpetuating the condition as stated by Rosenfarb *et al*[19] is face-to-face contact between people and families who display high levels of expressed emotion, which increases the likelihood of relapse of acute symptoms. The concept of expressed emotion include hostility and critical comments. The overly strict and religious parents fulfill the exposure of the patient to highly expressed emotion as she experienced an abusive and critical father in her childhood years. Presently, the husband had been critical of her because of the burnout as a caregiver to her excessive demands and her maltreatment of their only child. This now resulted in the hesitation of the patient to share her present condition with her family.

In the study of Gonzales-Rodriguez *et al*[1], it was shown that female sex and the reproductive age are actually protective factors against development of delusions because these groups of people possess the protective effects of estrogen. Psychological factors protecting the patient would be the presence of precipitating factors attributed to a better outcome on recent studies[1,12]. Furthermore, McFarlane[16] stated that a good social support is a protective factor for schizophrenia. Acknowledgement and support from the husband and siblings for the need of psychiatric treatment were given. Also, her husband provided financial support for medications and basic needs as she was on sick leave.

Freud's psychosexual theory of development states that it is driven by conflictual process between biological/sexual drives *vs* social expectations. Over the course of childhood, sexual impulses shift their focus as the name of each stage implies. He stressed the importance of personality development in

childhood, which has life-long effects during adulthood. Therefore, if a person is fixated at a certain stage of psychosexual development it would manifest negatively later in life[13]. In each stage of Freud's psychosexual developments there is a corresponding Erik Erickson's psychosocial development, which largely focus on the effects of culture and society in the development of personality[20].

The first stage, which is oral stage, occurs from birth to 18 mo of age. The focus of libido is at the mouth so oral gratification is the primary concern at this stage. An infant would be satisfied by feeding, rooting and sucking. With the demands of feeding being fulfilled appropriately by the mother, this stage would be resolved[13]. However, in this case, the mother of the patient had a divided attention being a working mother and not able to fulfill the demands of the patient at this stage.

The study of Olin *et al*[21] identified that faulty mothering would lead to an anxiety-laden self in the infant, which will cause profound damage to self-esteem. In this case, the patient was left under the care of young elder siblings whenever the mother would work as a market vendor. Hence, oral gratification was not fulfilled appropriately.

Furthermore, Erikson's concept of trust *vs* mistrust in early development states that individuals who never went through the healthy experience of having his or her needs satisfied by a significant relationship, which is the mother would result in an inadequate development of the virtue of hope[20]. Also, exposure to a distressing family set up like domestic violence would also worsen lack of trust in relationships. This now would manifest as insecurity and anxiety. The patient had been anxious ever since childhood in socializing with other people. The patient was noted to have struggles with social interactions up to present.

The next stage wherein the patient had failed resolution was the anal stage. This occurs at 1-3 years of age with the focus of libidinal drive is at the anus related with the experience of toilet training[13]. The patient was raised by parents who were overly strict disciplinarians, being particular with cleanliness and devout Pentecostals. According to Kosky *et al*[22], the concept of highly expressed emotion includes hostility and critical comments that greatly increases the risk for psychosis. The critical father in her childhood years with maltreatment led to the inadequate resolution of this phase. The patient poorly developed the virtue of will or independence leading to feelings of shame or doubt in her abilities.

The experiences of past trauma and influence of sociocultural input led to inadequate resolution of psychosocial conflicts namely trust *vs* mistrust that led to the development of an avoidant personality trait in the patient. Autonomy *vs* self-doubt leading to feelings of shame in the patient led to the poor responses of the patient to life stressors, such as unplanned pregnancy, change in religion and expectation from relatives and cultural beliefs.

These led to intrapsychic conflicts. The superego that functions under the moral principle dictated to the patient to preserve her moral obligations as a devout Pentecostal and pressured the patient with shame from the unplanned pregnancy. On the other hand, the id functions under the pleasure principle dictating the preservation of the relationship with her husband and go against her cultural belief and expectations from parents and relatives, which compelled her to change her religion. The ego that functions as a mediator between the two would have a hard time creating a compromise, hence leading to ego disintegration.

Freud suggested that neurosis of patients with schizophrenia is based on withdrawal of the ego boundary cathexis wherein patients have an impaired transference attachment[13]. Patients with paranoid schizophrenia suffer from a deficit in understanding correctly what others think about the patient and what their future attitudes or actions towards the patient might be[23]. Patients manifest with anxieties involving contact with others grounded on the fear of fusion with others hence patients tend to isolate themselves. This was manifested by the patient as she would tend to isolate herself than interact with others.

Patients with schizophrenia believe that they are bad or evil persons and have ruined their family. They may claim to have committed an unpardonable sin and be ashamed of themselves. This was manifested in the patient as she had feelings of shame in regards to her actions.

The theory of mind deficit on the other hand states that delusions of reference can be explained, at least in part, by the patient's inability to put themselves in another person's place and thus correctly assess their behavior and intentions[23]. It is the reduced ability to form a valid hypothesis about another person's state of mind with regard to oneself. Paranoia or more generally speaking delusional ideation in this view is a result of disturbed cognitive and social metarepresentation. Thus, these theories explain the paranoid perception of ridicule from others by the patient thereby manifesting as low self-esteem with social withdrawal.

The severe preoccupation to her foul body odor was related to her paranoid perception of ridicule from others through mechanisms of introjection and projection. The patient internalized the expectations and demands of her parents to be a strict devout Pentecostal and be an extremely conservative woman in her early life. Thus, the patient projected to people around her including family, coworkers and even strangers whom she perceived as persecuting objects judging her negatively for her over valued belief that she did something wrong for changing her religion and getting pregnant before being married. When the persecuting objects reintrojected, they became an internal persecutor in the form of foul body odor.

The emergence of delusion of foul body odor led to the formulation of other defense mechanisms such as denial wherein the patient avoided awareness of aspects of external reality that were difficult to face by disregarding sensory data. The patient had a strong conviction and denied the absence of foul body odor, which led to the persistence of the delusion and causing a strained marital relationship. The patient also manifested displacement as the patient was angry at herself, which was displaced from her husband and child. This may explain the possible child neglect and maltreatment.

The persistence of the delusion, strained marital relationship and child neglect and maltreatment by the patient led to the development of post-psychotic depression. The patient also manifested with sublimation wherein she had increased goal directed activities in an attempt to control anger outbursts and prevent harm to self and others. She chose to tire herself out by doing household chores repeatedly. All of these manifestations fulfill the classical picture of DD.

CONCLUSION

Schizophrenia and DD have certain defining features that separate the two. However, at times it may be difficult to actually classify one from the other. One must be able to carefully examine and assess the history of the patient to help them share early life experiences of past traumatic events. Developing a therapeutic alliance is vital in achieving this goal through empathy, support and warmth between the patient and physician. History of PTSD actually predisposes patients with schizophrenia to develop depressive disorders. This case report supported the recent studies associating the two disorders.

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Jessica Maciuch, Leonard A Jason

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Abstract

BACKGROUND

The literature is mixed about the occurrence of alcohol intolerance among patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Surveys that asked respondents with ME/CFS whether they experienced alcohol intolerance within a recent time frame might produce inaccurate results because respondents may indicate that the symptom was not present if they avoid alcohol due to alcohol intolerance.

AIM

To overcome this methodologic problem, participants in the current study were asked whether they have avoided alcohol in the past 6 mo, and if they had, how severe their alcohol intolerance would be if they were to drink alcohol.

METHODS

The instrument used was a validated scale called the DePaul symptom questionnaire. Independent *t*-tests were performed among the alcohol intolerant or not alcohol intolerant group. The alcohol intolerant group had 208 participants, and the not alcohol intolerant group had 96 participants.

RESULTS

Using specially designed questions to properly identify those with alcohol intolerance, those who experienced alcohol intolerance *vs* those who did not experience alcohol intolerance experienced more frequent/severe symptoms and domains. In addition, using a multiple regression analysis, the orthostatic intolerance symptom domain was related to alcohol intolerance.

CONCLUSION

The findings from the current study indicated that those with ME/CFS are more likely to experience alcohol intolerance. In addition, those with this symptom have more overall symptoms than those without alcohol intolerance.

Key Words: Myalgic encephalomyelitis/chronic fatigue syndrome; Alcohol intolerance; Orthostatic intolerance; DePaul symptom questionnaire; Symptom burden; Methodology

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Core Tip: The findings from the current study indicated that those with myalgic encephalomyelitis/chronic fatigue syndrome are more likely to experience alcohol intolerance.

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INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic illness characterized by persistent debilitating fatigue, post-exertional malaise, cognitive impairment, and sleep dysfunction[1]. In addition to these core symptoms, individuals with ME/CFS may also present with a variety of other symptoms. Symptom occurrence patterns have been previously proposed as a method of determining ME/CFS subtypes[2,3].

In response to anecdotal observation of alcohol avoidance in individuals with ME/CFS, several studies have attempted to quantify alcohol intake. The majority of these studies reported decreased alcohol intake in ME/CFS, but results are inconsistent across studies. Woolley *et al*[4] reported that 66% of respondents chose to reduce alcohol intake, with the most common justifications being “increased tiredness after drinking (67%), increased nausea (33%), exacerbated hangovers (23%) and sleep disturbance (24%).” The same study also reported increased impairment in the ability to work, engage in social or leisurely activities, and memory function in those with reduced alcohol intake[4]. Weigel *et al*[5] and van't Leven *et al*[6] also reported reduced alcohol intake in ME/CFS compared to the general population and non-fatigued controls, respectively. In contrast, Hamaguchi *et al*[7] reported no significant difference in alcohol intake in participants with ME/CFS.

Studies focusing on alcohol intolerance or sensitivity as a potential symptom of ME/CFS have produced similarly inconsistent findings. Jason *et al*[8] found a statistically significant higher prevalence of alcohol intolerance in participants with ME/CFS compared to non-fatigued controls. Within ME/CFS populations, De Becker *et al*[9] found that 59%-64% of participants who met either the Holmes or Fukuda diagnostic criteria for ME/CFS reported alcohol intolerance. Chu *et al*[10] found that 66% of participants with ME/CFS reported an increased sensitivity to alcohol after becoming ill. However, Nisenbaum *et al*[11] found no significant difference in alcohol intolerance between fatigued and non-fatigued respondents.

