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ORIGINAL ARTICLE

# Psychosomatic symptoms related to exacerbation of fatigue in patients with medically unexplained symptoms

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## Abstract

**Background:** Medically unexplained symptoms (MUS) are common conditions that cause various somatic complaints and are often avoided in primary care. Fatigue frequently occurs in patients with MUS. However, the somatic and psychiatric symptoms associated with fatigue in patients with MUS are unknown. This study aimed to clarify the intensity of fatigue and the related somatic and psychiatric symptoms in patients with MUS.

**Methods:** A total of 120 patients with MUS aged 20–64 years who visited the Department of Psychosomatic Medicine, Toho University Medical Center Omori Hospital, between January and March 2021 were considered. The participants' medical conditions were assessed using the Chalder Fatigue Scale (CFS), Somatic Symptom Scale-8 (SSS-8), and Hospital Anxiety and Depression Scale (HADS). We estimated the relationship between CFS, SSS-8 and HADS by using Spearman's rank correlation. Additionally, linear multiple regression analysis with CFS as the objective variable was used to identify symptoms related to fatigue.

**Results:** Fatigue was significantly associated with all symptoms observed ($p < 0.01$). Linear multiple regression analysis revealed that "dizziness," "headache," and "Sleep medication" were extracted as relevant somatic symptoms ($p < 0.05$), independent of anxiety and depression, which were already known to be associated with fatigue in MUS.

**Conclusion:** The intensity of anxiety, depression, headache, and dizziness were all associated with the intensity of fatigue in MUS patients. On the contrary, sleeping medication was associated with lower levels of fatigue in MUS.

KEYWORDS
anxiety, depression, fatigue, functional dizziness, medically unexplained symptoms

## 1 | INTRODUCTION

Medically unexplained symptoms (MUS)[1] are somatic and psychiatric dysfunctions that organic status cannot explain. Somatic symptoms perceived by patients with MUS range from headaches and dizziness to fatigue.[2] Psychiatric symptoms, such as depression and anxious, are also associated with MUS.[3] Patients with MUS frequently visit primary care facilities because they exhibit various symptoms.[4] The clinical concept of MUS[5] includes disease groups such as somatic symptomatology and functional body syndromes, which generally have lower quality of life, general functioning and family functioning compared with healthy individuals.[6] However, medical personnel often avoid MUS because it is difficult to explain the mechanism of these symptoms occurring in patients through clinical examinations and tests.[7] Then, about 20%–25% of MUS patients develop chronic symptoms, making treatment even more difficult.[2]

Fatigue is also a common symptom in healthy individuals and is a nonspecific and subjective symptom. Therefore, medical personnel often underestimate fatigue.[8] However, fatigue has been reported that the economic burden and social loss caused by fatigue are significant.[9] For example, it has been reported that chronic fatigue can generate as much as $9 billion in economic losses in the year.[10] Furthermore, chronic fatigue syndrome, also treated as one of the MUS, significantly reduces the quality of life and functioning of patients and their families due to its severity.[11] Therefore, addressing fatigue before it becomes chronic might be important. Unfortunately, research on early detection or intervention for fatigue is scarce. However, a previous randomized controlled trial study demonstrated that early intervention with psychoeducation for infectious mononucleosis was preventive for fatigue in primary care.[12]

However, because MUS patients report various complaints, correctly assessing fatigue and related symptoms efficiently in a busy clinical setting is challenging. Therefore, in this study, we investigated somatic and psychiatric symptoms of patients with MUS to clarify the symptoms associated with the level of fatigue.

## 2 | METHODS

### 2.1 | Study design

This study was a cross-sectional study.

### 2.2 | Setting and participants

Participants were selected aged 20–64 years who exhibited MUS and visited the Department of Psychosomatic Medicine, Toho University Medical Center Omori Hospital, between January and March 2021. No formal sample size calculation was performed for this study because this study was exploratory.

There are no clear diagnostic criteria for MUS. Nevertheless, patients in this study were defined as those with somatic complaints examined by multiple physicians who concluded that organic dysfunctions could not adequately explain their symptoms or pathology, citing previous studies.[13,14]

### 2.3 | Measures

The participants' age, gender, medical therapy, fatigue, somatic symptoms, anxiety, and depression were extracted from their medical records.

Fatigue was assessed by the Chalder Fatigue Scale (CFS).[15] The total CFS score ranges from 0 to 42, with higher scores indicating more significant fatigue.

Somatic symptoms were evaluated using the Somatic Symptom Scale-8 (SSS-8).[16,17] The SSS-8 is a scale of 8 general symptoms such as "gastrointestinal upset" and "dizziness," comprising a 5-point scale ranging from "0 (not at all)" to "4 (very much)," with higher scores indicating more severe somatic symptoms.

Anxiety and depressive symptoms were also assessed using the Hospital Anxiety and Depression Scale (HADS).[18,19] The HADS is a self-assessment scale comprising 14 questions, half of which address anxiety and the other half address depressive symptoms. Both anxiety and depression were scored from 0 to 21, with higher scores indicating a higher degree of impairment in life.

