



Sub-typing CFS patients on the basis of ‘minor’ symptoms

Malvin N. Janal^{a,*}, Donald S. Ciccone^a, Benjamin H. Natelson^b

^a *Fatigue Research Center and Department of Psychiatry, New Jersey Medical School, BHSB-F1522, Box 1709, University of Medicine and Dentistry of New Jersey, Newark, NJ 07101, United States*

^b *Fatigue Research Center and Department of Neurosciences, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, United States*

Received 13 May 2005; accepted 10 January 2006

Abstract

The diagnosis of chronic fatigue syndrome (CFS), an illness characterized by medically unexplained fatigue, depends on a clinical case definition representing one or more pathophysiological mechanisms. To prepare for studies of these mechanisms, this study sought to identify subtypes of CFS. In 161 women meeting 1994 criteria for CFS, principal components analysis of the 10 ‘minor’ symptoms of CFS produced three factors interpreted to indicate musculoskeletal, infectious and neurological subtypes. Extreme scores on one or more of these factors characterized about 2/3 of the sample. Those characterized by the neurological factor were at increased risk of reduced scores on cognitive tests requiring attention, working memory, long-term memory or rapid performance. In addition, the neurological subtype was associated with reduced levels of function. Those characterized by the musculoskeletal factor were at increased risk for the diagnosis of fibromyalgia (chronic widespread pain and mechanical allodynia) and reduced physical function. Those characterized by the infectious factor were less likely to evidence co-occurring fibromyalgia, and showed lesser risk of functional impairment. The prevalence of disability was increased in those with the highest scores on any of the subtypes, as well as in those with high scores on multiple factors. Depression and anxiety, while frequently present, were not more prevalent in any particular subtype, and did not increase with the severity of specific symptom reports. Results suggest that subtypes of CFS may be identified from reports of the minor diagnostic symptoms, and that these subtypes demonstrate construct validity.

© 2006 Published by Elsevier B.V.

Keywords: Chronic fatigue syndrome; Subgroup analysis; Pathophysiology; Women

Chronic fatigue syndrome (CFS) is an illness characterized by medically unexplained fatigue producing a substantial reduction in activity, and accompanied by rheumatological, infectious and neuropsychiatric symptoms. Because its diagnosis depends on a clinical case definition (Holmes et al., 1988; Fukuda et al., 1994), the illness criteria might represent the end result of one or more pathophysiologic mechanisms. In order to identify these potential mechanisms, the authors of the 1994 case definition suggested that researchers develop and employ stratification strategies that might reveal subtypes of CFS. If reliable subtypes were identified, this would set the stage for the exploration of pathophysiologic mechanisms explaining the onset or maintenance of those symptoms. Our goal here, then, was to identify subgroups of CFS patients and to determine if that subgrouping

reduced the heterogeneity often present in illnesses defined by a clinical case definition.

We began working on stratification strategies by focusing on whether the illness began suddenly or gradually, and on whether the patient had a co-morbid psychiatric diagnosis. We reported that patients with more severe symptoms, a sudden onset, and no psychiatric illnesses had the most cognitive problems on neuropsychological testing (DeLuca et al., 1997a,b). These data suggested that some CFS patients had an underlying neurological etiology for their illness. Subsequently, we have shown that patients with CFS and fibromyalgia (FM), a medically unexplained syndrome characterized by widespread pain and tender points (Wolfe et al., 1990), show a greater degree of functional impairment than those with CFS alone (Ciccone and Natelson, 2003). We have also shown that the most severely ill CFS patients (Natelson et al., 1995) have reduced cardiac output relative to those who are less severely ill (Peckerman et al., 2003). These reports suggest heterogeneity of symptoms within the spectrum of CFS.

* Corresponding author. Tel.: +1 973 972 7924.

E-mail address: janal@njneuromed.org (M.N. Janal).

Others have also attempted stratification (see Jason et al., 2005 for a review). Wilson et al. (2001) reported two overlapping clusters of CFS patients, both had symptoms of CFS, but one also had a pattern of symptoms consistent with a somatization disorder; this latter group was characterized by a wider variety of symptom reports, longer duration of fatiguing illness, greater female:male ratio, more disability, more medical visitation, more depression and more anxiety. Unfortunately, that clustering strategy relied on a large number of questions, and it is not clear whether the somatization group had only CFS, or CFS as well as a somatoform disorder. Another approach has been to identify other markers, such as major depressive disorder, to increase specificity in the diagnosis of CFS (Jason et al., 2002a, 2002b; King and Jason, 2005). Given the heterogeneity implicit in the case definition, however, it would be important to know if there was a simpler way to subtype CFS patients.