Surveys that ask respondents with ME/CFS whether they experienced alcohol intolerance within a recent time frame might produce inaccurate results since respondents may indicate that the symptom was not present if they have avoided alcohol in the designated time frame[12]. Due to this concern, in research there is a need to ask participants whether they have avoided alcohol in the past 6 mo, and if they have, how severe their alcohol intolerance would be if they were to drink alcohol. The failure to account for the effect of question wording may partially explain the inconsistency in findings related to alcohol intolerance in ME/CFS.

Despite inconsistent findings in the literature, alcohol intolerance has been identified as a clinically relevant feature of ME/CFS by Bansal[13], even suggesting that the ability to tolerate four or more drinks in one sitting should prompt healthcare practitioners to rethink an ME/CFS diagnosis. Chu *et al*[10] previously speculated that alcohol intolerance in ME/CFS might be related to underlying autonomic dysfunction, which would also explain the high prevalence of orthostatic intolerance and impaired temperature regulation in ME/CFS. Baraniuk[14] speculated that alcohol intolerance in ME/CFS may be related to the effect of acetate (a byproduct of ethanol breakdown) on mitochondrial function, which is already known to be impaired in ME/CFS[15,16]. The added stress of high acetate levels during alcohol consumption may cause more severe dysfunction in areas of the brain that are highly metabolically active[14]. However, to our knowledge, neither hypothesis has been directly investigated.

The present study aimed to provide insight into the role of alcohol intolerance in ME/CFS by identifying correlations between alcohol intolerance and other common symptoms. We hypothesized that alcohol intolerance correlates with measures of autonomic dysfunction (such as orthostatic and temperature intolerance), measures of neurocognitive dysfunction, and higher severity of physical

impairment. Further, we investigated whether alcohol intolerance may be used to distinguish a clinically relevant subtype of ME/CFS.

MATERIALS AND METHODS

Participants

The present study utilized a previously collected cross-sectional sample of adults with various chronic illnesses from a larger study[17]. Participant recruitment was conducted *via* email requests to national foundations as well as posts to social media outlets, research forums, and support group websites. Participants were directed to complete an online questionnaire after establishing informed consent. Approval was provided by the DePaul University Institutional Review Board for all study methods.

For the purposes of this investigation, participants were included if they reported a diagnosis of CFS, ME, or ME/CFS, and if they responded to the DePaul symptom questionnaire-2 (DSQ-2) questions used to classify alcohol intolerance ($n = 304$). Exclusion criteria consisted of a diagnosis of cancer, lupus, multiple sclerosis, post-polio syndrome, HIV/AIDS, or Gulf War syndrome.

Measures

Participants completed the DSQ-2[12], a self-report questionnaire that assesses ME/CFS symptomatology as well as social, occupational, and medical history, and demographic information. The DSQ-2 constitutes an addition of 34 items to the DePaul Symptom Questionnaire-1 (DSQ-1), which has previously shown favorable results for construct, convergent, and discriminant validity[18] and test-retest reliability[19]. The DSQ-2 is publicly available in the shared library of the Research Electronic Data Capture (REDCap)[20,21] and can be accessed at <https://redcap.is.depaul.edu/surveys/?s=4NJ9CKW7JD>.

Participants were asked to rate the frequency and severity of each symptom over the past 6 mo on 5-point Likert scales. For frequency, participants chose between the following options: 0 = none of the time; 1 = a little of the time; 2 = about half the time; 3 = most of the time; and 4 = all of the time. For severity, participants chose between the following options: 0 = symptom not present; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe. Composite scores were generated for each symptom by averaging respective scores for frequency and severity and multiplying by 25 for a 100-point scale. Higher scores indicate a higher burden of the designated symptom. Symptom domain scores were calculated by averaging the composite scores for each item within the following symptom domains, previously determined by exploratory factor analysis on DSQ-2 data, including post-exertional malaise, cognitive impairment, fever and flu, pain, sleep disruption, orthostatic intolerance, genitourinary, and temperature intolerance[12].

Table 1 lists the DSQ-2 questions used to classify alcohol intolerance. The DSQ-2 question relating to frequency of alcohol intolerance over the past 6 mo was omitted due to ambiguity as to whether responses reflected the frequency of drinking alcohol or the frequency of experiencing alcohol intolerance when drinking alcohol.

Participants were classified as alcohol intolerant if they met either condition: (1) Reported a severity of moderate or higher on alcohol intolerance within the past 6 mo (options 2-4 on question 1 in Table 1); or (2) Reported that they were avoiding alcohol ("Yes" on question 2), and their alcohol intolerance would be moderate or higher if they were to drink alcohol (options 2-4 on question 3 in Table 1).

Participants were classified as "not alcohol intolerant" if they met either condition: (1) Reported alcohol intolerance severity within the past 6 mo as "symptom not present" or "mild" (options 0-1 on question 1 in Table 1); or (2) Reported that they were avoiding alcohol ("Yes" or "No, I do not drink alcohol for other reasons" on question 2), and their alcohol intolerance would be mild or not present if they were to drink alcohol (options 0-1 on question 3).

For the linear regression, alcohol intolerance was coded as a linear variable based on the following conditions: (1) If the participant answered that they were avoiding alcohol ("Yes" on question 2), alcohol intolerance was coded as the score of how severe alcohol intolerance would be if they were to drink alcohol (question 3); and (2) If the participant was NOT avoiding alcohol, alcohol intolerance was coded as the score of alcohol intolerance severity in the past 6 mo (question 1).

In addition to the DSQ-2, participants were also asked to complete the MOS 36-item Short-Form Health Survey (SF-36)[22]. The SF-36 is a self-report measure that assesses health across eight general domains: Physical functioning; role limitations due to physical health problems (role physical); bodily pain; general health functioning; vitality; role limitations due to personal or emotional problems (role emotional); and mental health. Responses to each of the 36 items are recoded to a 100-point scale, and items are grouped together based on the eight domains. Subscale scores are then generated by averaging item scores within each domain, with higher scores indicating better functioning in the domain. Adequate psychometric properties have been demonstrated for SF-36 across diverse patient groups[23], and it has previously been shown to perform well in measuring fatigue-related functional impairment in ME/CFS[24].

Table 1 DePaul symptom questionnaire-2 questions used to classify alcohol intolerance

Question	Response options
Severity: Throughout the past 6 months, how much has alcohol intolerance bothered you?	0 = symptom not present 1 = mild 2 = moderate 3 = severe 4 = very severe
Over the last 6 months, did you avoid alcohol due to an alcohol intolerance (feeling sick after drinking alcohol)?	Yes No, I drank alcohol No, I do not drink alcohol for other reasons
If you were to drink alcohol, how severe would the intolerance be?	0 = symptom not present 1 = mild 2 = moderate 3 = severe 4 = very severe

Statistical analyses

Independent *t*-tests were performed using SPSS 26 for all DSQ-2 symptoms and SF-36 items. Participants were divided into a binary classification of “alcohol intolerant” or “not alcohol intolerant.” Due to the large number of items that were tested, we only considered findings significant if $P \leq 0.01$, and we used two-tailed significance levels.

Multiple linear regression was conducted to determine if composite symptom scores in the eight DSQ-2 domains were predictors of alcohol intolerance severity scores. Age and sex (coded in the data set as: 1 = male; 2 = female; and 3 = other) were also evaluated in the regression model.

RESULTS

Demographics

Table 2 describes the demographic characteristics of the sample separated by the binary alcohol intolerance classification. The alcohol intolerant group ($n = 208$) had a mean age of 45.48 (standard deviation = 16.49), and the not alcohol intolerant group ($n = 96$) had a mean age of 45.54 (standard deviation = 17.40). Both groups were predominantly female and Caucasian/White. The majority of the sample reported being on disability (50.0% for the alcohol intolerant group; 40.6% for the not alcohol intolerant group) and married/living with a partner (45.2% for the alcohol intolerant group; 55.2% for the not alcohol intolerant group).

t-tests were conducted on mean composite scores for 79 individual symptoms, mean composite scores for the 8 symptom domains (calculated by averaging composite scores for items within the symptom domain), and subscale scores for 8 SF-36 domains. Results of the independent *t*-tests for DSQ-2 symptoms are available in **Table 3**. Out of 79 individual symptoms, 33 (41%) were significantly different ($P \leq 0.01$). For every statistically significant symptom, mean composite scores were higher for the alcohol intolerant group, indicating a higher symptom burden (in terms of frequency and severity of the symptom).

Of the eight symptom domains, five domain scores were significantly higher for the alcohol intolerant group, including post-exertional malaise, cognitive impairment, pain, orthostatic intolerance, and temperature intolerance. The fever and flu, sleep disruption, and genitourinary domains were not significantly different between the two groups.

Results of the *t*-tests for the SF-36 are presented in **Table 4**. The alcohol intolerant group scored significantly lower on physical functioning and bodily pain. Higher scores indicate better functioning on the SF-36, so lower scores for the alcohol intolerant group would indicate worse functioning.

Results of the multiple linear regression are available in **Table 5**. The overall multiple linear regression was statistically significant [$R^2 = 0.14$, $F(10, 233) = 3.64$, $P \leq 0.001$]. Sex, age, and seven out of eight symptom domains did not significantly predict alcohol intolerance severity ($P \leq 0.05$). Only the orthostatic intolerance domain significantly predicted alcohol intolerance severity ($\beta = 0.21$, $P = 0.01$). We did not use the SF-36 domains as predictors as our interest was in assessing which symptoms might

Table 2 Demographic characteristics of the sample (n = 304) separated by binary alcohol intolerance classification

Characteristic	Alcohol intolerant, n = 208		Not alcohol intolerant, n = 96	
	mean (%)	SD or n	mean (%)	SD or n
Age	48.07	12.26	49.57	13.50
Sex				
Male	11.1	23	8.3	8
Female	87.5	182	88.5	85
Race				
White	95.2	198	99.0	95
Asian or Pacific Islander	1.4	3	1.0	1
Other	2.9	6	0	0
Latinx				
No	98.1	204	96.9	93
Yes	1.4	3	3.1	3
Education				
High school diploma or less	12.0	25	9.4	9
College degree or partial college	46.2	96	55.3	53
Graduate degree	41.3	86	34.4	33
Work status				
On disability	50.0	104	40.6	39
Working (full-time or part-time)	25.5	53	29.2	28
Retired	8.7	18	13.5	13
Unemployed	16.3	34	11.5	11
Student or homemaker	9.6	20	12.6	12
Marital status				
Married or living with partner	45.2	94	55.2	53
Never married	31.7	66	25.0	24
Divorced	16.8	35	14.6	14
Widowed	1.9	4	3.1	3
Separated	2.9	6	2.1	2

be related to alcohol intolerance rather than physical or mental functioning.

