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Conditions Comorbid with Chronic Fatigue in a Population-Based Sample

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Abstract

Background—Chronic fatigue syndrome (CFS) has been found to be comorbid with various medical conditions in clinical samples, but little research has investigated CFS comorbidity in population-based samples.

Objective—This study investigated conditions concurrent with a CFS-like illness among twins in the population-based Mid-Atlantic Twin Registry (MATR), including chronic widespread pain (CWP), irritable bowel syndrome (IBS), and major depression (MD).

Method—A survey was mailed to participants in the MATR in 1999. Generalized estimating equations were used to estimate odds ratios to assess associations between CFS-like illness and each comorbid condition.

Results—A total of 4,590 completed surveys were collected. Most participants were female (86.3%); mean age was 44.7 years. Among participants with a CFS-like illness, lifetime prevalence of CWP was 41%, IBS was 16%, and MD was 57%. Participants reporting at least one of the three comorbid conditions were about 14 times more likely to have CFS-like illness than those without CWP, IBS, or MD (95% confidence interval 8.1–21.3%). Only MD showed a temporal pattern of presentation during the same year as diagnosis of CFS-like illness. Age, gender, body mass index, age at illness onset, exercise level, self-reported health status, fatigue symptoms, and personality measures did not differ between those reporting CFS-like illness with and without comorbidity.

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Conclusion—These results support findings in clinically based samples that CFS-like illness is frequently cormorbid with CWP, IBS, and/or MD. We found no evidence that CFS-like illnesses with comorbidities are clinically distinct from those without comorbidities.

Introduction

Fatigue is a non-specific, subjective feeling of physical or mental tiredness. Fatigue that lasts six months or longer is defined as chronic fatigue (1). Some degree of fatigue is a common and usually transient symptom (2–4), whereas chronic fatigue is rare (5–6) and generally associated with marked functional impairment (7–9). Notably, in clinical settings, chronic fatigue has a remarkable tendency to occur with other clinically unexplained conditions. In particular, chronic fatigue syndrome (CFS), a condition of prolonged, debilitating unexplained fatigue (7–8), is often comorbid with one or more of these conditions (10–12) as well as with certain psychiatric disorders (13). Fibromyalgia, a common form of chronic widespread pain (CWP) with musculoskeletal tender points on examination (14), is observed in 33–70% of CFS patients (15–16). Likewise, a lifetime history of major depression (MD), as diagnosed by structured diagnostic criteria, is found in up to 74% of CFS patients (15). CFS also frequently co-occurs with irritable bowel syndrome (IBS) (7, 17). The literature on non-clinical samples is less complete but suggests that some of these comorbid conditions co-occur with CFS in community samples (18–20).

This strong degree of phenotypic comorbidity has indicated to some authors that CFS is not a distinct diagnostic entity. For example, it has been suggested that CFS is a *forme fruste* of more established conditions such as major depression (13). Others have proposed a more inclusive nosology of unexplained clinical conditions that considers CFS, fibromyalgia, IBS, multiple chemical sensitivity, and other related conditions as manifestations of a similar underlying process (11–12, 21), raising the issue of whether it is necessary to establish distinct case definitions for these disorders (22). Multiple investigations have found evidence for high rates of co-occurrence between CFS and pain related disorders in particular, specifically fibromyalgia and chronic widespread pain (20, 23–25). These investigations further demonstrated that individuals reporting increasing co-morbidity concomitantly reported greater mental fatigue (23) or anxiety and depression (20), but problematically, the temporality of these conditions was not assessed. Yet another line of argument suggests that, because the co-occurrence of CFS with other unexplained clinical conditions has been primarily described in highly selected clinical samples, referral and diagnostic biases could have resulted in spurious associations that do not exist in the community (26–27).

To better understand the pattern of conditions that are comorbid with CFS illness in the community, we conducted an epidemiological investigation in a U.S. population-based twin registry. We surveyed more than 4,500 participants for self-reported chronic and debilitating fatigue of unknown etiology (CFS-like illness), CWP, IBS, and symptoms of lifetime MD. Our goals were to: 1) determine if CFS-like illness and selected unexplained clinical conditions co-occur, 2) describe the temporal sequence of onset of CFS-like and comorbid conditions, and 3) compare the demographic and personal characteristics of people who reported CFS-like illness both with and without comorbid conditions.

