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Journal of Chronic Diseases and Management

Review Article

A Comparison of Case Definitions for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome

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Submitted: 07 April 2017

Accepted: 16 May 2017

Published: 21 May 2017

Keywords
- Case definitions
- Myalgic encephalomyelitis
- Chronic fatigue syndrome

Abstract

Many professionals have described the clinical presentation of myalgic encephalomyelitis (ME), but recent efforts have focused on the development of ME criteria that can be reliably applied. The current study compared the symptoms and functioning of individuals who met the newly-developed Institute of Medicine (IOM) clinical criteria to a revised version of the London criteria for ME. While 76% of a sample diagnosed with chronic fatigue syndrome (CFS) met the IOM criteria, 44% met the revised London criteria. The revised London criteria identified patients with greater physical impairment. The results of this study indicate the need for a standard case definition with specific guidelines for operationalization. The application of case definitions has important implications for the number of individuals identified with ME, the pattern of symptoms experienced by these individuals, and the severity of their symptoms and functional limitations. Sample heterogeneity across research studies hinders researchers from replicating findings and impedes the search for biological markers and effective treatments.

INTRODUCTION

A Comparison of case definitions for myalgic encephalomyelitis and chronic fatigue syndrome

Many researchers and physicians have attempted to identify and define criteria for myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). Melvin Ramsay, an early investigator of myalgic encephalomyelitis (ME), summarized its clinical presentation in monographs published in1986 and 1988 [1,2]. In his 1988monograph, he described the distinct features of the illness: (1) muscle fatiguability after minimal exertion and a delay in the restoration of muscle power; (2) cerebral dysfunction, and (3) impaired circulation. He also emphasized the daily variation in symptoms and physical findings, as well as the propensity for the illness to become chronic.

Following the release of Ramsay's monographs, a number of researchers and physicians developed the London criteria for ME. These criteria were derived from the work of Ramsay and others and require: (1) an identifiable viral illness that preceded the onset of symptoms; (2) abnormal levels of muscle fatiguability or weakness, preceded by relatively minor activity; (3) impairment in memory and concentration, typically coupled with other neurological and psychological disturbances (e.g., emotional lability, disturbed sleep, vertigo, tinnitus, etc.); and (4) fluctuation of symptoms, often in response to minimal exertion.

In 1994, Westcare, a British charity, published a report by the National Task Force on CFS / Post-Viral Fatigue Syndrome (PVFS) / ME that included a compendium of existing case definitions [3]. One set of criteria for ME was incorrectly labeled as "the London criteria;" these criteria notably deviated from the London criteria described above. Throughout the remainder of this article, we refer to these criteria as the "Westcare criteria." The Westcare criteria for ME require exercise-induced fatigue (as opposed to the muscle fatiguability or weakness required by the London criteria) that is triggered by minor exertion, impairment of short-term memory coupled with other neurological symptoms (similar to the London criteria), and the fluctuation of symptoms (similar to the London criteria). Researchers who regard Ramsay's emphasis on muscle fatiguability as too limiting may prefer the Westcare criteria.

In 2009 [4], updated the original London criteria for ME, again identifying the core symptoms that differentiate the illness

from other disorders. The revised criteria required three or more months of: (1) a new onset of significantly abnormal levels of muscle fatiguability or weakness, preceded by relatively minor activity, with symptoms typically worsening over the following 1-2 days; (2) central nervous system dysfunction; (3) impaired circulation; and (4) symptom fluctuation, from hour to hour and day to day [4].Thus, the main difference between the London and Westcare criteria for ME is the presence of muscle fatiguability or muscle weakness (required by the London criteria) as opposed to fatigue. Findings by [5], support the observation that individuals with ME experience delayed recovery time following the onset of exertion-induced muscle fatigue.