DISCUSSION

Prior research assessed alcohol intolerance, but respondents could indicate that the symptom was not present if they have avoided alcohol in the designated time frame. When participants were asked whether they have avoided alcohol in the past 6 mo, and if they had how severe their alcohol intolerance would be if they were to drink alcohol, those designated in the alcohol intolerant group evidenced a higher symptom burden (in terms of frequency and severity of the symptoms). A second unique finding was that the orthostatic intolerance symptom domain predicted alcohol intolerance.

The fact that orthostatic intolerance was the only variable related to alcohol intolerance is of theoretical importance. Others have suggested that alcohol intolerance might be related to underlying autonomic dysfunction, which might help explain the high levels of orthostatic intolerance and impaired temperature regulation in ME/CFS[10]. It is also possible that the added stress of high acetate levels, which are a byproduct of ethanol breakdown, may cause more severe dysfunction in areas of the brain that are highly metabolically active[14].

Table 3 Differences in composite DePaul symptom questionnaire-2 symptom scores

Symptom	Alcohol intolerant	Not alcohol intolerant	P value
	mean (SD)	mean (SD)	
Post-exertional malaise	79.53 (15.46)	71.99 (17.07)	< 0.01
Feeling drained	74.70 (21.53)	67.06 (23.31)	0.01
Minimum exercise	78.99 (20.48)	72.27 (20.62)	0.01
Worse after physical activity	80.83 (21.42)	74.22 (21.83)	0.01
Soreness	77.84 (19.87)	70.96 (20.40)	0.01
Fatigue	81.86 (15.10)	77.47 (15.88)	0.02
Heavy feeling	83.87 (22.56)	69.53 (30.82)	< 0.01
Muscle fatigue	76.80 (24.01)	64.32 (26.03)	< 0.01
Unrefreshing sleep	81.52 (18.83)	80.08 (20.80)	0.57
Cognitive impairment	61.53 (18.28)	54.92 (18.39)	< 0.01
Difficulty remembering	68.84 (22.51)	64.58 (25.17)	0.14
Difficulty finding right word	61.78 (23.69)	54.56 (23.02)	0.01
Difficulty understanding	51.02 (24.93)	44.14 (24.33)	0.02
Absent-mindedness	62.74 (24.94)	57.50 (22.73)	0.08
Slowness of thought	60.34 (24.78)	52.99 (25.70)	0.02
Only focus on one thing	68.96 (23.14)	59.38 (24.60)	< 0.01
Difficulty paying attention	72.84 (23.31)	66.97 (23.77)	0.04
Slowed speech	35.75 (27.80)	29.61 (24.33)	0.07
Mental tiredness	71.32 (21.74)	64.19 (23.55)	0.01
Fever and flu	37.71 (19.81)	33.74 (19.55)	0.1
Fever	16.36 (21.41)	14.71 (20.52)	0.53
High temperature	33.82 (26.14)	29.43 (26.09)	0.18
Flu-like symptoms	52.84 (25.87)	49.22 (27.97)	0.27
Prolonged viral illness recovery	38.16 (32.95)	35.68 (33.88)	0.55
Fluctuations in temperature	47.18 (31.83)	39.76 (31.38)	0.06
Pain	54.84 (22.94)	46.30 (21.86)	< 0.01
Stomach pain	45.11 (28.08)	36.33 (25.14)	0.01
Irritable bowel	51.98 (31.39)	44.01 (31.88)	0.04
Bloating	50.79 (28.83)	41.45 (25.80)	0.01
Muscle pain	71.45 (25.12)	63.15 (29.43)	0.02
Sleep disruption	57.63 (23.80)	51.52 (25.12)	0.04
Problems staying asleep	61.29 (28.62)	54.04 (29.16)	0.04
Waking up early	52.40 (28.64)	44.53 (30.07)	0.03
Problems falling asleep	61.29 (28.62)	54.04 (29.16)	0.39
Orthostatic intolerance	39.99 (23.21)	27.86 (22.93)	< 0.01
Graying or blacking out after standing	28.14 (29.39)	17.63 (24.90)	< 0.01
Blurred or tunnel vision after standing	35.52 (31.01)	25.13 (28.51)	0.01
Heart beats quickly after standing	50.12 (31.11)	35.66 (33.37)	< 0.01
Dizziness	45.91 (26.21)	33.85 (26.34)	< 0.01
Genitourinary	43.06 (26.18)	36.81 (23.43)	0.05

Urinary urgency	41.95 (30.88)	38.03 (31.99)	0.31
Bladder problems	36.96 (31.91)	29.82 (27.29)	0.05
Nighttime urinary urgency	50.18 (31.51)	42.37 (30.20)	0.04
Temperature intolerance	39.45 (22.76)	28.60 (19.98)	< 0.01
Chills or shivers	37.38 (26.16)	27.34 (24.01)	< 0.01
Low temperature	29.41 (28.02)	17.45 (20.80)	< 0.01
Cold limbs	51.02 (28.65)	41.02 (28.89)	0.01
Other			
Needing to nap daily	58.74 (28.63)	53.39 (30.80)	0.14
Sleep inversion	21.80 (30.09)	16.28 (26.85)	0.11
Joint pain	60.33 (31.88)	56.64 (30.99)	0.35
Eye pain	34.24 (29.25)	25.52 (25.32)	0.01
Chest pain	28.32 (23.57)	19.79 (24.24)	< 0.01
Headaches	53.32 (26.10)	45.18 (24.69)	0.01
Twitching	38.28 (26.15)	30.34 (24.25)	0.01
Muscle weakness	68.15 (25.56)	57.81 (25.92)	< 0.01
Sensitivity to noise	64.12 (25.50)	57.55 (27.95)	0.04
Sensitivity to light	58.53 (28.25)	51.04 (29.00)	0.03
Unable to focus vision	41.35 (26.21)	33.06 (22.82)	0.01
Unable to focus attention	56.63 (21.10)	53.89 (20.75)	0.31
Loss of depth perception	31.10 (31.76)	17.63 (24.22)	< 0.01
Nausea	39.42 (24.74)	26.04 (25.76)	< 0.01
Feeling unsteady	49.70 (28.00)	36.85 (25.48)	< 0.01
Shortness of breath	38.88 (27.26)	35.81 (26.07)	0.36
Irregular heartbeat	32.91 (26.82)	28.26 (26.79)	0.16
Losing weight	19.04 (25.04)	17.34 (19.65)	0.6
Gaining weight	52.70 (33.53)	47.58 (31.51)	0.3
Loss of appetite	30.37 (24.52)	31.12 (25.84)	0.81
Sweating hands	15.99 (23.28)	15.89 (24.97)	0.97
Night sweats	37.44 (29.32)	35.55 (30.20)	0.61
Feeling hot or cold	53.93 (26.88)	45.96 (26.93)	0.02
Sore throats	37.50 (25.00)	32.16 (24.11)	0.08
Lymph nodes	39.54 (28.82)	34.08 (27.50)	0.12
Sensitivity to smells	53.43 (30.68)	37.50 (30.99)	< 0.01
Sensitivity to mold	29.89 (37.74)	21.45 (29.94)	0.04
Temperature intolerance	72.52 (26.97)	55.60 (31.93)	< 0.01
Worse after mental activity	66.41 (24.31)	59.87 (28.53)	0.06
Feeling disoriented	40.44 (25.23)	33.68 (23.36)	0.03
Difficulty reading	50.96 (32.42)	39.34 (30.89)	< 0.01
Eye aching	40.44 (29.61)	30.66 (28.47)	0.01
Sensitivity to pain	53.50 (31.78)	44.35 (36.19)	0.04
Pain from pressure	27.00 (34.21)	24.87 (33.73)	0.62
Daytime drowsiness	64.24 (26.74)	60.53 (27.85)	0.27

Sensitivity to vibrations	36.34 (35.50)	21.68 (31.39)	< 0.01
Poor coordination	51.68 (28.56)	38.42 (25.08)	< 0.01
Sinus infections	25.00 (28.84)	23.68 (25.36)	0.69
Upright position intolerance	51.98 (32.87)	44.08 (32.86)	0.05

Table 4 Differences for short form-36 domain scores

Domain	Alcohol intolerant	Not alcohol intolerant	P value
	mean (SD)	mean (SD)	
Physical functioning	23.91 (20.45)	34.27 (21.86)	< 0.01
Role physical	2.00 (9.39)	4.39 (11.22)	0.12
Bodily pain	34.30 (22.50)	43.82 (26.36)	< 0.01
General health	23.28 (15.02)	25.51 (14.36)	0.29
Vitality	8.98 (10.74)	12.47 (13.75)	0.06
Social functioning	18.34 (20.03)	25.51 (22.38)	0.02
Role emotional	69.54 (42.15)	63.01 (43.94)	0.29
Mental health	67.08 (18.84)	66.48 (20.00)	0.83

Table 5 Linear regression for symptom domain scores, sex, and age

Feature	Unstandardized coefficients		Standardized coefficients	t	P	95%CI	
	B	SE	Beta			LL	UL
Constant	0.90	0.70	< 0.01	1.29	0.20	-0.47	2.27
Sex	-0.27	0.27	-0.06	-1.01	0.31	-0.79	0.25
Age	< 0.01	0.01	0.04	0.57	0.57	-0.01	0.02
PEM domain	0.01	0.01	0.15	1.82	0.07	0.00	0.02
Cognitive impairment domain	< 0.01	0.01	-0.04	-0.54	0.59	-0.01	0.01
Fever/flu-like symptoms domain	-0.01	0.01	-0.11	-1.39	0.16	-0.02	0.00
Pain domain	< 0.01	< 0.01	0.07	0.89	0.37	0.00	0.01
Sleep disruption domain	< 0.01	< 0.01	-0.03	-0.43	0.67	-0.01	0.01
Orthostatic intolerance domain	0.01	< 0.01	0.21	2.57	0.01	0.00	0.02
Genitourinary domain	0.01	< 0.01	0.12	1.73	0.08	0.00	0.01
Temperature intolerance domain	0.01	< 0.01	0.09	1.11	0.27	0.00	0.01

CI: Confidence interval; LL: Lower limit of the confidence interval; PEM: Post-exertional malaise; UL: Upper limit of the confidence interval.

