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ME/CFS Health Outcomes: The Interaction of Mode of Illness Onset and Psychiatric Comorbidity

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Abstract**—**The objective of this study was to examine the interaction between mode of illness onset and psychiatric comorbidity on the health outcomes of persons with ME/CFS. A total of 114 individuals with ME/CFS participated in this study. Individuals completed a battery of baseline measures including the fatigue severity scale and measures of disability. Findings indicated that those with sudden illness onset had more impaired physical health functioning. In addition, among individuals with sudden onset, those without psychiatric comorbidity had greater fatigue severity and lower overall physical health than those with psychiatric comordibity. In contrast, among individuals with gradual illness onset, those with psychiatric comorbity had higher fatigue severity than those without comorbid psychiatric disorders. The health outcomes of individuals who have ME/CFS with or without psychiatric comorbidity are impacted by the mode of illness onset and this suggest that it is important to examine these factors in future research.

Keywords**—**Health Outcomes, ME/CFS, Mode of Illness Onset, Psychiatric Comorbidity.

I. INTRODUCTION

ACCORDING to the Fukuda et al. [1] case definition, chronic fatigue syndrome (CFS) is marked by the presence of persistent or relapsing chronic fatigue that has been present at least 6 months with new or definite onset. This illness has more recently been referred to as ME/CFS (where ME stands for either Myalgic Encephalomyelitis or Myalgic Encephalopathy). ME/CFS can affect several areas of functioning including social, occupational, educational, and activities of daily living [2]. In addition, heterogeneity of patient groups has been a major source of concern for research and treatment purposes. A variety of factors, including mode of illness onset and comorbidity with other illnesses [3-6], have been noted across studies of ME/CFS as contributing to differences noted among persons with ME/CFS.

Several studies have examined the mode of illness onset as a predictor of CFS health outcomes [4,5-7]. In a twin study of ME/CFS, Claypoole et al. found that individuals with sudden ME/CFS onset tended to present with decreased information processing while those with gradual illness onset demonstrated information processing that was similar to those of their healthy twin. Jason et al.[5] also found that individuals with sudden as opposed to gradual illness onset reported more severe sore throat and increased fatigue after exercise. In an epidemiology study, Reyes et al. [6] found that individuals with sudden ME/CFS onset reported more illness symptoms than those with gradual onset. Another study found that individuals with sudden ME/CFS onset presented with more neurological defects than individuals with AIDS [7]. These studies suggest that mode of illness onset may be a significant predictor of ME/CFS illness outcomes, such that persons with sudden ME/CFS onset appears to have poorer health outcomes than those with gradual illness onset. However, the findings are not always consistent, as Levine [8] found that sudden illness onset was associated with better prognosis than gradual illness onset.

Jason et al. [5] also found that those with sudden onset had a greater likelihood of the presence of lifetime psychiatric diagnosis. This is in contrast to other investigators who found that individuals with an acute illness onset evidenced less comorbid psychiatric diagnoses [9], and less severe depressive symptoms [10] than those with gradual illness onset. The study by Jason et al. was a community-based study and used the Fukuda et al [1] CFS criteria whereas Deluca et al.'s study generated their sample from a healthcare setting and used the Holmes et al [11] CFS criteria. Differences noted in these studies may be due to the sampling and diagnostic criteria differences. While these studies examined differences in psychiatric comorbidity among those with gradual and sudden onset of ME/CFS, neither investigation explored possible interactions between mode of illness onset and psychiatric comorbidity.

Psychiatric comorbidity is another variable that appears to play a role in the heterogeneity of ME/CFS and outcomes [12-15]. Jason et al. [13] found that psychiatric comorbidity was related to greater physical fatigue, worse emotional role functioning and higher perceived stress. Wagner-Raphael, Jason and Ferrari [16] also found more impaired emotional role functioning among nurses with ME/CFS presenting with psychiatric comorbidity versus those without a co-occurring psychiatric condition. In a study of the prevalence of fatigue, Njoku et al [14] found that psychological distress was a significant predictor of fatigue severity. Wilson et al. [15]

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found that psychiatric comorbidity was associated with functional impairments in persons with ME/CFS, while [17] found that individuals with psychiatric comorbidity had more impaired social functioning than those without psychiatric comorbidity. These findings indicate that persons with ME/CFS and comorbid psychiatric disorders may experience more impaired functioning. It should be noted that studies have indicated that some individuals with ME/CFS do not have comorbid psychiatric disorders and for those persons, they tend to be more similar to individuals with mild multiple sclerosis and than those with psychiatric disorders such as major depression [18].

