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Mortality in Patients with Myalgic Encephalomyelitis and Chronic Fatigue Syndrome

Stephanie L. McManimen, Andrew R. Devendorf, Abigail A. Brown, Billie C. Moore, James H. Moore, and Leonard A. Jason

Center for Community Research, DePaul University

Abstract

Background—There is a dearth of research examining mortality in individuals with myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). Some studies suggest there is an elevated risk of suicide and earlier mortality compared to national norms. However, findings are inconsistent as other researchers have not found significant increases in all-cause mortality for patients.

Objective—This study sought to determine if patients with ME or CFS are reportedly dying earlier than the overall population from the same cause.

Methods—Family, friends, and caregivers of deceased individuals with ME or CFS were recruited through social media, patient newsletters, emails, and advocate websites. This study analyzed data including cause and age of death for 56 individuals identified as having ME or CFS.

Results—The findings suggest patients in this sample are at a significantly increased risk of earlier all-cause ($M = 55.9$ years) and cardiovascular-related ($M = 58.8$ years) mortality, and they had a directionally lower mean age of death for suicide ($M = 41.3$ years) and cancer ($M = 66.3$ years) compared to the overall U.S. population [$M = 73.5$ (all-cause), 77.7 (cardiovascular), 47.4 (suicide), and 71.1 (cancer) years of age].

Conclusions—The results suggest there is an increase in risk for earlier mortality in patients with ME and CFS. Due to the small sample size and over-representation of severely ill patients, the findings should be replicated to determine if the directional differences for suicide and cancer mortality are significantly different from the overall U.S. population.

Keywords

myalgic encephalomyelitis; chronic fatigue syndrome; mortality; suicide; cardiovascular

Myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) are controversial and complicated illnesses [1]. Although many case definitions exist, ME and CFS are characterized by a variety of symptoms including post-exertional malaise; neurocognitive impairment; sleep dysfunction; and immunological, autonomic, and gastrointestinal issues [2–5]. Most patients with ME and CFS experience functional impairment that prevents them

from completing normal daily activities, with approximately 25% of patients housebound at any given time [6,7]. However, few studies have examined whether ME and CFS increases the risk of mortality in patients, and the studies that have reported conflicting results[8].

Smith et al. [9] found that individuals with CFS were not at an increased risk of all-cause mortality or suicide. However, this sample was collected from a tertiary setting, which may have excluded more severely ill individuals that could not attend a clinic due to being housebound. Contrastingly, Jason et al. [10] found mean ages of death from a memorial list of patients were considerably lower than national norms when considering the leading causes of death for these individuals: heart disease, cancer, and suicide. Recently, Roberts et al. [11] found no differences in age-standardized and gender-standardized mortality ratios for all-cause mortality and or cancer-specific mortality. The Roberts et al. study included wide diagnostic criteria, with one definition only requiring 6 months of fatigue, which could encompass many individuals that do not have ME and CFS [12]. These lax criteria may explain why they were unable to find an increased risk of all-cause and cancer-specific mortality. However, Roberts et al. [11] did find an increased suicide-related mortality in patients compared to the general population, but it is unclear which case definition those patients met. It is possible some of the Roberts et al. patients that died by suicide only met the widest criteria used (i.e. 6 months of fatigue), which could have included some with primary major depressive disorder, which is a major limitation of the study. In a study in Spain by Jiménez-Ortiz [13], there was also an increased risk of suicide in a patient population.

There are many reasons why ME or CFS could increase the risk of mortality. Severely affected patients have displayed lower stroke volume and cardiac outputs when compared to controls and less ill patients [14,15]. Hollingsworth et al. [16] found left ventricular mass in patients to be reduced by 23%. This reduced cardiac volume was associated with the plasma volume but not the length of illness, suggesting that deconditioning is unlikely to be the cause of these abnormalities [17]. Additionally, it has been found that patients have a higher heart rate and reduced heart rate variability during sleep, a risk factor of coronary heart disease and death [18–20].