### 2.4 | Analysis

We estimated the relationship between CFS, SSS-8 and HADS by using Spearman's rank correlation. Moreover, multiple linear regression analysis was performed using the CFS as the dependent variable. The independent variables in the multiple linear regression analysis were age, gender, medical therapy, somatic symptoms, anxiety, and depression. However, because the SSS-8 includes items that screen for fatigue, the item "feeling tired or having low." was excluded from the variables in the linear regression analysis due to concerns about its impact on the analysis results. Considering multicollinearity, we also checked each variable's variance inflation factor (VIF).

All analyses were performed using EZR version 1.54.[20] Statistical significance was set at $p < 0.05$.

## 3 | RESULTS

We selected 132 patients, but a total of 12 patients with missing data were excluded from the final sample, resulting in 120 patients.

The participants' backgrounds are listed in Table 1. There were 43 men and 77 women with a mean age of 47.7 years. Most of the participants were on medication, most commonly antidepressants (62.5%).

The results of the correlation analysis are shown in Table 2, where CFS showed a significant positive correlation with the eight items of the SSS-8 and with the anxiety and depression scales of the HADS. A particularly strong correlation was found between CFS and depression ($r = 0.71$).

In the linear multiple regression analysis of CFS, "dizziness," "headaches," "anxiety," and "depression" were positively associated with CFS. On the contrary, "Sleep medication" was negatively associated with CFS. The values of VIF among the variables were low, there was no apparent multicollinearity, and depression had the most potent association with fatigue when the standard partial regression coefficient values were considered (Table 3).

## 4 | DISCUSSION

We investigated fatigue and related symptoms in MUS and found that fatigue in MUS is associated with anxiety, depression, headache, dizziness, and sleep therapy. MUS is a complex condition associated with multiple somatic and psychiatric symptoms.[21] Depression and anxiety are associated with MUS,[3] and these psychiatric states are also associated with fatigue.[22] In the present study, depression and anxiety were significantly associated with MUS fatigue, consistent with the results of previous studies. Furthermore, our results showed that the association between depression and fatigue was the most robust. This finding is also consistent with previous studies.[23,24] The relationship between depression and fatigue may be influenced by subjective factors such as happiness and by brain inflammation associated with the activation of the immune response.[25] Based on previous studies and our results, psychiatric symptoms can be one of the most critical factors of fatigue. However, in primary care, healthcare providers shunned psychiatric symptoms such as depression and anxiety that MUS patients are aware of.[7] In addition, it has been reported that MUS patients have few opportunities to discuss their psychiatric symptoms.[3] This barrier may delay treatment for the psychiatric symptoms of MUS, and fatigue may worsen or become chronic. Therefore, examining the psychiatric symptoms of patients with MUS carefully in primary care settings is necessary, even if they do not directly consult with us.

Furthermore, sleep disturbances are also associated with various psychiatric disorders, but their effects on fatigue are thought to be independent.[26] In our results, "Trouble sleeping" was not significantly associated with fatigue, but "Sleep medication" was a significantly negatively associated factor. Since the sample in this study had already been introduced to the treatment, its effect may have influenced the results. Therefore, the relationship between sleep disorder and fatigue may warrant reexamination.

Then, in this study, dizziness and headache were identified as a factor associated with fatigue in MUS patients. Previous studies have reported a clear positive correlation between chronic fatigue and physical symptoms in adolescents, with dizziness and headache, in particular, being more frequently associated with fatigue, along with low energy and heaviness in arms/legs.[27] Additionally, it has been suggested that autonomic dysfunction involving the anterior cingulate gyrus, amygdala, and other forebrain regions[28] in chronic fatigue syndrome may cause increasing dizziness due to orthostatic intolerance and heart rate variability. These changes lead to increased fatigue.[29] Furthermore, an association between chronic headache symptoms and exacerbation of fatigue has been reported.[30]

Functional dizziness may be associated with the dysfunction occurring in the anterior cingulate cortex,[31] hippocampus, and insula, which are associated with mood disorders.[32] Functional dizziness considered to be caused by dysfunction arising in these forebrain regions and other areas, has been reported that selective serotonin reuptake inhibitors may improve dizziness symptoms[33,34] Many

**TABLE 1** Clinical status and characteristics of the study sample ($n = 120$)

| | |
|---|---|
| Gender | |
| Male | 43 (35.8%) |
| Female | 77 (64.2%) |
| Age (years ± SD) | 47.7 ± 11.3 |
| Education (year) | 14.1 ± 2.0 |
| Medical therapy | |
| Antidepressant | 75 (62.5%) |
| Sleep medication | 29 (24.2%) |
| Anxiolytics | 50 (41.7%) |
| Questionnaire | |
| Chalder Fatigue Scale | 22.6 ± 8.9 |
| Somatic Symptom Scale-8 | 23.3 ± 7.1 |
| Hospital Anxiety and Depression Scale | 15.6 ± 8.0 |
| Anxiety | 8.0 ± 4.3 |
| Depression | 7.6 ± 4.8 |

