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Original Research Report

Comorbidity in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Nationwide Population-Based Cohort Study

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Background: *Previous studies have shown evidence of comorbid conditions in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).* **Objective:** *To estimate the prevalence of comorbidities and assess their associations using a nationwide population-based database of a Spanish CFS/ME cohort.* **Method:** *A nationally representative, retrospective, cross-sectional cohort study (2008–2015) assessed 1757 Spanish subjects who met both the 1994 Centers for Disease Control and Prevention/Fukuda definition and 2003 Canadian Criteria for CFS/ME. Sociodemographic and clinical data, comorbidities, and patient-reported outcome measures at baseline were recorded. A cluster analysis based on baseline clinical variables was performed to classify patients with CFS/ME into 5 categories according to comorbidities. A multivariate logistic regression analysis was conducted adjusting for potential confounding effects such as age and sex; response and categorical predictor variables were also assessed.* **Results:** *A total of 1757 CFS/ME patients completed surveys were collected. We identified 5 CFS/ME clusters: group 1—fibromyalgia, myofascial pain, multiple chemical hypersensitivity, sicca syndrome, epicondylitis, and thyroiditis; group 2—alterations of ligaments and subcutaneous tissue, hypovitaminosis D, psychopathology, ligamentous hyperlaxity, and endometriosis. These 2 subgroups comprised mainly older women, with low educational level, unemployment, high levels of fatigue, and poor quality of life; group 3—with hardly any comorbidities, comprising mainly younger women, university students or those already employed, with lower levels of fatigue, and better quality of life; group 4—poorly defined comorbidities; and group 5—hypercholesterolemia.* **Conclusion:** *Over 80% of a large population-based cohort of Spanish patients with CFS/ME presented comorbidities. Among the 5 subgroups created, the most interesting were groups 1–3. Future research should consider multidisciplinary approaches for the management and treatment of CFS/ME with comorbid conditions.*

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Key words: Chronic fatigue syndrome, Comorbid illness, Fibromyalgia, Multiple chemical sensitivity, Myalgic encephalomyelitis, Chronic pain.

INTRODUCTION

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is a multisystemic disease of unknown etiology that mainly affects young women between the ages of 25 and 40. Previous studies have reported a male/female ratio of 1:4 in some cohorts.[1] The high prevalence rates (0.2–6.4%) and the

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low employment rates (27–41%) for CFS/ME are responsible for the disease's significant social burden, with loss of productivity representing the highest cost.[2] The Centers for Disease Control and Prevention (CDC) estimated that 4–10 people per 100,000 in the United States have CFS/ME. According to the CFIDS Foundation, approximately 500,000 adults in the United States (0.3% of the population) have CFS/ME.[3]

CFS/ME should be suspected in a patient with symptoms of unexplained fatigue of a least 6 months' duration that do not substantially improve with rest. To qualify as CFS/ME, fatigue must be accompanied by 4 or more of the following symptoms: impaired short-term memory and concentration; sore throat; painful cervical or axillary nodes; muscle pain; oligoarthralgias without signs of inflammation; headache of a new type, pattern, or severity; nonrestorative sleep; and postexertional malaise (PEM) lasting more than 24 hours. In combination, all these symptoms must produce severe functional impairment, as proposed in the CDC/Fukuda case definition.[4]

In 2003, a new clinical working case definition for ME/CFS (also called 2003 Canadian Consensus Criteria) was proposed in the Canadian Consensus document, which excluded psychiatric cases.[5] This new definition is a useful complement to the 1994 CDC/Fukuda definition and allows a clinical diagnosis through common clusters of symptoms (muscular, cognitive, neurological, autonomic, and immune manifestations) and comorbid entities.