A strength of the current study was using a validated questionnaire, the DePaul Symptom Questionnaire, that differentiates the frequency and severity of symptoms as well as specifies threshold values for determining whether symptoms meet a necessary threshold of being a burden for the patient. When symptoms are measured only using occurrence as a binary outcome, patients who experience the symptom at relatively low frequencies and/or severities are counted, even if the symptom might not represent any burden to the respondent. It is only by using more differentiated surveys that allow these important characteristics to be assessed and using questionnaires that have been validated that more assurance can occur that symptoms such as alcohol intolerance are being accurately identified in patients.

There are several limitations in this study. First, all analyses relied on self-report data. Thus, there was no biological confirmation of alcohol intolerances in the respondents. In addition, the designation of ME/CFS was also based on self-report. Therefore, there was not an independent assessment of this illness by a medical health care professional. Finally, the sample was somewhat biased toward women

who were White, and the outcomes of a more sociodemographic sample is unclear.

CONCLUSION

In general, the findings from the current study indicated that those with ME/CFS are more likely to experience alcohol intolerance. It is very likely that this subtype of patients might have other biologic differences, and future research is needed to explore this hypothesis. The contribution of the current study was assessing the construct of alcohol intolerance in a more sophisticated way than has been attempted in previous investigations.

ARTICLE HIGHLIGHTS

Research background

There is a need to objectively measure alcohol intolerance among those with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Research motivation

There is a need to determine if those with ME/CFS with alcohol intolerance are more symptomatic than those without alcohol intolerance.

Research objectives

We aimed to carefully measure alcohol intolerance and determine its effects on those with ME/CFS.

Research methods

We collected data from patients with ME/CFS using a validated symptom questionnaire.

Research results

We were able to determine that those with alcohol intolerance were more symptomatic than those without it among a sample of patients with ME/CFS.

Research conclusions

It is important to measure alcohol intolerance carefully among patients who are not going to report using alcohol over the preceding months.

Research perspectives

It is possible to reliably and validly measure alcohol intolerance among those with ME/CFS, and this should guide future research in this area.

FOOTNOTES

Author contributions: Maciuch J and Jason LA contributed equally to this work, designed the research, performed the research, analyzed data, and wrote the paper.

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Steroid-induced psychosis related to pituitary adenoma status post trans-sphenoid excision and a history of psychiatric illness: A case report

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Abstract

BACKGROUND

Steroid-induced psychosis is a common adverse effect of steroid exposure. Reported cases were mostly related to rheumatologic disease. Despite its high incidence, there is only one case reported related to perioperative steroid replacement for pituitary adenoma surgery. This manuscript presents the second case of such and compared the two with the latest literature review of steroid-induced psychosis.

CASE SUMMARY

This is a case of an adult male with a chief complaint of auditory hallucinations and was referred by Neurosurgery to Psychiatry Out-patient department. He was diagnosed with pituitary adenoma who underwent trans-sphenoid excision of the mass from which steroid exposure led to steroid-induced psychosis. Also, patient had a history of psychiatric illness of severe depressive episode. At the out-patient department, patient was started on antipsychotic, Risperidone, which led to eventual improvement of his symptoms.

CONCLUSION

The two cases of pituitary adenoma surgery with steroid-induced psychosis had almost similar clinical profile with the latest literature review of steroid-induced psychosis. However, the present case highlights the association of psychiatric illness in predisposing an individual in developing it. Also, this manuscript emphasizes that early recognition of steroid-induced psychosis leads to better prognosis. Multispecialty treatment is vital in the holistic management of the patient with timely referral and close coordination.

Key Words: Steroid-induced psychosis; Dexamethasone; Complication; Pituitary adenoma; Perioperative supplementation; Case report

Core Tip: This case report supports the association between a history of psychiatric illness with higher incidence in developing steroid-induced psychosis. Also, the higher dosage of steroid exposure can cause earlier manifestation of psychotic symptoms. Steroid dosage was observed to be directly proportional to the severity of psychosis. Later improvement may be due to the delayed initiation of antipsychotics. Multispecialty treatment is vital in the holistic management of the patient with timely referral and close coordination. Lastly, proper determination of indication and minimum dose of steroids in patients undergoing pituitary surgery must be done so as to avoid any perturbing complications.

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INTRODUCTION

Steroid-induced psychosis is categorized by the *Diagnostic and Statistical Manual of Mental disorders*, fifth edition, as a form of substance/medication-induced psychotic disorder with the following criteria: psychosis occurred after exposure to psychedelic substances/medications, which cannot be better explained by another condition or substance and does not occur during the course of a delirium[1]. Lastly, it must cause significant distress and functional impairment. With those requirements, this condition is a diagnosis of exclusion, hence other potential differential diagnoses must be ruled out such as infectious, other substance-use related condition, metabolic, neurologic, vascular and other medical causes. The frequency of steroid-induced psychosis is estimated at under 5% from review of cases and clinical study literature, much of this focused on rheumatologic conditions[2]. Despite the high incidence of steroid-induced psychosis, there is only one case report about the occurrence of it after perioperative steroid replacement for pituitary adenoma surgery published by Mizutani *et al*[3] in 2015. Currently, there are no clear guidelines regarding the dose and period of steroid replacement for pituitary adenoma surgery hence, it varies in every institution. This report supports the highlighted risk of steroid psychosis associated with it.

This manuscript has the following objectives: (1) To present a rare case of an adult male with Pituitary adenoma status post transsphenoid excision with steroid-induced psychotic disorder and history of severe depressive episode; (2) To discuss the biological, psychological, and social factors in the development of his disorder, as well as treatment and management; and (3) To compare the findings of the latest literature review of steroid-induced psychosis with the two cases related with pituitary adenoma and discuss the currently suggested guidelines for the perioperative assessment and management of pituitary surgery.

CASE PRESENTATION

Chief complaints

Referred by his attending neurosurgeon for evaluation and management of auditory hallucinations status post Trans-sphenoid excision of Pituitary Adenoma.

History of present illness

18 years prior to consultation, the patient was apparently well until his wife left their family to work abroad as a factory worker and then cut off communications with them. Patient had a severe depressive episode in reaction to this event. He had a depressed mood and lost interest in his daily activities with associated poor sleep and poor appetite however denied thoughts of death and suicidal ideations. Patient had feelings of betrayal and worthlessness. Patient had a constant feeling of fatigue that slowed him down. He preferred staying in his room ruminating about what he did wrong to deserve the abandonment. Patient had diminished concentration at work and would often forget his tasks. The depressive episode lasted for 2 wk with no noted psychosis. No excessive alcohol drinking and no use of illicit drugs. No noted manic or hypomanic episodes. No medical condition noted. The patient coped by focusing on his furniture shop business and in taking good care of his two young children.

Interim revealed that the patient was apparently well until four years prior to consultation when the patient had an onset of intermittent flickering of vision. This was disregarded by the patient until two

years prior to consultation, the patient started to have visual field loss on the temporal side of the left eye. He thought of this as the result of his frequent exposure to direct heat of the sun as he works in his shop and felt that he was neglecting his health due to over working. Patient then decided to seek consultation with an optometrist to acquire eye glasses which he claimed to have provided temporary relief of his condition. However, one year prior to consultation, his right eye then started to have loss of vision on the temporal side also, however now with associated intermittent headaches. Patient noted that it affects his performance in making furniture however disregarded it. No noted depressive or manic episodes. No substance use or medications taken. No psychosis noted.

One year prior to consultation, due to the persistence of the problem with vision, the patient decided to seek consultation with an ophthalmologist and was diagnosed with bitemporal hemianopsia. The ophthalmologist explained that the problem with his vision were not primarily age-related eye diseases and that a mass in his brain was causing it. Upon hearing this, the patient asked about the etiology of this mass as he was shocked and anxious of it. Further testing was suggested and he was assured by the ophthalmologist that there was treatment of his condition. Patient complied with the advised and there were no depressive episodes noted as he confided all his worries to his partner. And so, MRI was immediately done showing heterogeneously enhancing sellar/suprasellar mass measuring 2.4 cm × 2.73 cm × 3.0 cm with considerations of pituitary macroadenoma or craniopharyngioma. The ophthalmologist referred the patient to a neurosurgeon in their local institution where consult was done. It was explained that surgical intervention was needed to address his problem in his vision however the nature of his disease and etiology was not understood by the patient. Patient felt anxious at first about the said procedure and the expenses for it. Patient decided to close his furniture shop and allocate his savings for his procedure. His partner assured him that she and other relatives will help him financially. Patient remained hopeful that he will be cured with the help of his doctors however, he was hold on queue for surgery in the government hospital during the pandemic. Hence, patient was repeatedly told to wait for schedule as elective surgeries were not the priority at the height of the pandemic. Patient understood the situation and that being safe from coronavirus disease 2019 (COVID-19) was his first priority. No noted depressive or manic episode. The patient then received a recommendation to seek consultation in our institution.

Upon consultation in our institution, preoperative endocrine studies were done to assess the hypothalamic-pituitary-adrenal axis: Serum growth hormone, 0.04 ng/mL; free thyroxine, 12.68 pmol/L; cortisol, 274.20 nmol/L; and ACTH, 23.70 pg/mL. Hence, the patient was diagnosed with a non-functioning pituitary adenoma. Patient was then scheduled for admission the next month for trans sphenoidal excision of sellar-suprasellar mass. Patient thought that the fast catering of service in the institution helped him feel relieved and that securing a schedule immediately made him feel hopeful once again. Even though, he still did not understand very well the nature and course of his disease, he chose to trust his doctors as he had great confidence with their competency as endorsed by a relative to him.

