



Assessment of Value of Fatigue Severity and Symptoms in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Fibromyalgia

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AK and LK designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors AI and GV performed the statistical analysis. Authors IL, MM and SR managed the analyses of the study. Authors LV, SG and SC managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background and Objective: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) remains a challenge for health care professionals because of its complex pathogenesis. Scales and questionnaires have been developed in order to assess the severity of syndrome. Fibromyalgia share similar clinical features with CFS/ME however have its own diagnostic criteria. Our study was performed to analyze impact of value of fatigue severity in patients with CFS/ME and fibromyalgia (FM).

Materials and Methods: One hundred and three CFS/ME patients and 21 fibromyalgia patients were included in study. CFS/ME patients were diagnosed using the diagnostic criteria of Fukuda et al. 1994. The diagnosis of fibromyalgia was established using the American College of Rheumatology (ACR) 1990 diagnostic criteria. Fatigue Severity scale (FSS) and Fibro Fatigue scale (FFS) were used to assess the severity of fatigue. Factor analysis was performed in order to detect most common combinations of clinical signs in patients with CFS/ME. The data were calculated using SPSS version 16.0.

Results: The most common clinical feature other than fatigue was un-refreshing sleep established in 71(68.9%) patients. The mean score of FSS within CFS/ME patients was 6.65 ± 0.256 . The highest mean scores -6.94 ± 0.243 were observed within statements – “Exercise brings on my fatigue”, “Fatigue is among my three most disabling symptoms”. The total score of FSS within CFS/ME patients was 59.94 ± 2.045 and 53.62 ± 8.880 in FM patients, ($p=0.008$). Fatigue was the most severe indicator according to FFS in CFS/ME patients with means score 5.76 ± 0.664 .

Conclusion: Most part of the CFS/ME patients suffered from un-refreshing sleep. CFS/ME patients had higher rates according to FSS than FM patients, which shows that fatigue in patients with CFS/ME is more intense, affecting their daily activities.

Keywords: Chronic fatigue syndrome; fibromyalgia; symptoms; severity.

1. BACKGROUND

Fatigue as entity is an overwhelming persisting sense of physical and mental tiredness, lack of energy, exhaustion, apathy and rapid inanition having an impact on daily activities and work [1,2].

Fatigue, including chronic fatigue, is one of the most common disabling conditions in different patients' populations accompanying as non-specific signs and symptoms in various somatic and neurological diseases as well as in disorders of psychosomatic and psychogenic origin. It is noticed in 6% to 45% of complaints in primary care [3]. Chronic fatigue syndrome (CFS) is the separate disorder characterized by persistent or relapsing fatigue and classified as neurological illness G93.3 in the International Classification of Diseases ICD-10 [4-6]. According to International Consensus this is a complex, acquired multi-factorial and multi-systemic disease defined as chronic fatigue syndrome/myalgic encephalitis (CFS/ME) or myalgic encephalomyelitis [6-8]. CFS/ME is a relatively common disease-evidence suggests a population prevalence of at least 0.4–0.5% [9]. Its clinical diagnosis is based on widely used US Center's for Disease Control and Prevention (CDC) case definition criteria which include unexplained by other causes fatigue of new onset and lasting for at least six months or longer and at least four out of eight additional symptoms: post-exertional malaise, impaired memory or concentration, un-refreshing sleep, muscle pain, multi-joint pain without redness or swelling, tender cervical or axillary lymph nodes,

sore throat, headache [10]. Diagnosis of CFS/ME has been confirmed by elimination of any other medical conditions that can cause similar symptoms and signs and by consideration of alternative diagnoses such as neurological focal damage, connective tissue disease, inflammatory arthritis, cardio respiratory disease, sleep apnoea, any tumors [7], anemia, hypothyroidism [11], hepatobiliary or renal problems [12].

Fibromyalgia patients usually complain about widespread pain and tenderness as main symptoms, but fatigue, sleep disorders, headaches, memory or concentration problems, mood disturbances, and stiffness are also common. The condition is more common in females [13]. The 1990 diagnostic criteria of ACR consist of: pain at least for 3 months, widespread pain in all 4 quadrants of the body including the axial skeleton, pain must be bilateral, above and below the waist, involving the trunk and extremities, 11 out of 18 positive tender points on physical examination [14].

