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# Chronic Fatigue Syndrome in Male Gulf War Veterans and Civilians

## A Further Test of the Single Syndrome Hypothesis

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### Abstract

Different modes of fatigue onset in male Gulf War veterans versus male civilians raise the possibility that chronic fatigue syndrome (CFS) may not be a single disease entity. We addressed this issue by comparing 45 male veterans with CFS to 84 male civilians who satisfied identical case criteria. All were evaluated for fibromyalgia (FM), multiple chemical sensitivity and psychiatric comorbidity. CFS was more likely to present in a sudden flu-like manner in civilians than veterans ( $p < .01$ ) and comorbid FM was more prevalent in civilians ( $p < .01$ ). These findings question the assumption that all patients with CFS suffer from the same underlying disorder.

### Keywords

- *comorbidity*
- *diagnosis*
- *fatigue*
- *medically unexplained illness*
- *veteran*

CHRONIC fatigue in the absence of physical exertion is called neurasthenia (ICD-10) in the United Kingdom but in the United States the term chronic fatigue syndrome (CFS) has become more popular. Case criteria for CFS, established by the Centers for Disease Control, stipulate that the fatigue must be new (or of definite onset) and produce substantial impairment in social or occupational functioning (Fukuda et al., 1994). The fatigue must also last for at least six months, fail to recover with rest, and be accompanied by one or more infectious, neuropsychiatric, and/or rheumatological symptoms. The case definition relies exclusively on self-reported symptoms and explicitly excludes individuals with medically explained fatigue. In the absence of an objective marker, however, it is possible that not all patients with CFS have the same disorder. Subgroups may exist that differ in pathogenesis but appear superficially similar by virtue of a common final pathway.

CFS presents in two ways: (1) sporadic with no apparent trigger other than infection for some patients; and (2) quasi-epidemic as in the case of Gulf War veterans. Although veterans are required to demonstrate good health prior to deployment, approximately 6 percent came forward with complaints of fatigue, pain, and/or cognitive dysfunction shortly after their return home (Fukuda et al., 1998). An epidemiological study found that 2.2 percent of these veterans fulfilled the case definition for CFS (McCauley et al., 2002). This is substantially higher than the 0.4 percent rate reported among civilians in a community sample (Jason et al., 1999).

Differences in fatigue onset and increased prevalence in males suggest that CFS in Gulf veterans may not be the same syndrome previously observed in civilians. In an earlier study comparing Gulf veterans with CFS to civilian cases we found that veterans were less likely to report sudden flu-like onset and were less physically impaired (Pollet et al., 1998). However, that study was limited by the fact that the civilian sample was predominantly female whereas the veteran sample was predominantly male. These differences were almost inevitable since most civilian care seekers with CFS tend to be female while the majority of veterans tend to be male. Furthermore, veterans had expected rates of minority membership while civilians were mostly White.

Nevertheless, differences in onset and prevalence raise the possibility that CFS is not a discrete illness but rather a group of disorders sharing a common final pathway. Veterans exposed to war-related

stress, for example, may develop a unique fatigue syndrome with illness characteristics different from those of civilian fatigue. Alternatively, failure to find differences in illness presentation between veterans and civilians would suggest a single underlying disease mechanism and perhaps a single diagnostic entity. We sought to address this issue in the present study by comparing male veterans with CFS to male civilians who satisfied identical diagnostic criteria (Fukuda et al., 1994). The existence of our federally funded Center which collected data from civilians for 12 years allowed us to assess enough men with CFS to allow for a matched comparison of male veterans and their civilian counterparts.

Finding differences between different CFS subtypes would also cast doubt on the single syndrome hypothesis which holds that all medically unexplained illnesses are manifestations of a common underlying etiology (Barsky & Borus, 1999). If male veterans and civilians with CFS have the same disorder, we would not expect to find differences in mode of onset, rates of comorbid illness, or functional impairment. However, our own preliminary data suggest that such differences may well exist (Pollet et al., 1998). Moreover, civilians with post-traumatic stress disorder (PTSD) are known to be at increased risk of an unexplained pain syndrome called fibromyalgia (Amir et al., 1997; Sherman, Turk, & Okifuji, 2000). Since veterans are known to be at greater risk for PTSD than civilians (Card, 1987) it follows that veterans with CFS should have higher rates of comorbid fibromyalgia than civilians with CFS.