Methods

Sample

All potential participants were members of the Mid-Atlantic Twin Registry (28), a population-based registry of twin pairs ascertained from birth and school system records of Virginia, North Carolina, and South Carolina. Although statistical analyses conducted in the

current study were not based on twin status, this registry was used because it is a large, well-described sample that allowed for the investigation of our primary outcomes of interest. The study protocol was reviewed and approved by the Institutional Review Boards of Virginia Commonwealth University, the University of Washington, and the University of North Carolina, and by the for-profit Western Institutional Review Board. All participants provided written informed consent.

Procedures

We mailed a survey to approximately 15,000 individual participants in the Mid-Atlantic Twin Registry in the last quarter of 1999 and received 4,590 responses, for a response rate of 31%. This response rate is a minimum, as the percentage of individuals who were mailed but never received the survey because of incorrect addresses is unknown. Shortly after the initial mailing, all human subjects research at Virginia Commonwealth University was halted by the US Department of Health and Human Services Office for Human Research Protections because of concerns about human subjects protection procedures at Virginia Commonwealth University (29–30). This shutdown, which was not directly related to the ethicality of the study reported here, lasted for more than one year and led to the early termination of this study. As a result, available data were limited to early responders to the survey, because the planned repeat mailings, non-responder telephone follow-up, and clinical evaluation were not conducted. An additional consequence was that zygosity data were available only for a minority of participants.

Fatigue Measures

Participants completed a questionnaire that captured the lifetime presence of fatiguing illnesses, patterned on the Centers for Disease Control and Prevention 1994 (hereafter CDC-94) criteria (1). “Any lifetime fatigue” was considered to be present when participants endorsed a “Yes” response to one of the following four stem questions: substantial lack of energy, extreme tiredness, fatigue, or exhaustion. If subjects reported experiencing any of these symptoms at any point in their lives, they were asked additional questions classified into three domains: (a) degree of social and occupational impairment (i.e., fatigue that caused a substantial reduction in work, school, social, or personal activities); (b) eight additional ancillary symptoms fundamental to the CDC-94 criteria for CFS (sore throat; tender glands; muscle aches or muscle pain; painful joints that were not red or swollen; sleep that was not refreshing; severe headaches; forgetfulness or memory problems; and worse fatigue lasting more than 24 hours after physical activity), and (c) temporality of the disorder (i.e., age of onset, duration, and age of offset).

With reference to the CDC-94 criteria, we defined “chronic fatigue” as experiencing at least one of the symptoms enumerated in the four stem questions for six or more months. We defined “CFS-like illness,” the category of fatigue that was of primary interest for our study, as chronic fatigue plus (a) the presence of impairment, (b) an endorsement of at least four of the eight ancillary symptoms (1), and (c) the absence of exclusionary conditions. Exclusionaryconditions were self-reported and included morbid obesity and other medical conditions that could explain fatigue, such as epilepsy, cancer, or inflammatory bowel disease. Body mass index was derived from self-reported height and weight (kg/m^2) and classified according to World Health Organization guidelines (less than 24.9 = normal, 25.0–29.9 = overweight, 30.0 or more = obese) (31). A body mass index of 40 kg/m^2 or more was considered exclusionary (1).

To assess the validity of our questionnaire, we conducted a pilot study at the University of Washington Chronic Fatigue Clinic to examine its sensitivity and specificity in patients with and without CFS. The questionnaire was administered to 40 clinic patients with physician-

diagnosed CFS, 20 patients with viral hepatitis from another clinic within the same hospital, and 21 non-patient controls who denied any fatigue or other medical or psychiatric conditions. The sensitivity of the questionnaire among CFS patients was 72.5%, and its specificity among patients with viral hepatitis and healthy control participants was 85% and 100%, respectively. These results suggest that a self-reported assessment of the CFS symptom criteria alone is good at identifying true positive cases and extremely good at identifying true negatives.