**TABLE 2** Correlation between the CFS, the SSS-8, and HADS ($n = 120$)

| | CFS | *p* Value |
|---|---|---|
| SSS-8 | | |
| Stomach or bowel problems | 0.34 | <0.001 |
| Back pain | 0.33 | <0.001 |
| Pain in your arms, legs, or joints | 0.26 | 0.004 |
| Headaches | 0.46 | <0.001 |
| Chest pain or shortness of breath | 0.28 | 0.002 |
| Dizziness | 0.43 | <0.001 |
| Feeling tired or having low energy | 0.58 | <0.001 |
| Trouble sleeping | 0.54 | <0.001 |
| HADS | | |
| Anxiety | 0.69 | <0.001 |
| Depression | 0.71 | <0.001 |

Abbreviations: CFS, Chalder Fatigue Scale; HADS, Hospital Anxiety and Depression Scale; SSS-8, Somatic Symptom Scale-8.

TABLE 3 Multiple linear regression analysis of Chalder Fatigue Scale ($n = 120$)

| | Unstandardized | | Standardized | | | |
|---|---|---|---|---|---|---|
| Independent variable | *B* | Standard error | *β* | *t* Value | *p* Value | VIF |
| Age | 0.03 | 0.05 | 0.04 | 0.61 | 0.55 | 1.57 |
| Gender | −1.86 | 1.03 | −0.10 | −1.37 | 0.17 | 1.15 |
| Antidepressant | 0.30 | 0.98 | 0.02 | 0.31 | 0.76 | 1.08 |
| Sleep medication | −2.53 | 1.18 | −0.12 | −2.15 | <0.05 | 1.21 |
| Anxiolytics | −0.01 | 0.99 | −0.01 | −0.01 | 0.99 | 1.13 |
| Stomach or bowel problems | −0.73 | 0.44 | −0.11 | −1.66 | 0.10 | 1.64 |
| Back pain | 0.59 | 0.44 | 0.09 | 1.36 | 0.18 | 1.50 |
| Pain in your arms, legs, or joints | −0.47 | 0.44 | −0.07 | −1.08 | 0.28 | 1.77 |
| Headaches | 0.83 | 0.40 | 0.14 | 2.09 | <0.05 | 1.59 |
| Chest pain or shortness of breath | 0.01 | 0.42 | 0.01 | 0.01 | 0.99 | 1.43 |
| Dizziness | 1.16 | 0.45 | 0.18 | 2.59 | <0.05 | 1.70 |
| Trouble sleeping | 0.85 | 0.47 | 0.13 | 1.78 | 0.08 | 1.88 |
| HADS-anxiety | 0.72 | 0.16 | 0.35 | 4.38 | <0.001 | 2.32 |
| HADS-depression | 0.70 | 0.13 | 0.38 | 5.33 | <0.001 | 1.85 |

*Note*: Multiple $R^2 = 0.72$, adjusted $R^2 = 0.68$.

Abbreviations: HADS, Hospital Anxiety and Depression Scale, VIF, variance inflation factor.

studies have suggested that serotonin is also involved in migraine and tension headaches,[35-37] and antidepressants are used for prevention and treatment.[38] Functional dizziness and headache, depression, and anxiety are all dysfunctions of serotonin-mediated brain regions, and this dysfunction may cause or exacerbate fatigue in MUS in a chain reaction. Symptoms accompanying chronic fatigue syndrome, as one of the MUS, are reported that were affected by decreased serotonin transporters in the anterior cingulate gyrus region.[39]

This study was robust in assessing the combined fatigue intensity and related symptoms of MUS in primary care settings. However, it has several limitations. First, the study used a questionnaire to assess participants' subjective symptoms. Few objective indices exist in symptomatology research, including our study, and the development of quantitative evaluation methods is expected. Second, the study did not compare the effects of pharmacotherapy or the relationship of other diseases with fatigue; therefore, it is uncertain whether the results regarding fatigue are specific to MUS. Third, while university hospitals in Japan often provide primary care, this study was conducted at a single medical institution which may have biased the characteristics of the sample. Fourth, although patients with MUS are not uniform due to various factors, such as region and race, our sample's background partly differs from previously reported characteristics of MUS concerning educational history and other factors.[40] These differences in background characteristics might also affect the sample's subjective fatigue and other symptoms.[24] Therefore, challenges remain regarding the generalization of our results. Finally, although this study evaluated the association between fatigue and somatic and psychiatric symptoms cross-sectionally, previous studies have suggested a bidirectional relationship between the fatigue and these symptoms.[41] Therefore, the causal relationship between fatigue and symptoms in MUS is an issue for future studies.

## 5 | CONCLUSIONS

A multifaceted study of symptoms related to fatigue intensity in MUS was conducted, and sleep therapy, headache, dizziness, anxiety, and depressive symptoms were associated with fatigue intensity in MUS.

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### CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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### ETHICS COMMITTEE APPROVAL

Instead of obtaining informed concent from the patients, information on the study implementation, including the purpose and overview of the study, was released on the Toho University Medical Center

Omori Hospital website. This ensured ample opportunities for patients to decline participation. Furthermore, all study procedures were conducted with the approval of the research hospital ethics committee (approval number M21095), with due consideration to the Helsinki Declaration, patient anonymity, and ethics.

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