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Review Article

Myalgic Encephalomyelitis Case Definitions

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Abstract This article reviews a Myalgic Encephalomyelitis (ME) case definition based on criteria offered over the past five decades. The current paper looks to review case definitions for ME based on Ramsay's definition [41], the "London" criteria [45], Hyde's Nightingale definition [16], and Goudsmit et al.'s criteria [11]. In general, these theorists have argued that ME is now defined differently than chronic fatigue syndrome because ME involves an acute onset, post-exertional malaise and neurocognitive problems, and fatigue is not a major criteria. We will compare these theorists to the recently published International Consensus Criteria for Myalgic Encephalomyelitis [3]. We will also attempt to consolidate aspects of different current definitions in order to suggest possible core features of ME. This article will also recommend the importance of providing explicit, objective criteria on specific key symptoms. In addition, structured interview schedules along with specific medical tests are recommended to assure this illness is assessed in a consistent way across settings. It is hoped these developments will lead to increased reliability of the ME case definition, as well as more frequent use of these criteria by investigators.

Keywords myalgic encephalomyelitis; case definitions

1 Introduction

Myalgic Encephalomyelitis (ME) was first described in literature of the 1930s, where an outbreak of Epidemic Neuromysthenia in L. A. County was called "atypical poliomyelitis" because of its resemblance to polio [9, 16]. Years later, an anonymous editorial in the 1956 issue of the *Lancet* coined the term benign Myalgic Encephalomyelitis [5]. It was called "benign" because the illness did not lead to patient death. Later, Ramsay [41] published a definition of this disease using the term Myalgic Encephalomyelitis (ME) and the term benign was dropped due to the seriousness of the disability created by the illness [17]. Ramsay, the consultant in charge of the patients who developed ME during the summer of 1955 at various hospitals in North London, became recognized as a world authority on this illness until his death. Ramsay [41] described "muscle fatiguability after minimal exertion plus the delay in the recovery of muscle power, often lasting up to five days; the involvement of the central nervous system, including cardinal features such as impaired memory and concentration as well as 'emotional lability,' but also disturbed sleep, frequency of micturition, hyperacusis, episodic sweating and other signs of autonomic dysfunction" (p. 30). In addition, ME involved a circulatory impairment (e.g., cold extremities, a grey pallor preceding reports of feeling unwell, and hypersensitivity to climate change). Ramsay considered ME to be an acute illness which often becomes chronic.

The London criteria [45], which were funded by the charity Westcare (now amalgamated with Action for ME). Based on Ramsay's concept [41], the "London criteria" were developed that recognized four cardinal features: (1) physical or mental fatigue or muscle weakness after minimal exertion which may persist long after exertion ends; (2) circulatory impairment (e.g., feeling hot when it is cold, postural hypotension); (3) one or more symptoms indicating the involvement of the central nervous system, such as impairment of memory and concentration and disturbed sleep patterns; (4) and the marked fluctuation of symptoms [4, 11]. When Jason et al. [22] attempted to operationalize these ME criteria by selecting individuals with post-exertional malaise, memory and concentration impairment, and fluctuation of symptoms, and then compared these patients to those meeting the current US definition of CFS [8], the ME criteria selected a more symptomatic group of patients.

Recent case definitions of ME have focused on central nervous system dysfunction as a cause for the symptoms associated with the illness, as well as using post-exertional malaise as a core symptom. Hyde [16] presented criteria that focused on vascular damage of the central nervous system for people with ME. The criteria included: (1) brain injury observed using a single photon emission computed tomography (SPECT) scan; (2) neurological changes that

demonstrate short-term memory loss, cognitive dysfunction, irritability, confusion, and perceptual difficulties, along with a decrease of these functions following physical or mental activity; (3) sleep dysfunction; (4) muscle dysfunction including pain and rapid loss of muscle function and/or strength following moderate physical or mental activity; (5) vascular and cardiac dysfunction; (6) and endocrine dysfunction [16]. It is suggested that post-exertional malaise may be related to cardiac dysfunction, which prevents adequate oxygen from reaching the brain, gut, and muscles. Furthermore, in some people with ME there may be cardiac irregularity making the heart unable to increase or decrease responses to physical activity, suggesting that people with ME are not receiving the adequate amounts of oxygen needed to perform physical activities [16].

Goudsmit et al. [11] presented ME criteria devised for the charity now known as Action for ME. The main difference between the Goudsmit et al. criteria and the "London criteria" was that the latter required an identifiable viral illness immediately preceding the development of ME. Goudsmit et al.'s criteria include: (1) new onset of muscle fatiguability precipitated by minor levels of activity; (2) symptoms indicating involvement of the brain and central nervous system; (3) periods of impaired circulation compatible with autonomic dysfunction; (4) fluctuation of symptoms from hour to hour and day to day; and (5) symptoms must be present for a minimum of three months. Post-exertional malaise is emphasized as a central feature of ME.

The ME case definitions have stressed post-exertional malaise, whereas the CFS case definitions have emphasized the construct of fatigue to define the illness [8, 14]. The Holmes et al. criteria [8] stipulated individuals needed to report six or more months of persistent or relapsing, debilitating fatigue not resolving with bed rest. A few years later, a revised Centers for Disease Control and Prevention (CDC) case definition for CFS [8] was developed, and it also required a person to experience six or more months of chronic fatigue of a new or definite onset, that is not substantially alleviated by rest, not the result of ongoing exertion, and results in substantial reductions in occupational, social, and personal activities. The CDC later developed an empiric case definition for CFS that involves assessment of symptoms, disability, and fatigue [44]. Using the CFS empiric criteria, the estimated rates of CFS have increased to 2.54% [43], which is ten times higher than prior CDC [46] and other investigator prevalence estimates [25]. Jason et al. [23] also found that 38% of those with a diagnosis of a Major Depressive Disorder were misclassified as having CFS using the new, more broadly based CDC empiric case definition. Therefore, the thresholds for casesness in the empiric criteria [44] may have led to the inclusion of individuals who might previously not have fulfilled the criteria.

In addition to problems associated with focusing on the construct of fatigue, a ubiquitous symptom within the general population, the Fukuda et al. case definition [8] uses polythetic criteria: a set of symptoms in which not all need to be present to make a diagnosis. Because Fukuda et al.'s criteria only require four symptoms out of a possible eight, critical CFS symptoms such as post-exertional malaise, and memory and concentration problems are not necessary for a person to receive a diagnosis of CFS. This increases the heterogeneity of the population and not only complicates identification of comparable samples, but is a likely cause of the inconsistent findings reported in the literature on CFS. As mentioned above, the earlier ME definition requires several primary symptoms. In addition, the patient community has felt that the term chronic fatigue syndrome trivializes the seriousness of this illness, as the illness is typified by many severe symptoms in addition to fatigue, and fatigue is generally regarded as a common symptom experienced by many otherwise healthy individuals in the general population [42].

