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ABOUT COVER

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ORIGINAL ARTICLE

Basic Study

Alcohol intolerance and myalgic encephalomyelitis/chronic fatigue syndrome

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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

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 (β = 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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CASE REPORT

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 transphenoid 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

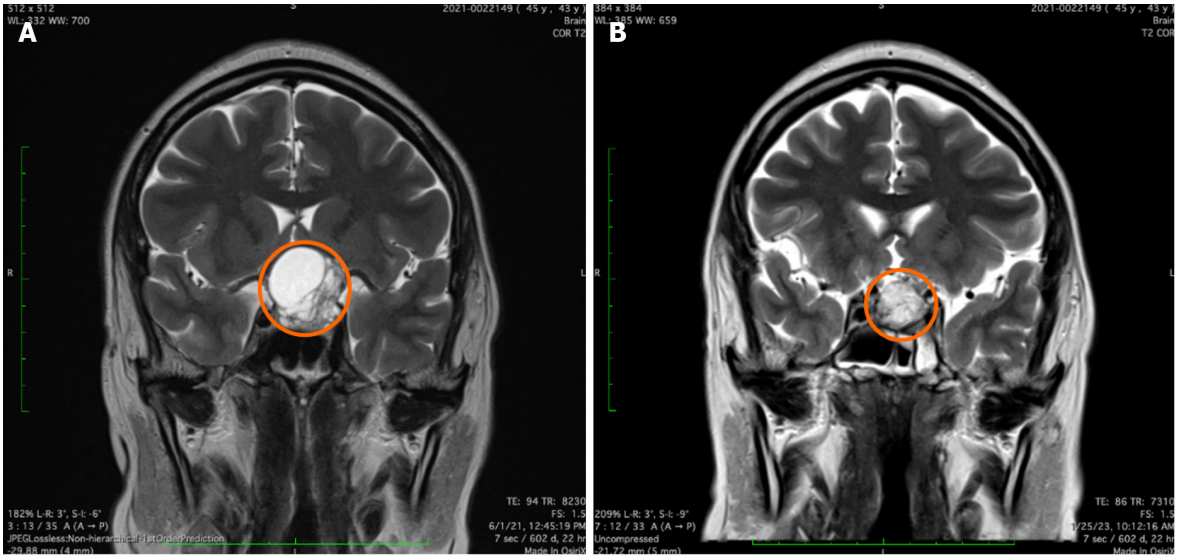

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Figure 1 Magnetic resonance image - T2 weighted image of the brain coronal view with the location of the mass encircled in red. A: Preoperative image; B: Postoperative image.

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 trans-sphenoid 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 *et al*[4], 2021)	Mizutani *et al*[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 1st 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 it 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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