

Toward an Empirical Case Definition of CFS

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ABSTRACT. The current case definition of chronic fatigue syndrome (CFS) was developed by consensus rather than empirical methods. From a practice point of view, if the case definition is not empirically-based, it is possible that some individuals with this illness might not be diagnosed, and others who do not have the disorder might be diagnosed. In the present study, 114 individuals with CFS were provided a theoretically driven questionnaire that featured neuropsychiatric, vascular, inflammatory, muscle/joint, infectious, and other symptoms. When symptoms using this classification were factor analyzed, a more interpretable factor structure was identified than when using symptoms from traditional case definition criteria. Factor scores from the new classification system were cluster analyzed, and four types of patient groups were identified. The field of CFS studies needs to be grounded in empirical methods for determining a case definition versus more consensus-based efforts. Such efforts will ultimately help social service providers better diagnose and provide services to those with this chronic illness. doi:10.1300/J079v34n02_04 [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2007 by The Haworth Press, Inc. All rights reserved.]

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Chronic fatigue syndrome (CFS) is an incapacitating illness affecting approximately 800,000 Americans (Jason, Richman et al., 1999), and the annual total value of lost productivity in the US due to this illness has been estimated to be \$9.1 billion (Reynolds, Vernon, Bouchery, & Reeves, 2004). Evengard, Jacks, Pedersen, and Sullivan (2005) screened 31,405 individual members from the Swedish Twin Registry, and reported the six-month prevalence of CFS-like illness to be 2.36%. Unfortunately, the international CFS case definition (Fukuda et al., 1994)

was developed by consensus rather than empirical means. 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). Some modifications to this case definition have recently been proposed, such as better specifying terms and criteria

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(Reeves et al., 2003). However, even this modification is not empirically-based.

As the CFS case definition was not empirically-based, there has been considerable debate over the validity of this construct (Sullivan, Pedersen, Jacks, & Evengard, 2005). Sullivan et al. (2005) used latent class analysis with a data base of 5,330 individuals in Sweden, and this method identified a syndrome strongly resembling CFS. Much discussion over the past decade has also concerned which symptoms to include or exclude in the case definition. 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. They concluded that eliminating muscle weakness, arthralgias, and sleep disturbance, and adding anorexia and nausea would strengthen the CFS case definition. In contrast, using the Fukuda et al. (1994) criteria, Jason, Torres-Harding, Carrico, and Taylor (2002) 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, Torres-Harding et al. (2002) also found that anorexia and nausea occurred with relatively low frequency and neither symptom uniquely differentiated those with CFS from controls. Further, Jason, Torres-Harding et al. (2002) found that 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, Herrell, Ashton, Goldberg, & Buchwald, 2000).

Recently, a new clinical case definition for ME/CFS has been developed in Canada (Caruthers et al., 2003). Rather than having a choice of four or more out of eight symptoms, as occurs with the Fukuda et al. (1994) criteria, specific symptoms are required, such as post-exertional malaise. Jason, Torres-Harding, Jurgens, and Helgersen (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 co-morbidity, more physical functional impairment, and more fatigue/weakness, neuropsychiatric, and neurology symptoms.

Unfortunately, both the Fukuda et al. case definition and the Canadian case definition were not empirically based. Empirically based approaches have been directed at attempting to better classify symptoms of individuals with chronic fatigue and CFS. For example, using factor analysis, Nisenbaum, Reyes, Mawle, and Reeves (1998) found three correlated factors (fatigue-mood-cognition symptoms, flu-type symptoms, and visual impairment symptoms). In a later study, Nisenbaum, Reyes, Unger, and Reeves (2004) found three factors among a sample of 1,391 chronically fatigued subjects; the factors were musculoskeletal, infection, and cognition-mood-sleep. A study by Jason, Taylor, Kennedy et al. (2002) used factor analysis to provide support for the existence of four distinct components of chronic fatigue: 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 that is not restorative). Unfortunately, these studies were based on individuals with chronic fatigue rather than exclusively CFS.

