Published in final edited form as:

Fatigue. 2015 ; 3(3): 164–172. doi:10.1080/21641846.2015.1041336.

Variability in Symptoms Complicates Utility of Case Definitions

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Abstract

Background—Ambiguities in case definitions have created difficulties in replicating findings and estimating the prevalence rates for chronic fatigue syndrome (CFS) and Myalgic Encephalomyelitis (ME).

Purpose—The current study examined differences in occurrence rates for CFS and ME cardinal symptoms (i.e. post-exertional malaise, unrefreshing sleep, and neurocognitive deficits).

Results—Findings indicated that there is a wide range of occurrence rates on critical symptoms of the case definition, suggesting that either the types of patients recruited differ in various settings or the questions assessing core symptoms vary in their wording or criteria among different researchers.

Conclusions—The polythetic nature of the case definition may contribute to the wide ranges of symptom occurrence that was found. In order to increase assessed reliability of the symptoms and case definitions, there is a need to better standardize data collection methods and operationalization of symptoms. This solution would reduce the heterogeneity often seen in populations of CFS patients.

Keywords

chronic fatigue syndrome; myalgic encephalomyelitis; symptom occurrence; operationalization

Individuals with chronic fatigue syndrome (CFS) and Myalgic Encephalomyelitis (ME/CFS) experience a number of symptoms including persistent fatigue, sleep disturbances, memory and concentration difficulties, and an intensification of the symptom complex following activity levels (i.e., post-exertional malaise) that would have been easily tolerated prior to becoming ill. [1, 2] Over the past two decades, 20 case definitions have been developed, but they have rarely been guided by empirical methods. [3] Instead, case definitions such as the Fukuda et al. [4] and Canadian criteria [2] were developed based on consensus methods. The lack of empirically defined criteria can lead to ambiguity on how to operationalize the case definitions. This can result in difficulties estimating the prevalence of these illnesses, replicating findings across studies, and determining which treatments are helpful to patients. [5–7]

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The most frequently used CFS case definition requires individuals to have persistent or relapsing fatigue for six months or longer. In addition, four or more of eight minor symptoms must be concurrently present for six or more months. [4] However, these polythetic criteria allow for an individual to be diagnosed with CFS without having some of the core main symptoms, such as post-exertional malaise, memory/concentration problems, or unrefreshing sleep. These three symptoms are the most prevalent symptoms for CFS, and are often considered cardinal symptoms of this illness. Jason et al. [11] found that a Classification and Regression Tree algorithm identified these three symptoms as accurately classifying over 95% of participants as either patients or controls.

The presence or absence of these cardinal symptoms is contingent upon how the researchers measure them. In one study, Jason et al. [8] found that occurrence rates for unrefreshing sleep fluctuated between 68.8% and 90.0% when the question of the symptom's presence was phrased differently. In a review article, Johnston et al. [5] found that CFS prevalence rates ranged from 0.17% to 8.34% depending on how samples were recruited and whether the illness was confirmed by self-report or medical examination. It is very likely that this large range of prevalence rates is at least in part due to ambiguities in the assessment of symptoms.

In an effort to better operationalize the Fukuda et al. criteria, Reeves et al. [9] developed what has been referred to as the empiric criteria. However, using these operationalized criteria from Reeves et al. [9], Jason et al. [10] found that 38% of individuals with Major Depressive Disorder would meet the CFS criteria. If individuals with other disorders are being classified as having CFS, this would complicate the interpretations of findings from different studies.

Furthermore, it is possible that the existing disparities in various epidemiologic, etiologic, and treatment studies is a result of the variability in the way essential, core symptoms are either measured or included in case definitions. The purpose of this study is to review the literature when using the Fukuda et al. [4] criteria to determine reported differences in CFS cardinal symptom occurrence. It was hypothesized that symptom occurrence for cardinal symptoms of CFS, including post-exertional malaise, memory/concentration problems and unrefreshing sleep would be highly variable across studies, and that those within community based studies would differ from other settings.

Methods

Procedures

Article selection was completed by searching for peer-reviewed studies on CFS from January 1995 through July 2014 within the Google Scholar and PubMed databases. Searches were conducted using the phrase: "Chronic fatigue syndrome", "Myalgic Encephalomyelitis", "Myalgic Encephalomyelitis/Chronic fatigue syndrome". Some researchers are advocating for Myalgic encephalomyelitis to be a distinct diagnosis from chronic fatigue syndrome. [2,11] ME has been recognized as a separate illness by the World Health Organization (WHO) since 1969. However, the Centers for Disease Control and Prevention (CDC) do not recognize ME as being distinct from CFS. [12,13] Therefore,

patients diagnosed with the CDC Fukuda criteria may be considered to have ME according to the WHO. Since there is no current consensus, both terms were utilized in this search. [14,15]

Articles were excluded if the full-text was not available. Full-text articles were excluded if the patients were not diagnosed using the Fukuda et al. [4] case definition. This criterion was selected as it is the most frequently used case definition for CFS. Articles were excluded if they did not report occurrence rates for post-exertional malaise, unrefreshing sleep, or neurocognitive deficits. In addition, articles that reported symptom occurrence rates for a sample that had been previously reported in another article were excluded as being duplicates.