CFS/ME has been associated with various comorbid entities including sicca syndrome, myofascial pain syndrome, anxiety/depression, plantar fasciitis, degenerative or mechanical spinal disease or tendinitis of the shoulder, and fibromyalgia (FMS).[6] Comorbidities may lead to a delay in diagnosis, may be confounding factors in the analysis of the clinical status and disease progression, and may also increase morbidity and mortality in these patients.[7]

In a recent study on the effect of FMS in patients with CFS/ME, our group found that this comorbidity was present in more than 50% of cases, determining a specific clinical profile and negatively affecting patients' quality of life.[8]

Prior studies may have mistakenly excluded individuals with these distinct comorbid illnesses, leading to delayed or conflicting diagnoses, contradictory treatments, suboptimal care, and inappropriate health care utilization. There is now an urgent need to define cellular and molecular pathomechanisms for targeted treatments able to distinguish between CFS/ME alone, CFS/ME with comorbid illness, and even other chronic fatiguing conditions. Against this background, and given the importance of performing a comprehensive multisystemic assessment of patients with CFS/ME, we designed the present study with the following objectives: (1) to assess the estimated prevalence of comorbidities in a large cohort of Spanish patients with CFS/ME and (2) to identify the differential characteristics of CFS/ME subsets who have comorbid illnesses.

METHODS

Study Population

Applying both the 1994 CDC/Fukuda definition[4] and 2003 Canadian Criteria,[5] a total of 1757 white patients from different geographical areas in Spain were referred to a single outpatient tertiary referral center (CFS/ME Unit, Vall d'Hebron University Hospital, Barcelona, Spain) with a diagnosis of CFS/ME between 2008 and 2015.

Patients were included in this nationwide cross-sectional retrospective cohort study at the time of diagnosis. Most were referrals with compatible clinical findings from primary or specialist care services from all over Spain, but primarily from Catalonia. Interviews were conducted by clinicians with experience in diagnosing the condition. Informed written consent was obtained from all participants before enrollment. The study was approved by the local Institutional Review Board and Clinical Research Ethics Committee. Clinical outcomes and sociodemographic data (age, sex, onset time and duration of fatigue and pain, marital status, occupation, employment status, and educational level) were recorded for each patient.

Patients were asked about the characteristics of symptoms, such as fatigue, chronic pain, sleep hygiene, and chronic headache (time of onset, course, and time of evolution). After verifying the CFS/ME diagnosis, all patients were evaluated by the Structural Clinical Interview DSM-IV-TR[9] to complete a comprehensive assessment for psychiatric conditions.

In case of any doubt, SCID-I and -II were administered by a specialist.[10]

Measures of Symptom Assessment

Fatigue and quality of life were scored through validated, self-administered questionnaires, using the Fatigue Impact Scale (FIS 40)[11] and the Short-Form-36 Health Survey (SF-36),[12] respectively.

The FIS 40, a 40-item questionnaire that includes 3 subscales of the perceived effect of fatigue: cognitive fatigue (10 items), physical fatigue (10 items), and psychosocial function (20 items), scoring each item from 0 (no fatigue) to 4 (severe fatigue). The total score is calculated by adding together responses from the 40 questions (range: 0–160). Higher scores indicate more functional limitations due to fatigue.

The SF-36 Health Survey questionnaire, a generic scale that provides a health status profile, was used to assess quality of life. The SF-36 comprises 36 questions that explore 8 dimensions of health status (physical function, role limitations due to physical health, bodily pain, general health, vitality, social functioning, emotional role, and mental health) and also 2 general subscales covering the physical and mental health domains.

Comorbid Illness Measures

A cluster analysis based on baseline clinical variables was performed to classify CFS/ME patients in 5 categories according to comorbidities. A multivariate logistic regression analysis was conducted adjusting for potential confounding effects such as age and sex; response and categorical predictor variables were also assessed.