Several scales have been implemented in order to assess the severity of fatigue and to differentiate CFS/ME patients from healthy controls. Fatigue Severity Scale (FSS) which was originally developed for multiple sclerosis and systemic *lupus erythematosus* patients [15] is well known and now widely used in a variety of medical and neurological disorders [16-18]. There are 9 indicators in this scale, self-report questionnaire measures how fatigue affects motivation, exercise, physical functioning, carrying duties, interfering with work, family and social life scoring each indicator on 7-point Likert scale. Another rating scale-the Fibro Fatigue scale (FFS) was constructed for measuring severity and treatment outcome in both groups of patients-with fibromyalgia and chronic fatigue syndrome. FFS is an observer's rating scale with 12 indicators measuring aches, muscular tension, fatigue, concentration difficulties, failing memory, irritability, sadness, sleep disturbances, autonomic disturbances, irritable bowel, headache, subjective feeling of infection [19].

The objective of this study was to analyze of CFS/ME case definition criteria symptoms and to determine the value of FSS and FFS measures for evaluation of severity of fatigue in CSF/ME and FM patients.

2. MATERIALS AND METHODS

2.1 The Study Population

The study population between 2010 and 2012, we enrolled 124 consecutive patients into a prospective observational study. CFS/ME patients were diagnosed using the diagnostic criteria of Fukuda et al. 1994. One hundred and three CFS/ME patients and 21 fibromyalgia patients were included in study. The Riga Stradinš University Ethics Committee approval was obtained.

Criteria for CFS/ME patients to be included in the study were the following:

1. Fatigue lasting at least for six months;
2. Additional criteria of Fukuda et al. [6], at least 4 out of 8:
 - post-exertional malaise-marked, rapid physical and/or cognitive fatigability in response to physical exertion with prolonged recovery period taking 24 hours or longer,
 - impaired memory and concentration,
 - un-refreshing sleep,

- muscle pain,
 - multi-joint pain,
 - tender lymph nodes,
 - sore throat,
 - headache.
3. Each patient's consent to be enrolled in the study.
 4. Patients' consent of HHV-6 and HHV-7 analysis in blood samples.

Exclusion criteria:

1. Anemia (Fe, B12 deficiency)
2. Cancer in the past, radiation therapy, chemotherapy
3. Radiation exposure
4. Pregnancy and postpartum period within 1st year
5. Endocrine disorders, including, diabetes mellitus, thyroid and adrenal diseases.
6. Orthostatic hypotension
7. Cardiac disorders (congestive heart failure, endocarditis, arrhythmias)
8. Renal disorders (uremia, electrolyte disturbance)
9. Hepatic disorders (hepatitis, cirrhosis)
10. Connective tissue diseases
11. Myopathy, myositis, peripheral neuropathies
12. CNS diseases with motor, sensory, cognitive and mental impairment (stroke, multiple sclerosis, traumatic brain injury, motoneuron diseases etc)
13. Infectious diseases (Lyme disease, EBV, CMV, HIV)
14. Trauma
15. Toxic substance influence (including alcohol, drugs)
16. Psychoorganic diseases (depression, affective and neurotic conditions)

The following were inclusion criteria of patients with fibromyalgia:

1. Patients who met the 1990 diagnostic criteria of ACR [14]:
 - Pain for at least 3 months,
 - widespread pain in all 4 quadrants of the body including the axial skeleton, pain must be bilateral, above and below the waist, involving both the trunk and extremities,
 - 11 out of 18 positive tender points on physical examination.
2. Each patient's consent to be enrolled in the study.

Exclusion criteria—as mentioned before.

