

## Causes of Death Among Patients With Chronic Fatigue Syndrome

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*Chronic fatigue syndrome (CFS) is a debilitating illness affecting thousands of individuals. At the present time, there are few studies that have investigated causes of death for those with this syndrome. The authors analyzed a memorial list tabulated by the National CFIDS Foundation of 166 deceased individuals who had had CFS. There were approximately three times more women than men on the list. The three most prevalent causes of death were heart failure, suicide, and cancer, which accounted for 59.6% of all deaths. The mean age of those who died from cancer and suicide was 47.8 and 39.3 years, respectively, which is considerably younger than those who died from cancer and suicide in the general population. The implications of these findings are discussed.*

Chronic fatigue syndrome (CFS) is a severe illness, affecting a higher proportion of women than men, and it can affect virtually every major system of the body. Neurological, immunological, hormonal, gastrointestinal, and musculoskeletal problems are all common among people with CFS (Friedberg & Jason, 1998). Descriptions of symptom complexes similar to CFS have occurred in the medical literature for centuries (Hyde, 2003), and it is a condition that occurs throughout the world. Because it is one of the more prevalent chronic health conditions (Jason et al., 1999), it is important to better understand whether those with this condition have a higher risk of mortality. Because few investigators have examined the issue of mortality and

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CFS, databases that can provide estimates would be of particular importance to public health officials and scientists from around the world.

Since the mid-1990s, the Fukuda and colleagues' (1994) case definition has been used by most researchers and health care personnel to define this syndrome. This CFS case definition stipulates that a person needs to experience chronic fatigue of new or definite onset, that is not substantially alleviated by rest, is not the result of ongoing exertion, and results in substantial reductions in occupational, social, and personal activities. This case definition also requires the concurrent occurrence of at least four to eight other symptoms (i.e., impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, multiple joint pain, new headaches, unrefreshing sleep, and postexertional malaise).

This case definition, however, has been criticized by several researchers. As an example, Jason and Taylor (2002) used cluster analysis to define typologies of chronic fatigue symptomatology. They found that a majority of individuals with moderate to severe symptoms were accurately classified into two distinct subgroups: one distinguished by severe postexertional fatigue and generalized fatigue that is alleviated by rest; and one characterized by severe overall symptomatology, severe postexertional fatigue, and generalized fatigue that is not alleviated by rest. Markedly high severity of postexertional fatigue was a key symptom that distinguished the two clusters that contained almost all participants with CFS from a third cluster containing almost none of the CFS participants. This symptom has been designated as a major criterion for the London definition of myalgic encephalomyelitis (ME; Dowsett, Goudsmit, Macintyre, & Shepherd, 1994), but as only one of eight possible symptoms within the Fukuda et al. (1994) criteria. In other words, some individuals who are diagnosed with CFS according to the Fukuda et al. case definition do not have one of the central features of this illness.

Jason and colleagues (2003) investigated differences between CFS as defined by Fukuda et al. (1994) and a set of criteria that has been stipulated for ME, which requires postexertional malaise. The ME and the 1994 Fukuda et al. criteria were compared with a group having chronic fatigue due to psychiatric reasons (CF-psychiatric). There were 22 significant symptom differences between the ME and CF-psychiatric group, but only eight significant symptom differences between the CFS and CF-psychiatric group. Those meeting the ME criteria were more symptomatic than those meeting only the 1994 criteria, especially in the neurological and neuropsychiatric areas. Chronic fatigue syndrome case definitions would be improved if more attention was devoted to developing operationally explicit, objective criteria and standardized interviews.

In spite of the debate in some quarters over the most appropriate criteria for CFS (Brimacombe, Zhang, Lange, & Natelson, 2002–2003; Linder, Dinser, Wagner, Krueger, & Hoffmann, 2002), other investigations have

been able to isolate CFS as an illness distinct from other syndromes. For example, Taylor, Jason, and Schoeny (2001) found diagnostic distinctions between CFS, fibromyalgia, somatic depression, somatic anxiety, and irritable bowel syndrome when employing a confirmatory factor analysis. In addition, Naschitz and colleagues (2003) found a particular dysautonomia in CFS that differs significantly from dysautonomia in patients with non-CFS fatigue, fibromyalgia, syncope, and hypertensives, as well as healthy controls, but not generalized anxiety disorder. In this study, the researchers computed blood pressure and heart rate changes during a head-up tilt test, and processed the data by image analysis methods.

Because other investigators have found cardiac and immunological dysfunction in patients with CFS (Evengard, Schacterle, & Komaroff, 1999; Lerner et al., 2003; Peckerman et al., 2003), it is possible that CFS might be associated with the occurrence of other health conditions and, as a result, perhaps decrease a patient's life expectancy. Macfarlane, McBeth, and Silman's (2001) prospective follow-up study over eight years in England found that mortality was higher in people with regional pain and widespread pain than in those who reported no pain at baseline. The excess mortality was almost entirely related to deaths from cancer, but there were also more deaths from causes other than disease (e.g., accidents, suicide, violence) among people with widespread pain. These findings may have implications for the long-term follow-up of patients with CFS, who often report chronic pain syndromes.