Operationalization

Post-exertional malaise (PEM) was classified as the occurrence rate for post-exertional fatigue, post-exertional malaise, and exhaustion or fatigue lasting longer than 24 hours after exertion. Neurocognitive deficits were classified as the occurrence rates of problems with concentration or impaired memory. Sleep deficits were classified as occurrence of unrefreshing sleep. Instruments used to measure symptoms during the diagnosis were included when they were reported.

Research Samples

Samples recruited from tertiary care settings may be demographically different than community samples. [16] As an example, Whiting et al. [17] found that many treatment studies required patients to be ambulatory. As a result, patients who were more severely impaired and could not physically get to the clinics were not included in the treatment trials. As a result, tertiary care samples may not generalize to the entire CFS population in the community. Therefore, sample recruitment was grouped into three categories: Primary/tertiary non-community, random community, and other. Primary/tertiary non-community samples were those that included a population that had been recruited at a primary or tertiary care setting. Random community samples were obtained through random sampling respondents of an entire community. Others involved samples that were not based on primary or tertiary care and were not a random sample (e.g., internet based).

Results

Our literature search identified 437 articles, including the 53 articles that met inclusion criteria for this study. Of these 53 articles, 43 (81.1%) were primary/tertiary non-community samples, six (11.3%) were random community samples, and four (7.6%) were other.

Symptom Occurrence

Figures 1–3 show the occurrence rates for cardinal symptoms across all 53 articles. The occurrence rate for post-exertional malaise ranged from 24.7% to 100% ($M = 84.7\%$, $SD = 17.31$). The occurrence rate for unrefreshing sleep ranged from 16% to 100% ($M = 88.6\%$, $SD = 14.66$). The occurrence rate for neurocognitive symptoms ranged from 16% to 100% ($M = 84.0\%$, $SD = 17.59$).

For the purpose of this research, Kendall's correlations were utilized to test for significant relationships between variables. This non-parametric test was chosen due to the small sample sizes and tied ranks of the occurrence rates. Post-exertional malaise was significantly correlated with neurocognitive symptoms, $\tau = .48$, 95% BCa CI $[-.106, .895]$, $p = .04$. However, there was no significant correlation between unrefreshing sleep and neurocognitive symptoms, $\tau = .26$, $p = .27$, nor between unrefreshing sleep and post-exertional malaise, $\tau = .11$, $p = .64$.

Sample Population

Table 1 illustrates data regarding symptoms from various samples. Post-exertional malaise occurrence rates with random community samples ($M = 70.3\%$, $SD = 4.0$) were significantly lower than the rates for articles with primary/tertiary non-community samples ($M = 87.8\%$, $SD = 16.1$), $U = 25.00$, $z = -2.69$, $p < 0.01$, $r = -.40$. There were no additional significant findings.

Table 2 reveals the data regarding the various forms of subjective diagnostic measures (e.g. SF-36, DePaul Symptom Questionnaire, or CDC Symptom Inventory) reportedly employed in each study. According to Table 2, the neurocognitive occurrence rates for articles using empirically validated symptom measures ($M = 80.1\%$, $SD = 13.7$), were significantly lower than articles that only reported the use of frequency or severity as a diagnostic measure ($M = 91.5\%$, $SD = 9.2$), $U = 66.50$, $z = -2.33$, $p < 0.05$, $r = -.41$. Occurrence rates for post-exertional malaise and unrefreshing sleep were not statistically significant.

Discussion

As shown in Figures 1–3, symptom occurrence for several of the core CFS Fukuda et al. [4] criteria varies considerably. Investigators are not only using different instruments to collect patient self-report data, but they are also using various threshold standards to determine if a symptom is present or not. If different severity and frequency thresholds are determining the presence of symptoms, this creates difficulties for researchers who are studying these patients. It is possible that the variation in symptoms is one of the reasons researchers experience difficulties estimating the prevalence for CFS or identifying the biomarkers consistently. Moreover, if patients who were recruited in primary/tertiary care non-community samples have higher rates of post-exertional malaise compared to those in random community samples, this would suggest additional challenges to identifying the true symptoms of patients in the CFS population, as most research in this area has been with primary/tertiary care patients.

Furthermore, the wide range of occurrence rates reported suggests comparisons across studies or findings of meta-analytic and systematic review papers may not be valid. Although the same case definition is utilized, the patients may not be comparable to one another due to differences in how the researchers operationalized the criteria or the polythetic nature of the case definition. If the studies are reporting very different occurrence rates of cardinal symptoms, it is possible their patient populations are significantly different.

As shown in Table 2, occurrence rates for neurocognitive deficits differ subject to how the symptom is operationalized. However, standardized neurocognitive measures might not be effective in assessing a number of the common symptoms of patients with neurocognitive problems, which would explain this finding. In order to address issues with reliability, it is imperative for researchers and clinicians to reach a consensus on how to effectively measure symptoms within case definitions. Varying occurrence rates for cardinal symptoms could be attributed to the differences in how each study operationalized the measurement of symptoms. Certain cardinal symptoms may be measured using objective testing. For example, it has been recommended that post-exertional malaise be measured over a two-day period. Patients would complete exercise tests 24 hours apart and both the performance levels and cognitive impairment levels are compared. [18,19] However, these patients must be ambulatory. This type of test would exclude patients that are bed-bound and more severely affected by the illness.