One hundred and three patients who had met inclusion criteria, 35 (34%) males and 68 (66%) females, with clinically diagnosed chronic fatigue syndrome/myalgic encephalomyelitis and 21 patients (all women) with clinically diagnosed fibromyalgia were included in this study. The mean age of the patients with CFS/ME was 37 years (range from 22 to 65), with FM—51 years (range from 26 to 62). Clinical diagnosis of CFS/ME was established by using the diagnostic criteria of Fukuda et al. [6]. 30 (29.1%) out of all patients had fatigue for 6 months, 62 patients (60.1%) -7 to 12 months, 11 patients (10.8%) for >12 months.

Patients with fibromyalgia were diagnosed using the 1990 ACR diagnostic criteria [14] excluding musculoskeletal disorders and other causes mentioned before.

2.2 Evaluation of Symptoms in the CFS/ME Patients' Group

Neurological (clinical) patients were thoroughly investigated by the competent neurologist group. Fatigue of new onset, persistent and lasting for at least six months was compulsory for CFS/ME diagnosis and this symptom was observed in all observed patients. Additional case definition criteria symptoms, i.e., post-exertional malaise-marked, rapid physical and/or cognitive fatigability in response to physical exertion with prolonged recovery period taking 24 hours or longer, impaired memory and concentration, un-refreshing sleep, muscle pain, multi-joint pain, tender lymph nodes, sore throat, headache, were observed and their values were calculated. However, subfebrile temperature, persistent fatigue and impaired thinking are usually not included in criteria symptoms, but we included these symptoms in our study because of many patients' complaints.

2.3 Instruments

2.3.1 Fatigue severity studies

Fatigue Severity Scale (FSS) [15,18,20] was administrated to 17 CFS/ME and 21 FM patients. The severity of fatigue in different situations within one week was estimated using the following 9 questions or statements of a self-administrated questionnaire: "Exercise brings on my fatigue"; "Fatigue is among my three most disabling symptoms"; "Fatigue interferes with carrying out certain duties and responsibilities"; "Fatigue interferes with my work, family, or social life"; "My fatigue prevents sustained physical functioning"; "My motivation is lower when I am fatigued"; "Fatigue causes frequent problems for me"; "I am easily fatigued"; "Fatigue interferes with my physical functioning". Grading of each indicator ranges from 1 to 7, what corresponds from "strongly disagree" to "strongly agree". Fatigue severity was calculated by mean score of FSS and total score of FSS.

2.3.2 Evaluation of fatigue using fibro fatigue scale (FFS)

Seventeen CFS/ME patients were assessed using the Fibro Fatigue scale [20]. Each of 12 indicators was rated from "0" (no symptoms) to "6" (severe symptoms). To aid the scoring, a short description (anchoring point) is given for scores 0, 2, 4, and 6. If the patient's condition falls somewhere in between the anchoring points, a score of 1, 3, or 5 (which are not defined) may be given.

2.4 Statistical Analysis

One sample t-test was used to calculate the mean scores, standard deviation and confidence interval. Wilcoxon test was used to compare the scores of total FSS in CFS/ME patients and fibromyalgia patients. We considered statistical test results as statistically significant at a level of $p < 0.05$. Factor analysis was performed in order to detect most common combinations of clinical signs in patients with CFS/ME. The data were calculated using SPSS version 16.0.

3. RESULTS

3.1 Impact of CFS/ME Case Definition Criteria Symptoms

The most common clinical sign in CFS/ME patients besides fatigue was un-refreshing sleep observed in 71 (68.9%) cases. 42 out of 50(48.5%) patients with muscle pain had moderate and 8-severe muscle pain. 45 out of 53(51.5%) patients suffering from joint pain had moderate and 8-severe joint pain. All clinical signs of patients with CFS/ME are shown in Table 1.

Factor analysis made 6 components out of 13 patients' symptoms. The results are shown in Table 2. The patients' symptoms after a strong cross-correlation were collected in a group - factors. Factor analysis showed which symptom combinations were the most common in the group of CFS/ME patients. Higher ratio showed stronger association of symptoms within the component, negative ratio showed the lack of the symptom within component. In our study, a strong association within the component showed "Post-exertional malaise" and "Joint pain" symptoms. Slightly less associated "Impaired thinking", "Impaired memory" and "Subfebrile temperature" symptoms. The results are shown in Table 3.