ME and CFS may also lead to lower systolic, diastolic, and mean arterial pressure, which are implicated in early signs of coronary dysfunction [21,22]. Hollingsworth et al. [23] found patients had a greater left ventricular work index while standing compared to controls, suggesting that patients' hearts were working harder while standing. As a result of lower cardiac output, patients are prone to orthostatic intolerance (OI), a condition in which symptoms worsen upon standing [24]. When assessing blood volume and cardiac function, research has found patients who experience OI have lower blood volume and blood pressure variability compared to controls [25,26]. Altogether, these findings may explain the increase in cardiovascular-related mortality from Jason et al. study [10].

Pain may also contribute to an increased risk of death. Prior research has linked chronic pain to an increased risk of suicide [27]. Fibromyalgia, an illness characterized by widespread pain, has been found to increase the risk of suicide [28–30]. Several studies have shown a direct link between the severity of pain and an increased risk of suicide after controlling for

psychiatric diagnoses in other illnesses [31,32]. This is of concern as patients with ME and CFS have been found to have lower pain thresholds [33].

Concurrent with the physical risk factors of mortality, patients experience many secondary impacts of this illness including stigma from family, friends, and healthcare providers compared to other chronic illness groups [34–36]. Patients are often delegitimized and socially isolated because of the invisible nature of the illness [37]. Patients also face significant changes in their quality of life (QOL), which have led to feelings of failure, loss, worthlessness, and insignificance [38]. Hvidberg et al. [39] found that the health-related QOL for patients with ME and CFS was substantially lower than patients with other conditions including: depression, schizophrenia, chronic renal failure, and various forms of cancer. In a severely affected Norwegian sample, approximately 75% of patients were housebound or bedridden most of the time [40]. Additionally, Nacul et al. [41] found both patients and their caregivers had significantly lower scores on the SF-36, a measure of disability, compared to the general population. Thus, this illness not only has major effects on the patients but has substantial deleterious effects on their caregivers, many of whom are family members.

Financial pressures exacerbate these experiences[42]. Taylor and Kielhofner [43] found that in studies reporting work status and job loss, up to 69% of patients were unemployed and as high as 89% of patients had suffered job loss due to the debilitating nature of this illness. Yet, patients generally must continue paying their ordinary housing and food, as well as medical expenses, which may not be covered by health insurance.

Because there is no definitive treatment approach and no FDA-approved drug, some patients may feel hopeless, believing they will never reach a full recovery [38,44,45]. Altogether, these circumstances compound the illness experience of patients and significantly decrease their QOL [46]. These findings suggest that some patients experience hopelessness about the prognosis of the illness, and some feel as though they are a burden to their caregivers, both factors are associated with an increased risk of suicide [47].

This study aimed to learn more about the relationship between mortality and ME and CFS. Unlike previous studies that utilized a database of deceased individuals, this study relied on self-reports from the caregivers, friends and family members of individuals who had ME or CFS and died. For the reasons cited above, we predicted that deceased individuals who had ME and CFS would have a lower mean age of death compared to national norms.

Method

Following approval from DePaul University's Institutional Review Board, 56 participants were recruited through a variety of means including postings on social media, emails, patient advocate news websites, and newsletters for patient organizations. All participants were recruited to complete a survey asking a variety of questions about an individual who is deceased that they knew well and had been diagnosed with ME or CFS. The questionnaire was hosted online using Research Electronic Data Capture (REDCap) [48]. Participants answered questions assessing their familiarity with the aspects of the patient's illness, how

involved they were in the patient's life, and how caring for the individual affected their own life. The participants were either family, friends, or caregivers of the patient. For brevity, all participants will be referred to as caregivers.

Symptomatology for the deceased individual was assessed using symptoms from the DePaul Symptom Questionnaire in addition to new symptoms (e.g. hypoglycemia) [49]. The questions were modified from the 5-point Likert scale to a 4-option question as follows: major problem, minor problem, not a symptom, and do not know. Additional questions assessed the onset of the illness, management of work and family life, and functional status. Participants also indicated if the patient had a caregiver, where the patient was living (e.g. nursing home), and if the patient was under the care of a medical professional. Finally, participants indicated the immediate cause of death, if it was recorded as being attributable to the illness, if they believed it was a direct result of the patient having the illness and why. Due to the small sample size, non-parametric tests were used to determine differences in demographics between deceased individuals by cause of death. Patients with missing data were excluded on an analysis-by-analysis basis.

