

Chronic Fatigue Syndrome: The Need for Subtypes

Journal: Neuropsychology Review, Vol. 15, No. 1, March 2005,
pp. 29-58
DOI: 10.1007/s11065-005-3588-2

Authors: Leonard A. Jason [1,4], Karina Corradi [1], Susan
Torres-Harding [1], Renee R. Taylor [2], and Caroline King [3]

Affiliations:

[1] DePaul University, Chicago, Illinois.

[2] University of Illinois at Chicago, Chicago, Illinois.

[3] Hines VA, Hines, Illinois.

[4] To whom correspondence should be addressed:

Center for Community Research, 990 W. Fullerton
Illinois 60614; e-mail: ljason@depaul.edu.

Abstract

Chronic fatigue syndrome (CFS) is an important condition confronting patients, clinicians, and researchers. This article provides information concerning the need for appropriate diagnosis of CFS subtypes.

We first review findings suggesting that CFS is best conceptualized as a separate diagnostic entity rather than as part of a unitary model of functional somatic distress. Next, research involving the case definitions of CFS is reviewed.

Findings suggest that whether a broad or more conservative case definition is employed, and whether clinic or community samples are recruited, these decisions will have a major influence in the types of patients selected.

Review of further findings suggests that subtyping individuals with CFS on sociodemographic, functional disability, viral, immune, neuroendocrine, neurology, autonomic, and genetic biomarkers can provide clarification for researchers and clinicians who encounter CFS' characteristically confusing heterogeneous symptom profiles.

Treatment studies that incorporate subtypes might be particularly helpful in better understanding the pathophysiology of CFS. This review suggests that there is a need for greater diagnostic clarity, and this might be accomplished by subgroups that integrate multiple variables including those in cognitive, emotional, and biological domains.

KEY WORDS: chronic fatigue syndrome; subtypes; immunology; neuroendocrinology.

Chronic fatigue syndrome (CFS) is an incapacitating illness affecting approximately 800,000 Americans (Jason et al., 1999f), and the annual total value of lost productivity in the United States due to this illness has been estimated to be \$9.1 billion (Reynolds et al., 2004).

Individuals with CFS have been found to differ with respect to characteristics such as the case definition utilized, psychiatric comorbidity, method of case ascertainment, functional disability, and viral, immunologic, neuroendocrine, neurology, autonomic, and genetic biomarkers (Jason et al., 2003a).

As a result of this heterogeneity, findings emerging from studies in a number of areas are, at best, discrepant, and at worst, contradictory. Heterogeneity among participant groups can also contribute to a lack of observable abnormalities in some laboratory studies (Friedberg and Jason, 1998).

There probably are different types of illnesses now contained within the CFS construct, which makes it even more difficult to identify commonalities in people with this diagnosis. This article will review the various demographic and clinical variables associated with onset, clinical expression, and severity of CFS, and then provide hypotheses regarding the identification of subtypes that emerge from the previously defined correlates.

It is important to determine which case definition to use in defining the syndrome. The benefit of classifying patients into diagnostic categories is that it facilitates communication among clinicians and researchers, selection of treatment methods, and prediction of response to treatment (King and Jason, 2004).

One of the greatest sources of diagnostic unreliability is criterion variance, differences in the formal inclusion and exclusion criteria used by clinicians to classify patients into diagnostic categories (Spitzer et al., 1975).

Which Case Definition to Use: Holmes, Fukuda, Canadian?

Currently, scientists throughout the world use the Fukuda et al. (1994) CFS case definition, which requires a person to experience six or more months of chronic fatigue of new or definite onset, that is not substantially alleviated by rest, not the result of ongoing exertion, and that results in substantial reductions in occupational, social, and personal activities.

To be diagnosed with CFS, individuals also need to have the concurrent occurrence of four or more symptoms that did not predate the illness and persisted six or more months since onset (i.e., sore throat, lymph node pain, muscle pain, joint pain, postexertional malaise, headaches of a new or different type,

memory and concentration difficulties, and unrefreshing sleep).

The article by Fukuda et al. actually called for subgrouping within the identified group of individuals with CFS, thus suggesting an awareness that a heterogeneous group was being identified.