Comorbidity Measures

The comorbid conditions assessed in the mailed survey were CWP, IBS, and MD. Lifetime CWP was based on the American College of Rheumatology criteria for fibromyalgia (e.g., respondents indicated “Yes” or “No” to questions assessing the experience of pain in muscles, joints, or bones for two weeks or more) (14). Lifetime IBS was defined according to the Rome II criteria (e.g., respondents indicated “Yes” or “No” to questions assessing the experience of pain or discomfort in their lower abdomen for at least three months) (32). MD was determined by a questionnaire (33–34) based on the DSM-IV-R criteria (35). As discussed in greater detail elsewhere (33–34) respondents were asked to respond to 12 items assessing MD (as “Yes,” “Maybe,” or “No”), with a minimum two-week duration of depression-related symptoms. An algorithm was then applied to these responses to categorize individuals as having MD. Questions measuring duration, onset, and offset of CWP, IBS, and MD-related symptoms were also assessed.

Other Measures

To assess functional status, we used the physical and mental health subscales of the Short Form-12 (36), a widely used assessment of health-related quality of life. Values for the continuous Short Form-12 summary subscale scores range from 0 to 100, with higher values reflecting better health. Levels of exercise were obtained by asking participants the number of times per week they exercised vigorously for at least 20 minutes. Personality dimensions of neuroticism and extraversion were derived from the Eysenck Personality Questionnaire (37) and were standardized after adjusting for the effects of age and gender.

Statistical Analyses

Analyses were conducted with SAS Version 9.1 (38). Odds ratios (OR) and 95% confidence intervals (CI) were calculated as measures of association between CFS-like illness status and each comorbidity. To examine categorical and continuous variables, we used linear and logistic regression models, respectively. Data for twins within a pair are inherently correlated, thus all regression analyses were conducted using robust generalized estimating equations (GEE) that statistically adjusts the standard error estimates to account for the non-independence of twins (39). Because estimates were not made based upon twin status, monozygotic and dizygotic twins are not treated differently, and accurate estimates can be obtained using GEE without reference to zygosity status. We also examined whether the associations between CFS-like illness and each comorbid condition differed by gender. As no appreciable differences were observed between genders, we present results for males and females combined.

To evaluate the temporal sequence of onset of CFS-like illness and the three comorbid conditions, we conducted an analysis among participants who reported both CFS-like illness and at least one comorbid condition. We compared the proportions of participants who: developed a CFS-like illness first; developed a CFS-like illness and a comorbid condition in the same year; and developed a comorbidity first. We report p-values from χ^2 tests that compared proportions of respondents in each group without respect to twin status, since this analysis included only one twin pair.

Next, among participants who reported CFS-like illness, we compared those with comorbidities to those without. Again, GEE was used to account for non-independence of twins within a pair (39). Least squares means and standard errors are presented for continuous variables and frequencies. ORs and 95% CIs are presented for categorical variables.

Results

Data on 4,590 individuals from the MATR were available for this analysis; 64.7% were females, whose mean age at interview was slightly younger than that of the males (42.2 ± 9.5 years vs. 44.4 ± 9.5 years). Only 16.6% of participants were members of twin pairs in which both twins participated; the remainder were singletons.

Of the 4,590 participants, 123 (2.7%) reported lifetime CFS-like illness. The mean age of those with CFS-like illness was 42.9 ± 9.0 years and 85.4% were female. Almost 83% of participants with CFS-like illness reported at least one comorbid condition (Table 1). Among participants with CFS-like illness, the prevalence of lifetime CWP was 41%, lifetime IBS was 16%, and lifetime MD was 57%. Participants reporting at least one of the three comorbid conditions were about 14 times more likely to have CFS-like illness than those without CWP, IBS, or MD (95% CI 8.1–21.3%). In the fully adjusted model, participants who reported lifetime CWP were over six times more likely to have CFS-like illness than those without CWP (95% CI 4.2–10.0%). Participants with lifetime MD symptoms were over four times more likely to have a CFS-like illness than non-depressed participants (95% CI 2.9–6.6%). After accounting for MD and IBS, CWP was most strongly associated with CFS-like illness.

Among participants with a CFS-like illness and CWP or IBS, there was no distinctive pattern of timing of onset (Table 2). However, CFS-like illness and MD most frequently presented in the same year.

Finally, as shown in Table 3, participants who reported CFS-like illness with and without comorbid conditions did not differ in demographic and personal characteristics, including gender; body mass index; physical health, mental health, neuroticism, and extraversion subscale scores; and age at onset of CFS-like illness.