A clinical case definition for ME/CFS, called the Canadian criteria, specified core symptoms, including post-exertional malaise, impairment of memory and concentration, unrefreshing sleep, arthralgia and/or myalgia; and several autonomic, neuroendocrine, and immune manifestations [2]. However, there are several problems with the Canadian ME/CFS case definition. First, stating that the illness is unexplained is counter to increasing evidence of a number of biological abnormalities that could explain this illness [24]. Further, the same concerns the patient community has had regarding the name CFS, persist with the term ME/CFS regardless of the inclusion of ME. This condition (ME/CFS) does not focus exclusively on those with a viral or sudden onset, as has been suggested by some theorists [15].

Another problematic issue, which pertains to most CFS case definitions, is the focus on six or more months of persisting or recurring fatigue. Some patients with ME are not chronically fatigued, but have problems with endurance or stamina, and lengthy times to recover following minimal degrees of activity [15]. A person who participates in very little activity (possibly to minimize ME symptoms) when compared to his or her same-age peers, and becomes exhausted upon minimal exertion should not be excluded. While normal fatigue is not activity limiting, the fatigue present in ME restricts the individual's activity to varying degrees, and Goudsmit et al. [10] have recommended pacing as a strategy to deal with this symptom. Therefore, rather than a sole focus on fatigue, it is critical to assess whether individuals have low stamina and endurance, and possibly have less fatigue because they are severely limiting their daily activities.

Several of the individuals who were involved in creating the Canadian ME/CFS criteria, as well as others, have

recently published what they refer to as an International Consensus Criteria for Myalgic Encephalomyelitis, which refers to ME-ICC [3]. These authors indicated that symptom severity impact must result in a 50% or greater reduction of a patient's premorbid activity level for a diagnosis of ME-ICC.[1] There are four major groupings and each are described below. To meet criteria, a person must have post-exertional neuroimmune exhaustion. Within the Neurological Impairment area, a patient must have at least one symptom from three of the following four symptom categories 1. neurocognitive impairments (e.g, difficulty processing information, short-term memory loss), 2. pain, 3. sleep disturbance, and 4. neurosensory, perceptual and motor disturbances (e.g., inability to focus vision, sensitivity to light, muscle weakness, feeling unsteady on feet).[2] The third category is Immune, Gastrointestinal and Genitourinary Impairments, and there needs to be at least one symptom from three of the following five symptom categories: 1. flu-like symptoms, 2. susceptibility to viral infections with prolonged recovery periods, 3. gastro-intestinal tract (e.g., nausea, abdominal pain), 4. genitourinary (e.g., urinary urgency), and 5. sensitivities to food, medications, odors or chemicals.[2] The final category is Energy Production/Transportation Impairments, and there needs to be at least one symptom from 1. cardiovascular (e.g., orthostatic intolerance), 2. respiratory (e.g., labored breathing), 3. loss of thermostatic stability (e.g., subnormal body temperature), and 4. intolerance of extremes of temperature.

The current paper evaluates criteria based on case definitions for ME which include Ramsay's definition [41], the "London" criteria [45], Hyde's Nightingale definition [16] and Goudsmit et al.'s criteria [11] (see Table 1). Specifically, it looks to use the past case definitions to identify possible consensus on cardinal features of ME: type of onset, post-exertional malaise, neurological and autonomic manifestations, pain, endocrine manifestation, sleep dysfunction, and immune manifestations. To stay true to the former case definitions, the present paper attempts to consolidate aspects of the past definitions presented in Table 2. We have also developed the DePaul Symptom Questionnaire (DSQ; [21]), which provides a structured way to gather standardized information to help diagnose many of these core aspects of ME (it was initially developed to operationalize the Canadian ME/CFS case definition). In addition, the current revised definition also incorporates Hyde's Nightingale definition [16] use of objective testing for more accurate diagnosis for both research and clinical purposes.

[1] The authors describe an approximately 50% reduction in activity as "mild". However, a better term than mild is probably needed to describe an illness state that causes a 50% reduction activity levels. In addition, some individuals might not experience a 50% reduction in activity as they continue to push themselves to maintain work and/or family commitments; yet they might have all the classic symptoms of ME.

[2] Requiring patients to meet three symptoms in this category may leave many out who meet everything else and do not have three of these symptoms.

2 Diagnostic system

We believe that it might be useful to separate possible diagnostic criteria for ME into level 1 and level 2 diagnostic ratings. To meet the level 1 rating for each symptom category, objective measures such as magnetic resonance imaging (MRI) would be required. To qualify for the level 2 rating, a self-report questionnaire, such as the DSQ [21] could be used to meet the criteria for each symptom category. Although objective medical tests are preferred over self-report measures, for some symptoms, there are not yet definitive answers in the literature regarding which tests are most accurate or reliable, and which cut off scores to use. Due to a lack of consensus in the field and the limited scope of this manuscript, the descriptions of objective tests that follow are considered experimental. Both level 1 and level 2 criteria will be included in a proposed scoring system (see Appendix A); however, at this time, we suggest that level 1 criteria are not required to receive a diagnosis.

2.1 Onset

Past case definitions are not consistent with regard to the type of onset involved in ME. Ramsay [41] described the onset of ME as acute and followed by persistent and profound fatigue, including other symptoms such as dizziness, muscle tenderness, headaches and pain. Ramsay used strict criteria to select those with a syndrome commonly precipitated by infection, though he included some patients reporting a more insidious onset [4]. In contrast, the London criteria specified that there needed to be an identifiable viral illness that preceded the development of ME [45]. Hyde's Nightingale definition [16] specified that ME had a biphasic infectious onset. Moreover, it was suggested that ME had a primary infectious phase with a 4–7 day incubation period and a secondary chronic phase that occurred 2–7 days after the first phase, and it was this phase that most characterized ME. Hyde's Nightingale definition also states ME could have a non-infectious onset that could be precipitated by toxic chemicals and referred to this as secondary ME [16]. Goudsmit et al. [11] supported this view by indicating that the onset of ME could be triggered by other factors such as immunizations, trauma, and exposure to other chemicals.