Unlike the first CFS criteria published by Holmes et al. (1988) (as specified by the Schluederberg et al., 1992 revision), the presence of anxiety disorders, somatoform disorders, and nonpsychotic or nonmelancholic depression prior to CFS onset does not constitute exclusionary conditions under the Fukuda et al. (1994) definition.

In addition, the Fukuda et al. criteria require the concurrent occurrence of at least four of eight symptoms (sore throat, muscle pain, etc.), as compared with eight or more required by the prior Holmes et al. (1988) CFS criteria. Jason et al. (2001e) compared the Fukuda and Holmes criteria and found that the Holmes criteria did select a group of patients with higher symptomatology and functional impairment.

More restrictive or more liberal criteria clearly have an effect on who is classified as having CFS but these different definitions also pose difficulties in interpreting results of related studies. For example, Komaroff and associates (1996) compared patients meeting the major criteria of the original U.S. CFS case definition (Holmes et al., 1988) with healthy controls and groups with multiple sclerosis and depression (91% of this sample met the CFS case definition). They concluded that eliminating muscle weakness, arthralgias, and sleep disturbance, and adding anorexia and nausea would strengthen the case definition.

In contrast, using the Fukuda et al. (1994) criteria, Jason et al. (2002c) compared individuals with CFS, melancholic depression, and controls, and in contrast to the Komaroff study, muscle weakness and arthralgias were reported in over half of participants with CFS and uniquely differentiated this group from controls. Jason et al. (2002c) also found that anorexia and nausea occurred with relatively low frequency and neither symptom uniquely differentiated those with CFS from controls. Further, Jason et al. (2002c) found a symptom currently not part of the Fukuda criteria, shortness of breath, did differentiate the groups. This symptom might play a role in neurally mediated hypotension, which has been connected to CFS (Poole et al., 2000).

Efforts to develop a case definition can be traced back even earlier. In 1955, there was an outbreak of a CFS-like illness at the Royal Free Hospital, and Ramsay (1981, 1988), the medical consultant in charge, published a definition of this disease using the term Myalgic Encephalomyelitis (ME) (Hyde et al., 1992).

The most prominent of the criteria include: (1) fatigue after minimal exertion (not daily fatigue) or delay of recovery of muscle power after exertion ends; (2) one or more symptoms that indicate circulatory impairment; (3) one or more symptoms that indicate central nervous system involvement (cerebral problems); (4) and fluctuating symptoms (Ramsay, 1981, 1988).

Dowsett and associates (1990) operationalized Ramsey's definition (ME) into criteria which bear some similarity to a case definition developed in Australia by Lloyd et al. (1990). Lloyd et al. stipulate that postexertional malaise, as well as memory and concentration difficulties, are central for a diagnosis.

In contrast, for the Fukuda et al. (1994) criteria, these symptoms are optional as they represent only two symptoms among a group of eight, of which a patient must have four. To date, there has only been one investigation comparing the Fukuda et al. (1994) CFS criteria with the ME criteria (Jason et al., 2003b).

Those meeting the ME criteria, in contrast to those meeting the CFS Fukuda et al. (1994) criteria, had significantly poorer neurological, neuropsychiatric, fatigue/weakness, and rheumatologic symptoms than those with chronic fatigue explained by psychiatric conditions.

Recently, a new clinical case definition for ME/CFS has been developed in Canada. The Canadian clinical case definition specifies that the illness needs to persist for at least 6 months (Carruthers et al., 2003). In addition, there must be a marked degree of new onset of unexplained, persistent, or recurrent physical or mental fatigue that substantially reduces activity level.

Postexertional malaise must occur with loss of physical or mental stamina, rapid muscle or cognitive fatigability, usually with 24 hr or longer to recover. There also needs to be unrefreshing sleep or sleep quantity or rhythm disturbance, and a significant degree of arthralgia and/or myalgia (there are a small number of patients with no pain or sleep dysfunction and a diagnosis can only be given when these individuals have a classical case with an infectious illness onset).

In addition, there need to be two or more neurocognitive manifestations (e.g., confusion, impairment of concentration, and short-term memory).

Finally, there needs to be at least one symptom from two of the following categories: autonomic manifestations (neurally mediated hypotension, light headedness), neuroendocrine manifestations (e.g., recurrent feelings of feverishness and cold extremities), and immune manifestations (e.g., recurrent sore throats).

