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 seden-
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 oxy-
gen uptake, and respiratory exchange ratio. Similar to the
patients were showing signs of physical deconditioning.

However, there is also an inconsistency in findings with
exercise testing. Although the researchers found signif-
ificant 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 dif-
fferences between patients and controls. This study also failed
to find significant differences in peak heart rate, endur-
ance, 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 dif-
fferences in endurance and respiratory exchange ratio. Since
the results are varying, it is difficult to determine which dif-
fferences 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 cur-
rent 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 dif-
fferences 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 popula-
tions from previous research are heterogeneous, which
could explain the inconsistencies in findings.

Methods

Measures

Participants were asked to complete a series of ques-
tionnaires 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 fre-
quency and severity scores of each PEM-related symp-
tom. 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 symp-
toms 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 mul-
tiplying 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]. Con-
versely, 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 se-
verity 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 inter-
net forums, and postings in patient organization news-
letters. Participants completed the study measures on-
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 [χ²(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,
**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 percentage of participants reporting that they were bedridden or could only walk around the house, \( \chi^2 (2) = 6.11, p < 0.05 \). 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.
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,

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.

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<table>
<thead>
<tr>
<th>Table 3: Illness characteristics by exercise test status (N = 177).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal results</strong></td>
</tr>
<tr>
<td>(N = 66)</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td><strong>Diagnosed by</strong></td>
</tr>
<tr>
<td>Medical doctor</td>
</tr>
<tr>
<td>Alternative practitioner</td>
</tr>
<tr>
<td>Self-diagnosed</td>
</tr>
<tr>
<td><strong>Fatigue/Energy problem duration</strong></td>
</tr>
<tr>
<td>6-12 months</td>
</tr>
<tr>
<td>1-2 years</td>
</tr>
<tr>
<td>Longer than 2 years</td>
</tr>
<tr>
<td>Since childhood or adolescence</td>
</tr>
<tr>
<td><strong>Illness onset</strong></td>
</tr>
<tr>
<td>Within 24 hours</td>
</tr>
<tr>
<td>Over 1 week</td>
</tr>
<tr>
<td>Over 1 month</td>
</tr>
<tr>
<td>Over 2-6 months</td>
</tr>
<tr>
<td>Over 7-12 months</td>
</tr>
<tr>
<td>Over 1-2 years</td>
</tr>
<tr>
<td>Longer than 2 years</td>
</tr>
<tr>
<td>Since childhood or adolescence</td>
</tr>
<tr>
<td><strong>Course of illness</strong></td>
</tr>
<tr>
<td>Constantly getting worse</td>
</tr>
<tr>
<td>Constantly improving</td>
</tr>
<tr>
<td>Persisting</td>
</tr>
<tr>
<td>Relapsing &amp; Remitting</td>
</tr>
<tr>
<td>Fluctuating</td>
</tr>
<tr>
<td><strong>Functional status</strong></td>
</tr>
<tr>
<td>Bedridden/Walk around the house</td>
</tr>
<tr>
<td>Can do light housework</td>
</tr>
<tr>
<td>Able to work</td>
</tr>
<tr>
<td><strong>Had PEM in past 6 months</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>PEM onset after activities</strong></td>
</tr>
<tr>
<td>1 hour or less</td>
</tr>
<tr>
<td>2-3 hours</td>
</tr>
<tr>
<td>4-10 hours</td>
</tr>
<tr>
<td>11-13 hours</td>
</tr>
<tr>
<td>14-23 hours</td>
</tr>
<tr>
<td>More than 24 hours</td>
</tr>
<tr>
<td><strong>Pre-illness level of exertion leads to PEM</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

*p < 0.05.
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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**References**