The current definitions all seem to agree that most cases of ME have an acute onset; however, there are some disparities between the different definitions regarding the type of onset needed for diagnosis of ME. To stay consistent with the current definitions, we believe that there is a consensus for the onset of ME that can be categorized into three groups: ME-viral, ME-infectious non-viral, and ME-other. ME-viral can be described as onset precipitated by a virus,

	Ramsay 1988	"London" Criteria 1994	Hyde Nightingale Definition 2007	Goudsmit et al. 2009
Onset	**Acute onset** ● Later followed by persistent and profound fatigue and other symptoms such as headache and pain	**Identifiable viral illness immediately preceding development of ME**	**Acute Biphasic Infectious Onset = Primary ME** ● Infectious process evident (not required) ● Non-Infectious Onset = Secondary ME	**Does not have to be viral** ● Often follows an infection but may also be triggered by other factors such as immunizations, trauma, and exposure to other chemicals.
Immune	**History of infection of the upper respiratory tract or gastrointestinal tract.** Low grade fever (max 100.4 F for a week)	**Symptoms suggesting persistent viral infection** (e.g., low grade temperature, feeling feverish, sore throat)	**Often preceded by a series of repeated minor infections** which would suggest either a vulnerable or an overwhelmed immune system.	**Symptoms suggestive of immune system dysfunction** and/or persisting infection
Time Period	***Not discussed**	**Must have had major symptoms for 6 months**	**None** ● Should be able to define disease at onset.	**Symptoms present during last 3mths (req.)** ● Exclude patients with debility which often follows illnesses such as the flu.
Post-Exertional Malaise	**Muscle fatigability** after physical exercise with 3 or more days elapse before muscle power is restored.	**Exercised induced fatigue precipitated by physical or mental exertion.**	**Testable Muscle dysfunction** ● Pain and rapid loss of muscle strength after moderate physical or mental activity	**Abnormal levels of muscle fatigability precipitated by minor levels of activity. Symptoms typically worsen after 24-48 hours.** ● Profile of Fatigue Related Symptoms
Neurological	**Cerebral dysfunction** ● Impairment of memory/concentration ● Emotional lability **Other common features** ● Using wrong word ● Sleep rhythm disturbance ● Hyperacusis ● Frequency of Micturition	**Impairment of short-term memory and loss of powers of concentration.** ● Usually coupled with other neurological and psychological disturbances, e.g., emotional lability, disturbed sleep, nominal dysphasia, vertigo, or tinnitus	**Testable Neurological** ● Brain injury observed on a SPECT scan ● Neurological changes that are measurable and demonstrate short-term memory loss, cognitive dysfunctions, increased irritability, confusion, and perceptual difficulties ● Neuropsychological dysfunction that can decrease in function following physical or mental activity	**Symptoms indicating involvement of the brain and CNS including cognitive impairment, disturbed sleep patterns, balance problems.**
Autonomic	**Circulatory impairment** ● Cold extremities, hypersensitivity to climate change and ashen grey facial pallor, 20-30mins before patient complains of being ill. **Other common features** ● Episodic sweating, Orthostatic tachycardia	**Symptoms** Bouts of inappropriate night/day-time sweating; Raynaud's phenomenon; postural hypotension; disturbances of bowel motility; photophobia; blurred vision; abnormally acute hearing; frequent urination	**Testable Vascular & Cardiac Dysfunction** ● POTS, Cardiac Irregularity, Raynaud's Phenomenon, Circulating Blood Volume Decrease, and Bowel Dysfunction	**Periods of impaired circulation compatible with autonomic dysfunction** e.g., sensitivity to heat and cold.
Pain	**Muscle spasms and twitches**	**Pain and coarse muscle twitch in exercised muscle is common.**	**Possibility of various pain syndromes** Tend to decrease over time but may increase due to external and chemical stressors.	**Muscular, arthritic or neuropathic in character**
Endocrine	***Not discussed**	**For research purposes those with endocrine disorders should be excluded.** ● Hypothyroidism, thyrotoxicosis, Addison's disease Cushing's syndrome, diabetes mellitus, hyperparathyroidism.	**Testable Endocrine dysfunction (Features are common but appear late)** ● Changes in serum TSH, FT3, FT4, Microsomal Ab, PTH, calcium, and phosphorous. ● Some ME patients: Shrinking of thyroid Uncommon Endocrine features. ● Pituitary-Adrenal Axis Changes, Pituitary-Ovarian and Axis Changes	***Not discussed**
Sleep Dysfunction	***See Neurological**	***See Neurological**	**Testable Major Sleep Dysfunction** ● Include all forms of sleep dysfunction	***See Neurological**
Other	**Variability of both symptoms and clinical findings during the day.** Tendency to become chronic.	**Fluctuation of symptoms precipitated by physical or mental exercise.** Physical Signs ● Pharyngitis ● Tender and possible enlargement of lymph nodes ● Muscle tenderness ● Positive Romberg test	**Biphasic infectious disease process** ● Primary infection phase: 4-7 day incubation period ● Secondary Chronic phase: 2-7 days after first phase and characterized by change in CNS. **Testable Vascular & Cardiac Dysfunction** ● Ehlers-Danlos Syndromes Group ● M.E. Associated Clotting Defects: ● Anti-smooth muscle Antibodies	**Fluctuation of symptoms from hour to hour and day to day.** Physical Signs ● Pharyngitis ● Tender and possible enlargement of lymph nodes ● Positive Romberg test

Table 1: Comparison of different case definitions.

ME-infectious non-viral can be described as onset precipitated by infections such as a Lyme disease, and ME-other can be described as onset precipitated by chemical exposure or trauma. To be classified as acute, onset should occur within a one week period. In contrast, the recent ME-ICC [3] criteria indicate that onset can be acute or gradual.

To determine the onset type, patients can be assessed through medical documentation indicating the type of onset, which would qualify for a level 1 diagnosis. The patient could also complete a self-report measure like the DSQ [21] to confirm the type of onset (viral, infectious, or chemical) and qualify as a level 2 diagnosis.

I. Acute Onset. An abrupt (acute) illness onset is required over one week. This may follow a virus, infection, or other factors (i.e. immunization or chemical exposure).

II. Post-exertional malaise and/or post-exertional fatigue. With activity (it need not be strenuous and may include walking up a flight of stairs, using a computer, or reading a book), there must be a loss of physical or mental stamina, rapid/sudden muscle or cognitive fatigability, post-exertional malaise and/or fatigue and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. The recovery is slow, often taking 2–24 hours or longer.