The presence of comorbid conditions was evaluated as follows. FMS was defined according to the 1990 ACR criteria[13]; myofascial syndrome was defined as pain, stiffness, and claudication of the temporomandibular joint.[14] Sicca syndrome was defined as the presence of dry mouth and dry eyes demonstrated by the Schirmer test[15]; Hashimoto thyroiditis was diagnosed based on a combination of clinical features, presence of serum antithyroperoxidase (anti-TPO) antibody, and appearance on thyroid sonogram.[16] Endometriosis was diagnosed using a gold standard test during laparoscopy and confirmed by taking endometrial biopsies for histological examination.[17] Multiple chemical hypersensitivity was diagnosed according to the 1990 consensus statement recommendations.[18] Ligamentous hyperlaxity (LHL) was based on revised 1998 Brighton criteria for the diagnosis of benign joint hypermobility syndrome.[19] Current anxiety, depressive, and personality disorders were clinically evaluated using the criteria defined in the DSM-IV-TR.[9]

Shoulder tendinopathy was assessed according to patient symptom history and ultrasound scan[20]; degenerative or mechanical spinal disease was diagnosed based on patients' history, physical examination, and an magnetic resonance imaging scan, which was used if lumbar degenerative disc disease was suspected and also to rule out other potential causes of the patient's symptoms[21]; the clinical diagnosis of plantar fasciitis was based on patient history, risk factors, and physical examination findings[22]; and epicondylitis was diagnosed by a physical examination and in some cases by tests such as X-ray, magnetic resonance imaging scan, or electromyography.[23] Currently, there is no consensus reference standard for the diagnosis of carpal tunnel syndrome, so a combination of symptoms, clinical findings, and electrophysiological testing was used.[24] Hypercholesterolemia (also called dyslipidemia) and hypovitaminosis D were defined as total blood cholesterol levels of 240 mg/dL (6.2 mmole/L) or above[25] and vitamin D insufficiency status by serum 25-OH-vitamin D levels less than 20 ng/mL.[26] Both total cholesterol levels and 25-OH-Vitamin D concentration in blood were measured at the local core laboratory.

Statistical Analysis

A descriptive analysis of the sample was performed using absolute and relative frequencies in the case of categorical variables and measures of central tendency and dispersion in the case of continuous variables. A classification analysis by hierarchical clusters was performed using the Ward method to classify patients with CFS/ME according to their comorbidities. To verify the relationship between the categorical variables and each cluster, a chi-square test was performed, and in the case of continuous variables, a nonparametric Kruskal-Wallis test was performed for independent samples. Type I (alpha) error was set at 5%. Statistical analysis was performed using R software (The R Foundation for Statistical Computing).

TABLE 1. Baseline Sociodemographic and Clinical Features Among the 1757 Spanish CFS/ME Cohort

Measures	*n* (%)
Age	
Mean age at diagnosis (y ± SD)	47.7 ± 10.5
Sex	
Male	169 (9.6)
Female	1588 (90.4)
Marital status	
Married	1162 (66.3)
Single	324 (33.9)
Divorced/separated	224 (33.4)
Widow/er	42 (12.1)
Occupation	
Unskilled work	827 (47.1)
Skilled work	386 (22.0)
Administrative/office work	311 (17.7)
Liberal profession	70 (4.0)
Housewife	61 (3.5)
Education/teaching	45 (2.6)
Student	26 (1.5)
Self-employed	18 (1.0)
Arts and crafts	12 (0.7)
Employment status	
Unemployed	1103 (62.8)
Employed	450 (25.6)
Never worked	204 (11.6)
Level of studies[a]	
Primary	350 (19.9)
Secondary	312 (17.8)
Preuniversity/vocational training	675 (38.4)
University graduate	377 (21.5)
Literate	14 (0.8)
Clinical features	
Onset time of fatigue (y ± SD)	37.7 ± 10.7
Onset time of pain (y ± SD)	37.5 ± 10.6
Duration of fatigue (mo ± SD)	128.7 ± 10.4
Duration of pain (mo ± SD)	121.2 ± 10.1
Nonrestorative sleep	1732 (98.6)
Superficial sleep	1309 (74.5)
Nightmares	835 (47.5)
Insomnia	1291 (73.5)
Chronic headache	1509 (85.9)

Data are expressed as mean ± SD for continuous variables, and as numbers of cases (percentages) for categorical variables.