In the CFS area, several investigators have explored links between CFS and other diseases (Levine, 1994). Endicott (1998) found patients with CFS had significantly poorer health up to the time of onset of CFS than a healthy control group, and that parents of patients with CFS had an increased prevalence of cancer and autoimmune disorders (Endicott, 1999). Grufferman and colleagues (1988) reported an outbreak of CFS in the Raleigh, North Carolina Symphony orchestra. Three of these members were later reported to have developed cancer (Johnson, 1996). Levine, Atherton, Fears, and Hoover (1994) reviewed data from the Nevada State Cancer Registry following an outbreak of a CFS-like illness in Nevada. These investigators found an upward trend in the incidence of brain/CNS tumors, although this could have been related to a national upward trend for this disease. Levine, Fears, Cummings, and Hoover (1998) also analyzed data from the Nevada Cancer Registry and found a higher incidence of non-Hodgkin lymphoma and primary brain tumors in two northern Nevada counties where an unexplained fatiguing illness was reported during 1984–1986. The higher incidence rate was in comparison with another county where no such illness had been reported. Finally, Joyce, Hotopf, and Wessely (1997) reported that among 2,075 people followed up in 19 published outcome studies of prolonged fatigue and CFS, there was one death by suicide and two unrelated deaths. In a more recent review, Cairns and Hotopf (2005) found eight

reported deaths in 12 studies. These mortality figures may underestimate the true number of deaths because not all of these investigators had either reported mortalities or had collected data on this topic.

The authors of a technical report issued by the Agency for Healthcare Research and Quality (2001) concluded that estimates of recovery/improvement or relapse from CFS are not possible because there are so few natural history studies and those that are available have involved selected referral populations. The authors recommended that studies need to be done to determine the long-term natural history of CFS in longitudinal cohorts that included representative samples.

Most CFS investigators believe that CFS can be a devastating and debilitating illness, but not a fatal one. Despite this common belief, it is conceivable that people with CFS might develop other serious secondary or cooccurring health problems. In populations with poor health, we would expect to find an increased susceptibility to many common diseases. Clearly, it is important to establish if CFS leads to other illnesses or a shorter life expectancy. In the present preliminary study, we reviewed the memorial list published by the National CFIDS Foundation, and we used this as a source for examining reasons for mortality in people with CFS. This database of information is limited due to the nature of the informal collection and presentation of data, but it still might provide intriguing data to warrant future scientific investigations.

## METHOD

### Participants

Participants in this sample included individuals who had been entered in the memorial list compiled by the National CFIDS Foundation. This list included individuals with ME Chronic fatigue immune dysfunction (CFIDS) who have died up to the summer of 2003. There are several other memorial lists available on the Internet, but the list from the National CFIDS Foundation was the most comprehensive. We decided not to pool entries from more than one list as this might have resulted in counting individuals twice. The National CFIDS Foundation Memorial List included both individuals who had been members of the National CFIDS Foundation as well nonmembers. Individual information for each entry was submitted by family or friends of the deceased. The sample totaled 166, with 164 reporting the sex of the individual, 145 reporting the cause of death of the individual, and 99 reporting the age of the individual.

### Procedure

Each individual report was entered into a database to record the entry, age, sex, and cause of death. Many causes of death were listed. To enable

appropriate statistical analyses, cause of death was coded into categories. The final categories included deaths caused by suicide, cancer (of all types), heart failure (of all types), infections, complications due to CFS/ME, liver or spleen or both failure, kidney failure, accidents and murder, other, and unknown. The other conditions included entries where there was only one individual in the category (i.e., ulceric gastritis, subdermal hematoma, abscess on groin/sepsis, unrelated to ME/CFS, under anesthesia for minor surgery, drug interaction/alcohol and medications, atypical pneumonia, pneumonia, aneurysm, adult onset asthma attack, blood clot following fracture, diabetes). The unknown condition referred to reports that specifically stated that the cause of death was unknown.

## RESULTS

Table 1 presents the reason for death among the 144 individuals where this information was available. The three leading causes of death were heart failure, suicide, and cancer, accounting for 59.6% of cases. In regard to gender, 74.4% of this sample were female and 25.6% were male, and this difference was significant at the  $p < .01$  level using a binomial test. There were also significant differences between males and females at the  $p < .01$  level for deaths due to suicide and cancer. Small sample sizes probably led to lack of significance on other variables.

