Frequency and characteristics of chronic fatigue syndrome in multiple sclerosis patients at a university hospital in Eastern Saudi Arabia

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Abstract:

BACKGROUND: Multiple sclerosis (MS) is a chronic, inflammatory demyelinating disease that affects various parts of the central nervous system. Fatigue, a common symptom, transient, prolonged, or chronic experienced by individuals with MS, can significantly impact daily functioning. It can be associated with underlying pathological processes or can have an idiopathic cause, such as chronic fatigue syndrome (CFS). The study aimed to assess the presence and etiology of fatigue in MS patients and its relationship with CFS.

MATERIALS AND METHODS: This cross-sectional study was conducted in the Eastern Province of Saudi Arabia. Data were collected using a questionnaire from a sample of 225 MS patients receiving care at our university hospital. The questionnaire included the Centers for Disease Control and Prevention (CDC) criteria for diagnosing CFS and the Expanded Disability Status Scale to evaluate fatigue in MS patients.

RESULTS: Of the total of 225 MS patients who participated in this study, 87.1% were diagnosed with relapsing-remitting MS, 6.7% with primary progressive MS, 3.6% with clinically isolated syndrome, and 2.7% with secondary progressive MS. About 53% had experienced fatigue that persisted for over 6 months. Analysis of CFS diagnosis revealed that 7.3% of patients met both CDC criteria and self-reported answers while 17.5% reported having CFS despite not meeting the CDC criteria. These findings highlight a significant lack of agreement between patient-reported diagnoses and established criteria, indicating poor agreement ($P = 0.028$).

CONCLUSION: The study found an association between CFS and MS, and a significant impact on daily functioning. The study revealed lack of agreement between patient-reported diagnoses and established criteria for CFS. This emphasizes the need for a standardized approach to diagnosis and evaluation of fatigue in MS patients.

Keywords:

Chronic fatigue syndrome, multiple sclerosis, myalgic encephalomyelitis

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Introduction

Numerous neurological and nonneurological disorders have ambiguous symptoms that make diagnosis and treatment difficult, particularly in individuals who also have fatigue. Moreover, many patients with no disease experience fatigue on a daily basis, and others have multiple, overlapping conditions that complicate the approach to such an unspecific symptom. Fatigue was defined by

a group of clinicians as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities."[1] It is usually associated with subjective weakness, lethargy, and a lack of energy. Fatigue may be transient, prolonged, or chronic and may be triggered by an obvious pathological process or may have an idiopathic cause, as is the case with chronic fatigue syndrome (CFS).[1] When the state of fatigue is not self-limiting, transient, or triggered by underlying conditions, CFS may be considered. The condition is characterized by profound disabling fatigue that lasts at least 6 months and may be associated with various self-reported impairments that possibly relate to neuropsychiatric, rheumatological, or infectious symptoms.[2,3] Usually, the diagnosis is given only after all other medical and psychiatric explanations have been ruled out. The estimated global prevalence of CFS is 1.45%, but has been reported to be up to 7.6% in some communities, with a strong female predominance in almost all settings.[4,5]

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating disease of the central nervous system that involves the various parts of sensory, motor, autonomic, and visual functions.[6] With a reported prevalence of 33/100,000 worldwide and 40/100,000 in Saudi Arabia, it is regarded as one of the most prevalent inflammatory neurological illnesses.[7] Fatigue, considered one of the most common presenting symptoms in MS, tends to have a tremendous effect on daily functions.[8] Up to 80% of MS patients experience fatigue, which many regard as their most incapacitating symptom. To help distinguish between fatigue and CFS, several diagnostic methods have been created.[9,10] Various assessment tools have been developed to assist in the distinction between fatigue and CFS. One of the most used tools is the Expanded Disability Status Scale (EDSS), developed by Kurtzke for the evaluation of the functionality of the central nervous system.[11] This clinician-administered assessment scale is used in MS patients to determine disease progression and response to therapeutic measures.[11] The symptom inventory, or what is commonly known as the Fukuda 1994 criteria, is another tool developed to assess the presence, severity, and frequency of eight main symptoms described by Fukuda *et al.,* in 1994.[3] This research conducted a cross-sectional study using a survey based on the Centers for Disease Control-Symptom Inventory (CDC-SI/Fukuda 1994) criteria and the EDSS. The study's aim was to assess the presence and etiology of fatigue and its association with CFS in MS patients being followed up or treated in the neurology department.