While several studies have examined the individual impact of mode of illness onset and psychiatric comorbidity on the health outcomes of individuals with CFS/ME, it is unclear what the interaction between psychiatric co-morbidity and type of onset and health outcomes of persons with ME/CFS. Evidence from the studies noted above suggests that persons with sudden ME/CFS onset and comorbid psychiatric disorders may experience poorer health outcomes. The objective of this study was to explore the interaction effect of mode of illness onset and psychiatric comorbidity status on markers of physical and mental health outcomes in individuals with ME/CFS. It was hypothesized that individuals with both sudden illness onset and psychiatric comorbidity would evidence significantly poorer health status than those with gradual onset and no psychiatric comorbidity.

II. Method

Participant Recruitment: Study participants were derived from a larger treatment trial investigating the effectiveness of non-pharmacologic interventions for individuals with ME/CFS [19]. Participants were recruited from a variety of sources, including physician referrals. Information about the non-pharmacologic treatment trial study was disseminated to medical colleagues through mailings and phone communication. In addition, study announcements for new participants were placed in local newspapers and recruitment offers were made at local ME/CFS support group meetings. These efforts were continued throughout the study period until the target enrollment numbers were achieved. Twenty-four additional individuals who were screened were excluded due to a variety of reasons (i.e., lifelong fatigue, less than 4 Fukuda symptoms, BMI > 45, melancholic depression or bipolar depression, alcohol or substance abuse disorder, autoimmune thyroiditis, cancer, lupus, rheumatoid arthritis). One hundred and fourteen individuals were recruited for the present study. Of the 114 individuals, 46% were referred by physicians, 34% were recruited by media (newspapers, TV, radio, etc.), and 20% stemmed from other sources (e.g., heard about the study from a friend, family member, person in the study, etc.).

Initial Screening. All participants were required to be at least 18 years of age, not pregnant, able to read and speak English, and considered to be physically capable of attending the scheduled sessions. Bedridden and wheelchair bound patients were excluded due to the practical difficulties of making appointments. Referrals to local physicians who treat ME/CFS and to support groups were offered to these individuals. After a consent form was filled out, prospective participants were initially screened by the third author, using a structured questionnaire. Because ME/CFS is a diagnosis of exclusion, prospective participants were screened for identifiable psychiatric and medical conditions that may explain ME/CFS-like symptoms. These measures were completed at DePaul University and took approximately two hours. After the initial interview was completed, the patients' information was reviewed to ensure that they met all eligibility requirements.

If found to be eligible for the study, all participants attended a medical appointment with the study physician in order to confirm the diagnosis of chronic fatigue syndrome. After confirmation that the individual fully met the criteria for ME/CFS according to the Fukuda et al. [1] case definition, individuals completed a battery of baseline measures (described below).

III. Measures

The CFS Questionnaire. This screening scale was initially validated by Jason et al. [20]. Hawk, Jason, and Torres-Harding [21] recently revised this ME/CFS Questionnaire, and administered the questionnaire to three groups (those with ME/CFS, Major Depressive Disorder, and healthy controls). The revised instrument, which was used in the present study, evidences good test-retest reliability and has good sensitivity and specificity [21]. This scale was used to collects demographic, health status, medication usage, and symptom data, and it used the definitional symptoms of ME/CFS [1]. For each Fukuda et al. case definition symptom, participants rated the intensity of each symptom they endorsed on a scale of 0 to 100, where 0 = no problem and 100 = the worst problem possible. The mode of illness onset was derived from an item on this measure. Illness onset duration of one month defined the sudden illness onset group whereas onset duration of longer than one month signified gradual illness onset.

The Structured Clinical Interview for DSM-IV (SCID) [22] Axis I: This interview was used to establish the presence of a current psychiatric diagnosis. The professionally administered SCID allows for clinical judgment in the assignment of symptoms to psychiatric or medical categories, a crucial distinction in the assessment of symptoms that overlap between ME/CFS and psychiatric disorders, such as fatigue, concentration difficulty, and sleep disturbance [4]. A psychodiagnostic study [23] validated the use of the SCID in a sample of ME/CFS patients. The presence of current Axis 1 psychiatric comorbidity was ascertained from the SCID. Psychiatric comordity status utilized in the present study was characterized as ME/CFS without a psychiatric diagnosis and ME/CFS with psychiatric comordity (involving any Axis 1 disorder).