Table 2 presents mean ages of death for individuals in the memorial list. Due to small sample sizes, only the three largest categories were examined. For heart failure, cancer, and suicide, employing an ANOVA, there was a significant difference in ages ( $F(2,52) = 7.88, p < .01$ ). In addition, those who died from suicide were significantly younger than those who died from heart failure.

**Table 1** Causes of Death in Individuals With Chronic Fatigue Syndrome

Cause of death	<i>n</i>	Percent of total sample	Percent male	Percent female	Significance
Suicide	29	20.1	17.2	82.8	*
Heart failure	29	20.1	34.5	65.5	
Cancer	28	19.4	17.9	82.1	*
Complications of CFS/ME	16	11.1	31.3	68.8	
Unknown	14	9.7	28.6	71.4	
Other	12	8.3	25.0	75.0	
Infections	5	3.5		100.0	
Accidents/murder	5	3.5	20.0	80.0	
Liver and/or spleen	4	2.8	75.0	25.0	
Kidney failure	2	1.4	50.0	50.0	
Total	144	100			

\*Significant at  $< .01$ .

**Table 2** Mean Age and Standard Deviation by Cause of Death

Cause of death	<i>n</i>	Age (mean)	Standard deviation
Suicide	17	39.3	12.69
Heart failure	21	58.7	15.57
Cancer	17	47.8	16.68
Complications of CFS/ME	7	35.6	13.73
Unknown	10	46.6	13.70
Other	9	44.4	3.84
Infections	3	48.3	17.62
Accidents/murder	4	46.2	20.76
Liver and/or spleen	1	69.0	
Kidney failure	2	50.0	4.24

## DISCUSSION

The authors examined causes of death in a sample of individuals that were listed on a memorial list from the National CFIDS Foundation. Among those listed, approximately 20% died from each of the following three causes: heart failure, suicide, and cancer. The number deaths of women reported was approximately three times the number deaths of men reported. Further, those who died from suicide were significantly younger than those who died from heart failure. Overall, at least among this group of individuals, there were increased risks of death associated with heart failure, suicide, and cancer.

The fact that approximately 20% of the sample died of heart failure is of importance given the growing evidence of cardiac problems among patients with CFS. For example, Streeten and Bell (2000) found that the majority of patients with CFS had striking decreases in circulating blood volume. The blood vessels in patients with CFS were constricted dramatically, and efforts to restore normal volume have met with limited success. Martinez-Lavin and colleagues (1997) studied 19 fibromyalgia patients, of whom 10 had CFS. The patients were asked to stand upright after they had been resting in a supine position, which represents a stressful challenge to the body. The patients showed a decrease in the intensity of the sympathetic transmission to the heart, and this reduction was even more pronounced for the patients with comorbid CFS. By comparison, controls evidenced increases in the intensity of sympathetic transmission to the heart. When lying down, there was a trend among patients for an elevated heart rate, whereas when standing up, there was a drop in sympathetic output. The authors suggest that the sympathetic system might be incapable of responding to a stressful challenge. Another line of research has been pursued by the Natelson et al. research group at New Jersey Medical School. They recently found that in response to postural stress, 81% of patients with CFS, but none of controls, experienced ejection fraction decreases (suggesting left ventricular

dysfunction in the heart) and those with more severe symptoms had greater decreases (Peckerman, Chemitiganti, et al., 2003). Patients with CFS might have lower cardiac output, and the resulting low flow circulatory state could make it difficult for patients to meet the demands of everyday activity, and it could also lead to fatigue and other symptoms (Peckerman, LaManca, et al., 2003).

The present study found that approximately 20% of the sample had died from cancer, and this is of theoretical interest given the immune abnormalities reported in patients. People with CFS appear to have two basic problems with immune function: immune activation as demonstrated by elevations of activated T lymphocytes, including cytotoxic T cells and elevations of circulating cytokines; and poor cellular function, with low natural killer cell cytotoxicity and frequent immunoglobulin deficiencies (most often IgG1 and IgG3; Patarca-Montero, Mark, Fletcher, & Klimas, 2000). For example, Antoni, Fletcher, Weiss, Maher, Siegel, and Klimas, (2003) found that patients with low natural killer cell activity (NKCA) and a state of overactivation of lymphocyte subsets (e.g., CD2+CD26+% activation markers) had the greatest fatigue intensity and greatest fatigue-related impairments in emotional and mental functioning. It seems that the Th2 cytokines are dominant over the Th1 cytokines. In addition, Suhadolnik and colleagues (1997) found a novel low-molecular-weight (37 kDa) binding protein in a subset of individuals with CFS who are severely disabled by their disease. A European team (De Meirleir et al., 2000) has also found increased levels of 80 kDa and 37 kDa RNase L in patients with CFS. The ratio of this 37 kDa protein to the normal 80 kDa protein was high in 72% of patients with CFS but only in 1% of the healthy controls and in none of the depression and fibromyalgia control patients.