Using factor analysis with samples of individuals with CFS, Friedberg, Dechene, McKenzie, and Fontanetta (2000) found three factors (cognitive problems, flu-like symptoms, and neurological symptoms) whereas Ray, Weir, Cullen and Phillips (1992) found four components: emotional distress, fatigue, somatic symptoms, and cognitive difficulty. With a pediatric sample, Rowe and Rowe (2002) used confirmatory factor analysis, and found support for muscle pain and fatigue, neurocognitive, abdominal head and chest pain, neurophysiological, and immunological factors.

Using cluster analysis, Jason and Taylor (2002) found that the majority of individuals with moderate to severe symptoms can be accurately classified into two important subgroups: one distinguished by severe post-exertional fa-

tigue, and fatigue that is alleviated by rest; and the other distinguished by severe overall symptomatology, severe post-exertional fatigue, and fatigue that is not alleviated by rest. Hickie and associates (1995) found two distinctive subtypes: (a) a "somatization-like" group, including those who have a higher prevalence of CFS symptoms and atypical symptoms, greater disability attributed to CFS and psychiatric symptoms, and a greater percentage unemployed and; (b) a "CFS" group, including those individuals with lower prevalence of CFS and atypical symptoms, less disability attributed to CFS and psychiatric symptoms, and a greater percentage employed. This study has been replicated in a multi-site study (Wilson et al., 2001).

Sullivan, Smith, and Buchwald (2002) used latent class analysis with 32 symptoms of patients with CFS, FM (Fibromyalgia), and CFS and FM, and the findings supported the notion that CFS and FM have more similarities than differences. Taylor, Jason and Schoeny (2001) used a confirmatory factor analysis, which supported diagnostic distinctions between five syndromes (FM, CFS, somatic depression, somatic anxiety, and IBS). Linder, Dinser, Wagner, Krueger, and Hoffmann (2002) used artificial neural networks to classify patients with chronic fatigue (including CFS and idiopathic chronic fatigue), lupus erythematosus, and FM. They were able to achieve a sensitivity of 95% and a specificity of 85%. Those chronic fatigue symptoms that had the highest accuracy were "acute onset of symptoms" and "sore throat," which supports the hypothesis of an infectious etiology.

Corradi, Jason, and Torres-Harding (2006) recently classified individuals with CFS into three sub-groups according to: medical evidence of possible inflammatory processes (as evidenced by abnormal eosinophils count, antinuclear antibodies, abnormal rheumatoid arthritis factor, and abnormal sedimentation rate in the presence of an additional inflammatory marker); medical evidence of possible current infection (as evidenced by abnormal results on Sedimentation rate without the presence of an inflammatory marker, or lymphocytes count); and an "other" group without evidence of either of the aforementioned organic

processes (cases with more muscular, autonomic, and neurological abnormalities). Individuals from the "other" group had significantly more physical disability than those in the inflammatory group. However, those in the inflammatory group were significantly more likely to have mental difficulties (based on the mental component summary of the SF-36) and a current psychiatric diagnosis.

Summarizing the literature above, there is some empirical support for individuals with CFS having neuropsychological or cognitive problems (Friedberg et al., 2000; Jason, Taylor, Kennedy et al., 2002; Ray et al., 1992; Rowe & Rowe, 2002), infectious symptoms (Corradi et al., 2006; Friedberg et al., 2000; Linder et al., 2002; Nisenbaum et al., 1998, 2004; Rowe & Rowe), and muscle/joint difficulties (Nisenbaum et al., 2004; Rowe et al., 2002) and these symptoms are reflected in the CFS research (Fukuda et al. 1994) and Canadian clinical case definitions (Carruthers et al., 2003). Two more specific symptoms, unrefreshing sleep (Nisenbaum et al., 2004; Jason, Taylor, Kennedy et al., 2002) and post-exertional malaise (Jason, Taylor, Kennedy et al., 2002; Jason & Taylor, 2002) are also prominent features in the empirical studies as well as the two CFS case definitions. Finally, two additional clusters of symptoms identified in the CFS studies include vascular (Rowe & Rowe, 2002; Jason, Torres-Harding et al., 2002) and inflammatory (Corradi et al., 2006) symptoms; and both are featured in the Canadian clinical case definition (Carruthers et al., 2003) but not in the Fukuda et al. criteria.