III. One or more neurological manifestations:

Impaired memory (self-reported or observable disturbance in ability to recall information or events on a short-term basis)
Difficulty focusing (disturbed concentration may impair ability to remain on task, to screen out extraneous/excessive stimuli)
Difficulty finding the right word
Frequently forget what wanted to say
Absent mindedness
Slowness of thought
Difficulty recalling information
Need to focus on one thing at a time
Trouble expressing thought
Difficulty comprehending information
Frequently lose train of thought
New trouble with math or other educational subjects.

IV. Autonomic manifestations: Neurally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness, feeling unsteady on the feet–disturbed balance, shortness of breath.

V. Subtypes:

A. Pain (or discomfort) that is often widespread and migratory in nature. At least one symptom from any of the following:
Myofascial and/or joint pain. Myofascial pain can include deep pain, muscle twitches, or achy and sore muscles. Pain, stiffness, or tenderness may occur in any joint but must be present in more than one joint and lacking edema or other signs of inflammation. Abdominal and/or head pain. May experience eye pain/sensitivity to bright light, stomach pain, nausea, vomiting, or chest pain. Headaches often described as localized behind the eyes or in the back of the head. May include headaches localized elsewhere, including migraines. Headaches would need to be more frequent than they were before, which would indicate new pattern, of a new type as compared to headaches previously experienced (i.e., location of pain has changed, nature of pain has changed), or different in severity type as compared to headaches previously experienced by the patient.

B. Endocrine manifestations: Recurrent feelings of feverishness and cold extremities, subnormal body temperature and marked diurnal fluctuations, sweating episodes, intolerance of extremes of heat and cold, marked weight change-loss of appetite or abnormal appetite, worsening of symptoms with stress.

C. Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance. May include unrefreshing sleep, prolonged sleep (including frequent naps), disturbed sleep (e.g., inability to fall asleep or early awakening), and/or day/night reversal.

D. Immune manifestations: Recurrent flu-like symptoms, nonexudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to tender to palpitation–generally minimal swelling noted, new sensitivities to food, odors, or chemicals

VI. Exclusionary conditions:

A. Any active medical condition that may explain the presence of symptoms such as:
1. Untreated hypothyroidism
2. Sleep apnea
3. Narcolepsy
4. Malignancies
5. Leukemia
6. Unresolved hepatitis
7. Multiple Sclerosis
8. Juvenile rheumatoid arthritis
9. Lupus erythematosus
10. HIV/AIDS
11. Severe obesity (BMI greater than 40)
12. Celiac disease
13. Lyme disease.

B. Some active psychiatric conditions that may explain the presence of symptoms such as:
1. Schizophrenia or psychotic disorders
2. Bipolar disorder
3. Active alcohol or substance abuse except as below:
a) Alcohol or substance abuse that has been successfully treated and resolved should not be considered exclusionary.
4. Active anorexia nervosa or bulimia nervosa-except as below:
a) Eating disorders that have been treated and resolved should not be considered exclusionary.
5. Depressive disorders with melancholic or psychotic features.

C. May have presence of concomitant disorders that do not adequately explain symptoms, and are, therefore, not necessarily exclusionary.
1. Psychiatric diagnoses such as:
a) Anxiety disorders
b) Somatoform disorders
c) Depressive disorders
2. Other conditions defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, such as:
a) Multiple food and/or chemical sensitivity
b) Fibromyalgia
3. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented.
4. Any condition that was treated with definitive therapy before development of chronic symptomatic sequelae.
5. Any isolated and unexplained physical examination, laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition.

Table 2: Criteria for possible consensus ME.

2.2 Post-exertional malaise

The majority of past case definitions conclude that post-exertional malaise is an essential feature of ME. Most also note the characteristic delay in recovery of muscle strength after exertion ends. Hyde's Nightingale criteria state that post-exertional malaise can be precipitated by both mental and physical activity; post-exertional malaise is defined as pain with rapid loss of muscle strength after moderate physical or mental activity, but also suggests that post-exertional malaise might be due to vascular dysfunction or peripheral nervous or spinal dysfunction [16]. Others have suggested that post-exertional malaise is due to mitochondrial dysfunction [4,37] (due to mitochondrial damage and/or inhibition of the oxidative metabolism) as a consequence of excessive (prolonged) oxidative stress (after exertion) [18,56]. Pall [39] has suggested that oxidative stress might help explain the pathophysiology among patients with ME.

Goudsmit et al. [11] describe post-exertional malaise as a new onset of abnormal levels of muscle fatigability that is precipitated by minor levels of activity with symptoms getting worse during the next 24 to 48 hours. There are some minor differences between how the case definitions define post-exertional malaise in ME. Ramsay [41] suggests that post-exertional malaise is a cardinal feature of ME and describes it as muscle fatigability that results from a minor degree of physical exercise with which three or more days elapse before full muscle power is restored. The London criteria support Ramsay, in that post-exertional malaise is precipitated by physical exertion, but also add the component of mental exertion as a precipitator of postexertional malaise. The London criteria also suggest that exercise-induced fatigue should be relative to the patient's previous exercise tolerance, but there is no specific time period for which full muscle power should be restored [45]. The recent ME-ICC [3] criteria are compatible, as a person must have post-exertional neuroimmune exhaustion, which is characterized as marked, rapid physical and/or cognitive fatigability in response to exertion.

There does appear to be a consensus that post-exertional malaise is a cardinal feature of ME; the definition recognizes post-exertional malaise as prolonged restoration of muscle power following either mental or physical exertion with recovery often taking 2–24 hours or longer. Post-exertional malaise can potentially be measured by increases in the expression for sensory, adrenergic, and immune genes following moderate exercise, and this would qualify as a level 1 rating [33]. Other examples include pain threshold before and after exercise [35, 60], neuropsychological/cognitive tests before and after a treadmill test [29], and repeated exercise tests [57]. To meet the criteria for level 2, the DSQ [21] could be used to confirm symptoms of post-exertional malaise (e.g., feeling dead heavy feeling after exercise, feeling drained or sick after exercise) [40].

2.3 Neurological manifestations

All of the ME criteria stipulate the presence of neurological manifestations as a major feature of ME, however, there are some differences regarding the extent of dysfunction. Ramsay [41] and the London criteria [45], describe neurological dysfunction as a number of symptoms including an impairment of short-term memory and concentration. Hyde's Nightingale definition states that neurological dysfunction should include observable injury to the brain and central nervous system, measurable neuropsychological changes that demonstrate short-term memory loss, cognitive dysfunction, increased irritability, confusion, and perceptual difficulties. Furthermore, Hyde's Nightingale definition suggests that there are important neuropsychological changes following physical or mental activity [16]. Goudsmit et al.'s criteria [11] require symptoms that indicate involvement of both the brain and central nervous system.