Materials and Methods

This cross-sectional study was conducted at a university hospital in the Eastern Province of Saudi Arabia. The aim was to evaluate the frequency of CFS in male and female MS patients, using a questionnaire-based approach. The study population comprised MS patients recruited from the MS clinic. Inclusion criteria consisted of individuals diagnosed with MS, while patients with other identifiable medical conditions, such as depression or hypothyroidism, that could potentially cause fatigue were excluded. This criterion was considered important, as it is one of the criteria for the diagnosis of CFS. The study was conducted between December 14, 2022, and March 30, 2023. Ethical approval was obtained from the Institutional Review Board Vide Letter No. IRB-2022-11-525 dated 12/12/2022, and written informed consent was taken from all participants in the study.

We utilized a questionnaire based on the CDC-SI/Fukuda 1994 criteria and the EDSS. To ensure the quality of the questionnaire, four experts evaluated the parameters for each question. The Delphi technique was employed, involving multiple rounds of questionnaires and feedback to reach a consensus or identify areas of agreement or disagreement. The final questionnaire was then distributed to all registered MS patients at the hospital who agreed to participate in the study, resulting in a random sample of 225 participants who met the inclusion criteria.

The Arabic translation of the questionnaire of four sections for this study was carefully reviewed by an Arabic language expert for consistency. The first section included the consent form and contact details. The second elicited demographic information such as sex, nationality, age, occupation, and place of residence. The third section gathered medical history, including MS diagnosis, type, and duration, CFS diagnosis, current and past functional status, and comorbidities. The fourth section had the CDC-SI/Fukuda 1994 criteria for CFS diagnosis and the EDSS to assess disability levels in MS patients and track changes over time. The questions used for diagnosing CFS based on the CDC guidelines can be found in Table 1.

To evaluate adherence to the CDC guidelines for diagnosing CFS, the study utilized a questionnaire administered to the participants. Table 2 illustrates the specific questions used to assess patient responses. Two questions were particularly important for evaluating adherence to the guidelines. The first question asked participants if they had been previously diagnosed with CFS by their physicians. Out of the total sample size of 225 patients, 47 (20.9%) patients responded affirmatively, indicating that they had received a diagnosis of CFS. To further evaluate adherence to the CDC guidelines, the group of patients who reported a CFS diagnosis as well as the group who did not were asked a second

question on the specific symptoms outlined in the CDC criteria for diagnosing CFS. The authors then assessed their responses according to the CDC guidelines for CFS diagnosis. We collaborated with analytics to determine which patients satisfied the criteria and which did not, based on their reported symptoms.

Table 1: Characteristics of multiple sclerosis patients (*n*=225)

Characteristics	N (%)
Sex	
Male	83 (36.9)
Female	142 (63.1)
Nationality	
Non-Saudi	11 (4.9)
Saudi	214 (95.1)
Age (years)	
<25	44 (19.6)
From 25 to 40	142 (63.1)
>40	39 (17.3)
Employment	
Student	21 (9.3)
Not employed	80 (35.6)
Retired	12 (5.3)
Employed	112 (49.8)
Place of residence	
Northern region	2 (0.9)
Southern region	3 (1.3)
Eastern region	199 (88.4)
Western region	4 (1.8)
Central region	17 (7.6)
Which type of MS have you been diagnosed with?	
Relapsing-remitting	196 (87.1)
Primary progressive	15 (6.7)
CIS	8 (3.6)
Secondary progressive	6 (2.7)
When 'were you' diagnosed with MS? (months)	
<6	8 (3.6)
>6	217 (96.4)
Have you been diagnosed with chronic fatigue syndrome?	
No	178 (79.1)
Yes	47 (20.9)
Do you have any other diseases? "Multiple responses allowed/possible"	
MS only	165 (73.3)
Diabetes	22 (9.8)
Obesity	14 (6.2)
Mental disorders	16 (7.1)
Thyroid	16 (7.1)
Other CNS disorders	13 (5.8)
Rheumatism	8 (3.6)
Sleep apnea	4 (1.8)
Drugs	3 (1.3)
Narcolepsy	2 (0.9)
CHF	2 (0.9)
Lupus	1 (0.4)

