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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 which ask 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 those participants with Alcohol Intolerance or Not Alcohol Intolerance. The Alcohol Intolerant group had 208 and the Not Alcohol Intolerant group had 96 participants.

RESULTS

Using specially designed questions to properly identify those with Alcohol Intolerance, we found those who experienced Alcohol Intolerance *vs* those who did not evidenced a higher symptom burden on a number of domains and symptoms. In addition, using a multiple regression analysis, the Orthostatic Intolerance symptom domain was related to Alcohol intolerance.

CONCLUSION

The findings from the current study indicate that those with ME/CFS do have Alcohol Intolerance. In addition, those with this symptom have more overall other symptoms than those without Alcohol Intolerance.

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

Maciuch J, Jason LA. Alcohol intolerance and myalgic encephalomyelitis/chronic fatigue syndrome. *World J Neurol* 2023; In press

Core Tip: The findings from the current study indicate that those with myalgic encephalomyelitis/chronic fatigue syndrome do have alcohol intolerance.

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 ability to work, engage in social or leisurely activities, and memory function in those that 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, and 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 which 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 4 or more drinks in one sitting should prompt healthcare practitioners to rethink an ME/CFS diagnosis. Chu *et al*[10] have 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 has speculated that alcohol intolerance in ME/CFS may be related to the effect of acetate (a byproduct of ethanol breakdown) on mitochondrial function[14], 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 aims to provide insight into the role of alcohol intolerance in ME/CFS by identifying correlations between alcohol intolerance and other common symptoms. We hypothesize that alcohol intolerance will correlate with measures of autonomic dysfunction (such as orthostatic and temperature intolerance), measures of neurocognitive dysfunction, and higher severity of physical impairment. Further, we hope that this study helps determine 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 chronic fatigue syndrome (CFS), Myalgic encephalomyelitis (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 which 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, 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: post-exertional malaise, cognitive impairment, fever and flu, pain, sleep disruption, orthostatic intolerance, genitourinary, 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); (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 the 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].

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 8 DSQ-2 domains were predictors of alcohol intolerance severity scores. Age and gender (coded in the data set as: 1 = "Male", 2 = "Female", 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 48.07 (SD = 12.26), and the Not Alcohol Intolerant group ($n = 96$) had a mean age of 34.27 (SD = 21.86). Both groups were predominantly female and Caucasian/White. Majority of the sample reported being on disability (50.0% for "Alcohol Intolerant," 40.6% for "Not Alcohol Intolerant") and married/Living with a partner (45.2% for "Alcohol Intolerant," 55.2% for "Not Alcohol Intolerant").

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 8 symptom domains, 5 domain scores were significantly higher for the Alcohol Intolerant group: 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 in statistically significant domains.

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]. Gender, age, and 7 out of 8 symptom domains did not significantly predict alcohol intolerance severity ($P \leq$ 0.05). Only the orthostatic intolerance domain significantly predicted alcohol intolerance severity ($\square$ = 0.21, P = 0.01). We did not use the SF-36 domains as predictors as our interest was in assessing which symptoms might be related to Alcohol Intolerance rather than physical or mental functioning.

DISCUSSION

Prior research had 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].

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 just using occurrence as a binary outcome, patients might experience the symptom at relatively low frequencies and/or severities and then be counted, when 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, and 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, so 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 indicate that those with ME/CFS do have alcohol intolerance. It is very likely that this subtype of patients might have other biologic differences that future research will be needed to explore. The contribution of the current study is assessing this alcohol intolerance construct 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 wanted to both 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 reliability and validly measure Alcohol Intolerance among those with ME/CFS, and this should guide future research in this area.

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