Results

Data was collected for 56 individuals who were deceased and that had been diagnosed with ME or CFS. As shown in Table 1, the majority of the deceased were female (66.1%) with the remaining 33.9% male. Almost all (98.3%) were Caucasian/White, with just one person (1.7%) that was Asian or Pacific Islander. There was only one person (1.7%) of Latino or Hispanic origin. Regarding marital status, 46.6% were married, in a civil union, or living with a partner; 29.3% were never married at the time of their death; 24.1% were divorced, widowed, or separated. For education, 33.3% had completed high school or less; 22.8% completed some college; 22.8% had a standard college degree; and 21.1% had a graduate degree. There was a significant effect of marital status within the top three causes of death, $p < .05$, with those that died by suicide being more likely to have never been married compared to those that died from cardiovascular problems or cancer. However, that could be a result of the small sample size. There were no significant differences in gender, ethnicity, race, or education level between the top three causes of death ($p > .05$).

Table 2 shows the number and percentages for each cause of death. As shown in the table, suicide was the most frequent cause of death, listed for 26.8% ($n = 15$) of the sample. The top three causes (cardiovascular problems, cancers, and suicide) constituted 67.9% of the overall sample. The "Other" category is composed of causes of death that did not fall into any of the other categories.

Table 3 displays the means and standard deviations for age of death in the top three causes and all-cause mortality in patients compared to the overall U.S. population [50]. There was a significant difference, $p < .0001$, for age of death between the patients and the overall U.S. population for all-cause mortality, the top three causes within the patient population, and cardiovascular problems. Suicide and cancer did not reach statistical significance, but this could be a result of the small sample size for the patient population. There is an overall trend of patients with ME and CFS dying at an earlier age than the general U.S. population.

Table 4 displays symptomatology characteristics for the top three causes and all-cause mortality in patients. Symptom data refers to the percentages of caregivers that reported the deceased experienced that symptom as a “major problem.” There was no statistical significance between suicide, cardiovascular, and cancer mortality for any of the additional illness characteristics. However, it is important to note that these rates of symptoms considered to be major problems are high, making this a very impaired group of patients. Almost half of this sample (48.2%, n = 27) was bedbound; 37.5% (n = 21) were homebound; 7.1% (n = 4) could work part-time; 7.1% (n = 4) could work full-time. This indicates that the current sample was more impaired than the general population of patients with ME or CFS, as several studies suggest that about 25% of patients are bedbound [6,7]. Additionally, 96.2% of the deceased were under the care of a medical professional at the time of death. There was no significant differences between the top three causes, but 93.3% of those that died by suicide and 100% of those that died by cardiovascular issues or cancer were under the care of a medical professional. Most of the caregivers (83.7%) attributed the patient’s cause of death to ME or CFS. Although it was not significantly different, rates of caregiver attribution differed by cause of death as follows: 92.9% for suicide, 91.7% for cardiovascular, and 62.5% for cancer.

Discussion

Causes of death in a sample of individuals with ME and CFS were provided by caregivers through an online questionnaire. Similar to Jason et al., approximately two-thirds of the sample reportedly died from suicide, cardiovascular problems, and cancer¹⁰. Unsurprisingly, more of the deceased individuals reported on were female, as this illness tends to disproportionately affect women [51,52]. Interestingly, as shown in Table 1, more males than females were reported to have died by suicide in this study (53.33% male and 46.67% female), which was the only cause of death to display this pattern.

It should be noted that individuals with ME and CFS are reportedly dying at a younger age compared to the overall population. However, only all-cause and cardiovascular-related mortality reached statistical significance. The all-cause mean age of death for this sample was 55.9 years. This is compared to the mean of 73.5 years for the US population [50]. Most strikingly, individuals in this sample died of cardiovascular problems at an average age of 58.8. The average age of death for cardiovascular problems in the United States is 77.7, a stark contrast from the average age found in patients in this sample and the prior study [10,50]. In the current study, the mean age of death for cancer was 66.3 versus the mean age of death for cancer in the United States of 71.1. Individuals that died by suicide were at a mean age of 41.3 years as opposed to 47.4, the average age of death from suicide in the United States. These differences suggest that, although the mean age of death differs significantly depending on the cause, ME and CFS may increase the likelihood of all causes and cardiovascular mortality.