Concurrent with the publication of the original London criteria, an international working group developed a case definition for chronic fatigue syndrome [6]. This case definition requires: (1) six or more months of fatigue of definite onset; (2) a significant reduction in social, occupational, or personal activities; and (3) four of the following eight symptoms: post-exertional malaise, unrefreshing sleep, impairment in memory or concentration, headaches, muscle pain, joint pain, sore throat, or tender lymph nodes [6]. These CFS criteria differ from the ME criteria described above in that they are polythetic; the ME criteria require a specific set of symptoms, whereas any combination of four symptoms could fulfill the Fukuda et al. CFS criteria. While certain core symptoms, such as post-exertional 'malaise' (or post-exertional worsening of symptoms) and cognitive impairment, must be present to meet the ME criteria, an individual could fulfill the Fukuda et al. CFS criteria without these symptoms. Due to symptomatology variation among patients who fulfill various case definitions, several studies have compared the characteristics of individuals who meet the different ME and CFS criteria.

Jason [7], operationalized the 'Westcare' criteria for ME [3], using a standardized questionnaire and applied these criteria to a community-based sample. This study compared 17 participants who met the Westcare ME criteria to 18 participants who were diagnosed with CFS using the Fukuda et al. criteria. The results indicated that the Westcare ME criteria selected a more symptomatic group of individuals than the [6], criteria for CFS. However, this study was limited in its symptom assessment; the questionnaires measured symptom occurrence but did not assess symptom severity.

Several years later, Jason [8], attempted to synthesize the work of a number of theorists and practitioners in order to operationalize the various descriptions and criteria for ME [2-4,9,10]. The resulting criteria require an acute illness onset, post-exertional malaise, neurological manifestations, and autonomic dysfunction. When Jason [11], applied these ME criteria to a tertiary care sample diagnosed with CFS [6], only 24% met this ME case definition. The individuals who met the ME case definition were more functionally impaired than those who fulfilled only the [6], CFS criteria. Additionally, those who met the ME criteria had higher resting and standing pulse rates, reported more autonomic symptoms, and demonstrated poorer performance on the Trail making test, a measure of processing speed and executive functioning. These studies demonstrate how differences in criteria and the operationalization of criteria lead to samples with vast differences in impairment and symptomatology.

Recently, the Institute of Medicine (IOM) published a clinical case definition for the illness (using the name Systemic Exertion Intolerance Disease) that requires individuals to evidence a substantial reduction in functioning, post-exertional malaise, unrefreshing sleep, and either cognitive dysfunction or orthostatic intolerance [12].While previous articles have compared individuals who met various ME criteria to those who fulfilled the most commonly used CFS criteria, none has compared the revised London Criteria [3], to the new IOM criteria [12]. In this study, we examined differences in functioning between individuals who met the revised London criteria for ME [3], and those who met the IOM criteria [12].We hypothesized that individuals who met the revised London Criteria would evidence greater physical impairment than those who met the IOM criteria.

METHODS

Participants

DePaul sample: Following approval from DePaul University's Institutional Review Board, adults with a self-reported diagnosis of CFS, ME/CFS, or ME were recruited from several sources: support group websites, national foundations, research forums, and social media outlets. Participants completed all study measures online. Of the 350 participants in this sample, 88.1% were female and 11.9% male. The majority (96.8%) of the sample identified as Caucasian, 0.9% as Asian, and the remaining 2.3% selected "Other" for their race. Regarding the highest level of education achieved, 42.0% of the sample had obtained a graduate or professional degree; 28.7% held a standard college degree; 19.0% had attended college for at least one year; 7.5% had completed high school; and 2.9% had not completed high school. Approximately half of participants (48.3%) were on disability, and only 22.1% of the sample was working part- or full-time. The mean age of the sample was 47.1 (*SD*= 16.8).

Solve ME/CFS initiative bio bank sample: The Solve ME/CFS initiative recruited participants with a physician diagnosis of ME or CFS for its Bio Bank sample. At the time of analysis, a total of 561individuals had completed study measures. This sample was 75.9% female and 24.1% male. The majority were married (60.9%); 0.7% were separated; 2.4% were widowed; 15.1% were divorced; and 20.8% were never married. Almost all participants were Caucasian (98%), although 0.4% identified as African-American, 0.2% as Asian or Pacific Islander, 0.2% as American Indian, and 1.3% selected "Other." Many participants (41.7%) were on disability; 1.7% was students; 2.4% were homemakers; 15.4% were retired; 13.9% were unemployed; 24.9% were working. In regards to education, 4.3% completed high school or less; 24.2% completed at least one year of college; 71.5% had a standard college degree. The mean age of the participants was 54.8 (*SD* = 12.5).