The present study used the categories above to develop a theoretically derived set of symptoms to compare with those from the CFS Fukuda et al. case definition. It was hypothesized that the factor analysis from the theoretically derived symptoms would provide a better factor solution than those derived from the Fukuda et al. criteria. The practical implications of such research is that if a better case definition is developed, it could help social service workers better diagnose individuals with this condition, and this could lead to more tailored and appropriate interventions for those with this chronic condition.

METHOD

Participant Recruitment. The DePaul Institutional Review Board approved this study. Participants were recruited from a variety of sources, including physician referrals. Individuals were recruited to participate in a non-pharmacologic treatment trial, and only baseline data are presented in the current study. Information about the study was disseminated to medical colleagues through mailings, phone communication, and invited grand rounds. In addition, study announcements for new participants were placed in local newspapers and recruitment offers were made at local CFS support group meetings. These efforts were continued throughout the study period until the target enrollment numbers were achieved. One hundred and fourteen individuals were recruited.

Of the 114 individuals, 46% were referred by physicians, 34% were recruited by media (newspapers, TV, radio, etc.), and 20% stemmed from other sources (e.g., heard about the study from a friend, family member, person in the study, etc.). There were no significant demographic differences for patients recruited from these varying sources. Twenty-four additional individuals who were screened were excluded due to a variety of reasons (i.e., lifelong fatigue, less than four Fukuda symptoms, BMI >45, melancholic depression or bipolar depression, alcohol or substance abuse disorder, autoimmune thyroiditis, cancer, lupus, rheumatoid arthritis). Approaches to reduce attrition included use of letters and telephone reminders of all appointments, flexibility regarding working around vacations and medical and other crises, reimbursement for transportation costs, and participant honoraria.

Of the 114 participants, 16.7% are male and 83.3% are female. The average age is 43.8 years. Regarding ethnicity, 87.7% are Caucasian, 4.4% are African-American, 4.4% are Latino, and 3.5% are Asian-American. As for marital status, 49.1% are married/living with someone, 33.3% are single, and 17.6% are either divorced or separated. In terms of work status at the baseline, 24.6% were on disability, 23.7% were unemployed, 20.2% were working part-time, 19.3% were working full-time, 6.1% were retired, 4.4% were part-time students, .9%

were full-time students, and .9% were working part-time and on disability. In terms of education, 47.4% had earned a standard college degree, 21.8% had a graduate or professional degree, 21.1% had partial college, 9.7% had a high school/GED degree or less. In regard to psychiatric co-morbidity, 62.3% had a lifetime Axis I diagnosis, and 38.6% had a current Axis I diagnosis.

Initial Screening. All participants were required to be at least 18 years of age, not pregnant, able to read and speak English, and considered to be physically capable of attending the scheduled sessions. Bedridden and wheelchair-bound patients were excluded due to the practical difficulties of making appointments. Referrals to local physicians who treat CFS and to support groups were offered to these individuals. After a consent form was filled out, prospective participants were initially screened by the third author, using a structured questionnaire.

The CFS Questionnaire. This screening scale was initially validated by Jason, Ropacki et al. (1997). This scale is used to collect demographic, health status, medication usage, and symptom data, and it uses the definitional symptoms of CFS (Fukuda et al., 1994). Hawk, Jason, and Torres-Harding (in press) recently revised this CFS Questionnaire, and administered the questionnaire to three groups (those with CFS, Major Depressive Disorder, and healthy controls). The revised instrument, which was used in the present study, evidences good test-retest reliability and has good sensitivity and specificity.

The CFS Questionnaire was designed to assess the diagnostic criteria for CFS as specified by Fukuda et al. (1994). For each symptom, participants were asked to indicate if the symptom had been present for six months or longer, if the symptom began before the onset of their fatigue or health problems, and how often (never, seldom, often/usually, or always) the symptom is experienced. Participants were also asked to rate the intensity of each symptom they endorsed on a scale of 0 to 100, where 0 = no problem and 100 = the worst problem possible. This is a numerical rating scale (NRS), which has been shown to be a consistently valid measure of symptom intensity, particularly for pain intensity (Jensen & Karoly, 1992). These

intensity ratings were used in all analyses below.

To measure the Fukuda et al. (1994) case definition symptoms, items were designed to measure the presence and intensity of the eight minor symptoms (i.e., impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep, and post-exertion malaise) as specified by the Fukuda et al. (1994) case definition.