CHF=Congestive heart failure, CIS=Clinically isolated syndrome, CNS=Central nervous system, MS=Multiple sclerosis

Regarding statistical analysis, descriptive statistics are presented in the form of numbers and percentages for categorical variables. The median and interquartile range are reported for nonnormally distributed numerical values. To compare categorical variables between patients diagnosed and those not diagnosed with CFS, the Chi-square test and Fisher's exact test were utilized. Cohen's kappa agreement was employed to measure the agreement between CDC criteria and patients' answers regarding the presence of CFS. The analysis was conducted using the Statistical Package for the Social Sciences version 28 for Windows software (SPSS, IBM Corporation, Armonk, NY, USA), and $P < 0.05$ was considered statistically significant.

Results

A total of 225 multiple sclerosis patients were included in the study. Most of the patietns were Saudi (95.1), were female (63.1%), were 25–40 years old (63.1%), and 49.8% were employed [Table 1]. Most patients (87.1%) were diagnosed with relapsing-remitting MS, 6.7% with primary progressive MS, 3.6% with clinically isolated syndrome, and 2.7% with secondary progressive MS. Furthermore, 96.4% of patients had had an MS diagnosis for at least 6 months or longer, but 3.6% had a shorter duration of diagnosis.

Table 2 shows the CDC criteria for diagnosing CFS. The study found that 53.3% of the patients had experienced fatigue for more than 6 months, while 40.4% had had fatigue for <6 months. The impact of fatigue on different activities was assessed: for 42.2%, personal activities were affected, social activities of 43.1% were affected, vocational activities of 43.1% were affected, and for 19.1%, educational activities were affected. On the examination of headaches, it was found that 44.9% experienced worsening headaches, 38.7% did not have any headaches, 17.8% had severe headaches, and 7.6% had new headaches. As regards sleep disturbances, 54.2% did not feel refreshed after waking up from sleep. Factors contributing to sleep disturbances: 28.4% had trouble with nocturnal enuresis, 24.4% had daytime exhaustion, and 14.2% had muscle cramps during sleep. Memory or concentration impairments were reported by 52.4% of patients, muscle pain by 50.7%, postexertional malaise by 29.8%, joint pain by 25.3%, new headaches by 20.0%, and tender lymph nodes by 3.1%.

According to the CDC criteria, 24% of the 225 subjects in the study would be diagnosed with CFS. However, based on the questionnaire used, only 20.9% of the patients had been diagnosed with CFS by their physicians [Table 3]. In addition, 73.3% of the patients

were solely diagnosed with MS, but the remainder had other comorbidities. Of the participants, 49.8% experienced intermittent fatigue, 28% attributed their fatigue to effort, 7.6% had mild fatigue, and 6.2% have had fatigue only once.

Table 2: Distribution of patients according to Fukuda 1994 criteria for diagnosing chronic fatigue syndrome (*n*=225)

Fukuda 1994 criteria	N (%)
What does your fatigue feel like?	
Intermittent	112 (49.8)
Related to effort	63 (28.0)
It happened once	14 (6.2)
Not severe	17 (7.6)
How long have you been suffering from fatigue? (months)	
<6	91 (40.4)
6	14 (6.2)
>6	120 (53.3)
Daily activities have been affected by fatigue (multiple choice)	
Personal activities	95 (42.2)
Vocational activity	97 (43.1)
Social activity	97 (43.1)
Educational activity	43 (19.1)
If you had headache, describe it "multiple responses allowed/possible"	
No, I don't have headache	87 (38.7)
New	17 (7.6)
Severe	40 (17.8)
Worsening with time	101 (44.9)
How do you feel when you wake up?	
Not refreshed	122 (54.2)
Refreshed	103 (45.8)
Which of these causes affect your sleep?	
Exhaustion all day	55 (24.4)
Muscle cramps during sleep	32 (14.2)
Nocturnal enuresis	64 (28.4)
Other reasons	74 (32.9)
Other symptoms "multiple responses allowed/possible"	
Brain fog	42 (18.7)
Muscle pain	114 (50.7)
Tender lymph nodes	7 (3.1)
Impaired memory or concentration	118 (52.4)
Polyarthralgia	57 (25.3)
Postexertional malaise	67 (29.8)
New headache	45 (20.0)

Table 4 illustrates the current and past physical and functional status of the participants. In the current assessment, 76.4% of patients exhibited the ability to walk independently, while the remaining participants had various limitations as indicated in the table. Regarding their previous physical and functional status, 83.1% of patients were able to walk without any assistance, but the remaining participants had certain limitations as specified in the table.

