RESEARCH ARTICLE

Differences in ME and CFS Symptomology in Patients with Normal and Abnormal Exercise Test Results

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Abstract

Post-exertional malaise (PEM) is a cardinal symptom of myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS), which often distinguishes patients with this illness from healthy controls or individuals with exclusionary illnesses such as depression. However, occurrence rates for PEM fluctuate from subject to how the symptom is operationalized. One commonly utilized method is exercise testing, maximal or submaximal. Many patients with ME and CFS experience PEM after participating in these tests, and often show abnormal results. However, some patients still exhibit normal results after participating in the exercise testing. This study examined the differences between two patient groups with ME and CFS, those with normal results and those with abnormal results, on several PEM-related symptoms and illness characteristics. The results suggest those that displayed abnormal results following testing have more frequent and severe PEM, worse overall functioning, and are more likely to be bedbound than those that displayed normal results.

Keywords

Myalgic encephalomyelitis, Chronic fatigue syndrome, Post-exertional malaise, Exercise testing

Myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) continue to be controversial illnesses, and over 20 case definitions developed in the past two decades to diagnose them [1]. However, the case definitions have rarely specified how to operationalize the fundamental symptoms. As a result, there is an inconsistency in how the critical criteria are applied and as a result the prevalence of cardinal ME and CFS symptoms varies from study to study [2].

One such symptom is post-exertional malaise (PEM), an exacerbation of the entire symptom complex after physical activity which can last for 24 hours or more. This experience can be triggered by mundane, everyday tasks such as simply getting dressed in the morning [3]. PEM was found to be a cardinal symptom of ME and CFS as it was one of three symptoms that accurately classified patients and controls over 95% of the time [4]. However, there have been multiple methods utilized, objective and subjective, to determine if a patient experiences PEM.

PEM has been objectively demonstrated with submaximal and maximal exercise tests. With a submaximal exercise test, patients walk or pedal on a stationary bike with the workload increasing every minute until the heart rate reaches 75% of the age-predicted heart rate or 80% of the rate corresponding to the anaerobic threshold [5,6]. Studies using submaximal exercise testing have found several significant differences between patients and sedentary controls. For example, Riley, et al. [7] found that patients have a reduced aerobic capacity. Rowbottom, et al. [8] found that patients had an increased perception of exertion which was coupled with physical deconditioning. Wallman, et al. [9] showed that patients have significant differences in peak heart rates, work rates, oxygen uptake, and respiratory exchange ratio. Finally, Montague, et al. [10] did not find differences in cardiac function at a resting state, but the results indicated patients had a reduced exercise capacity.

In contrast, for a maximal exercise test, patients pedal on a stationary bike while increasing the workload until exhaustion, which is measured by heart rate of 85% of age-predicted maximum and a respiratory exchange ratio of 1:1 or greater when the ventilatory threshold is reached [11-13]. Studies using maximal exercise tests have also

found multiple differences between patients and sedentary controls. De Becker, et al. [11] found higher resting heart rates, lower maximal heart rate, lower maximal workload and oxygen uptake, and a decreased exercise capacity in patients with ME and CFS. Sisto, et al. [14] found differences in peak heart rate, endurance, peak oxygen uptake, and respiratory exchange ratio. Similar to the Rowbottom, et al. [8] study, Fischler, et al. [15] found that patients were showing signs of physical deconditioning.

However, there is also an inconsistency in findings with exercise testing. Although the researchers found significant results for some measures, Sisto, et al. [14] found patients can withstand a maximal treadmill test without experiencing an exacerbation in fatigue or other illness symptoms. Bazelmans, et al. [16] did not find evidence of physical deconditioning as there were no significant differences between patients and controls. This study also failed to find significant differences in peak heart rate, endurance, peak work rate, and peak oxygen uptake. Similarly, Sargent, et al. [17] and Cook, et al. [18] also failed to find significant differences in peak heart rate and peak oxygen uptake. The Cook, et al. [18] study also failed to find differences in endurance and respiratory exchange ratio. Since the results are varying, it is difficult to determine which differences actually exist between patients and controls. This inconsistency also makes it difficult to determine effective treatment methods since studies are producing different results.