Participants were also asked to indicate whether they had a number of other symptoms commonly experienced by people with CFS. We grouped a set of these symptoms (some of which are part of the Fukuda et al. criteria and some are not) into the following theoretical constructs: neuropsychological or cognitive problems (absent minded, need to focus on one thing at a time, difficulty recalling information, concerned with driving, slowness of thought, memory/concentration problems), infectious symptoms (fever chills, recurrent flu-like, sore throat, tender/sore lymph), muscle/joint difficulties (muscle pain, pain in multiple joints, muscle weakness), vascular (headaches, shortness of breath, dizziness, dizzy after standing, unsteady on feet) and inflammatory (allergies, chemical sensitivities, new food/drug sensitivities, gastrointestinal symptoms). We also included two more specific symptoms, unrefreshing sleep and post-exertional malaise (and they were not placed into any of the above categories) that are also prominent features in the empirical studies as well as the two CFS case definitions. Grouping of these symptoms into the categories occurred prior to data analysis.

Next, a semi-structured psychiatric interview was administered by the third author. The Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) Axis I was used to establish psychiatric diagnoses. The professionally administered SCID allows for clinical judgment in the assignment of symptoms to psychiatric or medical categories, a crucial distinction in the assessment of symptoms that overlap between CFS and psychiatric disorders, e.g., fatigue, concentration difficulty, and sleep disturbance (Friedberg & Jason, 1998). A psychodiagnostic study (Taylor & Jason, 1998) validated the use of the SCID in a sample of CFS patients. Because CFS is a diagnosis of exclu-

sion, prospective participants were screened for identifiable psychiatric and medical conditions that may explain CFS-like symptoms. These measures were completed at DePaul University and took approximately two hours. After the initial interview was completed, the patients' information was reviewed to ensure that they met all eligibility requirements. If an individual was eligible for the study, a medical appointment was set up. Conversely, if an individual was not eligible, the third author discussed with him or her alternate treatment options.

Medical Assessment of CFS. The physician screening evaluation included an in-depth medical and neurological history, as well as general and neurological physical examinations. The evaluation also included a structured instrument, a modified version of the CFS questionnaire (Komaroff, Fagioli, Geiger et al., 1996). This instrument assesses the signs, symptoms, and medical history to rule out other disorders. Relevant medical information was gathered to exclude possible other medical causes of chronic fatigue, including exposure histories to tuberculosis, AIDS, and non-AIDS sexually transmitted diseases. Information on prescribed and illicit drug use was also assessed and recorded. With adult females, results of recent Pap smears and mammograms were obtained. Finally the histories of all symptoms related to CFS were gathered.

Laboratory tests in the battery were the minimum necessary to rule out other illnesses (Fukuda et al., 1994). Laboratory tests included a chemistry screen (which assesses liver, renal, and thyroid functioning), complete blood count with differential and platelet count, erythrocyte sedimentation rate, arthritic profile (which includes rheumatoid factor and antinuclear antibody), hepatitis B, Lyme Disease screen, HIV screen and urinalysis. A tuberculin skin test was also performed. Finally, an anterior-posterior and lateral chest x-ray was conducted if one had not been obtained within eight months of the study. The project physician performed a detailed medical examination to detect evidence of diffuse adenopathy, hepatosplenomegaly, synovitis, neuropathy, myopathy, cardiac or pulmonary dysfunction.

RESULTS

Factor Analysis

Two principal component analyses were conducted, with study 1 involving the eight Fukuda et al. symptoms (i.e., impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep, and post-exertion malaise), and Study 2 involving the 24 symptoms comprising neuropsychologic, infectious, muscle/joint, inflammatory, and vascular categories, and unrefreshing sleep and post-exertional malaise. On each sample, the Bartlett's test of sphericity was $< .01$ and the Kaiser-Meyer-Olkin measure of sampling adequacy was $\geq .80$.