Discussion

In this population-based study, we found that the prevalence of self-reported CWP, IBS, and MD was relatively high among participants with a history of lifetime CFS-like illness. The association of CFS-like illness with an additional comorbid diagnosis was strongest for CWP, intermediate for MD, and weakest for IBS. Notably, about 83% of participants with a CFS-like illness had at least one of the three comorbid conditions examined. As our findings in this population-based sample were consistent with those from clinically ascertained samples (15–16), the strong tendency of CFS-like illness to co-occur with these other conditions is unlikely to be an artifact of clinical ascertainment.

An association between two disorders can result from causal processes or from multiple non-causal processes, such as chance, bias, confounding, and effect-cause associations. One reason for non-causal associations is overlap in diagnostic criteria (10). We cannot exclude such overlap as an explanation for our findings. In this regard, we note that muscle pain is a component of the definitions of both CFS-like illness (1) and CWP (14), and that fatigue is part of the definitions of both CFS-like illness (1) and MD (35). However, the strength of the associations between CFS-like illness and CWP and MD in particular suggests that these are not chance findings.

The temporal sequence in which events occur can provide a hint as to which is the primary and which are subsequent events. There was a significant tendency for the onsets of CFS-like illness and MD to occur in the same year. Other than this intriguing suggestion of a temporally close (but causally indeterminate) relation between CFS-like illness and MD, the patterns of onset did not provide any strong evidence of temporality.

We also assessed whether individuals reporting CFS-like illness with and without comorbidity differed in any clinically meaningful ways and found no significant associations. Of the 123 individuals with CFS-like illness, 83% had at least one comorbid condition, while 17% had none. The personality construct of emotional instability (traditionally referred to as “neuroticism”) may be a prospective predictor of CFS-like illness (40), because we did find a trend, albeit non-significant, toward higher neuroticism in individuals with comorbid CFS-like illness. Apart from neuroticism, none of the tested variables appeared to distinguish the two groups. This finding provides some evidence that CFS-like illnesses with and without comorbidities are not clinically or etiologically distinct entities. Nevertheless, as the number of subjects with CFS-like illness but without comorbidities was small, our finding must be replicated in larger samples.

This study has several noteworthy limitations. First, it is possible that the observed associations could have resulted from several possible sources of bias. Our scientific aims were thwarted by the lengthy suspension of human subjects research activities at Virginia Commonwealth University (29–30), a development that hindered our ability to minimize response bias. It also prevented us from using the twin sample to its full capacity to conduct twin analyses. Second, because our assessments were based solely on questionnaires, our findings are subject to self-report biases, including poor recall of temporal data. It is reassuring, however, that the prevalences and associations reported here are similar to those previously reported in the literature. Third, we could not verify any health data or conduct tender point examinations to assess CWP, so that some participants may have been misclassified. Finally, as our data were cross-sectional, we could not address the etiology of fatiguing illnesses.

Despite the qualified nature of our findings, we argue that, given the relative paucity of data on chronically fatiguing illnesses, these results from a community-based sample have substantial relevance to the field. They reinforce prior findings that CFS-like illness frequently co-occurs with a range of other disorders. Because CFS-like illness without comorbidities is actually rare, researchers and clinicians can anticipate substantial complexity in their studies and clinical care. In particular, research that does not exclude patients with comorbidities would be most relevant to clinicians.

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Table 1

Adjusted odds ratios and 95% confidence intervals describing associations between comorbid conditions and CFS-like illness.

Comorbid Conditions	CFS-like illness present (n=123, 3%) n (%)	CFS-like illness absent (n=4467, 97%) n (%)	OR[1] (95% CI) Adjusted for age and sex	OR[2] (95% CI) Adjusted for age, sex, other comorbidities
Lifetime history of CWP				
Yes	50 (41)	314 (7)	9.1 (6.3–12.5)	6.7 (4.2–10.0)
No	73 (59)	4140 (93)	1.0	1.0
Lifetime history of IBS				
Yes	20 (16)	220 (5)	3.3 (2.0–5.6)	1.7 (1.0–3.1)
No	103 (84)	4204 (95)	1.0	1.0
Lifetime history of MD				
Yes	69 (57)	797 (18)	5.3 (3.7–7.7)	4.4 (2.9–6.6)
No	53 (43)	3638 (82)	1.0	1.0
Any comorbidity[3]				
Yes	102 (83)	1131 (26)	14.3 (8.1–21.3)	-[4]
No	21 (17)	3279 (74)	1.0	

Abbreviations: CI = confidence interval; CFS = chronic fatigue syndrome; CWP = chronic widespread pain; IBS = irritable bowel syndrome; MD = major depression; OR = odds ratio

[1] ORs describe the association between each comorbid condition and chronic fatigue-like illness, adjusted for age and sex, and after taking into account relatedness of twin pairs.