Medical Examination: The physician screening evaluation included a general and neurological physical examination. Laboratory tests in the battery were the minimum necessary to rule out other illnesses [1]. Laboratory tests included a

chemistry screen (which assesses liver, renal, and thyroid functioning), complete blood count with differential and platelet count, erythrocyte sedimentation rate, arthritic profile (which includes rheumatoid factor and antinuclear antibody), hepatitis B, Lyme Disease screen, HIV screen and urinalysis. A tuberculin skin test was also performed. If the TB skin test was positive, a follow-up chest x-ray was conducted to rule out tuberculosis. The project physician performed a detailed medical examination to detect evidence of diffuse adenopathy, hepatosplenomegaly, synovitis, neuropathy, myopathy, cardiac or pulmonary dysfunction. This medical examination was used to confirm the diagnosis of ME/CFS, according to the Fukuda et al. [1] criteria and to rule out exclusionary medical conditions.

Medical Outcomes Study-Short Form-36. (MOS-SF-36). Participants completed the Medical Outcomes Study 36-item Short-Form Survey (MOS) [Ware & Sherbourne, 1992], a reliable and valid measure that discriminates between gradations of disability. This instrument encompasses multi-item scales that assess physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, and mental health. The MOS Physical composite score (PCS) and Mental composite score (MCS) were utilized in the present investigation as combined measures of the eight MOS subscales to rate global impairment of physical and mental functioning. The PCS and MCS have good validity and reliability as well as adequate sensitivity and specificity in discriminating the gradations of health status among groups [24]. Higher scores indicated better health, lower disability, and less impact of health on functioning. Reliability and validity studies for the 36-item version of the MOS have shown adequate internal consistency, discriminant validity among subscales, and substantial differences between patient and nonpatient populations in the pattern of scores [25, 26]. The SF-36 has also indicated sufficient psychometric properties as a measure of functional status in a ME/CFS population [27].

Fatigue Severity Scale (FSS). Krupp et al.'s [28] Fatigue Severity Scale was used to measure fatigue. This scale includes 9 items rated on 7-point scales and is sensitive to different aspects and gradations of fatigue severity. Previous findings have demonstrated the utility of the Fatigue Severity Scale [28] to discriminate between individuals with ME/CFS, MS, and primary depression [29].

Statistical Analyses

The relationship between sociodemographic factors (gender and age) and the mode of illness onset and psychiatric comorbidity status were examined with chi-square tests. An analysis of variance was used for exploring the impact of mode of illness onset and psychiatric comorbidity on physical and mental health outcomes. The effect size for the analysis of variance was based on the partial eta squared generated from the SPSS. In order to interpret the strength of the effect sizes, Cohen's [30] guidelines were used; 0.01 = small effect, 0.06 = moderate effect and 0.14 = large effect. In cases of significant effects, a Bonferroni mean comparison was used for post-hoc testing.

IV. Results

Preliminary analysis

We first examined whether there were any gender or age difference among the two mode of illness groups (i.e., sudden versus gradual onset). Participants were placed into two age categories based on the median age of the sample (i.e., 18-46; 47-74). No significant gender [χ^2 (1, N =110) = 0.15, p = 0.70] or age [χ^2 (1, N =110) = 0.04, p = 0.84] differences were found among the two illness onset groups. We next examined whether there were any gender and age differences among those with and without psychiatric illness. There were no significant gender [χ^2 (1, N =114) = 0.00, p = 1.00] or age [χ^2 (1, N =114) = 0.04, p = 0.85] differences among those with and without psychiatric illness.

The Overall sample consisted of 39% with psychiatric comorbidity and 61% without psychiatric comorbidity. In terms of mode of illness onset, it was 33% and 67% respectively for sudden and gradual illness onset. Among the 43 individuals who had comorbid psychiatric disorders, 67% had a gradual CFS onset while 33% had a sudden onset [χ^2 (1, N = 43) = 5.23, p = 0.02]. There was an equal percentage of individuals with psychiatric comorbidity in each illness onset group, averaging 39% respectively for gradual illness (N =29) and sudden illness onset groups (N = 14). Similarly, among those without psychiatric comorbidity, 67% had a gradual illness onset while 33% had a sudden illness onset and this difference was also significant [χ^2 (1, N = 67) = 7.90, p = 0.01]. Also, there was an equal percentage of individuals without psychiatric comorbidity in each illness onset group averaging 61% respectively for gradual illness (N = 45) and sudden illness onset groups (N = 22).