Fukuda et al. Symptoms

For study 1, with the Fukuda et al. symptoms, three factors had eigenvalues > 1.0 . Using a varimax extraction method, a three-factor solution explained 65% of the variance. The factor loadings ($> .40$) for each of these factors are in Table 1. Four symptoms loaded on Factor 1, which we referred to as pain/cognitive. The combination of pain symptoms, memory/concentration problems and post-exertional malaise is a large and diverse set of symptoms. Two symptoms were on Factor 2 (Headache/Sleep symptoms), and both symptoms could involve

neurological issues. Finally, the two items loading on Factor 3 are the clearest to interpret as they both involve immunologic symptoms.

Cronbach's alpha was computed for the three factors (Factor 1, .60; Factor 2, .39; Factor 3, .56). Cronbach's alpha scores were low due to the limited number of items (4, 2 and 2 respectively), and sample size. Nonetheless, two of the three scores approached the cutoff range for acceptable scale reliability. In general, the factor structure is not easily interpretable based on theoretical issues in the CFS literature.

Theoretically Derived Symptoms

For study 2 with the 24 theoretically derived symptoms, seven factors had eigenvalues > 1.0 , but there was a clear difference with the scree plot between the first six and the seventh factor, so only six were retained. Using a varimax extraction method, a six-factor solution explained 61% of the variance. The factor loadings ($> .40$) for each of these factors are in Table 2. Factor 1 refers to neurocognitive items (e.g., slowness of thought), Factor 2 refers to vascular items (e.g., dizzy after standing), Factor 3 refers to inflammation items (e.g., chemical sensitivities), Factor 4 refers to muscle/joint symptoms (e.g., pain in multiple joints), Factor 5 refers to infectious symptoms (e.g., sore throat), and Factor 6 refers to sleep/post-exertional symptoms (e.g., unrefreshing sleep). Symptoms in the first five factors had been assigned to those categories prior to data analysis. No predictions had been

TABLE 1. Factor Analysis of Fukuda et al. Symptoms Following Varimax Rotation

| | Pain/ Cognitive | Sleep/ Headaches | Immune |
|-----------------------------------|--------------------|---------------------|--------|
| Eigenvalue | 2.77 | 1.14 | .99 |
| Cumulative variance explained | 34.67 | 52.76 | 65.10 |
| Pain in multiple joints | .84 | | |
| Post-exertional malaise | .69 | | |
| Impaired memory and concentration | .63 | | |
| Muscle pain | .59 | | |
| Headaches | | .79 | |
| Unrefreshing sleep | | .69 | |
| Sore throat | | | .80 |
| Tender/lymph node | | | .74 |

TABLE 2. Factor Analysis of Theoretically Derived Symptoms Following Varimax Rotation

| | Neuro- cognitive | Vascular | Inflam- mation | Muscle/ Joint | Infectious | Sleep/ Post-Exert |
|-------------------------------|---------------------|----------|-------------------|------------------|------------|----------------------|
| Eigenvalue | 3.66 | 2.85 | 2.38 | 2.26 | 1.97 | 1.45 |
| Cumulative variance explained | 15.2% | 11.9% | 9.9% | 9.4% | 8.2% | 6.1% |
| Slowness of thought | .81 | | | | | |
| Absent minded | .77 | | | | | |
| Difficulty recalling info | .71 | | | | | |
| Need to focus on 1 thing | .69 | | | | | |
| Impaired memory/concentration | .68 | | | | | |
| Concern with driving | .49 | | | | | |
| Dizzy after standing | | .79 | | | | |
| Dizziness | | .72 | | | | |
| Unsteady on feet | | .67 | | | | |
| Shortness of breath | | .56 | | | | |
| Headaches | | .50 | | | | |
| Chemical sensitivity | | | .74 | | | |
| Food/drug sensitivity | | | .74 | | | |
| Allergies | | | .69 | | | |
| Gastrointestinal symptoms | | | .42 | | | |
| Pain in multiple joints | | | | .74 | | |
| Muscle pain | | | | .73 | | |
| Muscle weakness | | | | .52 | | |
| Sore throat | | | | | .72 | |
| Fever and chills | | | | | .66 | |
| Tender/sore lymph | | | | | .57 | |
| Flu-like symptoms | | | | | .46 | |
| Unrefreshing sleep | | | | | | -.68 |
| Post-exertional malaise | | | | | | .62 |

made for the two symptoms in Factor 6 (because the two variables are inversely correlated, high scores on one domain are associated with low scores on the other domain).