Table 5 presents a comparison of categorical variables between individuals diagnosed with CFS and those without the diagnosis. The analysis employed Chi-square and Fisher's exact test. The findings revealed that 34.1% of patients younger than 25 years were diagnosed with CFS, in contrast to 17.6% of patients aged between 25 and 40 years. Of the individuals older than 40 years, the diagnosis rate was 35.9%. The *P* value associated with this analysis was 0.013.

Table 6 reveals several significant differences between patients diagnosed with CFS and those without a diagnosis. Patients with CFS had a higher prevalence of exhaustion related to effort (61.1% vs. 17.5%, *P* = 0.001) and showed more frequent reports of some impact of fatigue on their daily performance (90.7% vs. 69.6%, *P* = 0.002). Moreover, a higher percentage of patients with CFS experienced severe headaches (29.6% vs. 14.0%, *P* = 0.004) and reported worsening headaches over time (59.3% vs. 40.4%, *P* = 0.018) compared to patients without the diagnosis. In addition, a higher proportion of patients with CFS reported feeling groggy upon waking up (72.2% vs. 48.5%, *P* = 0.003).

The comparison between the CDC criteria and patients' reported answers, as shown in Table 2, revealed that most patients (82.5%) did not meet the criteria for CFS based on their answers or the CDC definition. Of the 47 patients who reported a prior diagnosis with CFS by their physicians, only 17 (7.3%) patients fulfilled the CDC guidelines for diagnosis. On the other hand, of the 178 patients without a previous CFS diagnosis, 37 (17.3%) patients met the CDC criteria. Therefore, it appears that 24% of the total patient population in our study would be eligible for a CFS diagnosis according to the CDC guidelines.

Table 3: Comparison of chronic fatigue syndrome diagnosis according to the Centers for Disease Control and Prevention diagnosis based on patient's answers

Patient's response regarding whether they received a CFS diagnosis from their physician	Chronic fatigue syndrome diagnosis according to CDC		Total N (%)	Kappa	P-value
	No N (%)	Yes N (%)			
No	141 (82.5)	37 (17.3)	178 (79.1)	0.146	0.028
Yes	30 (17.5)	17 (7.3)	47 (20.9)		
Total	171 (76.0)	54 (24.0)	225 (100)		

CFS=Chronic fatigue syndrome, CDC=Centers for Disease Control

Table 4: Distribution of multiple sclerosis patients according to current and previous Expanded Disability Status Scale (*n*=225)

Expanded disability status	N (%)
Current physical and functional status	
I can walk without any help	172 (76.4)
I use a single crutch	21 (9.3)
I use crutches to walk	9 (4.0)
I can't walk for distances longer than 5 m, I use a wheelchair	4 (1.8)
I can walk few steps, I use a wheelchair	12 (5.3)
Most of time in bed, I can do my daily activities	2 (0.9)
Most of time in bed, I can't do my daily activities	5 (2.2)
Previous physical and functional status	
I can walk without any help	187 (83.1)
I use a single crutch	21 (9.3)
I use crutches to walk	5 (2.2)
I can't walk for distances longer than 5 m, I use a wheelchair	2 (0.9)
I can walk few steps, I use a wheelchair	4 (1.8)
Most of time in bed, I can do my daily activities	3 (1.3)
Most of time in bed, I can't do my daily activities	2 (0.9)
I'm wheelchair bound	1 (0.4)

Furthermore, it was found that though 17.5% of the patients reported having CFS, they did not meet the CDC criteria. The agreement between the CDC criteria and patients' reported answers, as measured by Cohen's kappa, was quite low at 0.146, indicating poor agreement. This lack of agreement was statistically significant, with $P = 0.028$.

Discussion

The study's findings reveal an association between MS and CFS. The research also sheds light on the adherence of our study participants to the CDC guidelines for the diagnosis of CFS. We found that only a small proportion of patients diagnosed by their physicians met the CDC criteria, while a higher percentage of patients who had not been diagnosed also met those criteria, even though they had not been diagnosed by their physicians.