Upon admission, the patient had routine laboratory tests done including pre-operative Head computed tomography (CT) scan – plain. Patient was started on Dexamethasone 4 mg/tab 1 tablet twice a day among other drugs for perioperative preparation. The patient was referred to Internal Medicine for cardiopulmonary clearance and to Anesthesiology for pre-operative orders. There was no noted anxiety in the patient. Pt. had good sleep and appetite. No depressive episode noted. On his first hospital day, patient claimed that he was emotionally prepared for the day of his operation with the help of his faith and he had no anxiety or fear related to it as he prayed for guidance and strength. He was grateful for receiving the chance to be operated on even though there was still the pandemic. No depressive or manic episode noted. On his second hospital day, the patient underwent cardiopulmonary clearance and was classified as having 3.9% risk in developing cardiac complications with low to intermediate risk in developing pulmonary complications. These risks and possible complications like excessive bleeding and other possible morbidity were explained and understood by the patient. No noted depressive or manic episode noted. Oral Dexamethasone was shifted and increased to 4 mg/mL intravenous every 6 h. Patient received a total of 12 mg of Dexamethasone before the operation.

On his third hospital day, patient was primed for operation and oriented about the procedure to be done. Patient thought that everything would work out well and he will soon regain his normal vision. No anxiety or fear was noted at the operating room. The patient then underwent surgery under general endotracheal anesthesia *via* endoscopic endonasal approach. There were no surgical complications during and after the procedure. Patient continued to receive Dexamethasone 4 mg intravenously every six hours. No complications of anesthesia immediately post operation. However, at the post-anesthesia care unit, patient experienced a transient elevated blood pressure ranging from (140-150/100-110) for which patient was started on Nicardipine drip 10 mg in 90 cc Plain Normal Saline Solution titrated at 5 mL/h to maintain blood pressure of ≤ 140/90.

On the fourth hospital day and post-operative day (POD) 1, the patient has recovered from immediate effects of anesthesia with stable vital signs, fully awake, conversant and able to follow commands. Patient was for Head CT scan prior to transfer to the ward however was uncooperative due to persecutory delusion that the nurses and doctors are planning to harm him. Patient had an anxious mood and withdrawn behavior. At this time, there were no noted fever, headache, disorientation and problem with attention in the patient. After verbal pacification and assurance by his live-in partner, the

patient agreed to do the imaging test. Even after the procedure, the patient claimed that his vision improved however now characterized as blurry with white hazy smoke for both eyes. Patient thought that this will just be temporary and hoped that it will soon fade. No depressive or manic episodes noted.

On the fifth hospital day and POD 2, the patient continued to receive Dexamethasone 4 mg/mL intravenously every six hours. The patient was now at the surgery ward and was observed by his lived-in partner to have persistence of his anxious mood however now associated with poor sleep. Patient claimed to be having an auditory hallucination that he heard the nurses planning to put poison in his medications. Patient also had a delusion of thought broadcasting that people around him could read his mind. Also, patient had a command hallucination of telling him to run away from the hospital. The patient acted on his persecutory delusion and became agitated. He began pulling out all of his intravenous lines and demanded to go home. He then refused to take all of his medications. Patient and live-in partner then opted for discharge against medical advice despite the explanation of the patient's condition, risks and consequences of their decision including disability, infection and death. Patient was given home medications including Dexamethasone to be tapered over 11 days (PODs 3, 4, and 5 - 4 mg/tab 1 tablet every 6 h for 3 d, PODs 6, 7, and 8 - 1 tablet thrice a day for 3 d, PODs 9, 10, and 11 - 1 tablet twice a day for 3 d, PODs 12 and 13 - ½ tablet twice a day for 2 d).

For PODs 3, 4, and 5, patient went back to his house together with his live-in partner still with persistence of his psychosis however the episodes were intermittent. The patient only wanted to stay inside their house, closed and covered all the windows, due to fear of the outside light. Patient falsely believes that he was implanted with magnets and that if he were to go out he would be dragged away. Patient claimed that a voice told him to run away and so he did. His eldest son tried to calm him down however was not verbally pacified. Patient was apprehended and brought back to their house. No consultations were done despite the persistence of psychotic episodes. His family did not want to seek psychiatric consultation as they fear that the patient will be institutionalized which they deemed unnecessary. Patient continued his home medications as supervised by his live-in partner.

For PODs 6, 7, and 8, the patient was already able to go out of their house however falsely believed that the people around him could read his mind. No agitation or aggression noted. Patient was able to care for himself and had good interaction with family.

For the last of the days of dexamethasone tapering doses, the only psychosis that persisted was the auditory hallucination of a voice telling him to run away. However, the patient had better impulse control and did not act on it.

In the interim, patient was able to function again by being able to do self-care, relate well at home, and socialize with other people but this was lower level unlike his baseline functioning due to the persistence of blurred vision. As he could no longer work in his furniture shop, drive his motorbike, and had difficulties doing house hold chores. Hence, patient had lowered self-esteem. However, the patient did not experience any depressive or manic episodes. No feelings of worthlessness and hopelessness. As the patient was supported by his partner financially and emotionally and was able to confide his worries to her most of the time. Due to the persistence of his auditory hallucination and blurring of vision, the patient decided to have a follow-up consultation with his Neurosurgeon and was then referred to the Psychiatry department for evaluation and management regarding his hallucinations; hence, consult.

History of past illness

Patient was diagnosed with Pituitary adenoma in August 2022 for which he underwent trans-sphenoidal excision of sellar-suprasellar mass last September 15, 2022. Patient had a history of severe depressive episode without psychotic symptoms last 2005, however, no consult was done and no medications taken. Patient had no history of seizures, head trauma, and loss of consciousness. No comorbidities like hypertension, cardiac disease, diabetes, or thyroid disease. The patient also denies any substance use.

Personal and family history

There is no psychiatric or neurologic condition present in the family. No one in the family had substance abuse or attempted suicide. There is no history of diabetes, hypertension, cancer, neurologic diseases, cardiac diseases, and stroke in the family.

Physical examination

Patient had an unremarkable physical and neurologic exam except for the remarkable visual acuity of the patient: 20/400, right eye and no light perception, left eye.

Laboratory examinations

Laboratory tests requested were all unremarkable except for the lipid profile indicating hyperlipidemia. Patient had low high-density lipoprotein and elevated low density lipoprotein, triglycerides, and total cholesterol. At the psychiatry out-patient department, postoperative hormone status was rechecked and revealed unremarkable results with normal morning cortisol level of 20.38 µg/dL.

Imaging examinations

Magnetic Resonance Image - T2 Weighted Image of the Brain Coronal view with the location of the mass presented in [Figure 1](#): (1) Preoperative image - heterogeneously enhancing sellar/suprasellar mass measuring 2.4 cm × 2.73 cm × 3.0 cm with considerations of pituitary macroadenoma or craniopharyngioma; and (2) Postoperative image - interval decrease in size of the sellar-suprasellar mass that appears as a T1W/T2W isointense signal surrounding a fat intensity signal, now measuring 1.5 cm × 1.9 cm × 1.8 cm which still abuts the bilateral carotid arteries and obliterates the suprasellar cistern. The residual intrasellar tumor noted may have caused the minimal improvement of the patient's visual acuity as its mass effect, however this does not contribute to the psychosis experienced by the patient.

FINAL DIAGNOSIS

Patient had a final diagnosis of International Classification of Disease-10: Psychoactive substance-induced (steroid) psychotic disorder with delusions and hallucinations; Severe depressive episode without psychotic symptoms; Pituitary adenoma status post trans-sphenoid excision, Hyperlipidemia and Diagnostic Statistical Manual 5: Substance/medication induced (steroid) psychotic disorder; Major depressive disorder, single episode, without psychotic features.

TREATMENT

For the management, ideally the patient should have tapering or if possible discontinuation of steroid therapy at the onset of his psychosis during admission. Referral to Psychiatry department should have been done at the ward level and atypical antipsychotic should have been started by that time as well. The biological treatment of choice given for the patient was Risperidone. According to the recent review of efficacy and safety of medications used in the management of steroid-induced psychosis, atypical antipsychotics had established effectiveness in treating steroid psychosis. Among other atypical antipsychotics, Risperidone and Olanzapine were more effective for the positive symptoms such as hallucinations and delusions present in steroid psychosis[4]. Olanzapine was noted to be related to more adverse metabolic effects[5]. In the patient, his body mass index is within normal however his lipid profile revealed hyperlipidemia. Hence, Risperidone 2 mg/tab 1 tablet once a day at bed time, was started for the patient at the Out-patient department upon referral by Neurosurgery. This was the minimum dose to check efficacy and be able to go low and slow in the dosaging of his medication. The increase in his dosage, Risperidone 2 mg/tab 1 tablet twice a day, was done after 4 wk of administration with minimal response.

Ideally, the psychological treatment should also have been started for the patient in his admission. Standard nonpharmacological methods such as nursing by familiar faces, adequate ambient lighting, regular assurance and reorientation, de-escalation and gentle distraction when necessary should have been done at the ward[2]. As well as, psychoeducation and supportive psychotherapy however these were catered at the out-patient department.

Intermediate treatment plans were to continue his medication, supportive psychotherapy, and continue referral and coordination with the multispecialty team for the holistic care of the patient.

Long term treatment plans include tapering and subsequent discontinuation of antipsychotic medication and still with regular follow up consultation for observation of his overall condition. Socially, the minimum goals were to maintain his good interpersonal relationship and ensure good family support.

OUTCOME AND FOLLOW-UP

Patient had recovered from the effects of steroid. Patient continued consultation for long-term treatment plans.