We reasoned that parsing subjects by their pattern of symptoms might achieve this goal. Tseng and Natelson (2004) employed factor analysis to evaluate patients' symptom patterns based on their self-report of the severity of the 10 symptoms which made up the 'minor symptoms' used in the original case definition of CFS (Holmes et al., 1988). ('Minor' was dropped at the time of the 1994 case revision by Fukuda et al., when the number of symptoms necessary for diagnosis was also reduced.) While patients continued to respond to queries about all these symptoms in this study, the Fukuda criteria were used for entry. That analysis produced infectious, neurological and musculoskeletal factors. The occurrence of these three factors led us to two a priori hypotheses. First, we hypothesized that patients with high musculoskeletal scores would have higher rates of diagnosed FM than those in the other subtypes. Second, we hypothesized that those with high neurological scores would evidence more cognitive dysfunction than those in the other subtypes.

Because CFS is primarily a problem in women's health, we tested these hypotheses in a large group of women patients, in order to eliminate sex-related variability. We sought to determine whether one or more of these factors characterize most women with CFS, and how many of these patients satisfied criteria for membership in two or more subtypes. Finally, we sought to validate this grouping strategy on the basis of the degree to which it might reduce uncertainty in identifying those at increased risk of FM, cognitive difficulties, reduced quality of life and reduced functional status.

1. Method

1.1. Subjects

We collected data from 176 women who met the 1994 case definition of CFS (Fukuda et al., 1994). Patients came to our tertiary University-based Chronic Fatigue Syndrome/Fibromyalgia Center via newspaper advertisement, media reports, physician referral or information provided on a University website.

1.2. Procedure

All prospective subjects completed a paper and pencil screen for CFS. Individuals screening positive for CFS were asked to sign informed consent; if

they agreed, they then received a psychiatric diagnostic interview. Patients were excluded if they ever had schizophrenia, mania, or eating disorders, or a drug or alcohol abuse problem within 2 years of intake. Eligible patients visited the Center at the New Jersey Medical School for a complete history and physical examination, as well as blood tests (Schluederberg et al., 1992), to rule out medical causes of fatigue, that was conducted by a physician's assistant or a nurse practitioner, trained and supervised in the diagnoses of CFS and FM by a physician with expertise in these disorders (BHN). On the same day, patients completed a cognitive assessment battery administered by a research assistant under the supervision of a neuropsychologist.

1.3. Assessment

Patients rated the severity (during the past month) of the 'minor' symptoms from the 1988 case definition for CFS (feverishness, swollen glands, sore throat, new-onset headache, muscle pain, weakness, joint pain, post-exertional fatigue, sleep problems and cognitive problems) on a six-point Likert scale ('none', 'mild', 'moderate', 'substantial', 'severe' or 'very severe').

'Sudden' illness onset was defined if the entire symptom complex was reported to have appeared within a 3-day period; otherwise it was labeled as 'gradual'. Fibromyalgia was diagnosed according to the 1990 criteria of the American College of Rheumatology (Wolfe et al., 1990), which requires the report of spontaneous, four-quadrant pain, as well as pain on palpation at 11 or more tender points. The presence of an Axis I psychiatric disorder, the date of the onset of the disorder, and whether it existed within the preceding month, i.e., "current" diagnosis, was determined using a computerized version of the Diagnostic Interview Schedule (DIS-III-R) (Marcus et al., 1990). This assessment provided diagnoses of mood and anxiety disorders, as well as exclusionary diagnoses.

Cognitive function tests assessed attention, complex information processing, visual and verbal memory and psychomotor function. Information on 15 variables was derived from seven standard tests (California Verbal Learning Test, Revised Osterrieth Complex, NES Continuous Performance Test, Trail Making Test, Grooved Pegboard, PASAT and WAIS-R).

Ratings of physical function included reports of 'days spent in bed' and 'days cut down activity', during the past month. In addition, all subjects completed the Medical Outcomes Survey (SF-36), a 36-item assessment of functional status and quality of life (Ware et al., 1993), which was scored to produce summary measures of physical (PCS) and mental (MCS) function; ranging from 0 to 100, lower scores on each of these measures indicates poorer performance.

1.4. Data analysis

Patients' symptom severity ratings were summarized with relative frequencies. Severity ratings were entered into a principal components (PC) analysis to identify independent groups of related items. All PCs with eigenvalues greater than unity were accepted, and this solution was then rotated using the varimax technique. From this analysis, factor scores were computed by a regression method that reflected the extent to which each of the factors characterized each of the patients. Groups were then formed by collecting patients who displayed an extreme score (upper tertile) on each factor, and on each of the eight combinations of high factor scores. The number of symptoms endorsed as 'moderately' severe or greater, and the sum of symptom severity scores were compared between the eight groups by a one-way ANOVA. The dependency of co-occurring subtypes was evaluated via a one-sample z -test between observed and expected rates. To evaluate the differences between subtypes for rates of co-morbid diagnoses, Chi-square was used to measure overall effects and logistic regression was used to evaluate odds ratios (OR) between subtypes. To evaluate the main effects and interactions between subtypes on continuous measures of functional status, ANOVA was used. Here, results were summarized as mean and standard deviations, and effect sizes were indexed as η^2 (eta squared). Chi-square and omnibus F -tests employed a type I error rate (significance level) of 5%. To control experiment-wise error rates, post hoc comparisons employed a type I error rate of 1%.