The most frequent cause of death was suicide, occurring among 26.8% of patients in the sample. Roberts et al. [11] found a seven-fold increased risk of mortality as a result of suicide in a population of individuals with this illness in the United Kingdom; as a result of these findings, the authors suggested this result highlighted the importance of screening for

psychiatric comorbidities. Kapur and Webb [53] incorrectly interpreted that this increased rate of suicide was due to depression and suggested treating the depression would help lower the suicide risk. However, the authors failed to note that 60% of the patients in the Roberts et al. [11] study that died by suicide did not have a depression diagnosis. Therefore, although depression may influence suicidal ideation, it would be incorrect to attribute all suicide-related death in ME and CFS to untreated depression as other factors in the patient's life may also influence suicidal ideation or the development of symptoms of depression.

Many studies have shown there are distinct differences between depression and ME or CFS. Compared to patients with depression, patients with ME and CFS have shown significantly lower scores on the SF-36, a different degree of disability and pattern of impairment [54]; different reporting of widespread body pain [55]; distinct brain physiology [56]; and differences in white matter volume [57]. These differences suggest that, although some patients also suffer from depression, as do some patients with other serious illnesses, ME and CFS are different from solely psychiatric illnesses such as major depressive disorder [58]. Thus, alternative reasons should be considered for why some patients experience suicidal ideation instead of treating these thoughts as a result of an untreated mood disorder.

As stated, several factors may contribute to an individual with ME or CFS having suicidal thoughts or actions and the development of depression-like symptoms including: lack of treatment options and low recovery rates [59–61]; increased levels of pain and disability [33,41]; greatly diminished quality of life [39,41,54]; stigma and the beliefs sometimes held by family, friends, and even physicians that the illness is not real or is just depression [62–65]; job loss and subsequent poverty [66,67]; and social and familial isolation [68,69]. McInnis et al. [70] found that patients with ME and CFS experience unsupportive social interactions significantly more often than healthy individuals or patients with more legitimized autoimmune illnesses (i.e. rheumatoid arthritis, lupus erythematosus, and multiple sclerosis) so they are experiencing people telling them that they are overreacting or are emotionally and physically abandoning the patient.

Recently, Jiménez-Ortiz [13] attempted to clarify the circumstances surrounding the risk of suicide and depression in people affected by ME and CFS in Spain. The study found a 12.75% risk of suicide in the patient population compared to a risk in the general Spanish population of 2.3%. Additionally, the incidence of depression, a risk factor for suicide, among the patients was 57.25% compared to just 4% of the general population. Findings suggested that a lack of medical care, not being listened to by physicians, needing daily support from family, and not having the ability to earn a living outside of the home were all factors that contributed to an increased risk of suicide in these patients. There were also several factors found to contribute to risk for depression and hopelessness in patients: improper treatment by medical professionals, job loss, loss of friendships, and being sent for psychological or psychiatric treatment. This is the first study to assess external factors that may increase the risk of suicide or the development of depression in a patient with ME or CFS. Unfortunately, the current study and others like it [10,11] did not assess the reasons why these patients died by suicide because the data were collected after death. Future research should investigate these factors similar to the Jiménez-Ortiz [13] study that may be influencing suicidal ideation and their relationship with depression in patients instead of

attempting a psychological autopsy and attributing it to depression. The findings of such research might be instrumental in efforts directed to reducing stigma and providing better medical care, daily support from family, and economic resources that might reduce suicidal ideation and action. In addition, the findings of such research would help determine how these severely impacted individuals may be helped by multidisciplinary health care settings better attending to their needs.