It is the consensus across current case definitions that neurological manifestations is a cardinal feature, and therefore it should be incorporated into the ME definition. However, ME-ICC [3] criteria indicate that to meet criteria for the Neurological Impairment area, a patient must have at least one symptom from three of the following four symptom categories 1. neurocognitive impairments (e.g, difficulty processing information, short-term memory loss), 2. pain, 3. sleep disturbance, and 4. neurosensory, perceptual and motor disturbances (e.g., inability to focus vision, sensitivity to light, muscle weakness, feeling unsteady on feet). Unfortunately, with these criteria, a person could have pain, sleep disturbance, and neurosensory disturbance but no neurocognitive impairments. Among the ME case definitions, there does appear to be a consensus for neurological manifestations [41]. The Hyde Nightingale [16] and Goudsmit et al. [11] definitions include the component of central nervous system dysfunction as a main feature of neurological dysfunction in ME. And so, there does appear to be a consensus for a definition to include central nervous system dysfunction, which can be measured with objective testing as well as short-term memory loss, loss of powers of concentration, cognitive dysfunction, increased irritability, confusion, and perceptual difficulties to describe neurological manifestations in ME.

Level 1 dysfunction can potentially be measured through the use of functional magnetic resonance imaging (fMRI), SPECT, or positron emission tomography (PET) scans indicating brain injury [16,31]. Level 2 can be measured with the DSQ [21] to confirm self-report symptoms of neurological manifestations (e.g., slowness of thought, difficulty finding the right word to say) or neuropsychological/cognitive tests such as the Cambridge Neuropsychological Test Automated Battery (CANTAB; [7]).

2.4 Autonomic manifestations

Most case definitions of ME suggest that autonomic manifestations should be included as a major criterion. The Ramsay [41], Hyde Nightingale [16], and Goudsmit et al. [11] definitions require autonomic dysfunction to meet the criteria for ME [16]. Hyde's Nightingale definition requires that a person with ME must meet the criteria for autonomic dysfunction through the use of objective testing [16]. However, the London criteria [45] list autonomic dysfunction as a minor feature of ME. Research suggests that autonomic manifestations are the cause of many symptoms associated with ME and with the majority of the current case definitions in agreement that autonomic manifestations should constitute a major symptom category; so it does appear that there is a consensus for the ME definition to list autonomic manifestations as a cardinal feature [16]. The ME-ICC [3] case definition has a category called Energy Production/Transportation Impairments, and there needs to be at least one symptom from 1. cardiovascular (e.g., orthostatic intolerance), 2. respiratory (e.g., labored breathing), 3. loss of thermostatic stability (e.g., subnormal body temperature), and 4. intolerance of extremes of temperature. However, a person could meet criteria by having a number of symptoms within this category that are not reflective of autonomic dysregulation (e.g., one of the symptoms in number 3 involving the respiratory category is having recurrent feelings of feverishness with or without low grade fever).

To meet the level 1 diagnostic criteria, autonomic manifestations can potentially be measured using a tilt table test showing decreased blood pressure and/or increased heart rate [16]. For level 2 diagnostic criteria, autonomic manifestations can be assessed by the DSQ [21] to confirm dysfunction (e.g., irregular heartbeats, feeling unsteady on feet) or the Composite Autonomic Symptom Scale (COMPASS) [38].

2.5 Pain

There is consensus among the current case definitions that while pain is experienced by many patients, it is not a major symptom category of ME. Ramsay's criteria [41] describe pain as muscle spasms and twitching. While the London criteria [45] also suggest pain as being muscular in nature, the criteria also add the component that pain can be exacerbated by exercise. Hyde's Nightingale definition [16] suggests that people with ME can have various pain syndromes that can be divided into early and late findings. Early findings of pain can include: headaches associated with neck rigidity and occipital eye pain, migratory muscle and arthralgia pain, and cutaneous hypersensitivity. Late findings of pain can include any of the early findings and also fibromyalgia-like pain syndromes [16]. Goudsmit et al. [11] describe pain in ME as being muscular, arthritic, and neuropathic in character.

Though pain is a common symptom in ME, few of the definitions include it as a major criterion. The London criteria [45] focus more on muscle tenderness and mention headaches exacerbated by exercise, while Hyde's Nightingale definition [16] lists pain as a specific symptom but suggests that pain tends to decrease over time and could be increased by external stressors, implying that pain may not be a constant symptom. Goudsmit et al. [11] point out that pain is a common symptom present in many disorders and not discriminative enough for inclusion as a criterion. For the ME-ICC [3] criteria, pain is within the Neurocognitive Impairments, and it is necessary to have one symptom from three of four categories, and pain is one of these categories (therefore, as with the other criteria, pain would not be required for a ME-ICC diagnosis). With consensus between case definitions that the presence of pain does not improve the diagnostic precision, it might be possible to acknowledge pain as a secondary feature of ME.

For a level 1 rating, pain might be measured by increases in the expression for sensory, adrenergic, and immune genes following moderate exercise [33]. To diagnose pain for a level 2 rating, symptoms of pain can be assessed with the DSQ [21] (e.g., feeling pain or aches in muscles, experiencing headaches) or the well validated McGill Pain Questionnaire [36].

2.6 Endocrine manifestations

Endocrine manifestations are less important within the current ME case definitions. Both Goudsmit et al.'s [11] and Ramsay's [41] definitions do not discuss endocrine dysfunction as a major feature of ME. While the London criteria discuss endocrine dysfunction, they do so only as means for exclusion, suggesting that certain endocrine disorders such as hypothyroidism, thyrotoxicosis, Addison's disease, Cushing's syndrome, diabetes mellitus, and hyperparathyroidism might parallel symptoms of ME and should be ruled out [45]. Conversely, Hyde's Nightingale definition acknowledges endocrine dysfunction as a common feature of ME that tends to appear late and manifests with changes in serum TSH, FT3, FT4, Microsomal Ab, PTH, calcium, and phosphorous. For the ME-ICC [3] criteria, neuroendocrine dysfunction is not one of the main categories, nor is it required. There does appear to be a consensus that endocrine manifestations are not a required symptom category for ME.

Level 1 diagnosis for neuroendocrine manifestations might be measured by abnormal levels of circulating cortisol [55]. To meet level 2 criteria, neuroendocrine manifestations can be measured with the DSQ [21] confirming neuroendocrine symptoms (e.g. feeling hot or cold, night sweats).