[a] These items do not add up to the total population ($n = 1757$) because of missing values.

RESULTS

A total of 1757 patients with CFS/ME, predominantly women (90.4%), were included. Table 1 shows the main sociodemographic data and clinical findings of the study population. Mean age at diagnosis was 47.7 ± 10.5 years (range: 10–80 years). Two-thirds (66.3%) of participants were married, 47.1% were unskilled workers, and at the time of inclusion in the study 62.8% were unemployed. The mean age of onset of fatigue was 37.7 ± 10.7 years, mean age of onset of pain 37.5 ± 10.6 years, and mean durations of fatigue and pain were 128.7 ± 10.4 and 121.1 ± 10.1 months, respectively. Recurrent headache was reported by 85.9% of subjects, nonrestorative sleep by 98.6%, superficial sleep by 74.5%, and nightmares and insomnia by 47.5% and 73.5%, respectively.

Table 2 shows the absolute values and the percentages of common cluster of symptoms (2003 Canadian Consensus Criteria) of the participants. The 2 symptoms found to be most prevalent were cognitive (81.7%) and neurological disturbances (79.5%), followed closely by muscular symptoms (75%). However, autonomic dysfunction and immune disturbances were present only in 62.8% and 42.9%, respectively.

The distribution of patients according to cluster analysis is shown in Tables 3 and 4.

Cluster 1 comprised comorbidities characterized by pain, such as FMS, myofascial syndrome, and epicondylitis; immune phenomena such as sicca syndrome and thyroiditis; and multiple chemical hypersensitivity.

Cluster 2 showed higher prevalence of LHL, psychopathological domains, endometriosis, and decreased vitamin D. These 2 previous subgroups were composed mainly by older women with elementary level of education, not in employment, who presented with high levels of fatigue and poor quality of life.

Cluster 3, with a very low presence of comorbidity, included relatively younger women, with university studies and in employment, with lower levels of fatigue and better quality of life.

Cluster 4 that included patients with poorly defined comorbidities (some comorbidity from each group though, without any that stands out).

Cluster 5, the main comorbidity was the metabolic syndrome, in the form of dyslipidemia.

The most salient results are the presence of sicca syndrome, psychopathology, ligamentous alterations, and subcutaneous tissue in more than 80% of patients. Cluster analysis classified our patients into 5

TABLE 2. Prevalence of Symptoms in 1757 Spanish CFS/ME Subjects Based on the 2003 Canadian Criteria

Symptoms clinical	Manifestations	*n* (%)
Muscular	Fatigue or postexertional malaise or both	1738 (98.9)
	Muscle weakness	1711 (97.4)
	Generalized chronic pain	1582 (90.0)
	Marked muscle contractures	1569 (89.3)
	Difficulty performing fine movements due to pain	1538 (87.5)
	Myoclonic	706 (40.2)
	Falls due to loss of tone	386 (22.0)
Cognitive	Concentration impairments	1689 (96.1)
	Alterations in short-term memory consolidation	1652 (94.0)
	Difficulty reading	1614 (91.9)
	Difficulty with information processing	1566 (89.1)
	Episodes of nominal aphasia	1518 (86.4)
	Alterations during task planning	1513 (86.1)
	Confusion and forgetfulness	1498 (85.3)
	Temporospatial disorientation	1252 (71.3)
	Auditory and visual agnosia	620 (35.3)
Neurological	Sensorial hypersensitivity	1592 (90.6)
	Noise	1359 (85.4)
	Light	1190 (74.7)
	Ataxia or dissymmetry or both	1373 (78.1)
	Visual alterations	1229 (69.9)
	Blurred vision	1093 (88.9)
	Flashing lights	642 (52.2)
	Amaurosis	191 (15.5)
Autonomic	Dizziness or cephalic instability	1457 (82.9)
	Episodes of orthostatic hypotension	1384 (78.8)
	Motor incoordination, with or without falls	1345 (76.6)
	Vertigo	1343 (76.4)
	Frequent palpitations	1315 (74.8)
	Difficulties in visual accommodation	1313 (74.7)
	Reduced libido/anorgasmia/impotence	1284 (73.1)
	Intestinal dysbiosis/irritable bowel syndrome	1252 (71.3)
	Profuse sweating	1201 (68.4)
	Alterations in urination	996 (56.7)
	Tremors	757 (43.1)
	Collapse due to loss of postural tone	433 (24.6)
	Syncope	261 (14.9)
Immune	Migratory arthralgias	1500 (85.4)
	Generalized morning numbness	1409 (80.2)
	Recurrent fever	1271 (72.3)
	Recurrent sore throat	1269 (72.2)
	Painful lymph nodes	997 (56.7)
	Mouth ulcers	943 (53.7)
	Herpes	866 (49.3)
	Candidiasis	637 (36.3)
	Raynaud phenomenon	550 (31.3)
	Allergy to multiple medications	415 (23.6)
	Allergy to multiple metals	248 (14.1)
	Intolerance of food	187 (10.6)
	History of sinusitis	158 (9.0)
	Facial swelling	102 (5.8)