Newcastle sample: Individuals were referred to the Newcastle sample that had a suspected diagnosis of ME or CFS. Participants completed a written informed consent process, then provided a comprehensive medical history and were examined by an experienced physician. A total of 99 individuals completed

survey measures by hard copy. This sample was 99.0% Caucasian and 1.0% multiracial, and participants were predominantly female (81.0%). While 36.7% of participants were working, 30.6% were on disability. With regard to education level, 20.4% had a graduate or professional degree; 29.0% had a college degree; 24.7% had completed at least one year of college; 14.0% had a high school degree; and 11.8% had not completed high school. The average age of the sample was 45.8 (*SD* = 13.9).

Norway sample 1: Individuals who were 18 years or older and diagnosed with CFS by a physician or medical specialist were invited to participate in a randomized controlled trial of a CFS self-management program. Participants were recruited from the Oslo area through healthcare professionals, the waiting list for a patient education program, CFS patient organizations, and the Oslo University Hospital website. The study was approved the Regional Committee for Medical Research Ethics (Health Region North) and the Privacy Ombudsman for Research at Oslo University Hospital. Following a written informed consent process, 176 individuals participated in the study.

This sample was 86.3% female and 13.7% male. Almost all participants were Caucasian (99.4%), though 0.6% was Asian or Pacific Islander. Only 4.0% of participants were working, while 90.3% were on disability. Regarding education, 9.8% of participants had a graduate or professional degree, 40.2% a standard college degree, 42.0% a high school degree, and the remainder had not completed high school. The mean age of the sample was 43.6 years (*SD* = 11.9).

Norway sample 2: Individuals 18 years or older who were receiving services from a multidisciplinary CFS/ME Center was invited to participate in this study. Some participants resided in a medical ward for the severely ill, while others were receiving outpatient services. The project gained approval from the Privacy Ombudsman for research at Oslo University Hospital. All participants (n = 64) took part in a comprehensive medical history interview and a detailed medical examination conducted by experienced consultant physicians and a psychologist. The examinations were conducted to rule out exclusionary medical and psychiatric conditions. Participants completed a written informed consent, and the study measures were completed by hard copy in Norwegian.

This sample was 81.3% female, and the majority identified as Caucasian (98.4%); 1.6% identified as Asian. Most participants (93.8%) were on disability, while 4.7% were working. With regard to education, 12.5% held a graduate or professional degree; 25.0% held a standard college degree; 45.3% had a high school degree; and 17.2% had not completed high school. The mean age of the sample was 35.3 years (*SD* = 11.9).

Measures

The DePaul symptom questionnaire: All participants completed the DePaul Symptom Questionnaire [14], a self-report measure of ME and CFS symptomatology, demographics, and medical, occupational, and social history. This measure was developed to classify individuals by a variety of ME and CFS case definitions. Participants must rate the frequency and severity of 54 symptoms on 5-point Likert scales. Frequency is assessed using on the following scale: 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. Likewise, severity is rated on the following scale: 0=symptom not present, 1=mild, 2=moderate, 3=severe, 4=very severe. The DSQ has evidenced good test-retest reliability among both patient and control groups [15]. A factor analysis of these symptoms [15], resulted in a three-factor solution; all factors evidenced good internal consistency. The DSQ is available in the shared library of Research Electronic Data Capture [16].

Medical outcomes study 36-Item short-form health survey: The SF-36 is a self-report measure physical and mental functioning within the context of one's health status [17]. Lower scores indicate that an individual's health is negatively impacting his or her functioning. The SF-36 evidences strong psychometric properties, including internal consistency and discriminative validity [18].