Table 1
Reported rates of the severity of each ‘minor’ symptom of CFS

Symptom	None	Mild or moderate	Substantial	Severe or very severe
Feverishness (%)	36.0	30.4	17.4	16.2
Swollen glands	24.2	33.5	16.1	26.0
Sore throat	19.4	35.1	22.5	23.2
New onset headache	13.0	19.3	23.0	44.7
Muscle pain	4.3	13.7	15.5	66.4
Muscle weakness	9.9	14.3	24.2	51.6
Joint problems	14.9	14.3	19.9	50.9
Post-exertional fatigue	1.9	8.7	11.2	78.3
Sleep problems	0.6	8.0	13.7	77.6
Memory problems	0.6	20.9	22.2	56.3

2. Results

2.1. Sampling and demographics

Of the 176 women enrolled, 161 (91.4%) provided complete data; only they are considered in the following. With a mean age of 39.7 year (S.D. = 8.8), 146 (90.7%) were white, and all but 26 (83.9%) had at least 1 year of college; 67.1% of the sample reported a gradual onset of symptoms; 56.3% met criteria for FM; 12.9% met criteria only for current MDD, 14.3% met criteria only for a current anxiety disorder and 12.9% met criteria for both current MDD and current anxiety disorder; 22.4% reported disability.

2.2. Symptom severity

Table 1 shows that a majority of subjects reported ‘severe’ or ‘very severe’ muscle pain, muscle weakness, joint pain, post-exertional fatigue, sleep disturbance and memory/attention problems. Forty percent reported new headaches, but fewer reported ‘severe’ or ‘very severe’ feverishness, swollen glands or sore throat.

2.3. Principal components analysis (PCA)

PCA of the 10 symptoms yielded three factors accounting for 35.7, 15.1 and 11.4% of variability in symptom severity. Factor 1, *Musculoskeletal* (MUSC), collected symptoms of muscle pain (rotated loading = .83), muscle weakness (.81), joint pain (.83), post-exertional fatigue (.45) and sleep

disturbance (.40). Factor 2, *Infectious* (INF) collected feverishness (.75), swollen glands (.77) and sore throat (.84). Finally, Factor 3, *Neurological* (NEURO) collected symptoms of memory or attention problems (.78), headache (.65), post-exertional fatigue (.60) and sleep disturbance (.38). These factors tended to display simple structure, in that all items except sleep and post-exertional fatigue loaded on only one factor. Thus, the minor symptoms of CFS may be factored into three independent components.

2.4. Typology

Table 2 shows the prevalence of single and multiple subtypes of CFS defined by upper tertile scores on each of the three factors. As shown, 28.7% of the sample were not characterized by an extreme score on any factor, 43.9% were characterized by an extreme score on only one factor, 23.0% by an extreme score on two factors and 4.5% by an extreme score on all three factors. Table 2 also shows that the group not characterized by an extreme score on any factor endorsed fewer symptoms as at least ‘moderately’ severe ($F(1, 155) = 41.1, p < .001$), and had lower total symptom severity scores ($F(1, 155) = 83.0, p < .001$) than the other subtypes. For these reasons, we will label this group as ‘MILD’.

To determine if the co-occurring rate of two and three subtypes exceeded chance expectations, expected values (i.e., assuming independence) were computed as the product of singly occurring subtypes; expected rates (95% confidence limits) were: MUSC + INF = 1.7% (0.5, 5.9); MUSC + NEURO = 2.4% (0.8, 6.8); INF + NEURO = 2.3% (0.8,

Table 2
Frequency (%) of occurrence of extreme (upper tertile) factor scores defining each subtype ($N = 157$), the mean (S.D.) number of symptoms endorsed as ‘moderate’ or greater severity, and the mean (S.D.) sum of symptom severity ratings for each subtype

Subtype	N (%)	Symptoms endorsed \geq moderate	Sum severity
MILD	45 (28.7)	6.5 (2.0)	23.0 (6.7)
MUSCculoskeletal only	21 (13.4)	7.7 (1.4)	31.0 (4.3)
INFfectious only	20 (12.7)	8.3 (1.6)	31.1 (7.7)
NEUROlogical only	28 (17.8)	7.5 (1.4)	30.0 (5.1)
MUSC + INF	18 (11.5)	9.7 (0.5)	42.8 (2.3)
MUSC + NEURO	8 (5.1)	8.4 (1.1)	36.5 (4.4)
INF + NEURO	10 (6.4)	9.3 (1.3)	38.3 (6.6)
MUSC + INF + NEURO	7 (4.5)	9.7 (0.5)	45.1 (2.0)

6.8) and MUSC + INF + NEURO = 0.3% (0.02, 2.0). By this method, rates of MUSC + INF and MUSC + INF + NEURO each occurred significantly more often than would have been expected by chance. Greater than expected rates suggest that these two subtypes may arise from a different pathophysiology than their constituents.