Table 1. Clinical signs of CFS/ME patients

Clinical features	CFS/ME patients (n=103)	95% CI
Un-refreshing sleep	71(68.9%)	60.0–77.9
Post-exertional malaise	66(64.1%)	54.8–73.4
Headaches	66(64.1%)	54.8–73.4
Tender lymph nodes	66(64.1%)	54.8–73.4
Joint pain	53(51.5%)	41.8–61.2
Muscle pain	50(48.5%)	38.8–58.2
Sore throat	50(48.5%)	38.8–58.2
Subfebrile temperature	34(33.0%)	23.9–42.1
Persistent fatigue	32(31.1%)	22.1–40.0
Muscle weakness	41(39.8%)	30.4–49.3
Impaired thinking	18(17.5%)	10.1–24.8
Impaired concentration	16(15.5%)	8.5–22.5
Impaired memory	13(12.6%)	6.2–19.0

Table 2. Total variance explained

Component	Initial eigenvalues			Rotation sums of squared loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	1.923	14.791	14.791	1.633	12.560	12.560
2	1.591	12.237	27.028	1.613	12.405	24.965
3	1.499	11.532	38.561	1.517	11.668	36.633
4	1.299	9.995	48.556	1.441	11.082	47.714
5	1.234	9.491	58.046	1.195	9.190	56.904
6	1.017	7.822	65.868	1.165	8.964	65.868
7	0.953	7.333	73.202			
8	0.839	6.454	79.656			
9	0.761	5.852	85.508			
10	0.696	5.357	90.865			
11	0.638	4.905	95.770			
12	0.529	4.069	99.839			
13	0.021	0.161	100.000			

Extraction Method: Factor analysis. Component 1: Impaired memory, Persistent fatigue, Subfebrile temperature; Component 2: Muscle weakness, Muscle pain, Impaired concentration; Component 3: Un-refreshing sleep, Impaired thinking, Headaches; Component 4: Joint pain, Sore throat; Component 5: Tender lymph nodes; Component 6: Post-exertional malaise.

Table 3. Rotated component matrix (a) of CFS/ME patient's symptoms

Component	Symptoms	Component					
		1	2	3	4	5	6
1	Impaired memory	0.671					
	Persistent fatigue	-0.657					
	Subfebrile temperature	0.612					
2	Muscle weakness		-0.814				
	Muscle pain	0.472	0.557				
	Impaired concentration		0.530			0.492	
3	Un-refreshing sleep			-0.787			
	Impaired thinking			0.675			
	Headaches		0.406	0.535			-0.494
4	Joint pain				0.806		
	Sore throat				-0.759		
5	Tender lymph nodes					-0.905	
6	Post-exertional malaise						0.850

Rotation Method: Varimax with Kaiser Normalization. a Rotation converged in 8 iterations.

3.2 The Assessment of Severity of Fatigue in CFS/ME and FM Patients Using Fatigue Severity Scale

The mean score of fatigue severity scale in patients with CFS/ME was 6.65 ± 0.256 . The highest mean scores -6.94 ± 0.243 were observed within statements—"Exercise brings on my fatigue" and "Fatigue is among my three most disabling symptoms". The results are shown in Table 4.

We compared the total score of FSS in CFS/ME patients and fibromyalgia patients. The total score of FSS in CFS/ME patients was 59.94 ± 2.045 while the mean score of FSS in fibromyalgia patients was 53.62 ± 8.880 . The difference was statistically significant, $p=0.008$. Results are shown in Fig. 1.

3.3 The Evaluation of Fatigue Severity in CFS/ME Patients Using Fibro Fatigue Scale (FFS)

Seventeen CFS/ME patients were analyzed using the Fibro Fatigue scale. Out of 12 indicators—fatigue was measured as the most severe symptom with mean result— 5.76 ± 0.664 . None of the patients suffered from irritable bowel disease. The results are shown in Table 5.