Case definitions

Institute of Medicine (IOM): To fulfill the IOM criteria [12], participants needed to report that they had experienced six or months of fatigue that caused a substantial reduction in functioning [13], and was not lifelong or the result of overexertion. Additionally, participants needed to endorse symptoms of post-exertional malaise, sleep dysfunction, and either cognitive impairment or orthostatic intolerance. To fulfill the post-exertional malaise requirement, they needed to report that one or more of the following symptoms occurred at least half the time at moderate severity (or higher): *dead, heavy feeling after starting to exercise*, *next-day soreness or fatigue after non-strenuous, everyday activities*, *mentally tired after the slightest effort*, *minimum exercise makes you physically tired*, or *physically drained or sick after mild activity*. To fulfill the sleep dysfunction requirement, participants needed to report that one or more of the following symptoms occurred at least half the time at moderate severity (or higher): *feeling unrefreshed after you wake up in the morning*, *need to nap daily*, *problems falling asleep*, *problems staying asleep*, or *sleep all day and stay awake all night*. To indicate the presence of cognitive impairment or orthostatic intolerance, participants needed to report that one of the following symptoms occurred at least half of the time at moderate severity (or higher): *problems remembering things*, *difficulty paying attention for a long period of time*, *difficulty finding the right word to say or expressing thoughts*, *difficulty understanding things*, *only able to focus on one thing at a time*, *slowness of thought*, *absent-mindedness or forgetfulness*, *feeling unsteady on your feet*, *shortness of breath or trouble catching your breath*, *dizziness or fainting*, or *irregular heartbeats*.

London criteria for ME: To operationalize the revised London criteria for ME [4], its first author (E.G.) reviewed the DSQ and identified scoring rules. To meet these criteria, participants needed to have symptoms from the following domains: muscle fatigue / post-exertional malaise, central nervous system involvement, and circulatory impairment. To demonstrate post-exertional malaise, participants needed to report that their symptoms worsen after minimal physical effort or endorse that one of the following occurs all of the time and is of at least moderate severity: *next-day soreness or fatigue after non-strenuous, everyday activities*, *minimum exercise makes you physically tired*, or *physically drained or sick after mild activity*. To

demonstrate central nervous system involvement, participants needed to indicate that they experience one of the following symptoms all of the time at mild severity or greater: *problems remembering things*, *difficulty paying attention for a long period of time*, *difficulty finding the right word to say or expressing thoughts*, *difficulty understanding things*, *only able to focus on one thing at a time*, *unable to focus vision or attention*, *loss of depth perception*, *absent-mindedness or forgetfulness*, *feeling unsteady on your feet*, or *dizziness or fainting*. Finally, to demonstrate circulatory impairment, participants needed to indicate that they experience one of the following symptoms all of the time at mild severity or greater: *cold limbs*, *feeling chills or shivers*, *feeling hot or cold for no reason*, *feeling like you have a high temperature*, *feeling like you have a low temperature*, or having *intolerance to extremes of temperatures*. Individuals with medical or psychiatric diagnoses that could explain these symptoms were excluded from analysis.

RESULTS

Case definition fulfillment

The IOM criteria [12], selected76% of participants in the current study, whereas 44% met the revised London criteria for ME [4], because participants could meet both case definitions, independent groups were created for the subsequent analyses. All individuals who met the revised London criteria [4], were included in the "London-Revised" group (n = 502). Individuals who met the IOM criteria, but who did not meet the revised London criteria, were included in the "IOM" group (n = 520).

Demographics

Table 1 presents demographic data for each group described above. Individuals in the IOM group were significantly older than those in the London-Revised group [F (1, 1001) = 4.74, p= 0.03]. Additionally, individuals in the IOM group had obtained higher levels of education than those in the London-Revised group [χ^2 (5, N = 997) = 15.01, p= 0.01]. No further significant demographic differences existed between these groups. Subsequent analyses control for differences in age and education level (education level was dummy-coded for use in analyses of covariance).

Functional status

Table 2 presents the groups' mean SF-36 subscale scores. The groups' scores were compared via analyses of covariance (ANCOVA), and a Bonferroni adjustment suggested that only results with a p-value of less than 0.006 should be deemed significant. The London criteria group had significantly worse scores on the following SF-36 subscales: Physical Functioning [F(1, 955) = 53.22, p < 0.001], Bodily Pain [F(1, 953) = 38.13, p < 0.001], General Health [F(1, 956) = 26.56, p < 0.001], Vitality [F(1, 957) = 15.10, p < 0.001], and Social Functioning [F(1, 958) = 46.20, p< 0.001]. The groups' Role Physical, Role Emotional, and Mental Health scores were not significant different.

DISCUSSION

The current study compared the functional status of individuals, who met the IOM criteria [12], to those who met the revised London criteria [4], While 75% of participants met the IOM criteria, 44% met the revised London criteria. The revised London case definition likely selected fewer participants due

Table 1: Demographic comparison.

