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Psychiatric comorbidities and chronic fatigue syndrome in patients diagnosed with fibromyalgia: a prospective study

Canan Emiroğlu[1], Nesrin Dilbaz[2]

[1]Department of Family Medicine, Ankara Etlik City Hospital, Ankara, Turkiye
[2]Department of Psychiatry, Faculty of Medicine, Üsküdar University, İstanbul, Turkiye

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ABSTRACT

Aims: Currently, fibromyalgia (FM) is still diagnosed solely on clinical grounds, as no serologic, imaging, or histologic markers are available. Chronic fatigue syndrome (CFS) shares many similarities with FM. The implication of similar etiological factors and mechanisms, the overlap in symptoms and signs, and the high prevalence of psychiatric disorders such as anxiety, depression, panic attacks, and somatization disorder in both conditions have led to suggestions that they may represent different manifestations of the same disease. The primary objective of this investigation was to assess the prevalence of comorbid psychiatric conditions 'including depression, anxiety, and somatization disorder' as well as CFS, among individuals diagnosed with FM, and to explore potential overlaps in their clinical presentation.

Methods: In this prospective, cross-sectional study, the prime MD scale was applied to 60 patients diagnosed with FM to investigate their overlap with psychiatric diagnoses. In addition, patients were evaluated according to the Fukuda Classification System to determine whether they could be diagnosed with CFS.

Results: The incidence rate of anxiety disorder was 33.3% and the incidence rate of somatoform disorder was 83.4%. Major depression was detected in 10 patients (16.7%) and dysthymia in 16 patients. Eight out of 60 patients (13.3%) did not have any psychiatric disorders, while the remaining 52 patients had at least one disorder or more than one disorder. Although 50 of 60 patients (83.3%) complained of fatigue, only 8 (13.3%) patients were diagnosed by meeting sufficient criteria for CFS.

Conclusion: Although FM and CFS are not the same clinical entity, they appear to be two conditions with overlapping symptoms, particularly psychiatric ones, which frequently coexist. The prevalence of psychiatric symptoms and diagnoses was notably higher among individuals who met the diagnostic criteria for both FM and CFS. Further research is needed to refine and evaluate the diagnostic criteria for both conditions.

Keywords: Fibromyalgia, fatigue, depression, anxiety, somatoform disorders

INTRODUCTION

Fibromyalgia (FM) is clinically characterized by chronic, widespread musculoskeletal pain accompanied by symptoms such as stiffness, fatigue, sleep disturbances, and headaches.[1] Patients often report mood disorders, including depression and anxiety, as well as cognitive impairments and increased sensitivity to stimuli, all of which contribute to challenges in daily functioning. FM is also frequently associated with a wide range of comorbid conditions, including allergic symptoms, dry eyes, palpitations, vulvodynia, dyspnea, premenstrual syndrome, dysmenorrhea, irritable bowel syndrome, weight fluctuations, sexual dysfunction, dysphagia, night sweats, restless legs syndrome, temporo-mandibular joint pain, chronic fatigue syndrome (CFS), Raynaud's phenomenon, and autonomic dysfunction.[2,3]

Recent research on FM, a condition lacking a clearly identified organic cause, suggests that its development may result from a complex interplay of genetic predispositions, hormonal, biochemical, and immunological factors, along with psychological traits and triggering events that enhance central nervous system sensitivity.[1,2,4] Symptom intensity can vary over time, with pain often beginning in localized areas before spreading to multiple muscle groups. This pain is heterogeneous, frequently described as burning, gnawing, or neuropathic, and is usually accompanied by muscle stiffness. Hallmark features of FM include increased pain sensitivity (hyperalgesia) and pain in response to normally non-painful stimuli (allodynia). Patients commonly report subjective sensations such as joint swelling and tingling (paresthesias), even when objective clinical signs are absent. Moreover, pain severity is often modulated by environmental and lifestyle factors, such as cold and damp weather, poor sleep quality, and physical or psychological stress.[4,5]

FM, the diagnostic criteria of which were first determined by the American College of Rheumatology (ACR) in 1990, was