The varying results make it difficult to generalize the findings to the entire ME and CFS patient population. Thus, it is beneficial to investigate the possible factors that may influence these inconsistent findings. The current study sought to determine what factors, if any, may have had an effect on previous exercise test research. It was predicted that there would be functional differences between the group of patients that reported normal results and the group that reported abnormal results. Specifically, it was hypothesized that those with abnormal test results are experiencing more severe and frequent symptoms and would be more functionally impaired than the group that reported normal results. Such findings would suggest that the patient populations from previous research are heterogeneous, which could explain the inconsistencies in findings.

Methods

Measures

Participants were asked to complete a series of questionnaires to gauge the frequency and severity of their illness using questions from multiple sources. Questions that measured PEM were pulled from the DePaul Symptom Questionnaire [19], Ramsay [20], the Jason, et al. [21] CFS screening study, the CDC Symptom Inventory [22], ME-ICC [23], the Chalder Fatigue Scale [24], and the Medical Questionnaire [25]. Additionally, participants were asked the following questions to determine if they participated in an exercise test: Did you ever have a cardiopulmonary test,

which is often called an exercise challenge? What type of test did you have? Did this exercise challenge show that you had normal or abnormal results? Were you asked to exercise on back-to-back days for this test?

To assess functioning levels, participants completed the Bell Ability Scale [26] and the SF-36 Physical Functioning subscale [27]. For the SF-36, participants answer questions assessing their physical functioning on a 3-point Likert scale, which is then converted to a 100-point scale. This measure has shown good discriminant validity and internal consistency [28]. Similarly, the Bell Ability Scale is a 10-point scale that also assesses a participant's current functioning level. Patients are given a list of functional status examples (e.g. able to work outside the home) and they endorse the number that best fits their current physical functioning. The scale was adapted to a 100-point scale to allow for more variability in scores for participants that feel their current functioning falls between two examples.

Domain composites

Domain composite scores were created from the frequency and severity scores of each PEM-related symptom. The severity of symptoms was rated on a 5-point Likert scale over the past 6 months as follows: 0 = Symptom not present, 1 = Mild, 2 = Moderate, 3 = Severe, and 4 = Very severe. Likewise, the frequency of symptoms was rated on a 5-point Likert scale over the past 6 months as follows: 0 = None of the time, 1 = A little of the Time, 2 = About half the time, 3 = Most of the time, and 4 = All of the time. For each symptom and factor, the scores were converted to a 100-point scale by multiplying them by 25. The frequency and severity for the symptom was then averaged to calculate the composite score. The DSQ has shown good test-retest reliability for patients and control groups [29]. Similarly, the CFS Screening Questionnaire has shown high discriminant validity and excellent test-retest reliability [21]. Conversely, The Chalder, et al. [24] Fatigue Scale has shown strong internal consistency, but fails to differentiate patients from individuals with multiple sclerosis [21]. Additionally, the CDC Symptom Inventory [22] has also shown issues with sensitivity and specificity [30]. The eleven items taken from questionnaires other than the DSQ have not been assessed on this frequency and severity scale previously.

Research sample

Participants were recruited using an international convenience sample of adult patients that self-identify as having ME or CFS. To be eligible, the individuals must be at least 18-years-old, capable or reading and writing English, and have a current, self-reported diagnosis or ME or CFS. Following approval from DePaul University's Institutional Review Board, individuals were recruited from multiple sources: social media, postings on internet forums, and postings in patient organization newsletters. Participants completed the study measures on-

Table 1: Demographics of participants reporting exercise test results (N = 177).