2.7 Immune manifestations

Immune dysfunction is common among ME patients and can be seen during the onset or through the patient's history

of infection. However, consensus between the current ME definitions suggests that immune dysfunction is not a required feature. Ramsay [41] indicates that a history of infection of the upper respiratory or gastrointestinal tract and a low grade fever serves as an indicator of immune dysfunction. Later definitions also support the notion of repeated infections as an indicator of immune dysfunction [45, 11, 16]. The London criteria [45] and Goudsmit et al. [11] indicate that people with ME can have symptoms suggesting persistent viral infection combined with feeling feverish. Hyde's Nightingale definition [16] also supports this notion by suggesting that ME can be preceded by a series of repeated minor infections suggesting a vulnerable immune system but also indicates that immune dysfunction can be caused by overwhelming stressors.

All the current definitions acknowledge that immune manifestations are a common feature in ME; however, other than Ramsay's definition, the more recent definitions indicate that immune manifestations are not a cardinal feature. The London criteria [45] specifically acknowledge immune dysfunction as a minor feature. Hyde's Nightingale definition [16] suggests that an infectious process is common in most cases but is not always present. It is also important to mention that Hyde's Nightingale definition [16] specifically refers to Primary ME, which is associated with immune pathologies, and Secondary ME, which is a non-infectious ME type disease that is associated with toxic chemical injury. As such, for Hyde's Nightingale definition [16], immune dysfunction may be related to onset, and since onset in ME can range from infectious to noninfectious, this suggests that immune dysfunction may not always be present. The Goudsmit et al.'s definition [11] does not mention immune dysfunction as a cardinal feature, instead, proposes it can be common among people with ME, but not a feature that distinguishes ME from other disorders. For the ME-ICC [3] case definition, immune issues are part of a required impairment called Immune, Gastro-Intestinal and Genitourinary, and as only one symptom from three of 5 categories are required, it is possible that no immune symptoms would be required. However, two of the categories have considerable overlap, flu-like symptoms that may be recurrent or chronic, and susceptibility to viral infections with prolonged recovery periods, but still if neither occurs, a person can still meet criteria by having symptoms from three other categories. The consensus among case definitions is that immune manifestations are not a cardinal feature of ME and may be related to the type of onset, suggesting that it may not always be present and is not a distinguishable feature of the illness. A consensus ME case definition might acknowledge immune manifestations as a secondary feature of ME.

For a level 1 rating, the presence of immune dysfunction could be measured by elevations in CD5+CD19+ subset and decreased natural killer cell cytotoxicity [34]. Other potential markers include immune activation [e.g., elevated cytokine levels, inflammatory markers (elastase etc.)], immune dysfunction (e.g., RNAse L fragmentation, Th1-Th2 cytokine markers), and immunosuppression [e.g., IgG subclass deficiencies (IgG1 and IgG3), NK Cell activity including perforin and granzyme levels]. To meet the criteria for level 2, immune manifestations in ME can be assessed using the DSQ [21] to confirm immune manifestations (e.g., feeling feverish, having a sore throat).

2.8 Sleep dysfunction

Sleep dysfunction is not discussed as a symptom in many of the current case definitions of ME. Sleep dysfunction is acknowledged within the London criteria, but only as a consequence of the neurological dysfunction of ME [45]. Hyde's Nightingale definition also states that sleep dysfunction is a required symptom of ME, but its presence can only be recognized through the use of an objective test [16]. Goudsmit et al. [11] do not discuss sleep dysfunction as part of their ME criteria. Though sleep dysfunction is acknowledged by both the London criteria [45] and Hyde's Nightingale definition [16] as a feature of ME, only Hyde's Nightingale definition recognizes it as a major feature. However, Hyde's Nightingale definition indicates that sleep dysfunction is related to swollen lymph nodes, suggesting that it is dependent on other symptoms [16]. The London criteria acknowledge sleep dysfunction as a secondary feature of neurological dysfunction in its criteria and do not mention it as an independent ME symptom category [45]. For the ME-ICC [3] criteria, sleep disturbance is within the Neurocognitive Impairments, and it is necessary to have one symptom from three of four categories, and sleep disturbance is one of these categories (therefore, as with the other criteria, sleep disturbance would not be required for a ME-ICC diagnosis). And so, with the majority of the current case definitions agreeing that sleep is not a major feature, there is a consensus that recognizes sleep dysfunction as a secondary feature of ME.

For a level 1 rating, un-refreshing sleep, disturbance of sleep quantity, or rhythm disturbance would be documented by polysomnography [49]. To meet the criteria for level 2, sleep dysfunction can be assessed by using the Pittsburg Sleep Quality Index [1], which measures sleep disruptions and sleep quality or the DSQ [21] to confirm sleep dysfunction symptoms (e.g., problems falling or staying asleep, feeling unrefreshed after waking up).

2.9 Time period needed for diagnosis

In regards to the time period, there is a lack of agreement between past case definitions. Some suggest a specific amount of time (i.e., 3 or 6 months), while others deny the need for a time period, or a time period is not discussed. Ramsay [41] does not mention whether or not a time period

is needed for diagnosis. However, the London criteria [45] and Goudsmit et al. [11] both require a minimum time period for diagnosis, requiring major symptoms to be present for 6 months and 3 months, respectively, to exclude patients with post-influenza debility. The Goudsmit et al.'s criteria [11] suggested the time period requirement is to exclude patients with debility that may follow illnesses such as the flu. In contrast, Hyde's Nightingale definition [16] suggests that a time period is not required because ME should be diagnosable at onset, due to its distinct biological features. For the ME-ICC [3] criteria, the six-month waiting period before diagnosis is no longer required. With regard to the current revised definition, it appears that there is a consensus for the time period needed before diagnosis [16]. Research has shown ME to have distinct biological features that clearly define the illness; the current revised definition recognizes that a time period is not needed for diagnosis.

3 Possible consensus ME criteria

In summary, the current review of ME case definitions focuses on the major features of the illness, and suggests that ME has an acute onset that can be categorized into three categories: ME-viral, in which ME is precipitated by a virus; ME-infectious non-viral, in which ME is precipitated by a non-viral infection such as a tick bite resulting in Lyme disease;[3] and ME-other, in which ME is precipitated by trauma or chemical exposure. The major symptom categories of ME include: post-exertional malaise, and neurological and autonomic manifestations. Postexertional malaise can be described as prolonged restoration of muscle power following either mental or physical exertion with recovery often taking 2–24 hours or longer. Neurological manifestations, which include short-term memory loss, loss of powers of concentration, cognitive dysfunction, increased irritability, confusion, perceptual difficulties, as well as evidence of central nervous system and/or brain injury. Autonomic dysfunction, which can incorporate neutrally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness, feeling unsteady on one's feet, disturbed balance, cold extremities, hypersensitivity to climate change, cardiac irregularity, Raynaud's phenomenon, circulating blood volume decrease, and shortness of breath. Secondary features of ME include pain, endocrine manifestations, immune manifestations, and sleep dysfunction.