Corresponding Author: Canan Emiroğlu, cananmemiroglu@gmail.com

defined as 'sensitivity in 11 of the 18 pain points, lasting longer than 3 months'.[6] The diagnostic criteria were revised in 2010 to remove tender points and instead include the Widespread Pain Index (WPI) as a key measure to assess the extent and distribution of pain in FM. The symptom severity scale (SSS scale) was specifically developed to quantify not only widespread pain but also the severity of associated symptoms, and it has been integrated into the updated diagnostic framework of FM.[7] Nonetheless, these tools enable the identification of chronic widespread pain characterized by a minimum of three pain regions even in individuals exhibiting significant variations in the severity of their condition. To correct these deficiencies, FM diagnostic criteria were revised in 2016. A modified definition of widespread pain 2016 has been provided, dividing the body into five zones of three pain zones each and requiring at least four pain zones.[8] It has been suggested that WPI ≥7 be added to the 2016 regulation in 2019.

The World Health Organization (WHO) has cited fibromyalgia as a rheumatological disease and FM is listed as "M97" in the International Statistical Classification of Diseases and Related Health Problems (ICD).[9]

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) shares many similarities with FM.[10] The involvement of similar etiological factors and mechanisms, the overlap in symptoms and clinical findings, and the high prevalence of psychiatric disorders-such as anxiety, depression, panic attacks, and somatization disorder-in both conditions have led to the hypothesis that they may represent different manifestations of the same disease.[10-12]

Depression and anxiety appear more prevalently in FM and CFS/ME than in other comparable medical conditions. However, the underlying reasons remain unclear. It is not yet known whether psychiatric disorders precede the onset of FM or CFS/ME and contribute to their etiology, or whether they develop subsequently as a result of chronic pain, fatigue, and general functional decline.[13]

The CFS/ME diagnostic guide published by "the National Institute for Health and Care Excellence (NICE)" in the year of 2007 is now being reviewed again.[14]

This study aims to determine how common psychiatric conditions-such as anxiety, depression, and somatization disorder-are in individuals with FM, alongside CFS. Additionally, it aims to evaluate whether these psychiatric comorbidities and CFS might reflect a single, unified clinical syndrome. The central hypothesis is that psychiatric disorders and CFS occur frequently among patients with FM.

METHODS

This article is based on a thesis completed before 2020 and the study was conducted after institutional approval. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this prospective study, 60 patients who applied to the tertiary hospital outpatient clinics and were determined to have PFS based on the criteria established by the American College of Rheumatology in 1990 by a Physical Therapy and Rehabilitation assistant or specialist doctor were evaluated. Illiterates, those with sensory and cognitive loss at a level that affects communication, those with CRP, RF, erythrocyte sedimentation rates outside normal limits, those with severe systemic disease, and those with a history of long-term drug use or psychoactive substance use were excluded from the study.

The prime MD scale was administered to all patients to assess overlap with psychiatric diagnoses such as somatoform disorders (either not otherwise specified or multi-somatoform disorder), major depression, anxiety disorders (including not otherwise specified, generalized anxiety disorder, or panic disorder), dysthymia, and hypochondriasis.[15] The validation and reliability of the Turkish version of Prime MD were established through a study conducted in 1996.[16]

Patients completed the self-report questionnaire section of the prime MD diagnostic tool, which gathered information on gender, age, occupation, marital status, and presenting symptoms. Clinicians also inquired about the duration of symptoms and the presence of any other diagnosed conditions that could explain these symptoms.

The questionnaire included 21 items: 15 related to somatoform disorders, 1 to hypochondriasis, 2 to mood disorders, and 3 to anxiety disorders. Patients responded with "yes" or "no" to each item. For any question answered affirmatively, additional structured questions were administered by the clinician, leading to diagnoses such as major depression, dysthymia, anxiety disorder, or panic disorder. Furthermore, all patients were assessed using the Fukuda Classification, a consensus-based diagnostic guideline for CFS adopted by the U.S. Centers for Disease Control and Prevention (CDC) in 1994, to determine whether they met the criteria for CFS.[17]

Before the diagnosis of FM was made to all patients, complete blood count, sedimentation rate, RF, CRP, SGOT, SGPT, albumin, alkaline phosphatase, total protein, globulin, phosphate, glucose, calcium, urea, creatinine, electrolytes, complete urinalysis, and thyroid function tests were performed as laboratory examinations.

Statistical Analysis

Statistics were conducted with SPSS (SPSS Inc., USA). The study data were examined by descriptive statistical analysis. The socio-demographic characteristics of the patients and the incidence of other parameters were evaluated.