DISCUSSION

Steroid psychosis is a common complication of steroid therapy. This case report presents the second patient who underwent perioperative steroid replacement for pituitary adenoma surgery and then experienced an adverse effect of steroid-induced psychosis. However, an important predisposing factor noted in this case was the history of psychiatric illness which was severe depressive episode. In the latest literature review of steroid-induced psychosis by Huynh *et al*[4] in 2021, majority of the cases were without history of psychiatric illness however history of anxiety and depressive disorders were

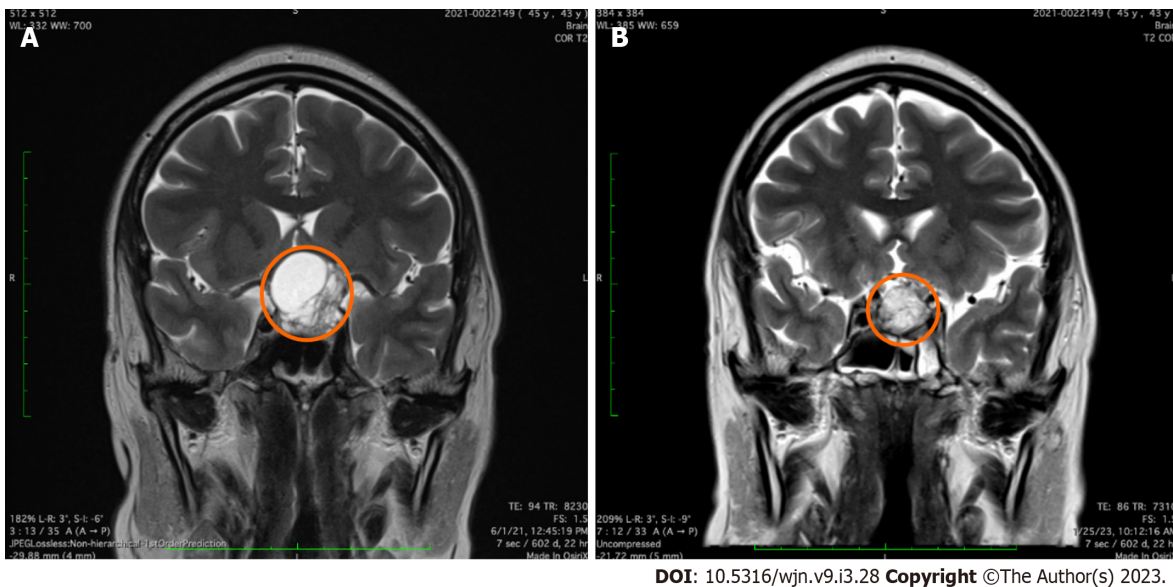


Figure 1 Magnetic resonance image - T2 weighted image of the brain coronal view with the location of the mass encircled in red. A: Preoperative image; B: Postoperative image.

identified in a few cases. This case report supports the association observed in various studies that a history of psychiatric illness and/or history of previous steroid-psychosis are associated with higher incidence in developing it[6-8].

In order to understand the history of mental illness in this case, the theoretical model of self-psychology developed by Heinz Kohut needs to be applied[9]. This theory focuses on external relationships and their impact on the development of self-esteem and self-cohesion[9]. Examining the patient's anamnesis, he did not experience developmental stunting as related to empathic failures in his mother. At an early stage he was not arrested in the evolution of the structure of the self. However, according to Kohut the needs of mirroring and idealization continues throughout life[9]. In the patient's adulthood when his wife was his self-object not satisfying his needs for idealizing and mirroring for the maintenance of the self that was the time he experienced disintegration of the self-object. When his wife left him and cut-off their relationship abruptly after all that he has done to help her he was not reciprocated leading to feelings of abandonment and betrayal which lead to the manifestation of severe depressive episode. The patient was able to cope by employing mature defense mechanism of altruism in committing himself to the needs of his children. Another important factor in his eventual recovery from depression was when he found a loving and supportive partner who accepted him and his children. These secured his sense of self once again.

However, the maintenance of his self-esteem was again challenged when he experienced blurring of his vision and eventually diagnosed with pituitary adenoma. He had poor understanding of the nature and course of his disease and had anxiety about the uncertainties of his condition. On top of that, patient experienced delays in treatment brought by the COVID-19 pandemic. The need for transphenoid excision of the pituitary adenoma precipitated the development of steroid-induced psychosis from receiving a high dose ranging from 26.7-106.7 mg of prednisone or its equivalent per day. Exposure to high dosage of steroids caused stress on the hypothalamus-pituitary adrenal axis leading to deleterious effects on cognitive function caused by a change of metabolic needs that can shrink the hippocampus[4]. The psychosis manifested brought about by the increase of dopamine that may be attributed to the induction of tyrosine hydroxylase by the steroid[4].

Several factors perpetuating the complication were identified including continuing exposure to steroid and late initiation of antipsychotic medications. Hence, the persistence of steroid-induced psychosis lowering the level of functioning of the patient at home and at work. Aside from that, there was also persistence of blurring of vision even after his operation. All of this led to him having a low self-esteem. However, no noted depressive episodes in response to these events.

As there are various protective factors identified as well, patient was eventually referred to Psychiatry and he was noted to have good adherence with treatment regimen which can be attributed to his trust and confidence to the medical team covering multispecialty treatment for his condition. Hence, the patient has sustained a positive outlook or optimism in his future. With good support system from partner and family, strong spirituality, and financial stability the patient had been able to recover from his complication.

In this manuscript, a summarized clinical profile of Steroid-induced Psychosis from the study of Huynh *et al*[4] was compared with the clinical profile of the 2 cases of Steroid-induced Psychosis associated with excision of pituitary adenoma presented in Table 1.

Table 1 Summarized clinical profile of steroid-induced psychosis compared with the clinical profile of the 2 cases of steroid-induced psychosis associated with excision of pituitary adenoma

Parameters	Latest literature review of steroid-induced psychosis (Huynh <i>et al</i> [4], 2021)	Mizutani <i>et al</i> [3], 2015	Aranas & Tangalin, 2023
Age	Mean age of 42.54 yr old	35 yr old	47 yr old
Sex	Cases were mostly male; Female sex – proven risk factor	Male	Male
Indication for steroids	Suppression of inflammatory processes and the immune system	Perioperative steroid replacement	Perioperative steroid replacement
Steroids (prednisone equivalent in average (mg/d)	Prednisone, Prednisolone, Methylprednisolone, Dexamethasone, Hydrocortisone, Triamcinolone, Betamethasone; (15-1250 mg of prednisone/d)	Hydrocortisone 10-300 mg/d; (2.5-75 mg of prednisone/d)	Dexamethasone 2-16 mg/d; (26.7-106.7 mg of prednisone or its equivalent per day)
Duration of steroid therapy	Shortest: < 2 d; Longest: 2 yr; Mostly within 3 d up to 6 mo	8 d	11 d
Onset of psychosis from 1 st dose of steroids	Earliest: < 24 h; Latest: After 2 yr of chronic use; Mostly within 2 da to up to 2 wk	4 d	1 d
Symptomatology	Most common: Delusions & hallucinations; Others: Insomnia, agitation, irritability, combativeness, confusion, cognitive impairment, mania, depression, and suicidal ideation	Elated and irritable mood, grandiose and persecutory delusions, anxiety, and agitation	Anxious mood, persecutory delusions, thought broadcasting, auditory hallucination, agitation
History of Psychiatric illness	Majority without psychiatric illness; Anxiety disorder; Depressive disorder	None	Severe depressive episode without psychotic symptoms
Steroid management following diagnosis of psychosis	Discontinued – quicker resolution; Tapered	Tapered (7 d)	Tapered (11 d)
Pharmacologic intervention	Typical antipsychotics: Haloperidol, Levomepromazine, perphenazine, & zuclopenthixol; Atypical antipsychotics: Risperidone, Olanzapine & Quetiapine; Mood stabilizers: Lithium & Valproic acid; Benzodiazepines: Clonazepam, diazepam, lorazepam, & Flunitrazepam	Atypical antipsychotic: Risperidone	Atypical antipsychotic: Risperidone
Recovery/Improvement	Earliest: 1 mo; Longest: 8 wk	4 d	3 wk

The mean age of patients in the latest review was 42.54 years old with more male cases identified in the study. This is close to the mean age of the 2 cases which is 41 years old with both being of male sex. However, according to studies female sex was a proven risk factor in developing the condition[2,10,11]. As for the common indication for steroid use in the review, it was generally for suppression of inflammatory processes and the immune system however for pituitary adenoma surgery the perioperative steroid replacement was for the prevention of associated complications related with hypoadrenalism[4]. The steroid dosage given for the cases included in the review ranges from 15-1250 mg of prednisone or its equivalent per day. The case of Mizutani *et al*[3] received a lesser steroid dosage range from 2.5-75 mg of prednisone/d while the present patient higher ranging from 26.7-106.7 mg of prednisone/d. The steroid utilized in this case report was Dexamethasone 2-16 mg/d, with 0.75 mg of it being equivalent to 5 mg of Prednisone. The higher the dose of steroid used has been implicated to be associated with higher incidence of steroid-induced psychosis[2]. For patients who received ≥ 40 mg/d of prednisone, the risk sharply increases to 4.6% and even more drastic increase for ≥ 80 mg/d rising to 18.4%[12,13].

In the latest review, the shortest duration of treatment was less than 2 d while the longest was 2 years. Mostly were within 3 d up to 6 mo. The case of Mizutani *et al*[3] had shorter duration of treatment and the present patient had longer exposure of steroid therapy, 8 and 11 d, respectively. The earliest onset of psychosis from the 1st dose of steroid exposure in the latest review was < 24 h. And the latest was after 2 years of chronic use. Mostly were within 2 d up to 2 wk. On the other hand, Mizutani *et al*[3] noted the presentation of psychosis in his case was at postoperative day 4 while in the present patient it was earlier at postoperative day 1. According to several studies, presentation of psychosis for most cases was < 2 wk of its induction, however, the more typical onset is at 3 or 4 d after initiation of steroid[14,15]. Although, it was also noted that symptoms can occur anytime even after discontinuation of steroid therapy[16]. This case report highlights that the higher dosage of steroid exposure can cause earlier manifestation of psychotic symptoms as observed from the 2 cases related to pituitary adenoma surgery. Also, the dosage was observed to be directly proportional to the severity of psychosis wherein the present patient had florid episodes of agitation when he was maintained on 106.7 mg/d of Prednisone.

In an older study of Lewis and Smith in 1983, most of the cases back then were most commonly presenting with delusions and a few had psychotic disorder without evidence of significant mood changes or features of delirium[10]. On the other hand, most common symptoms for all of the cases in the latest review were delusions and hallucinations however other psychiatric symptoms were also noted such as insomnia, agitation, irritability, combativeness, confusion, cognitive impairment, mania,

depression, and even suicidal ideation. Both cases related to pituitary adenoma had similar presentation with that of any typical steroid-induced psychosis in the latest review however there were no noted combativeness, mania, depression, and suicidal ideation among them.