Data are shown as number of cases (percentages).

TABLE 3. Estimated Prevalence of Comorbid Illnesses According to Cluster Analysis

Comorbidity	Clusters				
	G1 ($n = 320$)	G2 ($n = 220$)	G3 ($n = 415$)	G4 ($n = 318$)	G5 ($n = 455$)
Fibromyalgia	91.3	82.3	26.0	46.9	60.9
Myofascial pain syndrome	92.8	89.5	40.0	72.6	64.6
Sicca syndrome	95.3	90.0	49.6	86.5	89.2
Degenerative or mechanical spinal disease	85.6	86.4	30.4	39.0	55.2
Shoulder tendinopathy	96.3	97.7	17.6	89.6	26.2
Epicondylitis	90.0	88.6	5.1	82.7	5.3
Carpal tunnel syndrome	12.8	72.7	2.7	21.1	8.8
Plantar fasciitis	70.9	85.9	19.8	46.2	45.1
Hypovitaminosis D	11.6	28.6	7.0	9.4	13.6
Hypercholesterolemia	45.3	57.3	10.6	36.8	60.4
Multiple chemical sensitivity	71.6	37.7	14.2	20.4	24.8
Dysthymia	5.3	38.6	9.9	4.1	22.9
Panic disorder	4.1	41.4	9.9	8.2	20.0
Anxiety disorder	88.1	94.1	41.9	69.8	75.4
Personality disorder	1.3	13.2	1.9	3.5	6.6
Ligamentous hyperlaxity	46.3	49.1	15.9	31.1	25.7
Endometriosis	6.3	11.8	2.9	2.8	2.9
Hypothyroidism/Hashimoto thyroiditis	26.9	11.4	9.9	19.5	17.8

Data are expressed as percentages for each cluster.

independent groups according to the comorbidities studied. Group 1 comprised 18.2% of patients; group 2, 12.5%; group 3, 23.6%; group 4, 18.1%; and group 5, 25.9%.

DISCUSSION

In this large cohort of Spanish patients with CFS/ME, a high proportion (more than 80%) presented with associated comorbidities. These results are consistent with previous reports[27] but present a higher incidence than others.[28] These variation may be due to differences in the diagnostic criteria used and in the origin of the patients (i.e., referred from either primary setting or specialist care). Nevertheless, our results suggest that comorbidities play a major part in the functional limitations, which are entailed by CFS/ME and which prevent a high percentage of patients from carrying out their work or their studies in an effective manner.[29]

Collin et al.[30] analyzed a large UK CFS/ME adult cohort and noted that there is heterogeneity in symptom-based phenotypes. In this report, we conducted a formal cluster analysis that detected 5 different CFS/ME subgroups according to symptoms.

Let us look at each group or cluster of comorbid phenomena in more detail. Subgroup 1 comprises comorbidities characterized by pain, such as FMS, myofacial syndrome, and epicondylitis; immune phenomena such as sicca syndrome; and multiple chemical hypersensitivity.