Health outcomes, psychiatric comorbidity status and mode of illness onset

An ANOVA was used with fatigue severity as the dependent variable, and with mode of illness onset and psychiatric comorbidity as the independent variables. No significant main effects were found for psychiatric comorbidity status or mode of illness onset. A significant two-way psychiatric comorbidity status by mode of illness onset interaction was found for fatigue severity [F(1, 106) = 8.38, p = 0.01] and the effect size was moderate (partial eta squared = 0.07). Using Bonferroni mean comparisons, among individuals with ME/CFS without psychiatric comorbidity, those who had sudden illness onset had significantly greater fatigue severity than those who had gradual illness onset. In contrast, among persons with ME/CFS and psychiatric comorbidity, those with a sudden illness onset had directionally lower fatigue severity scores than those with gradual illness onset (See Table 1 and Figure 1). Among individuals with gradual illness onset, those with psychiatric comorbidity evidenced significantly greater fatigue severity than those with ME/CFS without psychiatric comorbidity.

TABLE I INTERACTIONS- MODE OF ILLNESS ONSET AND PSYCHIATRIC CO-MORBIDITY

	ME/CFS		ME/CFS with Psych	
Factor	Sudden M (SD)	Gradual M (SD)	Sudden M (SD)	Gradual M (SD)
Fatigue	6.35 (0.65)[a]	5.84 (0.73)[ab]	5.88 (1.33)	6.33 (0.55)[b]
MCS	46.26 (11.00)	41.85 (10.07)	37.32 (8.20)	39.76 (8.53)
PCS	23.34 (8.26)[a]	30.68 (7.11)[a]	26.48 (7.43)	27.32 (8.31)

Similar letters in each row indicate groups that are significantly different. Sample sizes were 21 for Sudden no Psych; 43 for Gradual no Psych; 14 for Sudden with Psych, and 28 for Gradual with Psych

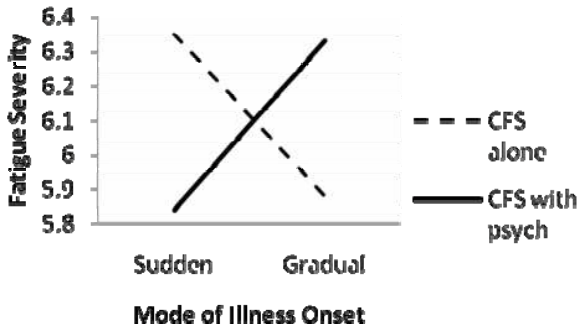

Fig. 1 Interaction between mode of illness onset and psychiatric comorbidity status for fatigue Severity

Next, a MANOVA was used to examine the relationship between the dependent disability variables tapping overall physical and mental functioning, and the independent variables of mode of illness onset and psychiatric comorbidity. A significant main effect of mode of illness onset was found for the physical component [$F(1, 106) = 6.32$, $p = .01$], with a moderate effect size (partial eta squared = 0.06). Persons with sudden illness onset ($M = 24.59$; $SD = 7.98$) had significantly lower physical functioning than those with gradual illness onset ($M = 29.35$; $SD = 7.73$). There was also an interaction effect for the overall physical functioning variable [$F(1, 106) = 3.97$, $p = .05$], with a large effect size (partial eta squared = 0.18). Bonferroni post-hoc testing indicated that among individuals without psychiatric comorbidity, those who had sudden illness onset evidenced significantly lower physical functioning than those with gradual illness onset (see Table 1 & Figure 2).

A significant main effect of psychiatric comorbidity status was found for the mental composite score [$F(1, 106) = 7.31$, $p = .01$], with a moderate effect size (partial eta squared = 0.07). Individuals with psychiatric comorbidity ($M = 38.95$; $SD = 8.40$) had significantly lower mental functioning than those without a psychiatric condition ($M = 43.30$; $SD = 10.51$).