	Normal results (N = 66)	Abnormal results (N = 111)	
	M (SD)	M (SD)	
Age	52.00 (10.77)	51.04 (11.49)	
	% (N)	% (N)	
Gender			
Female	86.4 (57)	85.5 (94)	
Male	13.6 (9)	14.5 (16)	
Race			
Black, african-american	1.5 (1)	0.0 (0)	
White	95.4 (62)	96.3 (104)	
American indian or alaskan native	3.1 (2)	1.9 (2)	
Asian or pacific islander	0.0 (0)	1.9 (2)	
Ethnicity			
Non-hispanic or latino	96.9 (63)	96.4 (106)	
Hispanic or latino	3.1 (2)	3.6 (4)	
Marital status			
Married/Living with partner	53.8 (35)	56.8 (63)	
Separated	3.1 (2)	0.9 (1)	
Widowed	1.5 (1)	2.7 (3)	
Divorced	23.1 (15)	15.3 (17)	
Never married	18.5 (12)	24.3 (27)	
Education level			**
High school or Less	6.1 (4)	10.9 (12)	
Partial college	28.8 (19)	10.9 (12)	
College degree	39.4 (26)	34.5 (38)	
Graduate/Professional degree	25.8 (17)	43.6 (48)	
Current work status			
On disability	37.9 (25)	50.0 (55)	
Student	1.5 (1)	0.9 (1)	
Homemaker	6.1 (4)	2.7 (3)	
Retired	12.1 (8)	17.3 (19)	
Unemployed	15.2 (10)	13.6 (15)	
Working part-time	16.7 (11)	11.8 (13)	
Working full-time	10.6 (7)	3.6 (4)	
Household income			
Less than $24,999	41.8 (23)	28.9 (28)	
$25,000 to $49,999	23.6 (13)	28.9 (28)	
$50,000 to $99,999	16.4 (9)	25.8 (25)	
$100,000 to $149,999	12.7 (7)	9.3 (9)	
$150,000 or more	5.4 (3)	7.2 (7)	

**$p < 0.01$.

line at their convenience using Research Electronic Data Capture (REDCap), an online survey tool [31]. A timeline was not utilized as this illness can be unpredictable and may have rapid declines in functioning any given day.

The full sample (N = 704) was 89.7% female and 10.3% male. The majority of participants were Caucasian (96.4%). Only 2% identified as being of Latino or Hispanic origin. For marital status, 56.4% were married; 2.6% were separated; 1.1% was widowed; 13.4% were divorced; and 26.5% were never married. Regarding education, 0.7% completed less than high school; 3.3% completed some high school; 6.6% completed high school or had a GED; 22.8% had at

least one year of college or specialized training; 33.7% had standard college degree; the remaining 32.9% had a graduate or professional degree. For work status, 42.2% were on disability; 3.0% were students; 4.9% were homemakers; 10.5% were retired; 16.8% were unemployed; 15.8% worked part-time; and the remaining 6.8% worked full-time. The majority of the participants were international with only 45.2% of individuals currently living in the United States.

Results

Exercise tests

One quarter of participants, 25.9% (N = 182), indicated they had participated in an exercise test. Of those individuals, 37.3% (N = 66) had normal results and 62.7% (N = 111) had abnormal results. Five of the participants that had exercise tests were omitted from the analyses due to missing results data. Only 20% (N = 35) of these participants were asked to exercise on back-to-back days. For those that only had a one-day test, 45.0% (N = 63) had normal results and 55.0% (N = 77) had abnormal results. For the participants that had a two-day test, 8.6% (N = 3) had normal results and 91.4% (N = 32) had abnormal results. Unfortunately, the majority of participants were unable to provide their results as they did not receive a copy from their physician or were only told they had "abnormal" results. Analyses were run with two groups: individuals with normal exercise test results and individuals with abnormal exercise test results. Since the results were similar when comparing the group with normal results from a one day test to the two groups with abnormal results individually, the groups were combined to all participants with abnormal test results and all participants with normal test results, regardless of if it was a one day or two day test. The individuals with abnormal results remained grouped together as they displayed similar results on functioning and symptomatology. The demographics for these two groups have been presented in Table 1. The abnormal results group had a significantly higher education level compared to the normal results group [$\chi^2 (3) = 12.39$, $p < 0.01$] so this was controlled for in subsequent analyses. No other demographic variables reached statistical significance, $p > 0.05$.

Functioning

Table 2 shows the functioning levels and composite scores for each PEM symptom and domain for the two groups. The abnormal results group had significantly lower scores for the SF-36 Physical Functioning subscale [$F (1, 155) = 8.48$, $p < 0.01$] and the Bell Ability Scale [$F (1, 154) = 4.33$, $p < 0.05$]. The lower scores indicate worse functioning for both measures, so the abnormal group displayed worse functioning on each of the disability measures.

For the composite scores, there were significant differences for the overall PEM composite [$F (1, 173) = 4.36$,

Table 2: Mean functioning levels of participants (N = 177).