Another 20% of patients died of suicide, possibly due to the losses that patients with this illness experience from family, friends, coworkers, and health care workers (Friedberg & Jason, 1998). Anderson and Ferrans (1997) found that 77% of individuals with CFS reported past negative experiences with health care providers, and 35% indicated that they no longer sought treatment because of minimal benefits. David, Wessely, and Pelosi (1991) found that 57% of respondents were treated badly or very badly by their doctors. Green, Romei, and Natelson (1999) also found that 95% of individuals seeking medical treatment for CFS reported feelings of estrangement, and 70% believed that others wrongly attributed their CFS symptoms to psychological causes. Asbring and Narvanen (2003) found that physicians regarded the illness as less serious than the patients. The physicians characterized the patients with CFS and fibromyalgia as illness focused, demanding, and medicalizing. Twemlow, Bradshaw, Coyne, and Lerma (1997) found that 66% of individuals with CFS stated that they were made worse by their doctors' care. Clearly, individuals who are extremely sick with an illness will feel even more alienated and demoralized if those

who are responsible for helping them are insensitive to their needs. Certainly, all of these factors, including demoralization, estrangement from the medical establishment, and unsympathetic responses may cause some individuals to develop depression as well. A sense of hopelessness concerning the illness and comorbid depression may also increase the risk for developing suicidal thoughts or behavior.

The fact that more women were reported to have died than men was not unexpected, given that there is a higher percentage of women with CFS than men. When examining individual cause of death categories, the authors found significant gender differences were found only for suicide and cancer. Analyses for gender differences in other causes of death, however, could not be done due to low sample sizes. Of interest, the only category where men had a higher reported percentage than women was with liver or spleen or both problems; yet the very low number of individuals in this category requires this finding to be viewed with caution.

When examining ages of death, we found that those dying of suicide were significantly younger than those dying of heart failure. Another intriguing finding was the overall ages of death for those dying of cancer, suicide, and heart failure. If one examines national rates of death for these conditions, the ages of death for these three conditions among the patients with CFS are considerable earlier. The median age of death for cancer in the United States is 72 (Reis et al., 2003, versus an average age of 47.8 for the CFS sample), the average age of death for suicide in the United States is 48 (Centers for Disease Control, 2003, versus an average age of 39.3 for the CFS sample), and the average age of heart failure is 83.1 (CDC, 2003, versus an average age of 58.7 years for the CFS sample). What this suggests is that those from this memorial list who did die of cancer, suicide, and heart failure were considerable younger than what would have been expected from the general population, which means that CFS might have increased the risk of death for at least this sample.

CFS is a condition that affects individuals throughout the world (Hyde, 2003). Most research on the epidemiology and pathophysiology of this syndrome, however, has occurred in either the United States, Europe, or Japan (Jason, Fennell, & Taylor, 2003). Given that CFS is one of the more common chronic health conditions, affecting potentially 42% of the population (Jason et al., 1999), it is imperative for international researchers and public health officials throughout the world to seriously study potential factors that might influence functioning and mortality of those with this condition.

The authors of the present study employed a sample from a self-help advocacy organization in the United States. It is probably the case that most individuals on this list were from the United States, but it is also likely that there were individuals on this list from other countries. The authors, before embarking on this investigation, did inspect lists that had been generated



from other self-help organizations in different locations, but the authors felt that the list from the United States was the most comprehensive. Unfortunately, the authors are not able to list the different countries where mortalities occurred, but this is an important task for future investigations. If mortality rates for CFS did differ by geographic location, this might have implications for either service delivery issues or for the etiology of the syndrome.

There are a number of methodological limitations in the present study. First, there was no independent confirmation of cause of death, and self-report data might have been inaccurate. It was not possible to interview the family members or seek independent confirmation of cause of death. In addition, data available from the memorial list often was not complete. Even when a cause of death was provided, more specific information was frequently missing (e.g., what type of heart failure or cancer caused the death). It also was unclear how representative the memorial list is and from what population it draws its data. Clearly, it is not possible to generalize the data from this memorial list to the overall population of patients with CFS.

We cannot underestimate this methodological flaw to the present study. In other words, it is possible that some of the deaths were either misdiagnosed or that the individuals did not even have CFS. We would urge future investigators on this topic to place more attention on the diagnostic criteria. Clearly, a study on causes of death related to a condition that may have been unreliably diagnosed is a serious issue. There are so few published findings in this area, however, that the current study could at minimum serve to stimulate additional, better controlled studies.

In spite of the above limitations, among this sample of participants with CFS, causes of death appear to cluster in three general domains: heart failure, suicide, and cancer. For each of these areas, there is supportive evidence that might help explain why heart failure, cancer, and suicide might be associated with deaths among people with CFS in this sample. Longitudinal prospective studies with community-based samples are needed in order to better understand the unique health risks associated with having CFS.

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