2.5. Construct validation and discrete measures of clinical function

To evaluate the utility of the typology, we evaluated associations between functional indices and subtype membership, factor severity and number of upper tertile scores.

2.5.1. Disability

Disability rates were related to the number of high factor scores ($\chi^2(3, N = 157) = 12.52, p < .01$). Table 3A shows that those with high scores on all factors were at increased risk of disability, while the MILD group was at significantly reduced risk of disability, and Table 3B shows that those with high scores on all three subtypes were at greater risk than those with either one or two subtypes ($\chi^2(1, N = 112) = 4.41, p < .05$). The risk of disability increased with increasing tertiles of the INF and NEURO factors, but not the MUSC factor. Logistic regression showed, in both cases, increased risk only among those in the highest tertile, where OR = 3.21 (95% CI = 1.30, 7.92) for INF and OR = 2.58 (95% CI = 1.09, 6.11) for NEURO subtype. Because differences could not be attributed to any specific subtype, disability risk appears to be most closely related to frequency and severity of symptoms reports.

2.5.2. Sudden onset

Table 3B shows that sudden onset was more likely among those in the upper tertile of all three factors than among those in the MILD group ($\chi^2(1, N = 49) = 4.41, p < .05$). However, those with one or two subtypes were not different from MILD ($\chi^2(1, N = 112) = 1.27, p > .25$), failing to suggest a graded

effect of number of symptoms. Analysis of rates shown in Table 3A failed to show a difference in sudden onset attributable to any specific subtype, or to increasing scores within any factor. Thus, increased risk of sudden onset appears limited to those showing the most and/or most severe symptoms.

2.5.3. FM

Analysis showed that tertile scores of the MUSC factor, but not INF or NEURO, were linearly related to risk of FM. Logistic regression showed that rates of FM were higher among those in the middle (63.5%, OR = 2.48, 95% CI = 1.12, 5.49) and highest tertiles of the MUSC factor (66.5%, OR = 2.78, 95% CI = 1.25, 6.16) than in the lowest tertile (41.2%). Thus, increased symptom reporting is not generally related to increased risk of an FM diagnosis; rather, FM risk increases specifically with increasing reports of MUSC symptoms.

2.5.4. Depression and anxiety

Table 3A shows rates of depression and anxiety disorder. While rates were highest in the MUSC and INF + NEURO subtypes, analysis failed to show difference in rates among subtypes ($\chi^2(7, N = 157) = 13.28, p < .07$ for depression and $\chi^2(7, N = 144) = 9.0, p > .25$ for anxiety). Further, rates did not vary with the number of upper tertile factor scores (Table 4B), or with increasing tertile scores on any factor.

2.6. Continuous measures of physical and mental function

2.6.1. SF-36 physical

A mean PCS score of 25.3 indicates that the average subject was severely impaired. Analysis showed that PCS also varied among subtypes ($F(7, 118) = 3.9, p < .001, \eta^2 = .19$). Table 4A shows the least impairment in the MILD group and more impairment in the MUSC + INF and MUSC + INF + NEURO groups, relative to the average subject. Table 4B shows declining PCS scores (poorer function) with

Table 3
Rates of reported 'sudden onset' and reported disability, and diagnoses of FM, MDD and anxiety disorder

	Disabled (%)	Sudden (%)	FM (%)	MDD (%)	Anxiety (%)
All subjects	28.7	32.5	57.1	28.5	26.4
(A) Sub-type (factor score in upper tertile)					
MILD	13.3*	23.8	55.6	20.5	25.0
MUSC	23.8	14.3*	76.2	52.6*	36.8
INF	25.0	40.0	36.8	22.2	16.7
NEURO	39.3	34.6	46.4	20.8	33.3
MUSC + INF	38.9	35.3	55.6	20.0	6.7
MUSC + NEURO	25.0	50.0	75.0	28.6	14.3
INF + NEURO	40.0	40.0	80.0	60.0*	50.0
MUSC + INF + NEURO	71.4*	71.4*	57.1	28.6	28.6
(B) Number of upper tertile factor scores					
0 ($n = 45$)	13.3	23.8	55.6	20.5	25.0
1 ($n = 68$)	30.4 ⁺	29.9	52.9	31.1	29.5
2 ($n = 36$)	36.1 ⁺	40.0	66.7	34.4	21.9
3 ($n = 7$)	71.4*	71.4 ⁺	57.1	28.6	28.6

⁺ Rate varies, $p < .05$, relative to full sample in A, and relative to MILD group in B.