If this consensus definition were operationalized, to meet full criteria for ME, patients must have an acute onset and qualify for the following three major ME symptom categories (post-exertional malaise, neurological manifestations, and autonomic manifestations) through objective testing (Level 1) or self-report measures (Level 2). Patients will be considered in remission if they meet one or less categories (i.e., only meets post-exertional malaise). In addition, for research purposes, a required period of 6 months of symptoms can be used to control for patients with infectious illnesses such as mononucleosis.

3.1 Medical and psychiatric evaluation

It is critical to do a medical evaluation [8] in order to identify exclusionary medical diagnoses that would explain fatigue and other symptoms, such as cancer or heart disease. Medical diagnoses that have been adequately treated (e.g., Lyme disease) or are not likely to cause the ME symptoms should not be considered exclusionary. Depression with melancholic or psychotic features is considered exclusionary, primarily due to findings that melancholic and psychotic processes represent distinct biological or endocrinological processes and may respond well to antidepressant or antipsychotic medications [47,48]. Table 1 lists disorders that should not be considered exclusionary, although they may present comorbidly with ME.

Psychiatric evaluation is essential to rule out psychiatric diagnoses that may be the cause of fatigue and preclude a diagnosis of ME. A semi-structured psychiatric interview, the Structured Clinical Interview for the DSM-IV (SCID; [52]) should be used. Test-retest reliability was assessed for the SCID and it had good quality Kappa scores [61]. 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 and psychiatric disorders, e.g., fatigue, concentration difficulty, and sleep disturbance. A psychodiagnostic study [54] validated the use of the SCID in a sample of patients with CFS. We believe psychotic disorders of any variety continue to be exclusionary. For our ME case definition, eating disorders (i.e., anorexia nervosa, bulimia nervosa) and substance abuse have been qualified to be exclusionary, but only if the diagnosis is current. A diagnosis of depression with melancholic features, substance abuse, or an eating disorder that has been appropriately treated and resolved should not be considered exclusionary.

4 Discussion

In this paper, we reviewed criteria for the ME case definition, and identified areas that we felt had sufficient consensus. To the extent a diagnostic category is unreliable, a limit is placed on its validity for any clinical research [51] and this complicates the identification of biological markers. Issues concerning reliability of clinical diagnosis are complex and have important research and practical implications [20]. The scientific enterprise depends on reliable, valid methods of classifying patients into diagnostic categories, and this

[3] We recognize that there a several tick-borne infections, one is Lyme disease (bacterial), another is viral (tick-borne meningoencephalitis TBEV or FSME).

critical research activity can enable investigators to better understand etiology, pathophysiology, and treatment approaches for ME, along with other disorders [27].

One of the key ways in which the ME criteria differ from other CFS diagnostic systems is that the onset of ME is sudden, and often linked with the presence of an infection. There is evidence for this proposition, as some cases of ME have been reported following acute mononucleosis, Lyme disease, and Q fever [28]. In addition, there is evidence that certain viruses (e.g., HSV-1, HHV-6, Epstein Barr virus, and cytomegalovirus) may influence the relapsing and remitting pathogenesis of ME [6]. ME patients may continue herpesvirus replication despite there being no herpesvirus DNA-emia, herpesvirus antigenemia or serum IgM antibody to structural virus [32]. These findings suggest ME may be due to latent herpesvirus replication. Lerner et al. [32] recently reported ME patients having EBV, HCMV, and HHV6 in single or multiple infections. It was found that 79 of 106 (74.5%) patients experienced long-lasting significant improvements in functioning after long-term herpesvirus subset-directed antiviral treatment.

Although there is good evidence that ME does occur suddenly, the maintenance of the illness might be due to host factors. Hickie et al. [13] followed up with people who had cases of mononucleosis (glandular fever), Q fever, and Ross River virus, respectively. The authors found that the percentage who went on to have CFS as defined by Fukuda et al. [8] was the same for all three of the infectious diseases (11% at 6 months). This suggests the reason these people develop CFS is associated with their host response. The syndrome was predicted largely by the severity of the acute illness, rather than demographic, psychological, or microbiological factors. In other words, it is the severity of the host response that determines the injury. In the same cohort study, Vollmer-Conna et al. [58] later found individuals with high levels of IFN gamma and low levels of IL10 were significantly more likely to experience severe acute illness following infection and were more likely to be symptomatic for a longer time. IFN gamma is one of several pro-inflammatory cytokines, and IL10 is one of several anti-inflammatory cytokines. On the other hand, research [62] has also shown that people with ME with different infections (causes) have many different upregulated genes. So a key issue involves whether these CFS subtypes are also ME-"subtypes" or distinct diseases (when applying the more strict ME criteria). White [59] summarized findings from five cohort studies involving post-infectious illnesses. These studies indicate that a post-infectious fatigue syndrome does exist, and it is not a mood disorder. The risk of prolonged fatigue or CFS as defined by Fukuda et al. [8] following post-infectious fatigue syndromes is five to six times that of common upper respiratory tract infections, and there is a 10–12% risk of Fukuda et al. defined CFS six months after infectious onset.

Neurotropic viral infections that replicate within and subsequently damage the central nervous system could be responsible for the appearance of lesions and the presence of focal epileptiform seizure activity in a ME viral onset subgroup. Magnetic resonance (MR) studies of encephalopathy and encephalomyelitis associated with acute EBV infection have found T2 prolongation over gray and white matter, brain atrophy, and periventricular leukomalacia [50]. An MR study examining a pediatric population of patients suffering from chronic EBV infection has shown evidence for the presence of lesions in the hippocampal region [12]. In some cases, cortical lesions caused by herpes virus infections fade before MR documentation can take place. Lesions can then reappear under specific conditions of environmental stimuli, a process that fits well with the relapsing and remitting hypothesis of ME.

At the present time, ME is used differently by different theorists, and our article is an attempt to increase dialogue and communications among the disparate parties. In other words, we are not comparing case definitions. Rather, we are only trying to highlight and summarize the characteristics of the illness described by ME theorists in the field. We have tried to summarize the opinions of a number of leading ME theorists in the hope that it will lead to more consensus among theorists and researchers when they try to use the ME criteria to identify groups for research purposes.