A second possible difference between veterans and non-veterans with CFS might be their higher risk of multiple chemical sensitivity (MCS), an unexplained illness thought to be caused by exposure to environmental toxins. MCS occurs in approximately one-third of civilian patients with CFS (Ciccone & Natelson, 2003), and yet toxic environmental exposure in these patients is rare. By contrast, Gulf veterans reported significant environmental exposures (e.g. burning diesel fuel, nerve gas, etc.), multiple vaccinations, and chemoprophylactic use of drugs such as pyridostigmine bromide. If such environmental agents are involved in the pathophysiology of CFS, then veterans with CFS should have higher rates of MCS than civilians with CFS. At issue in the present study was a head to head comparison of male veteran and civilian samples for the purpose of reconciling these competing claims.

## Methods and procedure

The participants were 45 male veterans from the Gulf War Research Center and 84 male civilians from the CFS Cooperative Center. All subjects fulfilled the 1994 case definition for CFS (Fukuda et al., 1994). Thus all subjects reported a new onset of fatigue severe enough to produce a substantial impairment in physical functioning and lasting six months or longer. In addition, subjects had to report recurring or continual problems, lasting at least six months, with four of the following symptoms: sore throat; tender lymph nodes as occur with an infection; myalgia; arthralgia; new onset of headache; unrefreshing sleep; difficulty with attention or concentration; and the complaint that even minimal exertion produced a dramatic worsening of the entire symptom complex. The veterans, all in the Veteran's Administration (VA)'s Gulf War Registry (Gray et al., 1998), came from 10 states east of the Mississippi River and responded affirmatively to a letter asking if they suffered from fatiguing illness. Subsequently, they filled out a screening questionnaire and reported symptoms consistent with CFS. Civilians were either self-referred in response to media reports or referred by their physicians and came mostly from states in the north-east USA. They completed a similar screening questionnaire and reported symptoms consistent with CFS. Patients with medical or psychiatric conditions that preclude a diagnosis of CFS were not eligible to enroll.

After screening positive, veterans and civilians were brought to the Center for a detailed history and physical examination as well as blood sampling to rule out common medical causes of fatigue (Schluederberg et al., 1992). Careful attention was devoted to determining if the illness had a sudden, flu-like onset or began gradually. Data from patients' original questionnaires as well as information elicited at the time of history and physical exam were evaluated to allow classification of patients into 'severe' and 'non-severe' CFS groups. 'Severe CFS' was defined as a patient fulfilling the more demanding 1988 case definition (Holmes et al., 1988) as well as endorsing at least seven of the minor symptoms (minimum of substantial, severe, or very severe intensity) in the month prior to intake (i.e.  $\geq 3$  on 0 to 5 Likert scales). Physical complaints required by the 1988 CFS case definition include: fever; tender glands; sore throat; new onset headache; muscle pain; muscle weakness; joint pain; prolonged fatigue; unrefreshing sleep; and

memory problems. All patients who fulfilled the less stringent 1994 case definition but not the 1988 definition were labeled as 'non-severe'.

The initial examination also allowed us to determine if the patient had multiple chemical sensitivity (MCS) as per our previous operational definition (Pollet et al., 1998). That diagnosis was made if a patient reported that exposure to more than one odorant produced symptoms in more than one body system plus reporting efforts to avoid those odorants. Fibromyalgia (FM) was diagnosed based on history and physical examination according to the American College of Rheumatology's clinical criteria (Wolfe et al., 1990). Patients also underwent a standardized interview, the computerized version of the Diagnostic Interview Schedule (DIS), to diagnose major psychiatric illness (Marcus, Robins, & Bucholz, 1990). The DIS is a structured interview designed for use by nonclinical (lay) personnel. Comparisons of lay versus physician DIS interviewers have demonstrated acceptable diagnostic reliability and validity (Helzer & Robins, 1988; Helzer, Spitznagel, & McEvoy, 1987). The version used in the present study relied on DSM-III R criteria (Robins & Helzer, 1985). Interviewers were tested periodically to ensure uniformity of administration. No patients were enrolled if they had a known medical cause of fatigue and none had a psychiatric exclusion for CFS (i.e. schizophrenia, bipolar or eating disorders, or substance/alcohol abuse within the past two years) (Fukuda et al., 1994).