	IOM Criteria		**London Criteria**		
	(N = 520)		(N = 502)		
	M	(SD)	M	(SD)	SIG.
Age	49.5	-14.8	47.5	-14.5	*
Other Demographic Information:	%	(N)	%	(N)	SIG.
Gender					
Female	83	-422	84	-412	
Male	17	-89	16	-80	
Race					
Caucasian	98	-496	98	-482	
Asian / Pacific Islander	1	-4	0	-1	
Black / African-American	0	-1	0	-1	
American Indian	0	0	0	-1	
Other	1	-7	2	-8	
Marital status					
Married / Living with partner	57	-291	53	-265	
Never married	24	-122	29	-145	
Divorced	16	-80	14	-69	
Widowed	2	-8	2	-8	
Separated	1	-7	2	-9	
Work status					
On disability	56	-281	62	-307	
Retired	10	-51	8	-39	
Unemployed	10	-49	10	-51	
Working (unspecified)	9	-44	7	-33	
Working part-time	7	-36	5	-25	
Working full-time	4	-20	4	-18	
Homemaker	3	-14	2	-10	
Student	2	-10	2	-11	
Educational level					
Graduate / Professional degree	16	-79	17	-83	*
Standard college degree	52	-264	41	-201	
Partial college	16	-83	20	-99	
High school degree or less	16	-79	22	-109	
* p < 0.05					

Table 2: SF-36 Score Comparison.

	IOM Criteria		London Criteria		
	(n = 520)		(n = 474)		
SF-36 Subscale	M	(SD)	M	(SD)	Sig.
Physical Functioning	37.8	(22.2)	27.8	(20.1)	***
Role Physical	3.8	(11.4)	3.1	(10.9)	
Bodily Pain	41.9	(22.8)	32.5	(22.4)	***
General Health	28.5	(16.4)	23.2	(13.9)	***
Vitality	14.7	(12.9)	11.8	(13.2)	***
Social Functioning	28.9	(21.0)	19.8	(19.9)	***
Role Emotional	65.4	(42.6)	65.2	(44.1)	
Mental Health	69.3	(17.5)	65.5	(20.4)	

** $p < 0.05$; *** $p < 0.001$

to the higher frequency thresholds for required symptoms. Statistical analyses demonstrated that individuals who fulfilled the revised London criteria for ME had greater physical impairment, less energy (vitality), and a decreased ability to engage in social activities due to their physical health.

These results are consistent with findings from previous studies suggesting that different case definitions select disparate groups of participants. For example, Jason [19], found that the [20], CFS criteria identified 93% of a physician-referred sample, while the Canadian ME/CFS clinical criteria, identified 73% of the same sample. A subsequent study [21], indicated that over 90% of patients met the [6], CFS criteria, but approximately 58% of patients fulfilled the International Consensus Criteria for ME [22]. These studies provide further evidence that the percentage of participants who meet ME or CFS criteria varies greatly based on the case definition applied [23].

An important limitation of the current study is that the DSQ was not specifically developed to assess the symptoms of the revised London criteria [24]. The DSQ was recently updated to include items that better assesses the London criteria; however, when the current samples were collected, this revised instrument was not available. Thus, caution should be exercised in interpreting the current study; validity challenges can be introduced when criteria are assessed using instruments not originally intended to measure them [25]. An additional limitation of this study is that the DePaul and Newcastle samples did not require proof of a physician diagnosis of ME or CFS; however, all participants included in the study's analyses fulfilled the symptom requirements of the IOM or revised London criteria.

Over the past decades, different names (ME, CFS, and ME/CFS) and criteria have been adopted to describe this illness [26]. However, there is now growing evidence indicating that the case definitions and the measures used to assess the condition have a marked effect on the number and type of participants who meet inclusion criteria [27]. In order to facilitate the replication of studies related to biological markers and treatments for ME, future work should seek to refine a research case definition such that it requires only pathognomonic symptoms and specifically defines how to measure these symptoms for research inclusion criteria.

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Cite this article

Sunnquist M, Jason LA, Nehrke P, Goudsmit EM (2017) A Comparison of Case Definitions for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome. J Chronic Dis Manag 2(2): 1013.