In relation to the phenomenon of pain, recurrent headache is included as a minor criterion in all the diagnostic/clinical definitions for CFS/ME; another working group[31] reported a higher prevalence of migraine with or without aura in CFS/ME subjects. FMS is an important comorbidity in view of its frequency (57% in our cohort) and its relationship to sex, as our group has reported in previous work.[32,8] We regard the distinction between FMS and CFS/ME as important, especially after the recent description of the new criteria for FMS currently awaiting validation,[33] which eliminate tender points and include the presence of an important group of symptoms such as sleep disorders and neurological and autonomic symptoms. In line with our results, Rusu et al.[34] demonstrated the relationship with sex in the comorbidity of FMS and CFS/ME, finding that the co-occurrence of the 2 entities was more prevalent in women of more advanced age and with greater limitations on their professional, social, and personal activities. Temporomandibular disorder was present in 67% of our cohort,

TABLE 4. Distribution of Sociodemographic and Clinical Features and Patient-Reported Outcome Measures Based on Cluster Analysis Among Patients With CFS/ME

	Clusters					
	G1 ($n = 320$)	**G2 ($n = 220$)**	**G3 ($n = 415$**	**G4 ($n = 318$)**	**G5 ($n = 455$)**	***P* value***
Age[a]						
Mean/SD	49.5 ± 9.4	50.6 ± 9.2	42.9 ± 11.7	48.3 ± 9.7	48.9 ± 9.7	<0.001
Sex[a]						
Male	21 (6.6)	8 (3.6)	64 (15.4)	30 (9.4)	44 (9.7)	<0.001
Female	299 (93.4)	212 (96.4)	351 (84.6)	288 (90.6)	411 (90.3)	
Marital status[a]						
Married	218 (68.3)	162 (73.6)	245 (59.6)	229 (72.0)	290 (63.7)	<0.001
Single	47 (14.7)	25 (11.4)	118 (28.7)	46 (14.5)	81 (17.8)	
Divorced/separated	45 (14.1)	26 (11.8)	43 (10.5)	34 (10.7)	72 (15.8)	
Widow/er	9 (2.8)	7 (3.2)	5 (1.2)	9 (2.8)	12 (2.6)	
Occupation[a]						
Unskilled work	189 (59.1)	116 (52.7)	144 (34.8)	164 (51.6)	201 (44.2)	<0.001
Skilled work	65 (20.3)	35 (15.9)	105 (25.4)	57 (17.9)	116 (25.5)	
Administrative/office work	57 (17.8)	37 (16.8)	79 (19.1)	57 (17.9)	73 (16.0)	
Education/teaching	4 (1.3)	3 (1.4)	14 (3.4)	13 (4.1)	11 (2.4)	
Self-employed	0 (0)	3 (1.4)	6 (1.4)	1 (0.3)	8 (1.8)	
Liberal profession	4 (1.3)	9 (4.1)	25 (6.0)	15 (4.7)	17 (3.7)	
Arts and crafts	0 (0)	3 (1.4)	7 (1.7)	0 (0)	2 (0.4)	
Student	0 (0)	1 (0.5)	20 (4.8)	0 (0)	5 (1.1)	
Housewife	1 (0.3)	13 (5.9)	14 (3.4)	11 (3.5)	22 (4.8)	
Level of studies[a]						
Primary	77 (24.1)	65 (29.5)	55 (13.3)	61 (19.2)	92 (20.2)	<0.001
Secondary	56 (17.5)	49 (22.3)	51 (12.3)	70 (22.0)	86 (18.9)	
Preuniversity/vocational training	130 (40.6)	69 (31.4)	190 (45.8)	126 (39.6)	160 (35.2)	
University graduate	56 (17.5)	32 (14.5)	117 (28.2)	60 (18.9)	112 (24.6)	
Literate	1 (0.3)	5 (2.3)	2 (0.5)	1 (0.3)	5 (1.1)	
Employment status[a]						
Employed	69 (21.6)	46 (20.9)	134 (32.3)	90 (28.3)	98 (21.5)	<0.001
Unemployed	200 (62.5)	158 (71.8)	236 (56.9)	187 (58.8)	307 (67.5)	
Never worked	51 (15.9)	16 (7.3)	45 (10.8)	41 (12.9)	50 (11.0)	
Total FIS 40 score[b]	135.5 ± 18.9	137.0 ± 18.5	121.0 ± 23.7	128.2 ± 23.6	131.1 ± 20.8	<0.001
Total SF-36 score[b]						
SF-36—Physical	24.5 ± 6.1	25.2 ± 5.6	27.0 ± 7.8	26.2 ± 7.2	25.8 ± 6.7	<0.001
SF-36—Mental	32.0 ± 12.4	29.1 ± 12.1	37.6 ± 12.6	33.2 ± 12.9	33.6 ± 13.1	<0.001