Patients self-reported the number of days they spent in bed, the number days with reduced activity in the past month, and their disability status. They completed the Medical Outcomes Study (MOS) Short Form-36 (SF-36), a commonly used vehicle for assessing functional status and health-related quality of life (Ware, Snow, Kosinski, & Gandek, 1993). Scores on SF-36 subscales range from 0 to 100 with higher scores reflecting better health (less disability). Finally, veterans completed a standard checklist of nine toxic exposures that might have occurred in the Gulf (e.g. smoke from burning oil wells, pesticides, debris from SCUDS, etc.). On average, 64 percent of the current veteran sample reported exposure to six or more potentially toxic chemicals.

Categorical (diagnostic) outcomes were compared using nonparametric statistics (Chi-square) while continuous outcomes (e.g. SF-36 scores) were compared using one-way analysis of variance and Bonferroni post-hoc comparisons (at the .05 level).

Table 1. Comparison of African American (black) male veterans, white male veterans, and white male civilians with chronic fatigue syndrome. Means and standard deviations shown for continuous measures

	(I) Black veterans (n = 15)	(II) White veterans (n = 30)	(III) White civilians (n = 82)	Statistical comparisons
<i>Demographics</i>				
Age	35.0 (10.2)	32.9 (6.7)	35.4 (8.5)	NS
Education (years)	13.1 (1.6)	13.1 (1.4)	15.8 (2.3)	III>I**; III>II**
Married/living together	53.3%	46.7%	50.0%	NS
Disabled	20.0%	13.3%	42.7%	III>II**
<i>Illness characteristics</i>				
Gradual onset	93.3%	90.0%	57.3%	I>III**; II>III**
Severe CFS (clinician rated)	60.0%	43.3%	62.2%	NS
<i>Comorbid illness</i>				
Fibromyalgia	6.7%	0.0%	22.0%	III>II**
Multiple chemical sensitivity	26.7%	26.7%	26.8%	NS
Depression	80.0%	36.7%	51.9%	I>III*; I>II**
PTSD	46.7%	26.7%	2.5%	I>III**; II>III**
Generalized anxiety	13.3%	6.7%	16.0%	NS
Psychiatric (axis I) diagnosis	93.3%	70.0%	60.5%	I>III*
<i>Functional impairment</i>				
Days cut down/month	7.4 (7.5)	7.3 (9.4)	14.2 (10.8)	III>II*
Days in bed/month	3.0 (3.1)	2.5 (4.8)	4.2 (7.1)	NS
<i>MOS Short Form-36</i>				
Physical function	51.4 (22.7)	56.6 (20.5)	55.2 (23.6)	NS
Physical disability	10.7 (23.4)	20.7 (28.4)	7.4 (15.6)	II>III*
Pain	33.1 (28.5)	41.2 (18.4)	42.8 (25.6)	NS
General health	27.9 (16.3)	26.0 (13.7)	25.8 (13.2)	NS
Fatigue (vitality)	20.6 (14.7)	20.7 (14.6)	14.0 (14.8)	NS
Social function	32.1 (21.2)	45.7 (25.5)	38.1 (25.4)	NS
Emotional disability	28.6 (31.6)	44.1 (43.6)	54.4 (44.9)	NS
Mental Health Index	42.3 (16.4)	57.1 (18.6)	57.1 (19.3)	III>I*; II>I*

\**p* < .05; \*\**p* < .01

All statistical tests were conducted using SPSS 12.0.1. Given the exploratory nature of this study, we did not control for inflated risk of Type I error due to multiple comparisons. Missing data reduced sample sizes for SF-36 comparisons (African American veterans = 14; white veterans = 29; white civilians = 68; white civilians without FM = 53).