	Normal results	Abnormal results	
	(N = 66)	(N = 111)	
	M (SD)	M (SD)	
SF-36 Physical functioning	30.40 (23.35)	21.77 (18.28)	**
Bell ability scale	36.18 (16.14)	32.33 (14.43)	*
All PEM symptoms	**67.65 (19.93)**	**72.74 (17.40)**	*
Muscle factor	**61.58 (23.67)**	**66.88 (23.00)**	
Muscle weakness after minor exertion	57.14 (28.90)	62.97 (29.78)	
Muscle fatigability after minor exertion	60.77 (28.63)	69.46 (24.82)	*
Muscle pain after minor exertion	55.08 (29.35)	60.97 (29.82)	
Next day soreness or fatigue after non-strenuous, everyday activities	66.54 (23.91)	72.13 (21.22)	
Dead, heavy feeling after starting to exercise	68.27 (27.61)	70.60 (28.15)	
General factor	**70.17 (19.42)**	**75.08 (16.55)**	*
Post-exertional malaise	70.70 (21.15)	75.24 (19.44)	
Prolonged generalized fatigue or malaise following previously tolerable levels of exercise	80.16 (21.26)	78.74 (23.24)	
Post-exertional exhaustion that is immediate or delayed	69.62 (22.09)	77.83 (16.84)	**
Symptoms worsen with exertion	72.85 (21.66)	80.78 (19.22)	**
Substantial reduction in pre-illness activity level due to low threshold physical and mental fatigability	80.08 (24.67)	84.70 (18.99)	
Fatigue/extreme tiredness	74.04 (20.29)	77.61 (18.32)	
Marked, rapid physical or cognitive fatigability in response to exertion	66.21 (25.07)	72.20 (23.18)	
Exhaustion not relieved by rest	65.96 (26.29)	75.23 (21.72)	**
Prolonged worsening of symptoms after physical activity	66.02 (23.72)	74.06 (22.14)	*
Minimum exercise makes you physically tired	71.15 (25.48)	73.75 (22.40)	
Physically drained or sick after mild activity	66.73 (23.83)	70.30 (22.74)	
Mentally tired after the slightest effort	59.62 (23.46)	65.00 (24.76)	

*$p < 0.05$, **$p < 0.01$.

$p < 0.05$]. This indicated that the abnormal results group was experiencing PEM-related symptoms more frequently and severely than the normal results group. Using an exploratory factor analysis, McManimen, et al. [32] found a two-factor solution for the construct of PEM: a muscle-specific fatigue (i.e. Muscle factor) and a generalized, full-body exhaustion (i.e. General factor). The abnormal group had significantly higher scores for "Muscle fatigability after minor exertion" within the Muscle factor [F (1, 169) = 6.34, $p < 0.05$]. Similar results were shown for the overall General factor domain composite [F (1, 173) = 4.22, $p < 0.05$] and four of the individual symptoms within the factor: "Post-exertional exhaustion that is immediate or delayed" [F (1, 169) = 9.10, $p < 0.01$], "Symptoms worsen with exertion" [F (1, 168) = 8.12, $p < 0.01$], "Exhaustion not relieved by rest" [F (1, 170) = 7.51, $p < 0.01$], and "Prolonged worsening of symptoms after physical activity" [F (1, 168) = 6.42, $p < 0.05$]. The other individual symptoms and the Muscle Factor composite scores were not significantly different, $p > 0.05$. However, with the exception of one symptom ("Prolonged generalized fatigue or malaise following previously tolerable levels of exercise"), there was a general trend of the participants in the abnormal results group having more frequent and severe symptoms than the participants in the normal results group.

Illness characteristics

Table 3 provides the illness characteristics for each group. The abnormal results group was more functionally impaired as they had a significantly higher percent-

age of participants reporting that they were bedridden or could only walk around the house, [χ^2 (2) = 6.11, $p < 0.05$]. No other illness characteristics were statistically significant, $p > 0.05$.

Discussion

To assess symptomatology differences, patients with ME and CFS rated the frequency and severity of several PEM-related symptoms. Additionally, their functional status was assessed using two disability measures, the SF-36 and the Bell Ability Scale. The participants were categorized into two groups based on their self-reported results, normal or abnormal, from prior exercise challenges. As shown in Table 2 and Table 3, the group that reported abnormal exercise test results displayed significantly lower functioning levels for the Bell Ability Scale and the SF-36 Physical Functioning subscale. In addition, this group was more likely to be bedbound and experience PEM-related symptoms at more frequent and severe levels compared to the group of participants that reported normal exercise test results.