An international group has recently suggested ME-ICC as a consensus ME case definition [3]. Based on our analysis, this case definition does contain similarities with themes identified with other ME criteria including the emphasis on postexertional malaise, and the rejection of the 6 month period of time to have elapsed from symptom onset. However, this ME-ICC case definition is different in several ways to what has been proposed in this article, including the lack of emphasis on sudden onset and a focus on only one symptom within both neurological and autonomic areas. In addition, the first CFS criteria developed in the US, the Holmes et al. criteria [14], were critiqued because the requirement of eight or more minor symptoms could inadvertently select for individuals with psychiatric problems [26]. The ME-ICC [3] case definition now requires eight symptoms, which is one more than what had been required in the ME/CFS Canadian criteria [2].

Jason et al. [19] found significantly higher current psychiatric comorbidity rates for those with Canadian ME/CFS criteria versus Fukuda CFS, but there were not significant differences between the ME criteria (as specified in the paper) and the Fukuda CFS criteria. Of interest, for the SF-36 measure of disability, for Role Emotional and Mental Health, the ME/CFS group was significantly worse than the Fukuda CFS comparison, but there was not a significant difference between the ME and Fukuda group. For all other subscales, the ME criteria had directionally

Appendix A Scoring sheet for the revised ME case definition

Myalgic Encephalomyelitis Case Definition Criteria Level 1 refers to objective medical tests. Level 2 refers to subjective self-report.			
Categories	Criteria and Tests	Meets Criteria	Diagnosis
I. Acute Onset • Types a. ME-Viral b. ME-Infectious Non-Viral c. ME-Other	Level 1: • Medical Results/Documents Level 2: • Self-Report of type of onset • DePaul Symptom Questionnaire (DSQ)	Onset Acute Onset____ ME-Viral____ ME-Infectious Non-Viral ____ ME-Other____ Level 1____ Level 2____	____ ME Full Meets criteria for categories I, II, III, and IV. Level 1____ Level 2____
II. Post-Exertional Malaise Example: - Feeling dead, heavy feeling after starting exercise. - Feeling drained or sick after mild activity	Level 1: • Sub-Maximal Exercise Challenge • Cardio-Pulmonary Exercise Testing: Lower VO2 peak and AT Level 2: • DSQ	Post-Exertional Malaise Level 1____ Level 2____	____ ME Not-Full Meets criteria for less than four of the major categories. Level 1____ Level 2____
III. Neurological Manifestations Example: - Slowness of thought - Difficulty finding right word to say	Level 1: • SPECT: Decreased cerebral blood flow • MRI: Lesioning • PET: Decreased metabolism of glucose and hypoperfusion • Romberg Test • PASAT Level 2: • DSQ	Neurological Manifestations Level 1____ Level 2____	
IV. Autonomic Manifestations Example: - Irregular heart beats - Feeling unsteady on feet	Level 1: • Tilt table test: ↓ Blood Pressure ↑ Heart Rate • SPECT: Hypoperfusion Level 2 • DSQ	Autonomic Manifestations Level 1____ Level 2____	____ Remission Was diagnosed with ME at one time, but is currently experiencing 0-1 Criteria categories.
V. Secondary Category Participant may meet the following categories, but are not required to meet any of the categories. a. Pain Example: - Pain or aching in muscles - Headaches b. Endocrine Manifestations Example: - Feeling hot or cold - Night sweats c. Sleep dysfunction Example: - Feeling unrefreshed after waking - Problems falling or staying asleep d. Immune Manifestations Example: - Having flu-like symptoms - Feeling feverish	Pain Level 1: • Increased Metabolites (Light et al. 2009) Pain Level 2: • DSQ • McGill Pain Questionnaire (MPQ) Endocrine Level 1: • Abnormal cortisol levels Endocrine Level 2: • DSQ Sleep dysfunction Level 1: • Polysomnography Sleep dysfunction Level 2: • Pittsburg Sleep Quality Index (PSQI) • DSQ Immune Manifestations Level 1: • Low NK cells Immune Manifestations Level 2 • DSQ	Secondary Category Pain Level 1____ Level 2____ Neuroendocrine Level 1____ Level 2____ Sleep Level 1____ Level 2____ Immune Level 1____ Level 2____	

worse scores when compared to the Canadian ME/CFS criteria. The lack of differences on the psychiatric items suggests that the ME criteria select individuals with less psychiatric co-morbidity and mental health issues than the Canadian ME/CFS criteria. It is possible that criteria which only require a sudden onset, post-exertional malaise, at least one neurocognitive symptom, and at least one autonomic symptom, identifies individuals with fewer emotional and mental health problems, but when additional symptoms are required, this selects for more physical and psychiatric impairment. This is of particular importance as Natelson and colleagues for the past 15 years have produced a series of studies that have found that their group of patients without psychiatric comorbidity had more problems with neuropsychological testing, more abnormalities on brain magnetic resonance imaging, more abnormalities in spinal fluid and higher levels of cerebroventricular lactate than patients who had psychiatric comorbidity (e.g., [30]).

Oftentimes, minimal information is presented in scientific articles, and available checklists for describing phenotypes have considerable overlap, arbitrary variations in wording and structuring, as well as inconsistency across research communities. There is clearly a need for improved standardization procedures and increased communication across research groups. In fact, there is already a greater push within the biological and biomedical communities to create minimal reporting guidelines for published research. For instance, the minimum information for biological and biomedical investigations (MIBBI) project serves as a compilation of "minimum information checklists" that outline the key information needed for reporting results of experimental studies using specific techniques (e.g., fMRI studies or studies using cellular assays) [53]. Other promising directions include the open-access online database (http://project-redcap.org/), which allows researchers to submit their own data and reporting methods and allows for easy access to reporting guidelines across the biological and biomedical fields, thus opening up the communication lines and enhancing standardization procedures. We hope that one day researchers will use these websites and guidelines to provide greater consensus regarding the utilization of case definitions as well as how they are operationalized.

In the near future, the state of the science will allow investigators to make clear decisions about which objective tests would fulfill each level 1 criterion. We feel that evidence based objective medical tests will be crucial for the future research of this illness, and there is already promising research on many of these areas. For ME to be diagnosed reliably across health care professionals, it is imperative to provide specific thresholds and scoring rules for symptomatic criteria, which we have tried to do. Without such standardization, symptom variability will be a function of the assessment procedure and etiological factors. In other words, by determining specific parameters and scoring rules for the symptomatic criteria, variability is likely to result in increased diagnostic reliability.

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