An additional 23.2% of individuals in this sample died as a result of cardiovascular problems. Prior research show various cardiovascular issues in patients with ME and CFS, which could explain why almost one quarter of this sample died as a result of these problems. Streeten et al. [71] found that patients had significant decreases in circulating erythrocyte volume. This results in the patient becoming anemic similar to primary autonomic failure. This finding is significant as anemia has been linked to an increased risk of mortality in several chronic conditions including kidney disease, congestive heart failure, and chronic obstructive pulmonary disorder [72,73]. Additionally, Richards et al. [74] found an increase of methemoglobin, which is unable to bind oxygen and is evidence of oxidative damage, in patients and an increased amount of stomatocytes (concaved erythrocytes due to membrane damage) in their blood compared to controls. These results indicate there are serious deficiencies in the cardiovascular system in patients, which could make them more susceptible to earlier mortality related to the cardiovascular system.

Another 17.9% of patients died as a result of cancer. Immune abnormalities and chronic manifestations of infections have been reported in CFS and ME [75]. Additionally, viruses such as the Epstein-Barr virus (EBV) have been implicated in the development of CFS [75]. Some of the infections thought to play a role in the etiology of this illness and immune-related conditions are also associated with the development of certain cancers through immunological abnormalities and infections [77–79]. For example, Chang et al. [80] found an association between CFS and non-Hodgkin lymphoma (NHL).

In addition to the reported earlier ages of death, caregivers are frequently attributing the death to ME or CFS. The majority of caregivers (83.7%) believed that ME or CFS should be implicated in the patient's death. This is disproportionate with the reported mortality rate. The National Institutes of Health (NIH) reported that only 16 patients died as a result of ME or CFS in 2014 [81]. The low mortality rate could be a result of this rate being based on the ICD-10 code for postviral fatigue syndrome [82]. Additionally, it is possible that ME or CFS is not listed when the primary cause of death is more apparent, such as with cancer.

Limitations

This study has several limitations. Most notably, these results are based on a caregiver's knowledge of the patient's cause of death. There was no confirmation of cause of death other than the self-report provided by the participant. Since the study was conducted after the patients died, we were unable to medically confirm the diagnosis of cancer, depression, or other health issues reported by the caregivers. Thus, inaccurate information may have been provided. A longitudinal, prospective study would provide the most accurate depiction of cause of death for patients. Jason et al. found a higher incidence of death than expected in

a ten-year follow-up of an epidemiological study [83]. In the ten years following wave one of the study, 12.5% of the patients in the CFS group had died compared to just 10.6% of the control group. The patients in this sample had died of septicemia or cancer at ages younger than is expected in the general population.

It is also unclear if this is an accurate representation of the overall population of patients. After the patient dies, it is possible that caregivers withdraw from the patient community since they may feel they no longer have a connection with surviving patients and caregivers. Thus, we might not have reached many caregivers who knew patients that died but were no longer in communication with the ME or CFS community. Additionally, this is a very impaired group of patients. Almost half of the patients reported on in this sample were bedbound, which is twice the rate found in prior literature [6,7]. However, it is possible the earlier mortality is related to illness severity and functional status. A longitudinal study would be able to better assess the relationship between illness severity and risk for earlier mortality. Thus, it is not possible to generalize these findings to the overall patient population. Despite these limitations, it is still important to note that there appears to be an increased risk of early mortality among the patients reported on in this sample.

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Table 1

Demographic characteristics of the top three causes of death and the overall sample

	Suicide	Cardiovascular Problems	Cancer	Total Sample
	(<i>N</i> = 15)	(<i>N</i> = 13)	(<i>N</i> = 10)	(<i>N</i> = 56)
	% (n)	% (n)	% (n)	% (n)
Gender				
Male	53.3 (8)	23.1 (3)	20.0 (2)	32.1 (18)
Female	46.7 (7)	76.9 (10)	80.0 (8)	67.9 (38)
Race				
White	93.3 (14)	100.0 (13)	100.0 (10)	98.2 (55)
Asian or Pacific Islander	6.7 (1)	0.0 (0)	0.0 (0)	1.8 (1)
Ethnicity				
Non-Hispanic	100.0 (15)	92.3 (12)	100.0 (9)	98.1 (53)
Hispanic	0.0 (0)	7.7 (1)	0.0 (0)	1.8 (1)
Education Level				
High School or Less	21.4 (3)	30.8 (4)	30.0 (3)	32.7 (18)
Partial College	42.9 (6)	7.7 (1)	10.0 (1)	23.6 (13)
College Degree	14.3 (2)	46.2 (6)	20.0 (2)	23.6 (13)
Graduate Degree	21.4 (3)	15.4 (2)	40.0 (4)	20.0 (11)
Marital Status				
Married	20.0 (3)	61.5 (8)	50.0 (5)	44.6 (25)
Separated, Widowed, Divorced	20.0 (3)	23.1 (3)	40.0 (4)	25.0 (14)
Never Married	60.0 (9)	15.4 (2)	10.0 (1)	30.4 (17)