The use of standardized subjective questionnaires, such as the DePaul Symptom Questionnaire (DSQ), could also reduce some of the current problems. [20] Jason et al. [21] found that when frequency and severity of symptoms thresholds are low, a third of the healthy controls would meet the CFS Fukuda et al. [4] case definition. However, when the thresholds were raised and required symptoms to be present at least half the time and at a moderate severity level, only 5% of the controls met the criteria. Therefore, not only is the development for a more definitive threshold that can accurately identify the existence and frequency levels for symptoms imperative, but having the larger scientific community develop consensus on such standards is essential, as well.

Objective measures, such as maximal exercise tests, have shown to have similar sensitivity, specificity, and accuracy as the DSQ. Snell et al. [22] found maximal exercise testing could identify 96% of CFS patients and 90% of control patients. The DSQ has accurately classified 96% of patients and 93% of controls when symptoms are of moderate severity for at least half of the time [21]. This illness is consistently one of the least funded by the National Institutes of Health. [23] Thus, it may be more desirable to utilize free diagnostic measures, such as the DSQ, compared to objective testing, which often requires sophisticated equipment and multiple days of testing.

To develop a better understanding of CFS and ME and to reduce criterion variance, researchers need to come to a consensus on which symptoms to require for the case definition. There are now a number of case definitions, and some require core symptoms, whereas others like the Fukuda criteria are polythetic. As one example of differences that occur in case definitions, Brown et al. [24] found that there were significant differences in the occurrence rates of CFS symptoms for individuals diagnosed with the Fukuda et al. criteria compared to those diagnosed with the Canadian criteria. [4, 2] The polythetic nature of the case definition allows for patients to be diagnosed without cardinal symptoms. Thus, it may be necessary to develop a consensus case definition that does not have a polythetic nature.

In addition, there are many problems with operationalizing case definitions other than the Fukuda criteria. Fluge et al. [25] have found that over 90% of individuals with CFS

according to the Fukuda criteria would meet the Canadian criteria. However, Pheby et al. [26] found only half of the patients meeting the Fukuda criteria also met the Canadian criteria.

Furthermore, as researchers work on developing standards for operationalizing the measurement of symptoms, there must be recognition that there is considerable variability today in multiple case definitions. This increases the seriousness of this reliability issue. What is now essential is for an open, transparent, inclusive process for developing a consensus on the core symptoms, how to measure them and what case definition to utilize. This could be accomplished by providing support for structural capacities that set up a mechanism for ongoing data collection and interactive feedback, and a process that is vetted by broad based gatekeepers representing scientists, patients and government groups. This would reduce the occurrence variance and lead to a more homogenous patient population, which would allow future research to develop better treatment studies compared to the heterogeneous population that is currently diagnosed.

Currently, there is an effort by the National Institutes of Health's Pathways to Prevention workgroup to examine these reliability issues. [27] In addition, the Institute of Medicine will examine issues relevant to the clinical case definition. [28] It is hoped that the discussion that emerges from these two scientific bodies will continue to work towards the efforts to reduce criterion variance for the existing case definition.

Acknowledgments

Funding

Funding was provided by NIAID (Grant numbers HD072208 and AI105781).

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Figure 2.
Occurrence rates by percentage across articles for unrefreshing sleep

Figure 3.
Occurrence rates by percentage across articles for neurocognitive deficits

Table 1
Means (M), Standard Deviation (SD) and Ranges of Symptom Occurrence in Percentages by Sample Recruitment

	Sample Recruitment					
	Primary/Tertiary Care Non-Community N=43		Random Community N=6		Other N=4	
	M (SD)	Range	M (SD)	Range	M (SD)	Range
Post-Exertional Malaise	87.8 (16.1) *	24.7–100	70.3 (4.0) *	65.0–75.0	68.4 (23.4)	36.0–90.6
Unrefreshing Sleep	88.8 (15.5)	16.0–100	85.6 (11.2)	66.7–95.0	92.0 (1.0)	91.0–92.9
Neurocognitive Deficits	85.6 (17.6)	16.0–100	75.9 (16.6)	50.0–100	79.8 (15.2)	54.0–93.8

* p<0.05.

Table 2
Means (M), Standard Deviation (SD) and Ranges of Symptom Occurrence in Percentages by Diagnostic Measures

	Diagnostic Measures				
	Validated Measures N=17		Frequency or Severity N=17		Sig.
	M (SD)	Range	M (SD)	Range	
Post-Exertional Malaise	82.0 (16.4)	36.0–100	87.5 (12.1)	65.0–100	0.446
Unrefreshing Sleep	89.8 (8.9)	66.7–100	83.5 (21.7)	16.0–100	0.799
Neurocognitive Deficits	80.1 (13.7)	54.0–100	91.5 (9.2)	66.3–100	0.019