[2] ORs describe associations between each comorbid condition and chronic fatigue-like illness, adjusted for age, sex, and the remaining 2 comorbid conditions.

[3] "Any comorbidity" describes participants who reported that they experienced CWP, IBS, or MD in their lifetime.

[4] A fully-adjusted OR is not presented, as each comorbid condition is already represented in the definition of the "Any comorbidity" variable.

Table 2

Temporal sequences of onset of CFS-like illness and comorbid conditions.

Conditions	Onset of fatigue earlier n (%)	Onset in same year n (%)	Onset of fatigue later n (%)	p-value[1]
CFS-like illness and CWP	12 (24)	21 (43)	16 (33)	p=0.29
CFS-like illness and IBS	5 (31)	3 (19)	8 (50)	p=0.31
CFS-like illness and MD	13 (19)	36 (53)	19 (28)	p=0.002

Abbreviations: CFS = chronic fatigue syndrome; CWP = chronic widespread pain; IBS = irritable bowel syndrome; MD = major depression

[1] p-values are derived from χ^2 tests that compared the proportions of participants who reported their age at the onset of CFS-like illness in an earlier year than that of the onset of the comorbidity to the proportions who reported their age at onset in the same year as or in a later year than the comorbidity. No adjustments for twin status were made, as only one twin pair was included in this portion of the analysis.

Table 3

Distributions of participant characteristics by comorbidity status.

Variable	CFS-like illness with any comorbidity	CFS-like illness without comorbidity	Adjusted OR[1] (95% CI)
Categorical	***n (%)***	***n (%)***	***n (%)***
Gender			
Males	14 (13.7)	4 (19.0)	0.61 (0.17–2.2)
Females	88 (86.3)	17 (81.0)	1.0
Vigorous exercise			
Never	49 (49.0)	10 (47.6)	1.0
1/week	32 (32.0)	5 (23.8)	1.46 (0.41–5.20)
2–3 times/week	15 (15.0)	5 (23.8)	0.70 (0.21–2.38)
4 or more times/week	4 (4.0)	1 (4.8)	0.84 (0.08–9.15)
Body mass index (kg/m^2)			
Normal, ≤ 24.9	35 (35.7)	9 (42.9)	1.0
Overweight, 25.0–29.9	38 (38.8)	7 (33.3)	1.21 (0.36–4.10)
Obese, ≥ 30.0	25 (25.5)	5 (23.8)	1.42 (0.47–4.28)
Continuous	***LS Mean (SE)*** [2]	***LS Mean (SE)***	***p-value***
Age at interview	44.75 (1.13)	44.73 (1.13)	0.83
Short Form-12			
Mental Health Score	43.97 (1.64)	50.05 (2.76)	0.28
Physical Health Score	46.65 (1.88)	45.06 (3.18)	0.72
Age at fatigue onset, mean years	31.9 (1.03)	29.9 (1.73)	0.46
Number of fatiguing symptoms	5.06 (0.17)	4.89 (0.28)	0.67
Eysenck Personality Scores[3]			
Neuroticism	0.88 (0.13)	0.11 (0.20)	0.16
Extraversion	−0.26 (0.15)	−0.34 (0.25)	0.81

Abbreviations: CFS = chronic fatigue syndrome; CI = confidence interval; LS = least square; OR = odds ratio; SE = standard error

[1] ORs describe the association between each characteristic and CFS-like illness/comorbidity status, adjusted for age and gender, and after taking into account relatedness of twin pairs.

[2] For each continuous characteristic, the LS Mean and SE are presented. They were obtained from mixed models that took into account relatedness of twin pairs and were adjusted for age and gender. The p-values were derived from t-tests that describe whether the means between participants with CFS-like illness and at least one comorbidity differ from the means of participants with CFS-like illness and no comorbidities.

[3] Studentized residuals with effects of age and sex regressed out.