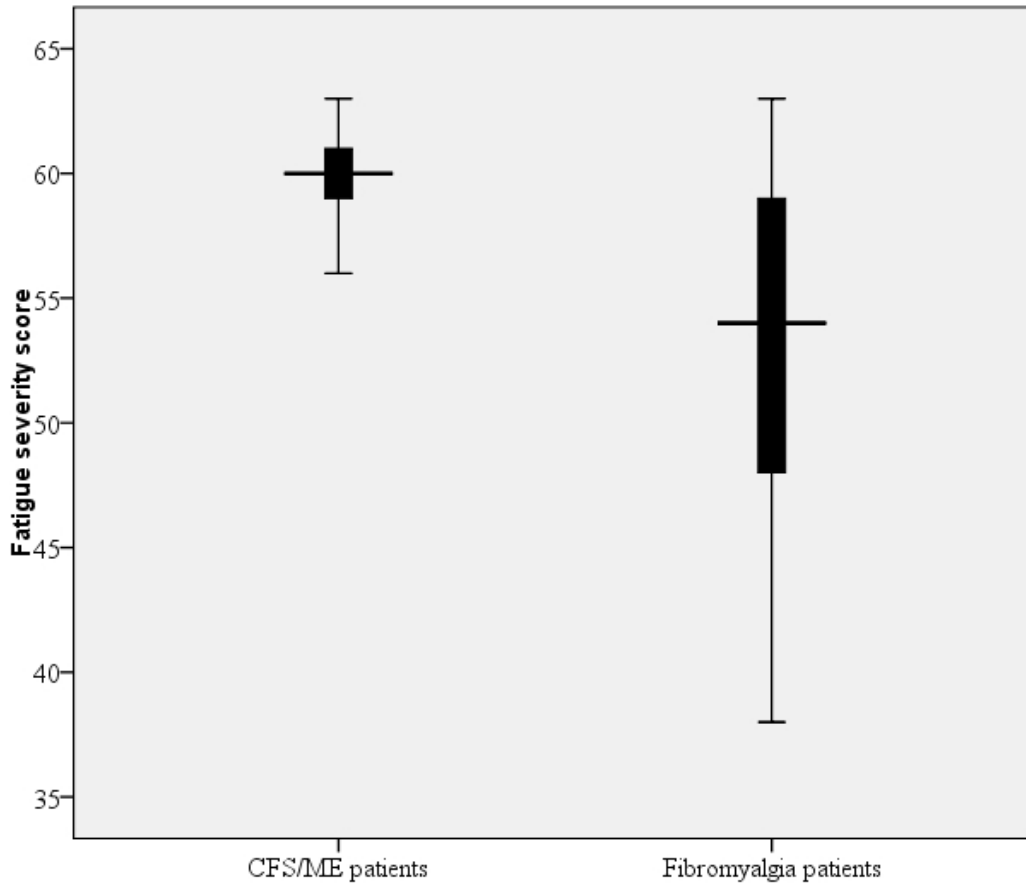


Fig. 1. Comparison of total fatigue severity scores between CFS/ME and fibromyalgia patients

Table 4. The mean scores of fatigue severity scale in patients CFS/ME

Fatigue severity scale	Mean score±SD	95% CI
Exercise brings on my fatigue	6.94±0.243	6.82–7.07
Fatigue is among my three most disabling symptoms	6.94±0.243	6.82–7.07
Fatigue interferes with carrying out certain duties and responsibilities	6.88±0.332	6.71–7.05
Fatigue interferes with my work, family, or social life	6.82±0.393	6.62–7.03
My fatigue prevents sustained physical functioning	6.71±0.470	6.46–6.95
My motivation is lower when I am fatigued	6.59±0.712	6.22–6.95
Fatigue causes frequent problems for me	6.35±0.606	6.04–6.66
I am easily fatigued	6.35±0.493	6.10–6.61
Fatigue interferes with my physical functioning	6.35±0.493	6.10–6.61
Total FSS	59.94±2.045	58.89–60.99
Mean fatigue score	6.65±0.256	6.46–6.85