The study revealed that of the 47 patients who had reported that they had been given a physician's diagnosis of CFS in the clinic, only 17 (7.3%) patients indicated that they fulfilled the CDC guidelines criteria for diagnosis. This suggests that a significant number of patients who had had a CFS diagnosis from their physicians did not meet the rigorous criteria set forth by the CDC. Such inconsistencies may be attributed to variations in the interpretation of symptoms or possible misdiagnoses by health-care providers. Further investigation would be beneficial to explore these discrepancies and understand the reasons behind the deviation from the CDC guidelines by some physician-diagnosed cases.

Interestingly, our results also showed that a significant number of patients who had not had prior CFS diagnosis met the CDC criteria. Out of the 178 patients who fell into this category, 37 (17.3%) patients were seen to meet the CDC criteria for CFS. This finding raises questions about the possible underdiagnosis or misdiagnosis of CFS in the broader population of individuals experiencing chronic fatigue. It suggests that health-care providers may need to be more vigilant in recognizing and diagnosing CFS in patients who present with symptoms that correspond with the CDC guidelines.

The low adherence to CDC guidelines by the physician-diagnosed cases of CFS indicates a need for increased awareness and education of health-care professionals. Improved understanding of the specific criteria for CFS diagnosis outlined by the CDC, including the hallmark symptoms and exclusionary conditions, can help the physicians to give more accurate and consistent diagnoses and facilitate appropriate management and treatment strategies for individuals with CFS.

Moreover, our study found no significant differences in factors such as sex, age, employment status, type of MS, and physical disability level between individuals diagnosed with CFS and those not diagnosed with CFS. This suggests that CFS in MS patients may not be influenced by these demographic or clinical characteristics.

Vercoulen *et al.*, did a multidimensional cross-sectional comparison study in patients with CFS and MS patients. They discovered that patients with MS suffered from significant fatigue, which impacted on their daily functioning but was unrelated to depression or an EDSS. Their study also showed that almost half of the MS patients reported feeling fatigued every day; 85% of the patients felt this at least once a week. The patients with MS experienced high severity levels of fatigue, almost as high what patients with CFS had.[12]

Furthermore, to differentiate MS from CFS and myalgic encephalomyelitis (ME), Jason *et al.*, conducted a cross-sectional online study using an approved self-report DePaul Symptom Questionnaire. The study participants were 106 patients with MS and 269 subjects with ME or CFS. Symptoms compared were fatigue, postexertional malaise, neurocognitive, neuroendocrine, autonomic, immune, sleep, and pain among others. Individuals with ME or CFS reported significantly more functional limitations and significantly more severe symptoms than those with MS. Prevalence rates in America were reported to be 0.42% for CFS versus 0.09% for MS.[13]

Our study found a relationship between MS and CFS. Moreover, we also found that 7% of patients' EDSS scores

Table 5: Association between chronic syndrome* and various independent variables among multiple sclerosis patients (*n*=225)