In the latest review, discontinuation and/or tapering of the steroid use were the management utilized following the diagnosis of psychosis. It was observed that discontinuation provided quicker resolution of symptoms. However, discontinuation may not be feasible for all medical indications, the benefit should always outweigh the risk in considering to withdraw steroids. As for the two cases of pituitary adenoma surgery, tapering was employed. The case of Mizutani *et al*[3] had a 7-d period of tapering while in the present patient, he had longer period for 11 d. There are no studies yet about recommended standard period of tapering and no established association if a shorter or longer period of tapering would lead to earlier recovery or improvement.

For the pharmacologic interventions, typical antipsychotics, atypical antipsychotics, mood stabilizers and benzodiazepines were utilized in the latest review. While for both cases of pituitary adenoma surgery, Risperidone, an atypical antipsychotic was utilized. The latest review of cases supports the high effectiveness of Haloperidol and Risperidone in managing adult patients exhibiting delusions or hallucinations after exposure to steroids[4]. However, it has been shown that there is greater preference in using atypical antipsychotics over the typical antipsychotics because of its lower adverse risk profile [15,17].

In the latest review, recovery or improvement was noted earliest by 1 mo and longest by 8 wk. And a great majority of patient completely recover within an average span of 2 wk after treatment initiation [4]. The case of Mizutani *et al*[3] had earlier recovery while the present patient had later improvement, at 4 d and 3 wk, respectively. This maybe due to the delayed initiation of antipsychotics which did not start at the onset of psychosis and did not overlap with the tapering period of steroid. Aside from that, the steroids given to the present patient was notably excessive when compared to the current suggested guidelines for the perioperative assessment and management of pituitary surgery by Inder *et al*[12] in 2002.

In the guidelines, no perioperative glucocorticoid cover should be given in patients with a normal hypothalamic-pituitary-adrenal (HPA) axis function and/or those in whom selective adenectomy can be performed. While for patients with abnormal HPA axis function, the preoperative steroid supplementation regimen recommends that a usual daily dose of prednisone is 5 mg/d (equivalent values: methylprednisolone 4 mg/d, dexamethasone 0.5 mg/d, hydrocortisone 20 mg/d) or 10 mg of prednisone every other day should be given followed by the regimen used for extensive pituitary surgery. The recommended hydrocortisone perioperative steroid regimen for extensive pituitary surgery is 50 mg IV every 8 h. On day 0 then taper dose by half per day, 25 mg IV every 8 h. On day 1 and so on until usual daily dose is reached. The present case received Dexamethasone 12 mg as its perioperative steroid dose which is equivalent to Hydrocortisone 320 mg. Hence, the present patient received more than 6 times greater than the recommended perioperative steroid dose by Inder *et al*[12] predisposing the patient to steroid psychosis. This highlights the importance of proper determination of indication and providing the appropriate minimum dose of steroids in patients undergoing pituitary surgery so as to avoid any perturbing complications.

CONCLUSION

For patients undergoing pituitary adenoma surgery, the indication for perioperative steroid replacement must be evaluated properly and the minimum dose should be utilized. Early recognition of steroid-induced psychosis would lead to better prognosis. Multispecialty treatment is vital in the holistic management of the patient with timely referral and close coordination.

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FOOTNOTES

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- 37 Role of lumbar puncture in clinical outcome of suspected acute bacterial meningitis

Saha A, Kanamgode SS, Malempati SC, Chaudhuri S, Scott J

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Retrospective Study

Role of lumbar puncture in clinical outcome of suspected acute bacterial meningitis

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Abstract

BACKGROUND

Meningitis remains a significant source of mortality and morbidity, with an incidence of 1 per 100000 persons in the United States. Guidelines recommend obtaining blood cultures and cerebrospinal fluid (CSF) studies in patients presenting with acute meningitis syndrome, and beginning treatment with broad spectrum antibiotics based on the age and certain predisposing conditions. In some patients however, the diagnostic lumbar puncture (LP) is not performed due to a multitude of reasons, ranging from increased intracranial pressure to failed attempt. In such situations, appropriate therapy is initiated empirically and often continued without establishment of a definitive diagnosis.

AIM

To determine whether a diagnostic LP in acute meningitis syndrome was associated with a better outcome and less duration of antibiotic therapy, along with potential causes for deferral of procedure.

METHODS

A retrospective study was conducted amongst the patients presenting to a 360 bedded community hospital in central Massachusetts with a diagnosis of acute meningitis syndrome between January 2010 – September 2022. The electronic health records were accessed to collect necessary demographic and clinical data, including etiology of meningitis, lumbar puncture results, reason for procedure deferral, duration of antibiotic therapy and clinical outcome. The patients were subsequently divided into two groups based on whether they received a LP or

not, and data was analyzed.

RESULTS

A total of 169 patients admitted with acute meningitis syndrome between September 2010-2022 were included in the study. The mean age of the participants was 54.3 years (SD +/- 19.2 years). LP was performed for 130 (76.9%) participants, out of which, 28 (21.5%) showed some growth in CSF culture. The most commonly identified organism was *streptococcus pneumoniae*. Amongst the 39 patients in whom LP was deferred, the major reasons recorded were: Body habitus ($n = 6$, 15.4%), and unsuccessful attempt ($n = 4$, 10.3%). While 93 (71.5%) patients with LP received antibiotic therapy, only 19 (48.7%) patients without LP received the antibiotics, with the principal reason being spontaneous improvement in sensorium without any diagnosed source of infection. The mean duration of antibiotic use was 12.3 days (SD +/- 5.6) in the LP group and 11.5 days (SD +/- 7.0) in the non-LP group ($P = 0.56$; statistically not significant). We observed higher long term sequelae in the non-LP group ($n = 6$, 15.4%) compared to the LP group ($n = 9$, 6.9%). Similarly, the death rate was higher in the non-LP group ($n = 7$, 18.0%) compared to the LP group ($n = 9$, 6.9%).

CONCLUSION

LP remains the cornerstone for diagnosing meningitis, but often CSF results are unavailable, leading to empiric treatment. Our study identified that body habitus and unsuccessful attempts were the most common reasons for LP not being performed, leading to empiric antibiotic coverage. There was no difference between the duration of antibiotics received by the two groups, but a lower proportion of patients without LP received antibiotics, attributed to a spontaneous improvement in sensorium. However, the residual neurological sequelae and death rates were higher in patients without LP, signifying a potential under-treatment. A LP remains crucial to diagnose meningitis, and a lack of CSF analysis predisposes to under-treatment, leading to higher neurological sequelae and increased chances of death.

Key Words: Meningitis; Acute meningitis syndrome; Lumbar puncture; CSF analysis; Acute bacterial meningitis; Suspected meningitis

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Core Tip: Cerebrospinal fluid (CSF) analysis is considered the gold standard for diagnosing meningitis, but often CSF results are unavailable and patients are treated empirically. There are a multitude of reasons for lumbar puncture (LP) deferral, predominantly unsuccessful attempts and body habitus. A lack of CSF analysis in patients with suspected meningitis is associated with prolonged antibiotic use in some and poor outcome in others secondary to potential under-treatment. Every patient with a clinical suspicion for meningitis should undergo LP, radiology-assisted if necessary, and have a CSF analysis to confirm or rule out meningitis to guide need for antibiotic therapy.

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INTRODUCTION

Acute bacterial meningitis (ABM) continues to be a significant cause of mortality and morbidity, with an incidence of 1 per 100000 in the United States[1]. However, the incidence is considerably higher in lower-income countries, such as the meningitis belt of Africa, where it is around 80 per 100000 individuals. The mortality rate is also significantly high, ranging from 10%-50%[2]. Many patients who receive inadequate treatment or survive the acute infection develop chronic neurological sequelae, significantly impairing their quality of life. The most commonly responsible organisms include *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B, with *Listeria monocytogenes* affecting certain age groups[3].

ABM is a medical emergency that requires prompt recognition, evaluation, and initiation of appropriate antimicrobial therapy based on the microbiome, susceptibility profile, and patient risk factors[4]. Early initiation of antibiotics has been significantly linked to better neurological outcomes with a lower risk of clinical deterioration and death[5]. The classic triad of headache, fever, and neck stiffness may not always be present in ABM and has poor sensitivity. Other symptoms include nausea, vomiting, altered sensorium, photophobia, and seizures. Diagnosing ABM requires a high index of clinical suspicion[6]. Immediate lumbar puncture, followed by broad-spectrum antibiotics and corticosteroids, remains the cornerstone of diagnosis and treatment. Vancomycin and ceftriaxone are the empirical antibiotics of choice, especially in areas with ceftriaxone resistance. Ampicillin is added for neonates, older patients, and immunocompromised

individuals. Glucocorticoids such as dexamethasone should also be initiated to decrease inflammation but discontinued if *Listeria monocytogenes* is confirmed[7]. Cerebrospinal fluid (CSF) findings are usually indicative, with an elevated leukocyte count being the most predictive, and gram stain is often used to guide therapy. However, cases of culture-confirmed meningitis without an elevated leukocyte count in the CSF have also been reported[8].

Many patients with meningitis present with an altered level of consciousness, but neuroimaging is not always necessary to rule out raised intracranial pressure before lumbar puncture[9]. The perceived need for baseline neuroimaging may delay lumbar puncture in the United States. Delays in lumbar puncture are associated with significantly lower diagnostic yield from CSF bacterial culture or polymerase chain reaction, and a delay in antibiotic administration is associated with increased mortality[10]. According to recent Swedish guidelines, neuroimaging prior to lumbar puncture is required only for patients who have signs of imminent brain herniation, focal neurological deficits (excluding cranial nerve palsies), or who have had cerebral symptoms for more than 4 d[10]. The use of Swedish guidelines instead of the Infectious Diseases Society of America guidelines has been shown to reduce unnecessary neuroimaging, decrease the time interval to initiation of therapy, and improve outcomes with a 33% reduction in overall mortality and a 24% increase in favorable neurological outcomes[9,10].

Rationale and knowledge gap

However, in certain cases, obtaining CSF may not be possible for various reasons, with the most common being unsuccessful attempts and the need for radiological guidance in the setting of obesity[11,12]. In such cases, empiric antibiotics may be initiated and continued in the absence of an established diagnosis, leading to unnecessary antibiotic use and potentially contributing to antibiotic-related complications and bacterial resistance.

Objective

We conducted a review of our experience regarding CSF sampling in patients for whom a diagnosis of meningitis was considered. We aimed to determine the percentage of patients who underwent a successful procedure, the reasons why some patients did not, and the impact of a successful procedure on patient treatment in terms of the duration of antibiotic therapy and overall outcomes.