These findings suggest there is a subgroup of patients with ME and CFS that is more functionally impaired than the rest of the patient population. Although both groups of participants endorsed PEM-related symptoms, the group with the abnormal results displayed higher frequency and severity for the symptoms. Since this group appears to be more impaired, they may have a lower threshold for exertion, which could result in them experiencing PEM

Table 3: Illness characteristics by exercise test status (N = 177).

	Normal results (N = 66) % (N)	Abnormal results (N = 111) % (N)	
Diagnosed by			
Medical doctor	89.4 (59)	98.2 (109)	
Alternative practitioner	1.5 (1)	0.0 (0)	
Self-diagnosed	9.1 (6)	1.8 (2)	
Fatigue/Energy problem duration			
6-12 months	1.5 (1)	0.9 (1)	
1-2 years	3.0 (2)	2.7 (3)	
Longer than 2 years	80.3 (53)	81.1 (90)	
Since childhood or adolescence	15.2 (10)	15.3 (17)	
Illness onset			
Within 24 hours	20.0 (13)	29.1 (32)	
Over 1 week	10.8 (7)	10.0 (11)	
Over 1 month	7.7 (5)	12.7 (14)	
Over 2-6 months	9.2 (6)	12.7 (14)	
Over 7-12 months	9.2 (6)	5.5 (6)	
Over 1-2 years	10.8 (7)	9.1 (10)	
Longer than 2 years	21.5 (14)	13.6 (15)	
Since childhood or adolescence	10.8 (7)	7.3 (8)	
Course of illness			
Constantly getting worse	15.2 (10)	28.8 (32)	
Constantly improving	3.0 (2)	1.8 (2)	
Persisting	13.6 (9)	14.4 (16)	
Relapsing & Remitting	12.1 (8)	9.0 (10)	
Fluctuating	56.1 (37)	45.9 (51)	
Functional status			*
Bedridden/Walk around the house	27.3 (18)	44.5 (49)	
Can do light housework	43.9 (29)	38.2 (42)	
Able to work	28.8 (19)	17.3 (19)	
Had PEM in past 6 months			
Yes	98.5 (65)	100.0 (111)	
No	1.5 (1)	0.0 (0)	
PEM onset after activities			
1 hour or less	33.3 (9)	20.0 (8)	
2-3 hours	22.2 (6)	20.0 (8)	
4-10 hours	25.9 (7)	10.0 (4)	
11-13 hours	3.7 (1)	5.0 (2)	
14-23 hours	3.7 (1)	10.0 (4)	
More than 24 hours	11.1 (3)	35.0 (14)	
Pre-illness level of exertion leads to PEM			
Yes	87.9 (58)	82.9 (92)	
No	12.1 (8)	17.1 (19)	

*$p < 0.05$.

more quickly than the group with normal test results. Conversely, the group with normal test results may require more exertion before the results would differ from those of healthy controls as they are not as functionally impaired as the group with abnormal test results.

This finding result in a heterogeneous patient population for research involving exercise testing, which may help explain the discrepant results found in previous studies. Additionally, since the group with abnormal exercise test results is more likely to be bedbound or housebound, it is possible that they are unable to make it to a tertiary clinic to participate in these research studies. As a result, the more severely impaired group patients with ME and CFS may be excluded from analyses comparing the full patient population to healthy control populations. This could prevent researchers from finding significant differences between patients and controls if the more impaired patients are unable to participate in research.

This study has several limitations. First, this study used an international convenience sample. All participants had a self-reported, current diagnosis of ME or CFS so there was no standardized diagnostic criteria necessary to participate in this study. The study also included participants from many settings and countries. Previous research has shown differences in patient populations between US and UK samples [33]. However,

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this may actually be seen as an advantage as it would allow for us to generalize the results across various settings (i.e. tertiary care, community, and primary care samples) and geographic locations.

Additionally, we do not have information on the types of tests that were performed, submaximal or maximal. The participants self-reported that they had previously received normal or abnormal exercise test results. Future research should examine the functional and symptomatic differences between the patients with normal and abnormal results in a controlled, standardized study to form a more homogenous patient sample.

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