**Results**

Of 84 civilians and 45 veterans with CFS, two civilians and 15 veterans identified themselves as African American. There were disproportionately more African Americans in the veteran (33.3%) than in the civilian sample (2.4%),  $\chi^2 = 24.6, p = .000$ . Because of this unanticipated difference in racial composition, our first step was to determine if race

was associated with other demographic factors or illness characteristics. Our ability to detect these differences, however, was compromised by the small size of the African American veteran group. Nevertheless, Table 1 shows that while African American and white veterans had equivalent years of schooling they had significantly fewer than white civilians,  $F(2, 124) = 24.17, p = .000$  (Bonferroni pairwise comparisons  $p < .05$ ). Interestingly, African American veterans were much more likely than white veterans to receive a diagnosis of major depression on the DIS,  $\chi^2(1) = 7.52, p = .006$ . The percentage of African American veterans with a lifetime psychiatric (Axis I) diagnosis was alarmingly high (93.3%) but not statistically different from the rate among white veterans (70.0%),  $\chi^2(1) = 3.15, p = .076$ . Perhaps as a result of this increased

depression, African American veterans scored lower on the Mental Health index of the SF-36 compared to white veterans, 42.3 versus 57.1, respectively (Bonferroni pairwise comparison  $p = .051$ ). African American and white veterans reported comparable levels of physical functioning, disability, and CFS severity. In view of the significant racial disparity between veteran and civilian CFS samples and given the fact that African American veterans were more likely to have comorbid depression than their white veteran counterparts, we elected to (a) eliminate two African Americans from the civilian sample leaving 82 white civilians and (b) divide participants into three groups instead of two as planned. As shown in Table 1, data for African American veterans are reported separately from white veterans.

The comparisons most likely to shed light on the existence of possible CFS subgroups were those involving (a) mode of illness onset (sudden versus gradual) and (b) rates of comorbid illness. Turning our attention to onset, fatigue was much more likely to present in a sudden flu-like manner in white male civilians than in white male veterans,  $\chi^2 = 10.47$ ,  $p = .001$ . While civilians were almost evenly split in mode of onset, 90 percent of veterans reported symptoms that began gradually. There were also dramatic differences in comorbidity with FM much more prevalent among white civilians than among white veterans, 22 percent versus 0 percent, respectively,  $\chi^2 = 7.85$ ;  $p = .005$ . This occurred despite a higher rate of PTSD in veterans ( $\chi^2 = 15.64$ ,  $p = .000$ ) that should have conferred an increased (rather than decreased) vulnerability to FM (Amir et al., 1997; Sherman et al., 2000). Rates of FM did not differ between African American veterans and white civilians despite a 15 percent difference in favor of the latter. The small number of African Americans included in the study suggests we should view this conclusion with caution. Contrary to expectations and despite endorsing substantial toxic exposure, veterans did not differ from civilians in their rate of MCS. Other than the previously noted rate of depression among African American veterans there were no other differences in CFS comorbidity.

Aside from differences in mode of onset and comorbidity, we also observed differences between veterans and civilians in functional impairment. The rate of disability among white civilians was substantially higher than it was among white veterans, 42.7 percent versus 13.3 percent ( $\chi^2 = 8.34$ ,  $p = .004$ ). Similarly, civilians reported almost twice as many days during the past month in which they cut

back on usual activities. A one-way analysis of variance yielded an  $F(2, 104) = 5.42$ ,  $p = .006$  and a significant Bonferroni pairwise comparison of white civilians versus white veterans ( $p = .016$ ). On the SF-36 civilians also reported higher levels of physical disability (Physical Role subscale) with an overall  $F(2, 108) = 4.25$ ,  $p = .017$ , and a significant Bonferroni comparison of white civilians versus white veterans ( $p = .013$ ).

The prevalence of FM in the civilian sample raises the possibility that observed differences in mode of onset and functional status might be the result of comorbid illness and not reflect inherent differences between civilians and veterans with CFS. We tested this hypothesis by excluding participants with comorbid FM and repeating the statistical comparisons reported above. The results were unaffected when civilians with FM were excluded suggesting that group differences were not an artifact of comorbid illness.

## Discussion

This is the first study to compare male veterans to male civilians with CFS. One reason this has not been done previously is the relative scarcity of civilian males with CFS. For the most part, civilians with CFS do not report a specific environmental stressor or traumatic event prior to onset (Taylor & Jason, 2001). By contrast, deployment-related stress usually precedes CFS in veterans (Kang, Natelson, Mahan, Lee, & Murphy, 2003). At issue in the present study was the possibility that while both groups may satisfy the same case definition, they nevertheless may not have the same disorder. Contrary to the single syndrome hypothesis, our results show that veterans and civilians differed on a broad range of illness characteristics. Perhaps the most striking differences were in mode of fatigue onset and rates of comorbid illness. Whereas almost all veterans with CFS reported a gradual onset of illness (90%) this was true for only about half the civilians (57.3%). We (Pollet et al., 1998) and others (McCauley et al., 2002) have reported this same outcome in mixed gender populations. Collectively, these findings suggest that CFS presents differently in veteran versus civilian populations and raises the possibility that CFS subgroups may have different underlying causes. The increased rate of sudden, mononucleosis-like onset of CFS in civilians is consistent with an infectious trigger (Zhang et al., 2000). By contrast, the gradual illness onset