RESULTS

The age range of the individuals with FM who took part in the research study spanned from 20 to 67 years, and the average was 42 years. Fifty-five (91.7%) were women and 5 (8.3%) were men. Upon examination of the educational status, it was found that 18 individuals (30%) had attained literacy or completed primary school, 17 individuals (28.39%) were classified as secondary or high school graduates, and 25 individuals (41.7%) had obtained a university or college degree. Of the 60 patients, 20 were housewives, 11 were civil servants, 3 were teachers, 4 were self-employed, 13 were retired, and 9 were health workers.

Eight (13.3%) of 60 patients diagnosed with FM had no psychiatric disorder. The remaining 52 patients had at least one disorder, and the majority had more than one disorder. The specifics of these disorders are outlined in Table 1, 2 (Figures 1, 2).

Table 1. Incidence rates of psychiatric disorders and chronic fatigue syndrome

Psychiatric disorders	n	%
Somatoform disorder-not otherwise specified	37	61.7
Multi-somatoform disorder	13	16.7
Major depressive disorder	10	16.7
Dysthymia	16	26.7
Anxiety disorder-not otherwise specified	6	10
Generalized anxiety disorder	14	23.3
Panic disorder	5	8.3
A history of depression in their past	8	13.3
A history of anxiety in their past	3	5
Chronic fatigue syndrome	8	13.3

Table 2. Distribution of psychiatric disorders in the study group consisting of 60 patients

Psychiatric disorders	n	%
None	8	13.3
Only somatization disorder	19	31.7
Only depressive disorder	1	1.7
Somatization disorder+depressive disorder	12	20
Somatization disorder+anxiety disorder	4	6.7
Depressive disorder+anxiety disorder	1	1.7
Somatization disorder+depressive disorder+anxiety disorder	10	16.7
Somatization disorder+anxiety disorder+panic disorder	3	5
Somatization disorder+depressive disorder+anxiety disorder+ panic disorder	2	3.3
Total	60	100

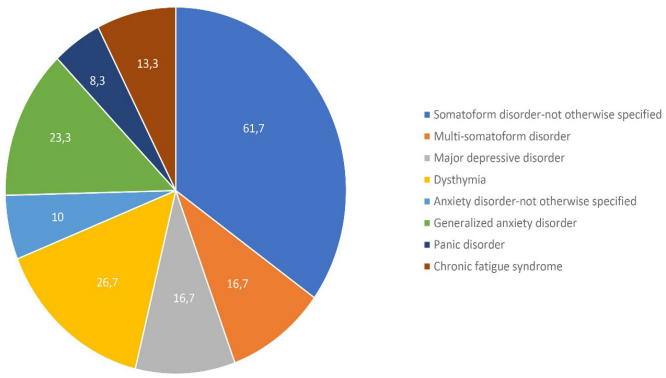

Figure 1. Incidence rates of psychiatric disorders and chronic fatigue syndrome

Although 50 out of 60 patients with FM (83.3%) had complaints of fatigue, only 8 (13.3%) patients were diagnosed by meeting a sufficient number of criteria for CFS. Of these 8 patients, 7 were women and one was male. Seven of them were married

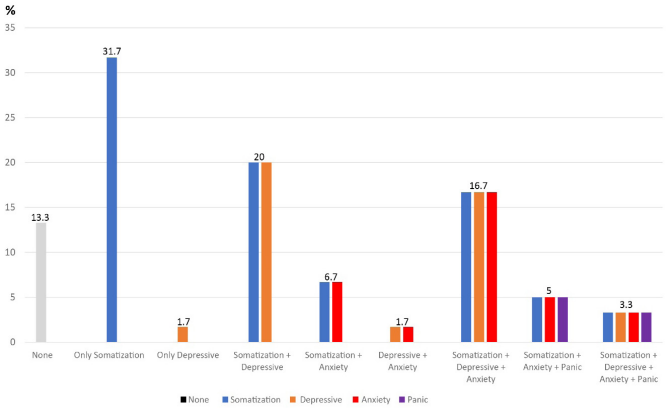

Figure 2. Distribution of psychiatric disorders in the study group consisting of 60 patients

and one was single. Three of them were housewives, 1 of them was a civil servant, 1 of them was self-employed, 2 of them were retired, and one of them was a nurse. The average age was 41. Due to the small number, other psychiatric disorders observed in patients with FM diagnosed with CFS could not be statistically evaluated. However, we still want to give the overlap rates here. Somatoform disorder-not otherwise specified was detected in 5 of 8 patients, multi-somatoform disorder in 3, major depressive disorder in 2, dysthymia in 4, anxiety disorder-not otherwise specified in 2, generalized anxiety disorder in 3, and panic disorder in one patient. The details of these disorders are summarized in Table 3 and Figure 3.