Cronbach's alpha was computed for five of the six factors and the values are within the moderate range (Factor 1, .84; Factor 2, .76; Factor 3, .71; Factor 4, .69; Factor 5, .61), indicating the factors are moderately reliable. Cronbach's alpha could not be computed on the sixth factor, as only two items (unrefreshing sleep and post-exertional malaise) loaded on this factor, and were negatively correlated, thus violating one of the assumptions of Cronbach's alpha.

Exploratory Cluster Analysis

Using the second principal component analyses, each individual had one score for each of the six factors in the second. We were now interested in determining if individuals with these six scores could be categorized into distinct clusters. In order to accomplish this we performed a hierarchical cluster analysis. In conducting the cluster analysis, we selected the squared Euclidean distance measure, which places individuals in clusters based on the distance between individuals. The squared Euclidean distance measure represents the sum of the squared differences across all of the variables. In combining cases into clusters, we used the

TABLE 3. MANOVA of 6 Factor Regression Scores and 4 Cluster Groups

| | Cluster 1 n = 43 | | Cluster 2 n = 21 | | Cluster 3 n = 28 | | Cluster 4 n = 22 | |
|-------------------------|---------------------|------|----------------------|------|---------------------|-----|----------------------|------|
| | M | SD | M | SD | M | SD | M | SD |
| Neurocognitive | .25 ^a | .90 | .25 ^b | .63 | .40 ^c | .93 | -1.24 ^{abc} | .65 |
| Vascular | .41 ^{ac} | .95 | .41 ^{bd} | 1.01 | -.65 ^{ab} | .79 | -.38 ^{cd} | .86 |
| Inflammation | .57 ^{abc} | 1.12 | -.75 ^a | .70 | -.19 ^b | .70 | -.17 ^c | .79 |
| Muscle/Joint | -.00 | .94 | .39 ^a | .98 | -.38 | .90 | .12 ^a | 1.11 |
| Infectious | .71 ^{abc} | .91 | -1.13 ^{ade} | .72 | -.14 ^{bd} | .71 | -.12 ^{ce} | .82 |
| Sleep/Post-Exert | .28 ^a | .73 | .47 ^b | 1.16 | -.87 ^{abc} | .92 | .11 ^c | .79 |

Rows with similar letters have means that are significantly different at the $< .01$ level (except for muscle/joint between clusters 2 and 4, and vascular, between clusters 2 and 4; and these are significant at the $< .05$ level).

agglomerative hierarchical clustering method. The method used to decide which cases should be combined at each step was the average linkage within-groups method. When we examined a dendrogram, four homogeneous clusters emerged. In addition, when looking at the agglomeration schedule, the coefficients indicated that there was a fairly large increase in the value of the distance measure, from a 5-cluster to a 4-cluster solution. Forty-three individuals were included in Cluster 1; 21 were included in Cluster 2; 28 in Cluster 3, and 22 in Cluster 4. Table 3 depicts the significant results of MANOVA analyses of the five factors. When a significant difference was detected, a Bonferroni t-test was used for multiple comparisons between cluster groups.

Cluster 1 scored highest on inflammatory and infectious symptoms, with second highest scores on vascular, neuropsychological scores, and unrefreshing sleep/post-exertional symptoms. This group of individuals appears to have the overall highest level of symptoms, particularly in inflammatory/infectious areas.

Cluster 2, in contrast, had the lowest level of inflammatory and infectious symptoms, but had highest scores on muscle/joint and unrefreshing sleep/post-exertional malaise (which means high post-exertional malaise and low unrefreshing sleep). These individuals also had relatively high scores on neuropsychologic and vascular symptoms. These individuals appear to be relatively impaired, but their symptom manifestation is very different from Cluster 1.

Cluster 3 had the highest score on neuropsychologic items, but the lowest scores on unrefreshing sleep/post-exertional malaise (which means high scores on unrefreshing sleep and low scores on post-exertional malaise), muscle/joint, and vascular symptoms. Relatively low scores were also evident on inflammatory and infectious items. In general, this cluster appears to be the least impaired than those in Clusters 1 and 2, except in cognitive areas and unrefreshing sleep.