Characteristics	Chronic fatigue syndrome		*P-value*
	No (*n*=171) N (%)	Yes (*n*=54) N (%)	
Sex			
Male	64 (77.1)	19 (22.9)	0.872
Female	107 (75.4)	35 (24.6)	
Nationality			
Non-Saudi	8 (72.7)	3 (27.3)	>0.999
Saudi	163 (76.2)	51 (23.8)	
Age			
<25	29 (65.9)	15 (34.1)	0.013
From 25 to 40	117 (82.4)	25 (17.6)	
>40	25 (64.1)	14 (35.9)	
Employment			
Student	16 (76.2)	5 (23.8)	0.617
Not employed	61 (76.3)	19 (23.8)	
Retired	11 (91.7)	1 (8.3)	
Employed	83 (74.1)	29 (25.9)	
Which type of MS have you been diagnosed with?			
Primary progressive	12 (80.0)	3 (20.0)	0.382
Secondary progressive	5 (83.3)	1 (16.7)	
Relapsing-remitting	150 (76.5)	46 (23.5)	
CIS	4 (50.0)	4 (50.0)	
When have you been diagnosed with MS? (month)			
<6	5 (62.5)	3 (37.5)	0.550
6	3 (75.0)	1 (25.0)	
>6	163 (76.5)	50 (23.5)	
Current physical-functional status			
I can walk without any help	133 (77.3)	39 (22.7)	0.301
I use a single crutch	16 (76.2)	5 (23.8)	
I use crutches to walk	4 (44.4)	5 (55.6)	
I can't walk for distances longer than 5 m, I use a wheelchair	4 (100.0)	0	
I can walk few steps, I use a wheelchair	9 (75.0)	3 (25.0)	
Most of time in bed, I can do my daily activities	2 (100.0)	0	
Most of time in bed, I can't do my daily activities	3 (60.0)	2 (40.0)	
Previous physical-functional status			
I can walk without any help	143 (76.5)	44 (23.5)	0.202
I use a single crutch	16 (76.2)	5 (23.8)	
I use crutches to walk	3 (60.0)	2 (40.0)	
I can't walk for distances longer than 5 m, I use a wheelchair	1 (50.0)	1 (50.0)	
I can walk few steps, I use a wheelchair	4 (100.0)	0	
Most of time in bed, I can do my daily activities	3 (100.0)	0	
Most of time in bed, I can't do my daily activities	0	2 (100.0)	
I'm wheelchair bound	1 (100.0)	0	
Do you have any other diseases?			
No	130 (78.8)	35 (21.2)	0.114
Yes	41 (68.3)	19 (31.7)	

*diagnosis based on Centers for Disease Control and Prevention criteria, CIS=Clinically isolated syndrome, MS=Multiple sclerosis

had deteriorated, which indicates a significant impact on their daily functioning. Besides, for most patients, fatigue was intermittent, affecting their daily social and vocational activities.

Clinically, exhaustion, loss of energy, daytime somnolence, or exacerbation of symptoms can all be present as fatigue.

Patients with ME/CFS and MS both have extremely high levels of incapacitating exhaustion, and their symptoms get worse after exertion. Fatigue, which interferes with and significantly limits everyday activities, is one of the most prevalent and disabling symptoms of people with MS. According to Hadjimichael *et al.,* compared to relapsing-stable and primary progressive MS,

Table 6: Comparison of exhaustion and headache for multiple sclerosis patients by chronic fatigue syndrome diagnosis (*n*=225)

Exhaustion and headache	Chronic fatigue syndrome		*P-value*
	Not diagnosed **N (%)**	**Diagnosed** **N (%)**	
Exhaustion related to effort			
No	141 (82.5)	21 (38.9)	<0.001
Yes	30 (17.5)	33 (61.1)	
Exhaustion happened only once			
No	158 (92.4)	53 (98.1)	0.197
Yes	13 (7.6)	1 (1.9)	
Exhaustion not worsening with time			
No	156 (91.2)	52 (96.3)	0.374
Yes	15 (8.8)	2 (3.7)	
Has fatigue affected your daily performance?			
No	52 (30.4)	5 (9.3)	0.002
Yes	119 (69.6)	49 (90.7)	
Do you have headaches?			
No	76 (44.4)	11 (20.4)	0.002
Yes	95 (55.6)	43 (79.6)	
Severe headache			
No	147 (86.0)	38 (70.4)	0.014
Yes	24 (14.0)	16 (29.6)	
Headache worsening with time			
No	102 (59.6)	22 (40.7)	0.018
Yes	69 (40.4)	32 (59.3)	
How do you feel when ou wake up?			
Not good	83 (48.5)	39 (72.2)	0.003
Refreshed	88 (51.5)	15 (27.8)	
Which of these affect your sleep?			
Exhaustion (morning)	35 (20.5)	20 (37.0)	0.067
Muscle cramps during sleep	25 (14.6)	7 (13.0)	
Nocturnal enuresis	49 (28.7)	15 (27.8)	
Other reasons	62 (36.3)	12 (22.2)	