* Rate varies, $p < .01$, relative to full sample in A, and relative to MILD group in B.

Table 4
Mean (S.D.) score on four measures of functional status in subtypes of CFS

	PCS	MCS	Days in bed (log ₁₀)	Days 'cut down'
All subjects	25.3 (3.9)	42.8 (10.0)	.56 (.44)	14.1 (10.0)
(A) Sub-type (factor score in upper tertile)				
MILD	29.3 (8.8)*	43.9 (8.7)	.39 (.37)	10.8 (10.0)
MUSC	24.2 (7.9)	42.9 (10.5)	.60 (.42)	15.1 (10.8)
INF	26.5 (7.3)	45.9 (8.2)	.46 (.37)	11.3 (7.8)
NEURO	24.2 (7.1)	41.2 (11.2)	.42 (.51)	16.4 (10.8) ⁺
MUSC + INF	20.0 (4.2)*	43.4 (10.2)	.83 (.36)*	16.9 (8.4) ⁺
MUSC + NEURO	23.4 (10.7)	47.9 (8.4)	.80 (.43) ⁺	9.7 (9.5)
INF + NEURO	25.4 (6.4)	34.7 (12.9)*	.88 (.52)*	20.9 (7.5)*
MUSC + INF + NEURO	17.6 (4.0)*	42.0 (10.1)	.79 (.37) ⁺	20.6 (8.4)*
(B) Number of upper tertile factor scores				
0 (n = 41)	29.8 (8.4)	43.9 (8.7)	.39 (.37)	10.8 (10.0)
1 (n = 55)	24.6 (7.7)*	43.1 (10.2)	.49 (.44)	14.4 (10.1) ⁺
2 (n = 30)	21.5 (5.5)*	40.8 (11.7)	.84 (.42)*	16.7 (9.0)*
3 (n = 7)	18.2 (3.9)*	42.0 (10.1)	.79 (.37) ⁺	20.6 (8.4)*

⁺ Mean varies, $p < .05$, relative to grand mean in A, and relative to MILD mean in B.

* Mean varies, $p < .01$, relative to grand mean in A, and relative to MILD mean in B.

increasing number of upper tertile scores ($F(3, 122) = 7.8$, $p < .001$, $\eta^2 = .16$). Relative to the MILD group, groups with one or more upper tertile scores evidenced poorer physical ability. PCS also declined with increasing tertiles of the MUSC and INF factors ($F(2, 99) = 7.1$, $p < .001$, $\eta^2 = .13$ and $F(2, 99) = 3.5$, $p < .05$, $\eta^2 = .07$, respectively).

2.6.2. SF-36 mental

A mean MCS score of 42.8 suggests that the average subject was moderately impaired. There were also differences among subtypes in MCS ($F(7, 118) = 2.3$, $p < .05$, $\eta^2 = .12$). Table 5A shows that the INF + NEURO group reported poorer function than the average subtype. Unlike PCS, MCS did not vary with either the number of high factor scores (Table 5B), or with increasing scores within any single factor (not shown).

2.6.3. Days in bed (DIB)

Table 5B shows that DIB increased with the number of upper tertile factor scores ($F(3, 120) = 7.6$, $p < .001$, $\eta^2 = .16$). Days 'cut down' (DCD) increased with particular subtypes as well as the number of subtypes ($F(7, 125) = 2.6$, $p < .05$, $\eta^2 = .12$ and $F(3, 129) = 3.3$, $p < .05$, $\eta^2 = .07$, respectively). Table 5A shows that activity was reduced among those in the NEURO group, as well as in all co-morbid groups except MUSC + NEURO, and Table 5B shows activity scores were inversely proportional to the number of upper tertile factor scores. In addition, middle and upper tertile NEURO scores were directly associated with DCD ($F(2, 107) = 5.2$, $p < .01$, $\eta^2 = .09$). Thus, results for PCS, DIB and DCD were similar; those most at risk for reduced function tended to have high scores on multiple subtypes or higher scores within each subtype. While these

Table 5
Mean (S.D.) score on three measures of neuropsychological performance in subtypes of CFS