MATERIALS AND METHODS

We conducted a retrospective study among patients admitted to a 360-bed community hospital in central Massachusetts. All patients who presented to the emergency department between January 2010 and September 2022 with a diagnosis of acute meningitis syndrome were identified and included in the study. Acute meningitis syndrome was defined as the presence of fever and headache with or without neck stiffness and clinical concern for meningitis[13]. The patients were divided into two groups based on whether they received a lumbar puncture to confirm the diagnosis of acute bacterial meningitis. Demographic, clinical, radiological, and microbiological data were reviewed. The patient groups were followed, and necessary data, including demographics, clinical course, CSF analysis results, reasons for procedure deferral, duration of antibiotic therapy, and overall outcome, were collected. The data were analyzed with respect to the duration of antibiotic use and overall outcome. A biomedical statistician performed the statistical review of the study.

RESULTS

During the study period, a total of 169 patients admitted with acute meningitis syndrome were included. The mean age of the participants was 54.3 years (SD +/-19.2 years) (Table 1). Lumbar puncture (LP) was performed for 130 (76.9%) participants, out of which, 28 (21.5%) showed some growth in CSF culture. The most commonly identified organism was *Streptococcus pneumoniae*. All cases of meningitis were community-acquired, with no post-surgical or post-traumatic etiology identified. Among the 39 patients in whom LP was deferred, the major reasons recorded were increased body mass index (BMI)/body habitus ($n = 6$, 15.4%) and unsuccessful attempts ($n = 4$, 10.3%). Three patients refused to provide consent for LP, three were hemodynamically unstable on pressors and started empirically on antibiotics, three had spinal deformities with a history of spinal surgery, and two had supratherapeutic international normalized ratio > 8 at presentation, while no reason was documented for 18 of them. All six patients with obese body habitus in whom LP was deferred had a BMI over 35 kg/m². While 93 (71.5%) patients with LP received antibiotic therapy, only 19 (48.7%) patients without LP received antibiotics, with the principal reason being spontaneous improvement in sensorium without any diagnosed source of infection. The mean duration of antibiotic use was 12.3 days (SD +/- 5.6) in the LP group and 11.5 days (SD +/- 7.0) in the non-LP group ($P = 0.56$; not statistically significant). We observed higher long-term sequelae in the non-LP group ($n = 6$, 15.4%) compared to the LP group ($n = 9$, 6.9%), predominantly focal neurological deficits, hearing loss, and cognitive impairment. Similarly, the death rate was higher in the non-LP group ($n = 7$, 18.0%) compared to the LP group ($n = 9$, 6.9%) ($P = 0.04$).

Table 1 Clinical profile of the participants

Variables	Frequency (%)	
	LP group, <i>n</i> = 130	Non-LP group, <i>n</i> = 39
Age		
≤ 40 yr	41 (31.5)	6 (15.4)
41 to 65 yr	58 (44.6)	12 (30.8)
> 65 yr	31 (23.9)	21 (53.9)
Gender		
Male	58 (44.6)	22 (56.4)
Female	72 (55.4)	17 (43.6)
Presence of comorbidities		
Diabetes	27 (20.8)	19 (48.7)
Hypertension	37 (28.5)	20 (51.3)
HIV infection	3 (2.3)	0 (0)
Carcinoma	3 (2.3)	1 (2.6)
History of brain tumor surgery	14 (10.8)	5 (12.8)
Presence of neck stiffness	58 (44.6)	21 (53.9)

HIV: Human immunodeficiency virus; LP: Lumbar puncture.

DISCUSSION

Key findings and discussion

Lumbar puncture remains the cornerstone for diagnosing meningitis, and early initiation of antibiotics after obtaining lumbar puncture without waiting for neuroimaging remains the standard of care[14]. In certain situations, although the clinical syndrome is consistent with meningitis, the diagnosis is not established due to an inability to obtain CSF results. This can be attributed to various factors. Morbid obesity, unsuccessful attempts, spinal deformities, or previous spinal surgery were the principal reasons identified in our study[14,15]. All six patients who had body habitus recorded as a reason for deferring LP had a BMI over 35 kg/m². Obesity makes it difficult to identify important landmarks and often requires longer LP needles to puncture the depth of skin tissue, which is not always readily available[16].

All 28 patients who had a confirmed diagnosis of bacterial meningitis through growth in the CSF culture were attributed to have acquired it from the community. Five of them were immunocompromised, with two being positive for human immunodeficiency virus on antiretroviral therapy and three on chemotherapy for malignancy within the last 6 mo of diagnosis. None of them had a history of trauma or brain injury in the past. There were 14 patients in the LP group who had a previous history of brain tumor surgery but did not have any active post-surgical complications or CSF leak, and all of them had sterile CSF cultures.

Delays in lumbar puncture have been associated with increased mortality in a study done using the national inpatient sample database on patients with cryptococcal meningitis[17]. Our study has shown that in a busy community hospital in central Massachusetts, not all patients admitted with a presumed diagnosis of meningitis had a lumbar puncture done, either on admission or during the hospital stay. There was also increased mortality in patients in whom a lumbar puncture was delayed. This could be attributed to potential undertreatment and delay in the initiation of antibiotics while waiting to obtain a radiology-guided lumbar puncture. Although CSF gram stain results can help guide treatment, empirical antibiotics are often warranted to cover potential organisms based on the patient's age, underlying comorbidities, sensitivity profile of the commonly causative organisms, and the microbiome[2,3]. However, it is difficult to differentiate between bacterial meningitis and aseptic meningitis as both the Meningitest and Bacterial Meningitis Score require CSF analysis[18], while blood cultures, white blood cell count, inflammatory markers, and other laboratory investigations may not be very predictive[5]. In such situations, the decision to defer antibiotics to evaluate another potential attributable cause of the presenting symptom complex may prove fatal. The lack of existing guidelines to aid in the management of such patients often leads to significant variability in treatment[19].

LP has traditionally been a procedure conducted by the internal medicine team. However, with an increasing number of patients undergoing spinal surgery and the recent obesity epidemic, ultrasound-guided LP has become the new norm. LP becomes more challenging with an increase in needle size, and landmarks become difficult to palpate[11,20]. This also leads to inadvertent delays in achieving a diagnosis, as radiology-guided lumbar puncture slots are not promptly available.

In our study, there was no significant difference in the duration of antibiotics received by the two groups, but a lower proportion of patients without LP received antibiotics. This was mostly attributed to a lack of an established diagnosis of meningitis in these patients. In such situations, the decision to empirically treat lies with the clinician and also depends on other potential confounding factors that can explain the symptom complex. Additionally, many patients experienced spontaneous improvement in sensorium and were deemed not to require antibiotics. However, the residual neurological sequelae and death rates were also found to be higher in these patients, possibly resulting from persistent underlying and untreated infection.

Strengths and limitations

The strengths of the study include a population presenting to a community hospital over a significant time period, which is representative of the general population and can be extrapolated to day-to-day clinical scenarios. Limitations involved the retrospective nature of the study and the smaller sample size included. Further large-scale studies are needed to develop an optimum guideline for the evaluation of meningitis in the absence of a definitive CSF analysis and to determine the best empirical antibiotic regimen for patients in whom LP is deferred.

CONCLUSION

Lumbar puncture remains the gold standard for diagnosing acute bacterial meningitis, but in certain cases, it may not be feasible to obtain CSF due to various factors. There is a definite association between deferral of lumbar puncture and poor outcomes in patients with suspected acute meningitis syndrome. Lack of CSF analysis may be associated with unnecessary antibiotic therapy in some and poor outcomes related to inadequate treatment in others. Clinicians should be aware of these challenges and make informed decisions based on clinical judgment, patient risk factors, and the need for empiric antibiotic therapy.

ARTICLE HIGHLIGHTS

Research background

The classic triad of headache, fever and neck stiffness is not always present in acute meningitis syndrome; however, diagnosis with lumbar puncture and immediate empirical antibiotic coverage remains cornerstone of therapy. In some cases, cerebrospinal fluid (CSF) analysis is also not available, leading to long term empiric antibiotics use or potential undertreatment.

Research motivation

We aimed to investigate the correlation between lumbar puncture in patients with suspected acute bacterial meningitis and their overall outcome, and determine if empirical therapy was beneficial.

Research objectives

To determine the percent of patients presenting with acute meningitis syndrome who underwent a successful diagnostic procedure, the reasons why some patients did not, and the impact a successful procedure had on patient treatment in terms of duration of antibiotic therapy and overall outcomes.

Research methods

We conducted a retrospective study among patients presenting with acute meningitis syndrome to a 360-bed community hospital in central Massachusetts. The patients were divided into two groups based on whether they received a lumbar puncture to confirm the diagnosis of acute bacterial meningitis. Data was collected and analyzed with respect to duration of antibiotic use and overall outcome.

Research results

A total of 169 patients admitted with acute meningitis syndrome were included. Lumbar puncture (LP) was performed for 130 (76.9%) participants, out of which, 28 (21.5%) showed some growth in CSF culture. Amongst the 39 patients in whom LP was deferred, 21 had no reason documented, 6 had increased body mass index ($n = 6$, 15.4%), and 4 had unsuccessful attempts. While 93 (71.5%) patients with LP received antibiotic therapy, only 19 (48.7%) patients without LP received the antibiotics with similar mean duration in both groups. Long term sequelae and death was higher in the non-LP compared to the LP group.

Research conclusions

Deferral of lumbar puncture is associated with poorer outcomes in patients with suspected acute meningitis syndrome. Lack of CSF analysis may be associated with unnecessary antibiotic therapy in some and poor outcomes related to inadequate treatment in others.

Research perspectives

Further prospective studies are needed to determine the exact reasons for deferral of lumbar puncture in patients. This will allow to identify potential caveats and ensure availability of adequate resources to obtain a CSF sample in all patients who need it.

FOOTNOTES

Author contributions: Saha A, Kanamcode SS and Scott J were involved in the conception of idea and study design; Chaudhuri S and Scott J provided administrative support; Scott J helped in provision of study materials or patients; Saha A, Kanamcode SS and Malempati SC were involved in collection and assembly of data; Saha A, Chaudhuri S and Scott J were involved in data analysis and interpretation; All authors were involved in manuscript writing; and the final draft was approved by all authors.

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