Data are expressed as mean ± SD for continuous variables, and as number of cases (percentages) for categorical variables.

[a] *P* value: chi-squared test.

[b] *P* value: Kruskal-Wallis test for independent samples.

* Statistical significance ($P < 0.005$).

a figure similar to that found in a study.[35] We believe that the coincidence in this group of comorbid entities characterized by increased pain threshold, such as CFS/ME, FMS, and temporomandibular disorder, suggests a possible common alteration in central processing mechanisms.[36]

Immune disorders, such as sicca syndrome and thyroiditis, were very frequent in this subgroup of patients with CFS/ME, reflecting the fact that immune-inflammatory phenomena are more frequent in females.[37] The presence of major immune-inflammatory disorders in tissues such

as the skin and mucous membranes in patients with CFS/ME is well known: examples are urticaria, lichen planus, atopic and seborrheic dermatitis, psoriasis, and Raynaud phenomenon (personal communication).

In our series, sicca syndrome, thyroiditis, and endometriosis were present in figures similar to those reported previously.[8,38] We also found that a high percentage of patients with immune-inflammatory processes presented with comorbid FMS. We stress the importance of the study of fatigue in immune-inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel disease.[39] In our view, this reinforces the pathogenetic hypothesis of immune abnormalities in CFS/ME, based on the (epi)-genetic susceptibility and the presence of multiple triggers during the clinical course of the illness.

The other differentiating element in the first cluster, multiple chemical hypersensitivity, was present up to 71.6 % of CFS/ME cohort, corroborating the results of previous studies.[3,40] As mentioned earlier, this finding suggests the possibility of a central sensitization mechanism. The presence of time of evolution of fatigue as a distinguishing factor supports the idea that multiple chemical hypersensitivity emerges progressively during the course of the condition.[41]

The differentiating elements in subgroup 2 were ligamentous and subcutaneous tissue alterations, LHL, psychopathological elements, endometriosis, and decreased vitamin D. Ligamentous and subcutaneous tissue alterations include ligament and intervertebral disc pathologies involving inflammatory process and were present in a higher incidence than that recorded in the age- and sex-matched healthy population.[42]

Recognition of ligament and intervertebral disc pathology has an important bearing on subsequent decisions regarding trauma and rehabilitation treatment. Together with the generalized muscular pain that characterizes CFS/ME and FMS, patients may often present with more intense pain in the shoulders, spine, feet, or hands. In the presence of these symptoms, a physical examination should be carried out along with ultrasound or magnetic resonance imaging to diagnose the specific pathology (for example, tendinopathy, intervertebral disc, or subcutaneous tissue pathology in the form of plantar fasciitis) that can then be treated by pharmacological and nonpharmacological means.

Another distinguishing element in this cluster was LHL. Several authors have noted the problem of fatigue in Ehlers-Danlos syndrome[43] and have also proposed a possible genetic connection between LHL and generalized anxiety,[44] which is a universal problem in CFS/ME and may suggest a relationship between CFS/ME, LHL, and anxiety.[6]

Regarding psychopathology, it is important to emphasize that psychiatric processes are relevant in CFS/ME; a number of primary psychiatric pathologies are exclusion criteria, and the study of psychopathology and cognitive-behavioral therapy is an important component of the evaluation of patients with CFS/ME.