Table 3. Distribution of psychiatric disorders in eight patients diagnosed with chronic fatigue syndrome

Psychiatric disorders	n	%
None	-	-
Only somatization disorder	-	-
Only depressive disorder	-	-
Somatization disorder+depressive disorder	3	37.5
Somatization disorder+anxiety disorder	1	12.5
Somatization disorder+anxiety disorder+panic disorder	1	12.5
Somatization disorder+anxiety disorder+depressive disorder	3	37.5
Total	8	100

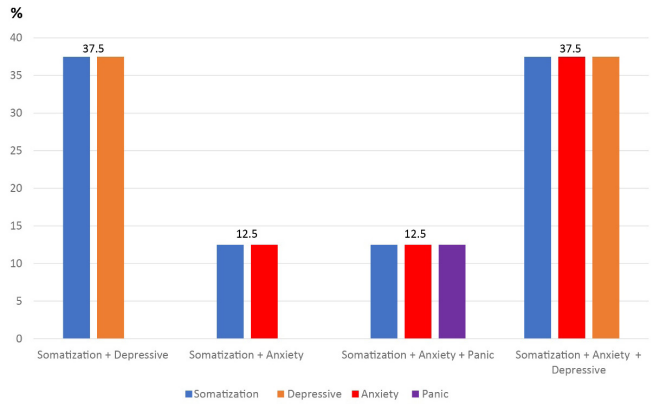

Figure 3. Distribution of psychiatric disorders in eight patients diagnosed with chronic fatigue syndrome

DISCUSSION

Interpretation of Findings

This study examined the co-morbidity and prevalence of psychiatric disorders-including somatization disorder, anxiety, depression-as well as CFS in patients diagnosed with FM based on ACR criteria. A secondary objective was to determine whether FM and CFS represent the same clinical condition. Psychiatric disorder were found in 85% and CFS was present in 13.3%. The relatively low prevalence of CFS among FM patients, as defined by the Fukuda criteria, suggests that FM and CFS are distinct conditions, although psychiatric symptoms are commonly observed in both. Notably, all patients with CFS had two or more psychiatric disorders. Due to the single-center design and limited sample size, a direct cause-and-effect relationship could not be established. However, the high rates of CFS and psychiatric symptoms among FM patients support the hypothesis that these disorders frequently co-occur. Moreover, while psychiatric disorders are prevalent in most FM patients, every FM patient diagnosed with CFS presented with at least two psychiatric disorders, indicating that CFS may act as a comorbidity that intensifies psychiatric symptoms in FM.

Comparison with Existing Literature

Although FM can occur across a wide range of age groups, studies suggest that it is most prevalent among individuals aged 50 to 59 years.[18] In this study, the mean age of participants was 42 years. A large majority of the participants (91.7%) were female. Numerous recent studies reports that FM is significantly more common in women, with a male-to-female ratio ranging from 1:8 to 1:9.[2-9,18,19]

One study highlighted that the 1990 ACR criteria may contribute to lower diagnosis rates in men.[20] Several hypotheses have been proposed to explain the gender disparity in FM. These include the possibility that women have a lower pain threshold, that women-particularly in Western countries-are more likely to seek medical attention for somatic or psychological symptoms, and that clinicians may be more inclined to diagnose FM in women, given its known higher prevalence in the female population.[19,20]

A review study reported that mood disorders are frequently observed in patients diagnosed with FM, with anxiety disorders ranging from 20% to 80%, and depressive disorders from 13% to 63.8%.[2] The findings of our study align with these results; we observed a lifetime prevalence of depression at 30%. In a meta-analysis by Løge-Hagen et al.[21] the prevalence of major depressive disorder in FM was found to be 25%, while the lifetime prevalence of depression was 65%. The discrepancy between these figures and ours may be attributed to the larger sample size used in their analysis.