Finally, Cluster 4 had the lowest scores for neuropsychologic items, and relatively low items for vascular, inflammatory, muscle/joint, infectious, and unrefreshing sleep/post-exertional malaise. Overall, this group of individuals appears to be less impaired than Cluster 1 and 2 patients, and has less cognitive impairment from those in Cluster 3.

DISCUSSION

The study's primary finding was that the symptom cluster as defined by the Fukuda et al. (1994) criteria did not result in interpretable factors, whereas, when using a larger group of theoretically defined symptoms, an interpretable set of factors did emerge. These findings suggest that theoretical and empirical approaches to determining critical symptoms of CFS have considerable merit. The field of CFS studies needs to be grounded in empirical methods for determining a case definition versus more consensus-based efforts. In addition,

since the case definition of 1994, considerable scientific developments have occurred (such as the identification of vascular and inflammatory processes (Corradi et al., 2006; Jason, Torres-Harding et al., 2002; Rowe & Rowe, 2002), and it is perhaps useful to consider integrating such developments into the CFS case definition.

The findings from this study provide empirical support for identifying five areas of functioning among those with CFS. These areas were based on theory and now they have empirical support. As was reviewed in the introduction, there is considerable support for identifying the following symptom clusters or symptoms in individuals with CFS: neuropsychological or cognitive problems (Friedberg et al., 2000; Jason, Taylor, Kennedy, Jordan et al., 2002; Ray et al., 1992; Rowe & Rowe, 2002), infectious symptoms (Corradi et al., 2006; Friedberg et al. 2000, Linder et al., 2002; Nisenbaum et al., 1998, 2004; Rowe & Rowe), muscle/joint difficulties (Nisenbaum et al., 2004; Rowe et al.), vascular issues (Rowe & Rowe, 2002; Jason, Torres-Harding et al., 2002), inflammatory problems (Corradi et al., 2006), unrefreshing sleep (Nisenbaum et al., 2004; Jason, Taylor, Kennedy et al., 2002) and post-exertional malaise (Jason, Taylor, Kennedy et al., 2002; Jason & Taylor, 2002). It is interesting that the Canadian clinical case definition (Carruthers et al., 2003) requires the assessment of vascular and inflammatory processes, whereas they are not criteria used by the current international case definition as defined by Fukuda et al. (1994). These findings suggest that a broader group of symptoms, ones which are theoretically derived, might be needed to more accurately identify critical symptoms of those with this illness.

Several prior factor analytic studies, including Nisenbaum et al. (1998, 2004) and Ray et al. (1992) have included items that assessed emotional distress items, and a psychological distress type factor did emerge. The present study did not include these items as we considered such items possible effects of having this illness. If one were to measure other chronic illnesses, such as AIDS or cancer, emotional consequences would surely be evident, and yet the case definitions do not refer to such emotional-type items.

Results from the cluster analysis were also of theoretical interest. Cluster 1, which comprised 38% of the sample, had the highest level of inflammatory and infectious symptoms. Borish, Schmalig, DiClementi, Streib, Negri, and Jones (1998) found evidence of low-level inflammation, similar to that of allergies, in a subgroup of individuals with CFS. Buchwald, Wener, Pearlman, and Kith (1997) found individuals with CFS and chronic fatigue to have significant abnormalities in C-reactive protein (an indicator of acute inflammation) and neopterin (an indicator of immune system activation, malignant disease, and viral infections) when compared to controls. Buchwald et al. stated that groups of individuals with active low-level inflammatory, infectious processes could be identified and that this was evidence of an organic process in these patients with CFS. The present study is supportive of these findings, and suggest that there is a group of patients with high levels of inflammatory and infectious symptoms.

Lutgendorf, Klimas, Antoni, Brickman, and Fletcher (1995) found that those patients with immune activation had the most severe cognitive deficits, while Natelson, Cohen, Brassloff and Lee (1993) found that those with ongoing inflammatory processes reported greater cognitive and mental disabilities. Corradi et al. (2006) also found those in an inflammatory group were significantly more likely to have mental difficulties. In contrast, findings from the present study suggest that there are two groups of individuals with cognitive problems, one having high levels of inflammatory/infectious symptoms (Cluster 1) and one group having low levels of inflammatory/infectious symptoms (Cluster 2), and that those with the highest levels of cognitive problems (Cluster 3) actually had relatively low levels of inflammatory/infectious symptoms. These discrepant findings could suggest that when all patients with CFS are grouped into one relatively heterogeneous group, the different symptom manifestations of subtypes are masked. As an example, Clusters 3 and 4 were derived from a larger cluster, and in this larger cluster the neuropsychologic problems were relatively low, as the average of the high scores for Cluster 3 were masked by the extremely low scores from Cluster 4.