In a study of 124 patients with CFS/ME,[27] 45.2% presented with psychiatric comorbidity, above all, mood disorders and anxiety. In agreement with our results, Janssens et al.[45] also found a higher prevalence of mood and anxiety disorders in patients with functional somatic syndromes, particularly CFS/ME, than in those without. These differences are probably owing to the fact that in our study the psychopathological disorders were evaluated thoroughly by a specialist, which favors their detection and the differentiation of the symptoms of CFS/ME.

In an early study of 132 patients,[46] our group found comorbid personality disorder, above all, obsessive-compulsive and avoidant disorders; patients with personality disorder had more depressive symptoms, while irritability, resentment, suspicion, and guilt were the symptoms most closely related to the total Personality Diagnostic Questionnaire-4+ (PDQ-4+) score. These results underline the fact that psychopathological disorders must be clearly and promptly identified because of their effect on quality of life and because successful treatment can help to optimize CFS/ME patient management.

Finally, vitamin D levels were lower than 20 ng/mL in 227 patients (12.9%) in this cohort (data not shown). Several authors have found a marked fall in vitamin D levels in CFS/ME[47] and have noted an improvement in fatigue and immune manifestations with oral vitamin D supplementation.[48] Among the pathomechanisms, a relationship between vitamin D levels and immune activation through NF-kB activity

has been reported, leading to dysregulation of the redox metabolism and low-grade chronic inflammation.[49]

More than 60% of cases, mainly in cluster 5, presented with hypercholesterolemia. The study by Maloney et al.[50] established that CFS/ME is a clinical process that induces metabolic syndrome (hypercholesterolemia, hypertriglyceridemia, and peripheral insulin resistance) and that early detection is vital to prevent cardiovascular complications. Early detection of metabolic syndrome in CFS/ME through a careful study of comorbidities can guide decisions regarding diet, personalized physical exercise programs, and pharmacological treatment with statins, antidiabetics, and antiaggregants to avoid complications.

The study has several noteworthy strengths and some limitations. The strong points are in the analysis of a large Spanish CFS/ME cohort recruited retrospectively at a single outpatient tertiary referral center, using both the 1994 CDC/Fukuda definition and 2003 Canadian Criteria for CFS/ME diagnosis. With such a large sample, we were able to record all the items for the study of the comorbidity clusters and the differentiation between them depending on the presence of these comorbid illnesses.

Several limitations of this study were noted. First, patients with CFS/ME were referred from a specialist outpatient clinical service that is a national reference center for the diagnosis of CFS/ME across Spain. This means that these patients may have presented with more severe fatigue, longer time of evolution of CFS/ME, and higher incidence of comorbidities than their counterparts in a primary health care setting. Second, as this was a cross-sectional measures study in which patients were included retrospectively, we could not assess their evolution over time. For this reason, we have recently initiated a longitudinal study of comorbid conditions in patients with CFS/ME.

CONCLUSIONS

In this large series of Spanish patients with CFS/ME, more than 80% of cases presented with comorbidities. Of the 5 comorbidity clusters created, subgroups 1 and 2 comprised mainly older and unemployed women with higher levels of fatigue and poor quality of life. In contrast, subgroup 3, characterized by the scarce presence of comorbidities, comprised younger employed women and with lower levels of fatigue and a higher quality of life.

These findings suggest that in the comprehensive assessment of patients with CFS/ME, together with the diagnosis and stratification of fatigue, a thorough assessment of comorbidities is mandatory in view of their specific involvement in the deterioration of the quality of life of these patients.

Future research is needed to confirm these results and to broaden our knowledge of different possible clinical subsets of patients with CFS. The temporal relationship of fatigue onset to the appearance of other comorbidities and clinical conditions should also be investigated, and the usefulness of early interventions assessed.

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