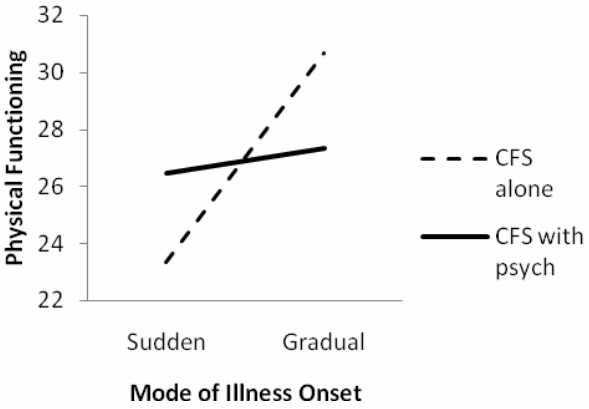

Fig. 2 Interaction between mode of illness onset and psychiatric comorbidity status for Physical Functioning

V. DISCUSSION

The present study investigated the impact of mode of illness onset and psychiatric comorbidity on the health status of individuals with ME/CFS. Among individuals without psychiatric comorbidity, those who had sudden illness onset evidenced significantly lower physical functioning and higher fatigue severity than those with gradual illness onset. These outcomes were hypothesized and suggest that sudden onset might have a variety of illness burdens that result in lower functioning and more severe fatigue. However, when examining those with psychiatric comobidity, the results indicated a reversal of effects, with greater fatigue severity among those with gradual onset rather than sudden onset (for those with psychiatric comorbidity, physical functioning did not vary as a function of type of onset). These types of findings point to complexities in the effects of psychiatric status and type of onset on major areas of functioning among patients with ME/CFS.

Among those with gradual illness onset, individuals with psychiatric comorbidity had significantly greater fatigue severity than those without psychiatric comorbidity. According to Deluca et al [9], individuals with gradual illness onset have more psychiatric comorbidity, and Deluca et al. concluded that there might be two types of patients, some with gradual onset with psychiatric comorbity and others with acute onset with less psychiatric comorbidity. The present study found that for the group with gradual onset, having the burden of both a chronic illness (ME/CFS) and a psychiatric condition might have led to more fatigue.

Claypoole et al. [3], Jason et al. [5], and Reyes et al. [6] had found that sudden illness onset was associated with poorer outcomes, and this could have been attributed to the etiology of viral or infectious processes leading to worse functioning among those with an acute illness onset. As is evident in Figure 1, among those with a sudden illness onset, individuals without psychiatric comorbidity had directionally higher fatigue severity than those with psychiatric comorbidity. It is possible that those with sudden onset were more likely to seek services for their sudden onset of symptoms if they also had a psychiatric condition. If those with sudden onset sought

services early and were satisfied with them, they might have been able to reduce their levels of fatigue severity. Among those with sudden onset with a psychiatric condition, 100% reported that treatments influenced their current fatigue illness, whereas among those with sudden onset without a psychiatric condition, only 35% indicated that treatments influenced their current fatigue illness. This suggests that among those with sudden illness onset, those with a psychiatric condition might more actively seek out supportive treatments. It may also be possible that experiences of fatigue among the sudden ME/CFS onset with a psychiatric condition group is more attributable to psychiatric fatiguing symptoms. Thus, treatment received for the condition may have been more helpful in reducing the severity of the fatigue. These findings for those with sudden onset are complex, and they suggest that the presence of current psychiatric disorders may impact the health outcomes of individuals with ME/CFS.

For physical functioning, among persons without psychiatric conditions, those with a sudden illness onset had more functional problems than those with gradual onset. Again, this might be explained by the nature of the onset of illness, which when sudden, can cause more trauma and difficulties for the individual, as was mentioned above. In contrast, there were no differential effects for sudden versus gradual onset for those with comorbid conditions. Still, there was a directional trend indicating that among those with a sudden onset, individuals with psychiatric comorbid conditions had better functioning than those without psychiatric comorbid conditions. Once again, it is possible that those with comorbid conditions with a sudden onset are more prone to seek services, which might help them in reducing functional limitations or tend to benefit from treatments that they receive for their psychiatric symptoms.

In terms of mental functioning, there was no significant mode of illness effect. But individuals with psychiatric comorbidity had significantly lower mental scores than those without a psychiatric condition. Given the high overlap between the assessment of mental functioning and psychiatric condition, it would be expected that this association would emerge.

In conclusion, mode of illness onset and psychiatric comorbidity was found to be associated with different health outcomes among people with ME/CFS. In the current study, among individuals with sudden illness onset, those without psychiatric comorbidity had higher fatigue severity and more physical impairment than those with psychiatric comorbidty. While sudden illness onset without psychiatric comorbidity is associated with poorer fatigue and physical health outcomes, gradual illness onset with psychiatric comorbity is related to poorer fatigue status. At minimum, this study suggests that it is important to assess for illness onset and psychiatric comorbidity when working with patients with ME/CFS. Additionally, there is a need for examining the interaction between these two factors when investigating the health outcomes of individuals with ME/CFS.

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