It is also evident from the cluster analyses that some individuals with CFS have relatively lower levels of critical symptoms, such as those within Cluster 4. Other investigators have also referred to patients with lesser disability of symptoms. Hadzi-Pavlovic, Hickie, Wilson, Davenport, Lloyd, and Wakefield (2000) used latent class analysis to classify patients with CFS into three classes: those with multiple severe symptoms, those with lower rates of cognitive symptoms and higher rates of pain, and those with a less severe form of multiple symptoms. In two follow-up studies of patients with CFS, persistent symptoms and disability at the follow-up were associated with eight or more symptoms at time one (Clark et al., 1995; Bombardier & Buchwald, 1995). Jason, Taylor, Kennedy et al. (2003) divided individuals with CFS into those who experienced a high and low frequency of symptoms. Those with high frequency were less likely to be working full-time, more likely to be unemployed, and more functionally disabled. It does appear that there are a group of individuals with CFS who have lower levels of symptoms, and it would be important to differentiate these groups from those with more severe symptomatology.

Jason, Corradi, Torres-Harding, Taylor and King (2005) have argued for the need to identify clinically significant CFS subgroups. The present study suggests that there might be important differences in those individuals with high levels of infectious/inflammatory processes versus those individuals with lower levels, and there might be a group with the highest levels of cognitive difficulties who have relatively lower symptoms in other critical areas. Depending upon the individual and subtype, these may include unique biological, genetic, neurological, psychological, and socio-environmental contributions. Subgrouping might provide investigators with a better understanding how CFS begins and how it is maintained, and in the best case, how it can be prevented, treated, and cured.

Clinical judgment remains an important role in diagnosing illnesses even for diseases, like lupus, which use a combination of clinical judgment, patient report, and objective measures to come up with a diagnosis. But the case definition is the critical beginning step in this

diagnostic process. Using a consensus-based approach or an empirical approach to defining this will have important influences on the precision for being able to diagnose this illness with specificity and sensitivity. If the illness category includes many who do not have this illness or does not include some with the illness, then this will make it more difficult to ultimately find biological markers for this illness and to better understand the pathophysiology of the illness. Having a reliable and valid case definition that is empirically derived is a critical first step for the diagnostic effort and greater diagnostic precision might impact the types of interventions that are developed for those with this illness. Social Service researchers have an important role to play in helping develop more reliable and valid case definitions for illnesses that are somewhat ambiguous and lack clear cut etiologic factors.

There were several limitations in the present study. The sample size was relatively small, and it is important to attempt to replicate the findings with a larger sample. In addition, the factor analysis for the Fukuda et al. (1994) symptoms involved only eight symptoms, and the small number probably limited the factor structure that was possible. Still, it is precisely for this reason that there might be a need to utilize a large number of symptoms to more accurately capture the CFS illness. It should also be noted that the principal component analyses accounted for similar proportions of variability in symptom ratings, however, internal reliabilities were better for the theoretically derived analyses. It should also be noted that there is no imperative for conceptually distinct symptoms to be empirically independent of one another in order to be valid. It is possible that the combination of cognitive and musculoskeletal symptoms in factor 1 of the Fukuda principal components analysis indicates that those symptoms are often comorbid.

In summary, the present study found that an empirically derived group of symptoms was able to better differentiate a meaningful group of factors than the current group of symptoms from the Fukuda et al. (1994) CFS case definition. Of interest, the larger group of symptoms included several areas (vascular, inflammatory) that are within the Canadian CFS case def-

inition (Carruthers et al., 2003), but not currently within the Fukuda et al. criteria. There is a clear need for longitudinal studies of the natural history of individuals with CFS, and for investigators to track those from different subgroupings. There is a need for more attention among CFS investigators in the development of empirically-based approaches toward diagnosing and understanding CFS.

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