Table 2Causes of death in patients with ME and CFS ($N=56$)

	<i>n</i>	%
Suicide	15	26.8
Cardiovascular Problems	13	23.2
<i>Heart Disease</i>	6	10.3
<i>Stroke</i>	4	6.9
<i>Pulmonary Embolism</i>	2	3.4
<i>Aortic Dissection</i>	1	2.6
Cancer	10	17.9
Influenza, Pneumonia, or Infection	9	16.1
Other	6	10.7
Accidents / Homicide	3	5.4

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Table 3

Means and standard deviations for age of death of the patients in the sample and the U.S.

	Patients with ME and CFS	U.S. Population (2014)	
	<i>M (SD)</i>	<i>M (SD)</i>	
All-Causes	55.9 (18.8)	73.5 (17.6)	***
Top Three Causes of Death	53.9 (17.1)	74.0 (3.2)	***
<i>Suicide</i>	41.3 (13.8)	47.4 (18.4)	
<i>Cardiovascular Problems</i>	58.8 (15.5)	77.7 (14.6)	***
<i>Cancer</i>	66.3 (10.5)	71.1 (13.5)	

 $p < .0001$

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Table 4

Illness characteristics by cause of death (N = 56)

	Suicide (n = 15)	Cardiovascular (n = 13)	Cancer (n = 10)	Overall (N = 56)
Symptom Data (Major Problem)	%(n)	%(n)	% (n)	%(n)
Fatigue	100.0(14)	100.0(12)	90.0 (9)	96.3(52)
Physically Exhausted after Mild Effort	100.0(15)	100.0(12)	90.0 (9)	96.3(52)
Unrefreshing Sleep	100.0(13)	100.0(10)	90.0 (9)	93.9(46)
Needing to Nap Daily	72.7(8)	90.9(10)	90.0 (9)	87.0(40)
Mentally Exhausted after Mild Effort	93.3(14)	100.0(12)	40.0 (4)	85.2(46)
Pain or Aching in Muscles	92.9(13)	91.7(11)	66.7 (6)	84.0(42)
Problems Falling Asleep	80.0(8)	80.0(8)	75.0 (6)	78.6(33)
Muscle Weakness	66.7(8)	90.9(10)	66.7 (6)	77.1(37)
Intolerant of Extreme Temperatures	85.7(6)	77.8(7)	55.6 (5)	77.1(27)
Joint Pain / Stiffness	72.7(8)	80.0(8)	50.0 (4)	76.2(32)
Difficulty Paying Attention	90.9(10)	72.7(8)	50.0 (5)	73.9(34)
Headaches	90.9(10)	81.8(9)	55.6 (5)	73.8(31)
Problems Staying Asleep	80.0(8)	80.0(8)	50.0 (5)	72.7(32)
Sensitivity to Noise	90.9(10)	60.0(6)	44.4 (4)	72.1(31)
Problems Remembering Things	81.8(9)	75.0(9)	50.0 (5)	70.8(34)
Sensitivity to Bright Lights	90.9(10)	60.0(6)	33.3 (3)	70.5(31)
Only able to Focus on One Thing at a Time	88.9(8)	72.7(8)	44.4 (4)	70.5(31)
Difficulty Expressing Thoughts	77.8(7)	66.7(8)	40.0 (4)	66.0(31)
Feeling Unsteady on His/Her Feet	60.0(6)	70.0(7)	50.0 (5)	63.8(30)
Irritable Bowel Problems	62.5(5)	72.7(8)	37.5 (3)	60.0(24)