Another meta-analysis revealed a wide variation in lifetime depression rates among FM patients, ranging from 40% to 80%, which reflects differences in study methodologies and diagnostic criteria.[22] Notably, this study emphasized that not all individuals with FM experience depression, and conversely, not all individuals with depression present with chronic pain or receive an FM diagnosis.

The association between FM and depression may be partly explained by symptom overlap-shared features such as fatigue, sleep disturbances, and cognitive dysfunction. Both biological factors (e.g., genetic predispositions) and psychological factors (e.g., adverse childhood experiences) have been proposed as underlying mechanisms.[22] Multiple studies have suggested a bidirectional relationship between FM and depression: FM may increase vulnerability to developing depression, while existing depression may predispose individuals to FM symptoms. Moreover, their co-occurrence appears to increase the likelihood of symptom onset at earlier stages in life.[23]

Clinical Implications

Due to the absence of identifiable biomarkers for the identification of CFS and FM conditions, the diagnosis continues to rely on clinical observations to this day. A notable distinction between the two conditions lies in the fact that the existence of any underlying medical reason for extreme exhaustion precludes individuals from being diagnosed with CFS. Conversely, there are no medical exemptions for the diagnosis of FM. Furthermore, individuals devoid of any other causative factor resulting in widespread pain are classified under FM, whereas those presenting with concurrent rheumatological diagnoses are categorized as having secondary FM.[24] Mckay et al.,[10] in a study with patients diagnosed with 101 CFS and 107 FM, examined the physical and psychological symptoms and their severity. They found that both groups experienced depression and anxiety at a certain rate. However, the hospital anxiety and depression scale scores were higher in the FM group. In our study group, 8 out of 60 PFS patients were diagnosed with CFS. However, it is not possible to make a complete comparison because this number is not suitable for statistical analysis. The fact that all these 8 patients have two or more psychiatric disorders may draw attention to the importance of the results of the Lifelines cohort study published in 2023.[25] The current investigation sought to evaluate the capacity of psychiatric conditions to forecast the emergence of FM and CFS in individuals experiencing pre-existing muscle pain or fatigue. A total of 148.614 individuals were included in the FM study group, while 136,423 individuals were part of the CFS study group. All of the patients were monitored for a period exceeding two years. In individuals who already experience fatigue, psychiatric disorders can serve as predictors for the development of self-reported CFS. However, these psychiatric conditions do not show the same ability to predict self-reported fibromyalgia (FM) or CFS in those who initially do not exhibit symptoms of pain or fatigue.[25]

Future Directions

Although muscle pain is the predominant symptom in FM and fatigue in CFS, psychoneuroimmunoendocrine studies on differential diagnosis are still ongoing.[26] Studies in the literature examining the pathophysiology of CFS and FM have investigated the expression profiles of circulating microRNAs. Some of these microRNAs have been shown to play a role in various pathological processes. Eleven of these microRNAs have been proposed as potential biomarkers for distinguishing CFS from FM.[27,28] However, there is another

recent study that claims CFS and FM are the same clinical entity.[29] These findings reinforce the need for objective biomarker assessments to better discriminate between the two syndromes.

Limitations

This investigation is subject to various limitations. First, it is a single-center and cross-sectional study. Second, further statistical analyzes could not be performed due to the low number of patients. Third, there were no control groups and these comparisons could not be made. For example, in patients with other rheumatological diagnoses or in those without a diagnosis of FM. Despite all these limitations, the prospective investigation examined both chronic fatigue and psychiatric disorders in patients with FM. While the diagnostic criteria and guidelines are still being updated, we have placed particular emphasis on FM and CFS because they are commonly observed in both primary and tertiary healthcare settings.

CONCLUSION

Among the patients with FM, significant association with psychiatric disorders and, partly, with CFS are observed. In particular, the incidence rates of psychiatric symptoms and diagnoses were found to be higher in patients who met the diagnostic criteria of both for FM and CFS. Although advances in diagnostic criteria and treatment approaches are ongoing, further research involving larger patient populations is needed, as the exact etiopathogenesis of FM and CFS remains unknown.

ETHICAL DECLARATIONS

Ethics Committee Approval

This article is based on a thesis completed before 2020 and the study was conducted after institutional approval.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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