	CPT-RT	Peg Board	Complex Figure Copy
All subjects	425.2 (76.2)	70.7 (15.2)	66.7 (5.8)
(A) Sub-type (factor score in upper tertile)			
MILD	401.8 (43.4) ⁺	67.2 (11.6)	68.4 (3.8) ⁺
MUSC	416.1 (64.6)	71.8 (11.5)	65.0 (4.4)
INF	398.4 (51.2)	67.0 (10.5)	66.3 (7.0)
NEURO	454.9 (94.6) ⁺	74.8 (18.4) ⁺	66.3 (8.0)
MUSC + INF	424.9 (83.1)	71.2 (13.6)	67.8 (3.3)
MUSC + NEURO	454.5 (107.1)	66.6 (8.3)	67.1 (2.5)
INF + NEURO	423.9 (50.5)	69.7 (15.4)	67.3 (2.5)
MUSC + INF + NEURO	528.4 (115.3)*	87.0 (33.7)*	60.1 (10.4)*
(B) Number of upper tertile factor scores			
0 (n = 41)	401.8 (43.4)	66.2 (9.2)	68.3 (3.8)
1 (n = 52)	426.9 (78.1)	73.0 (15.5)	66.6 (4.9)
2 (n = 25)	431.4 (81.1)	69.8 (12.5)	65.7 (7.8)
3 (n = 8)	528.4 (115.3)*	81.6 (34.3)*	62.4 (10.6)*

⁺ Mean varies, $p < .05$, relative to grand mean in A, and relative to MILD mean in B.

* Mean varies, $p < .01$, relative to grand mean in A, and relative to MILD mean in B.

measures suggest that physical performance was inversely proportional to symptom severity, they fail to implicate any particular subtype.

2.6.4. Cognitive function

To test our second hypothesis, that cognitive function would be most affected among those in the NEURO subtype, a one-way ANOVA was used to compare scores among the eight subtypes, and among those with one or more upper tertile factor scores. Results indicated differences among subtypes for the CPT reaction time task (CPT-RT), the Peg Board (PB) task and the Complex Figure Copy (CFC) task ($F(7, 141) = 4.0, p < .001, \eta^2 = .17$; $F(7, 142) = 2.1, p < .05, \eta^2 = .09$ and $F(7, 145) = 2.4, p < .05, \eta^2 = .10$, respectively). As shown in Table 5A, those in the upper tertile of the NEURO factor and those with upper tertile scores on all three factors showed reduced performance on the PB task and the CPT-RT measure, while only those with upper tertile scores on all three factors showed reduced CFC performance. Table 5B shows that, relative to the MILD group, performance on all three tasks declined only in the group with three upper tertile factor scores ($F(3, 145) = 6.4, p < .001, \eta^2 = .12$; $F(3, 146) = 3.8, p < .01, \eta^2 = .07$ and $F(3, 149) = 5.4, p < .001, \eta^2 = .10$, respectively). Thus, reduced performance of speed-dependent tasks characterized those with high NEURO scores or high scores on all three factors.

Analysis also indicated an interaction between NEURO and INF factors on tests of Immediate Recall, Digit Span Forward and Backward and WAIS Vocabulary ($F(4, 126) = 2.7, p < .05, \eta^2 = .08$; $F(4, 124) = 4.0, p < .01, \eta^2 = .11$; $F(4, 124) = 2.5, p < .05, \eta^2 = .07$ and $F(4, 125) = 3.7, p < .01, \eta^2 = .10$, respectively). Fig. 1 shows that among those all in the high tertile of INF factor, those in the middle or high tertile of the NEURO factor showed poorer performance than those in the low tertile. (Scores for groups defined by low and medium tertiles of the INF subtype (not shown), were not statistically different from the score shown by the high INF, low NEURO group.) There were no differences among subtypes on measures

of CPT false positives, delayed recall, trail-making or WAIS block design.

3. Discussion

Because CFS is defined by clinical criteria, similar symptoms may result from different causes. To address this issue of heterogeneity, Fukuda et al. (1994) recommended using stratification strategies to identify patient subtypes with different etiological or pathophysiological mechanisms. Toward this end, we categorized patients on the basis of their scores on a principal components analysis of severity ratings of the minor symptoms from the 1988 case definition of CFS. Groups derived from this analysis showed high levels of positive predictive value for FM. Those in the upper tertile of the MUSC factor were twice as likely to have FM as those in lower tertiles, and this association reduced unexplained variability in the occurrence in FM in CFS patients by about 5%. While this finding was not unexpected, it validates the hypothesized predictive value of this report. Supporting our second hypothesis, those in the upper tertile of the NEURO factor were significantly more likely to evidence reductions in cognitive function, particularly those dependent on processing speed. Interestingly, measures of attention and memory were also reduced in those patients who had high scores on both the NEURO and INF factors, but not the INF factor alone. At least 10% of the variance in each of these measures of cognitive function, a moderate-sized effect, was attributable to increasing scores on the NEURO factor. Finding more cognitive impairment in patients who report more neurological symptoms supports our hypothesis that some CFS patients may have a neurological basis for their symptoms. Thus, the sub-typing strategy was specific in showing that FM was more prevalent in the MUSC subtype; and that reductions in cognitive function were limited to the NEURO subtype, which sometimes interacted with the INF subtype. These data indicate that patients' symptom reports have good predictive value for test findings.