Table 5. The mean results and standard deviation of fibro fatigue scale items in patients CFS/ME

Fibro fatigue scale items	Mean score±SD	95% CI
Fatigue	5.76±0.664	5.42–6.11
Sadness	3.71±1.993	2.68–4.73
Aches and pain	3.47±1.546	2.68–4.27
Headache	3.41±1.734	2.52–4.30
Sleep disturbances	3.29±1.649	2.45–4.14
Muscular tension	3.12±1.269	2.47–3.77
Subjective experience of infection	2.76±1.147	2.17–3.35
Concentration difficulties	2.41±1.372	1.71–3.12
Irritability	2.18±1.468	1.42–2.93
Failing memory	2.12±1.166	1.52–2.72
Autonomic disturbances	2.06±1.478	1.30–2.82
Irritable bowel	-	-
Total FFS	34.29±6.283	31.06–37.52

4. DISCUSSION

CFS/ME still remains a challenge for health care professionals. There have been a lot of discussions about the possible etiologic factor, case definition and even existence of CFS/ME [4]. Previous studies in Latvia have analyzed human herpes virus 6 (HHV-6), also analyzed by Ablashi et al. [21], and HHV-7 [22], parvovirus B19 activation in CFS/ME, but there have been no studies analyzing fatigue severity or impact of CFS/ME case definition criteria symptoms.

Diagnosis of CFS/ME is based on diagnostic criteria due to lack of specific biomarkers. Symptoms, however nonspecific, should be obtained to make the diagnosis. The most common clinical sign in our CFS/ME patients other than fatigue was un-refreshing sleep established in 71 (68.9%) patients. According to scientific publications, sleep disorders are the most commonly overlooked diagnoses in CFS/ME patients. The sleep apnea has been discovered using polysomnography in some of the patients with CFS/ME. Previous studies have shown variable results of polysomnography findings in comparison with healthy controls. Some of the studies suggest that patients with CFS/ME might have characteristic findings in polysomnography, but some don't. This actually could explain why the CFS/ME patients usually feel sleepier and more fatigued than healthy people [23,11].

FSS is one of the most often used measurement scales to assess the severity of fatigue [18]. The higher mean score of FSS indicates more severe fatigue. Mean scores of healthy adults have been reported as 2.3±0.7 in Krupp et al. [15-17] and Neuberger studies, higher in Valko et al. [18] study–3.00±1.08. Mean score of our CFS/ME patients' FSS was 6.65±0.256 (SD) confirming severe fatigue. Although fibromyalgia and CFS/ME share a lot of similar symptoms including fatigue, the results confirmed that fatigue was more severe in CFS/ME patients; the total score of FSS was 59.94±2.045. Diagnostic criteria suggest that most important clinical sign within FM patients is pain [13] while fatigue and post-exertional malaise are more characteristic in CFS/ME cases [24]. Interesting, that none of the patients in this study suffered from irritable bowel disease.

The FFS confirmed the influence of fatigue in CFS/ME patients' everyday occurrence. According to FFS, fatigue was the most severe indicator in CFS/ME patients with means score 5.76 ± 0.664 (SD). Due to the overlap of symptoms, the scale has been developed to assess the severity of symptoms within CFS/ME, FM patients and change after the treatment [19].

The limitation of this study was the lack of control group in order to compare FSS to healthy adults. The other limitation was the lack of a chance to use the FFS in FM patients, to measure the clinical outcome after the treatment. We also didn't have a chance to perform polysomnography for all patients.

5. CONCLUSION

Most part of the CFS/ME patients suffered from un-refreshing sleep which might lead to more severe fatigue and increase the intensity of other symptoms. Factor analysis showed that some of the symptom combinations might be more common.

CFS/ME patients had higher total FSS rates than FM patients which shows that fatigue in patients with CFS/ME is more intense, affecting their daily activities. The mean score of fatigue severity scale in patients with CFS/ME was 6.65 ± 0.256 . The highest mean scores – 6.94 ± 0.243 were observed within statements–“Exercise brings on my fatigue” and “Fatigue is among my three most disabling symptoms”.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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