reported by veterans suggests that war-related stress may be etiologically significant for these individuals. We have previously reported data suggesting that CFS-like illness is sensitive to the stress of military deployment (Kang et al., 2003). While there is a monotonic relationship between deployment-related stressor intensity and rate of PTSD the relationship between deployment stress and CFS-like illness is more complex. As stressor intensity increases so does risk of CFS-like illness but only to a point after which no further increase is observed. This suggests that deployment stress may not be as closely linked with CFS as it is with PTSD but stressor intensity is nonetheless implicated in both.

We were led to expect higher rates of FM in veterans based on the known comorbidity of FM with PTSD (Amir et al., 1997; Sherman et al., 2000). As expected, veterans did have higher rates of PTSD than civilians but displayed no evidence of comorbid FM. On the other hand, previously reported rates of FM in population samples of Gulf veterans are low and comparable to rates in civilian samples (Bourdette et al., 2001). As we already noted, rates of CFS in male veterans are about 10 times higher than they are in male civilians (see McCauley et al., 2002 and Jason et al., 1999, respectively). Contrary to expectations, there were no differences in the prevalence of MCS between veterans and civilians despite increased toxic exposure in veterans. Previous studies have reported higher rates of MCS in symptomatic Gulf veterans compared to healthy controls (Black et al., 2000; Reid et al., 2001). Since we did not find differences in MCS between veterans and civilians with CFS, our results do not support an exposure hypothesis for medically unexplained fatigue in Gulf veterans. While they do not necessarily suggest differences in the etiology of veteran and civilian CFS subgroups we also found modest differences in functional status. In particular, fatigue-related disability in civilians with CFS was almost three times higher (worse) than it was veterans with CFS. This may be explained, in part, by the fact that most veterans, unlike most civilians, had good premorbid health.

Although our sample size of African American veterans was small, we chose to report their data since no previous article has compared black versus white men with CFS. Medically unexplained fatigue occurs far less often in men than women and even less often among non-whites (Buchwald et al., 1995). The racial composition of our armed forces serving in the Gulf, however, is such that

one-third of all male veterans with CFS were African American. The major difference we found between these racial groups was that African Americans had significantly higher rates of major depression on psychiatric interview as well as higher levels of impairment in self-reported mental health. This could reflect a disparity in care seeking for mental health or in treatment for depression. Practitioners should be aware of this possible disparity and consider assessing for depression in this population.

This study has a number of methodological limitations that prevent us from drawing definitive conclusions. First, we found unanticipated differences between African American and white veterans causing us to reduce the size of our veteran group. As a result, our ability to detect differences between veterans and civilians, especially those involving African Americans, was compromised. To avoid further attenuation of statistical power we chose not to adopt a more conservative significance level. This had the unfortunate effect of inflating the probability of Type 1 error (owing to multiple group comparisons). Another limitation derives from the fact that veterans and civilians were necessarily recruited from two very different clinical populations. One may reasonably expect them to differ on many salient characteristics such as premorbid health and socioeconomic status. We were able to identify and control for some of these pre-existing differences but by no means all. On the other hand, both groups were composed of care seeking individuals and both were evaluated using a common set of diagnostic criteria. Restricting the sample to care seekers is itself a limitation that prevents us from generalizing these results to the community at large. Similar differences may or may not obtain in noncare seeking veteran and civilian samples. Finally, we were unable to identify a sufficient number of female veterans with CFS to permit statistical comparisons with males. We cannot comment, therefore, on whether the observed group differences extend to women as well. Despite these limitations, the present comparison of medically unexplained fatigue in veterans versus civilians has allowed us to identify possible CFS subgroups that differ in mode of onset and in vulnerability to comorbid illness (FM). While preliminary, these findings call into question the assumption that all patients with CFS necessarily share the same illness characteristics or suffer from the same underlying disorder.

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