The INF subtype, in isolation, was distinguished by the lowest rates of FM, and by generally reporting less physical impairment than other subtypes. Rates of depression and anxiety disorders, while highest in MUSC and in INF + NEURO groups, were not statistically different among groups. MCS was also depressed in the latter group. Finally, functional status was poorer, and disability more frequent with higher scores on any (or many) of the factors. Thus, these last functional indices were related to CFS severity that is independent of particular subtype.

Further research is needed to validate each of these subtypes and the functional implications of our sub-typing strategy. One evaluation of the validity of this typology might determine if treatment has different benefits for different subtypes. For example, if heterogeneity in response to a drug were related to subtype, this might suggest testable hypotheses of different mechanisms related to either maintenance or pathophysiology of their symptoms. The typology might also be validated by different signs in new onset cases. For example, those showing

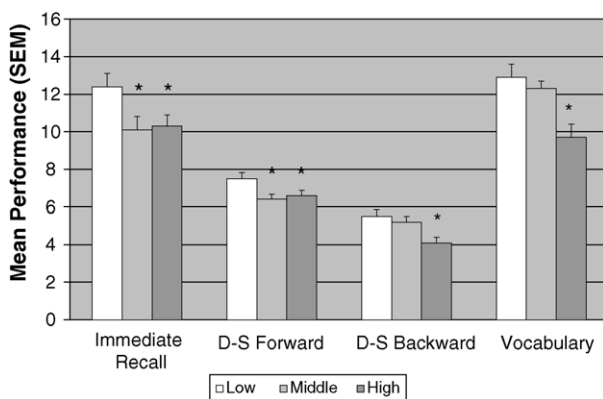


Fig. 1. Mean (S.E.M.) scores on tests of Immediate Recall, Digit Span Forward, Digit Span Backward and Vocabulary in groups defined by the low, middle and high tertiles of the neurological factor (open, lighter and darker grays), all in the high tertile of the INF factor ($N = 151$; asterisk (*) indicates $p < .05$).

an INF subtype would be expected to present with immunological evidence of infection more often than those showing the MUSC or NEURO subtype.

Several prior studies have examined the factor structure of the symptoms of chronic fatigue. Current results are in close agreement with those obtained in a community-based study reported by Nisenbaum et al. (2004), where a similar factor structure was found. Results less closely resemble a previous community-based study by this group (Nisenbaum et al., 1998), which failed to detect a musculoskeletal factor. Another large study reported by Jason et al. (2002) also found a factor structure similar to that reported here, but with an additional factor, perhaps due to the use of additional symptom reports. Importantly, however, the literature is beginning to show some consistency in the sub-typing strategy proposed here.

While rates of depression and anxiety appear higher than community rates, they may not be inconsistent with rates found in other chronic diseases. For example, a recent review of patients with multiple sclerosis, another fatiguing illness, showed an annual incidence (most comparable but less restrictive than our measure of 'current') of about 20% (Siegert and Abernethy, 2005), similar to rates found here. Further, the fact that rates of depression and anxiety did not increase with increasing factor scores fails to suggest psychiatric distress is a reaction to more CFS symptoms. Results are, however, consistent with our previous report showing that those with a psychiatric diagnosis were at reduced risk for cognitive problems (DeLuca et al., 1997b), in that those in the NEURO subtype were not at increased risk for either depression or anxiety disorders.

Several limitations should be acknowledged. First, while post hoc tests were corrected for multiple comparisons, several results were not hypothesized. While all studies benefit from replication, those latter effects are in particular need. Second, this study limited its analysis to women, and results are not generalizable to men. Third, no control group was included, so that apparently high rates of co-morbid complaints, particularly psychiatric disorders, are difficult to interpret. Finally, this cross-sectional analysis does not allow for causal inferences.

In summary, these analyses suggest that compelling information is contained in patients' reports of the severity of their CFS symptoms, and that different subtypes based on these reports have significant levels of positive predictive value for some clinical findings. Together, these analyses suggest that this sub-typing strategy reduced patient pool heterogeneity as follows: (1) patients high on the MUSC factor were more likely to have FM and least likely to report sudden onset; (2) patients in the INF subtype were at lower risk for FM as well as for impaired physical function; (3) patients in the NEURO subtype were at increased risk for reduced cognitive function and reduced physical ability; (4) those with the most severe symptoms of each subtype, or of all subtypes, were more likely to report disability, sudden onset, and to display cognitive difficulties; (5) the MILD subtype was at reduced risk for disability and cognitive problems, but at nominal risk for FM, psychiatric co-morbidity or sudden onset and (6) rates of depression and anxiety disorders were similar in all subtypes,

and their prevalence did not increase with symptom reports, suggesting that these disorders may reflect the general influence of chronic illness rather than a specific co-morbidity.

Acknowledgement

This study was supported by NIH grant AI-32247.