relapsing-worsening MS had a higher rate of severe fatigue.[14] Moreover, based on the results of the Fatigue Severity Scale scores, 74% of respondents reported severe fatigue. Long-lasting pathologic fatigue with severe effect on daily performance is a hallmark of CFS. This disorder is fundamentally characterized by the absence of any clear underlying disease and the existence of a variety of associated clinical characteristics. When using standardized instruments like the Medical Outcome Study Short-Form 36 (MOS) SF-36, physical and mental health scores appear to be affected in CFS just as much as they are in MS, if not more. We found that 91.8% of patients with CFS compared to only 70.6% of patients without a diagnosis of CFS reported that their fatigue interfered with daily functioning. A significant early symptom of MS is headache.[15] In our study, we discovered that only 47.1% of individuals without a CFS diagnosis had headaches, compared to 19.7% of patients with the condition. Another study found that a high percentage of MS patients (67%) reported that they had had headaches in the previous 4 weeks. It also revealed that these headaches were more common in young, physically unaffected patients without disease-modifying drugs, suggesting a connection to inflammatory activity, which is at its peak at the beginning of the disease. Therefore, young people with regular headaches should have a head MRI, and if the results are abnormal, a complete differential diagnosis should be made immediately.

To our knowledge, this study represents the first investigation into the presence and etiology of fatigue and its association with CFS in patients with MS within the Saudi population sampled at King Fahd Hospital of the University in Al Khobar. The aim of our study was to contribute to the existing knowledge on this topic and encourage further research in larger and more diverse populations, ultimately leading to a comprehensive understanding of the intricate relationship between CFS and MS-related fatigue.

The main limitations of the study were that the study design of this study was cross-sectional; all data were self-reported, and some were retrospective and therefore

could have been subject to reporting and recall bias. In addition, the research only involved a single hospital in the country; hence, a larger study involving more hospitals is recommended to improve the generalizability of the results.

Conclusion

The study showed an association between MS and CFS in MS patients registered at our university hospital in the Eastern Region of Saudi Arabia. Study findings indicate poor agreement and suggest the need for improved diagnostic criteria and better communication between patients and health-care professionals.

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Conflicts of interest
There are no conflicts of interest.

References

1. Chalah MA, Riachi N, Ahdab R, Créange A, Lefaucheur JP, Ayache SS. Fatigue in multiple sclerosis: Neural correlates and the role of non-invasive brain stimulation. Front Cell Neurosci 2015;9:460.
2. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol 2014;14:58.
3. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: A comprehensive approach to its definition and study. International chronic fatigue syndrome study group. Ann Intern Med 1994;121:953-9.
4. Lim EJ, Ahn YC, Jang ES, Lee SW, Lee SH, Son CG. Systematic review and meta-analysis of the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). J Transl Med 2020;18:100.
5. Líndal E, Stefánsson JG, Bergmann S. The prevalence of chronic fatigue syndrome in Iceland – A national comparison by gender drawing on four different criteria. Nord J Psychiatry 2002;56:273-7.
6. Induruwa I, Constantinescu CS, Gran B. Fatigue in multiple sclerosis – A brief review. J Neurol Sci 2012;323:9-15.
7. AlJumah M, Bunyan R, Al Otaibi H, Al Towaijri G, Karim A, Al Malik Y, *et al.* Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study. BMC Neurol 2020;20:49.
8. Ayache SS, Chalah MA. Fatigue in multiple sclerosis – Insights into evaluation and management. Neurophysiol Clin 2017;47:139-71.
9. Romani A, Bergamaschi R, Candeloro E, Alfonsi E, Callieco R, Cosi V. Fatigue in multiple sclerosis: Multidimensional assessment and response to symptomatic treatment. Mult Scler 2004;10:462-8.
10. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. Neurology 2013;80:409-16.
11. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444-52.
12. Vercoulen JH, Hommes OR, Swanink CM, Jongen PJ, Fennis JF, Galama JM, *et al.* The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996;53:642-9.
13. Jason LA, Ohanian D, Brown A, Sunnquist M, McManimen S, Klebek L, *et al*. Differentiating multiple sclerosis from myalgic encephalomyelitis and chronic fatigue syndrome. Insights Biomed 2017;2:11.
14. Hadjimichael O, Vollmer T, Oleen-Burkey M, North American Research Committee on Multiple Sclerosis. Fatigue characteristics in multiple sclerosis: The North American Research Committee on Multiple Sclerosis (NARCOMS) survey. Health Qual Life Outcomes 2008;6:100.
15. Gebhardt M, Kropp P, Hoffmann F, Zettl UK. Headache at the time of first symptom manifestation of multiple sclerosis: A prospective, longitudinal study. Eur Neurol 2018;80:115-20.