Recently, Jason et al. (2004) compared persons meeting the Canadian case definition, the Fukuda et al. (1994) criteria, and people experiencing chronic fatigue explained by psychiatric reasons. The Canadian criteria group, in contrast to the Fukuda criteria group, had more variables that significantly differentiated them from the psychiatric comparison group. The Canadian criteria selected cases with less psychiatric comorbidity, more physical functional impairment, and more fatigue/weakness, neuropsychiatric, and neurology symptoms.

Research has also been directed at attempting to better classify symptoms of individuals with chronic fatigue and CFS. For example, using factor analysis, Nisenbaum et al. (1998) found three correlated factors (fatigue-mood-cognition symptoms, flu-type symptoms, and visual impairment symptoms).

In a later study, Nisenbaum et al. (2004) found three factors among a sample of 1,391 chronically fatigued subjects; the factors were musculoskeletal, infection, and cognitionmood-sleep.

Friedberg et al. (2000) also found three factors (cognitive problems, flu-like symptoms, and neurological symptoms) in a sample of patients with CFS.

A study by Jason et al. (2002a) used factor analysis to provide support for the existence of four distinct components of chronic fatigue. The four were: Lack of Energy (fatigue intensity), Physical Exertion (fatigue exacerbated by physical exertion), Cognitive Problems (difficulties with short-term memory, concentration, and information processing), and Fatigue and Rest (rest or sleep is not restorative).

Results of the study by Jason et al. (2002a) were of theoretical importance because two of the primary dimensions of fatigue that emerged within the CFS-like group, postexertional fatigue and cognitive problems, corresponded closely with definitional criteria for CFS (Lloyd et al., 1990).

Postexertional fatigue and cognitive problems are part of the major criteria for the Canadian case definition for ME/CFS (Carruthers et al., 2003). Postexertional fatigue and cognitive problems appear to represent primary dimensions of CFS. A cluster analysis of the data mentioned above was performed to define a typology of chronic fatigue symptomatology (Jason and Taylor, 2002). With respect to CFS, findings suggested that a majority of individuals with moderate to severe symptoms can be accurately classified into two important subgroups: one distinguished by severe postexertional fatigue, and fatigue that is alleviated by rest and the other distinguished by severe overall symptomatology, severe postexertional fatigue, and fatigue that is not alleviated by rest. One key characteristic that

distinguished the two clusters that contained almost all participants with CFS to another cluster that contained only one CFS participant, was markedly high severity of postexertional fatigue.

Results from this investigation highlight the relative importance of this symptom as a diagnostic marker for CFS, and point to the potential utility in designating postexertional fatigue as a major criteria for CFS in future attempts to define the syndrome.

A second key characteristic, fatigue in relation to rest, distinguished individuals in two clusters that contained individuals with CFS, with those in one cluster differing most significantly from those in the second with respect to whether their fatigue was alleviated by rest. One of the major criteria for the current U.S. definition of CFS (Fukuda et al., 1994) requires that fatigue is not substantially alleviated by rest in order for an individual to receive a diagnosis.

Findings from this investigation suggest that this criteria may be more accurately designated as one of the secondary criteria for CFS, so that it does not artificially exclude those with CFS who may experience some symptom relief with rest. This recommendation has recently been included into the guidelines for the CFS case definition (Reeves et al., 2003).

A third result deserving of attention involves the finding for more severe cognitive problems in the clusters of patients with CFS versus the cluster with only one CFS patient. This finding highlights the importance of cognitive problems to the experience of CFS and supports the designation of cognitive problems as a major criteria, which it is for ME (Dowsett et al., 1994), the Canadian case definition for ME/CFS (Carruthers et al., 2003), and the Australian (Lloyd et al., 1990) criteria.

Based on the research reviewed in this section, we would encourage researchers to compare and contrast categories of patients meeting the Canadian Case definition and the Fukuda et al. (1994) criteria. In addition, the provision of standardized measures for assessment and scoring guidelines should reduce clinicians' difficulty with the criteria and their need to modify the criteria in clinical practice. In effect, the use of standardized measures should reduce criterion variance and improve diagnostic reliability (King and Jason, 2004).