Reference

- Ciccone, D.S., Natelson, B.H., 2003. Comorbid illness in the chronic fatigue syndrome: a test of the single syndrome hypothesis. *Psychosomatic Medicine* 62, 268–275.
- DeLuca, J., Johnson, S.K., Ellis, S.P., Natelson, B.H., 1997a. Sudden vs. gradual onset of chronic fatigue syndrome differentiates individuals on cognitive and psychiatric measures. *Journal of Psychiatric Research* 31, 83–90.
- DeLuca, J., Johnson, S.K., Ellis, S.P., Natelson, B.H., 1997b. Cognitive functioning is impaired in chronic fatigue syndrome patients devoid of psychiatric disease. *Journal of Neurology, Neurosurgery and Psychiatry* 62, 151–155.
- Fukuda, K., Straus, S.E., Hickie, I., Sharpe, M.C., Komaroff, A., Schluederberg, A., et al., 1994. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine* 121, 953–959.
- Holmes, G.P., Kaplan, J.E., Gantz, N.M., Komaroff, A.L., Schonberger, L.B., Straus, S.E., et al., 1988. Chronic fatigue syndrome: a working case definition. *Annals of Internal Medicine* 108, 387–389.
- Jason, L.A., Torres-Harding, S.R., Carrico, A.W., Taylor, R.R., 2002a. Symptom occurrence in persons with chronic fatigue syndrome. *Biological Psychology* 59, 15–27.
- Jason, L.A., Taylor, R.R., Kennedy, C.L., Jordan, K., Huang, C.F., Torres-Harding, S., Song, S., Johnson, D., 2002b. A factor analysis of chronic fatigue symptoms in a community-based sample. *Social Psychiatry and Psychiatry Epidemiology* 37, 183–189.
- Jason, L.A., Corradi, K., Torres-Harding, S., Taylor, R.R., King, C., 2005. Chronic fatigue syndrome: the need for subtypes. *Neuropsychopharmacology Review* 15, 29–58.
- King, C., Jason, L.A., 2005. Improving the diagnostic criteria and procedures for chronic fatigue syndrome. *Biological Psychology* 68, 87–106.
- Marcus, S., Robins, L.N., Bucholz, K., 1990. Quick Diagnostic Interview Schedule 3R Version 1. Washington University School of Medicine, St. Louis, MO.
- Natelson, B.H., Johnson, S.K., DeLuca, J., Sisto, S., Ellis, S.P., Hill, N., et al., 1995. Reducing heterogeneity in chronic fatigue syndrome: a comparison with depression and multiple sclerosis. *Clinical and Infectious Diseases* 21, 1204–1210.
- Nisenbaum, R., Reyes, M., Mawle, A.C., Reeves, W.C., 1998. Factor analysis of unexplained severe fatigue and interrelated symptoms: overlap with criteria for chronic fatigue syndrome. *American Journal of Epidemiology* 37, 183–189.
- Nisenbaum, R., Reyes, M., Unger, E.R., Reeves, W.C., 2004. Factor analysis of symptoms among subjects with unexplained chronic fatigue: what can we learn about chronic fatigue syndrome? *Journal of Psychosomatic Research* 56, 171–178.
- Peckerman, A., LaManca, J.J., Dahl, K., Qureshi, B., Natelson, B.H., 2003. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. *American Journal of Medical Science* 326, 55–60.
- Siegert, R.J., Abernethy, D.A., 2005. Depression in multiple sclerosis: A review. *Journal of Neurology, Neurosurgery and Psychiatry* 76, 469–475.
- Schluederberg, A., Straus, S.E., Peterson, P., Blumenthal, S., Komaroff, A.L., Spring, S.B., et al., 1992. Chronic fatigue syndrome research. Definition and medical outcome assessment. *Annals of Internal Medicine* 117, 325–331.
- Tseng, C.-L., Natelson, B.H., 2004. Few gender differences exist between women and men with chronic fatigue syndrome. *Journal of Clinical Psychology in Medical Settings* 11, 55–62.

- Ware, J.E., Snow, K.K., Kosinski, M., Gandek, B., 1993. SF-36 Health Survey. Manual and Interpretation Guide, first ed. The Health Institute, New England Medical Center, Boston.
- Wilson, A., Hickie, I., Hadzi-Pavlovic, D., Wakefield, D., Parker, G., Straus, S.E., Dale, J., McCluskey, D., Hinds, G., Brickman, A., Goldenberg, D., Demitrack, M., Blakely, T., Wessely, S., Sharpe, M., Lloyd, A., 2001. What is chronic fatigue syndrome? Heterogeneity within an international multi-centre study. *Australian and New Zealand Journal of Psychiatry* 35, 520–527.
- Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., et al., 1990. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. *Arthritis and Rheumatism* 33, 160–172.