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An Accurate Diagnosis of Myalgic Encephalomyelitis and Chronic Fatigue Syndrome requires strict Clinical Case definitions and Objective Test Methods

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Abstract

Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS) are subject to controversy. Although ME and CFS are often considered to be to be synonymous, the case criteria for ME and CFS define two distinct diseases with partial overlap.

ME, recognized as a new clinical entity in the 1950's, is characterized by distinctive muscular, neurological and autonomic symptoms. In contrast the core feature of CFS, introduced in 1988 and redefined in 1994, is chronic fatigue. Some researchers consider CFS to be equivalent to (incapacitating) chronic fatigue (CF). After the introduction of CFS, other criteria for ME, ME/CFS, CFS and CF were introduced and used in research studies, creating obfuscation and controversy. The use of various diagnostic criteria has hampered effective research into ME and CFS.

Next to the various diagnostic criteria, the assessment of symptoms is almost always based on questionnaires and subjective measures, e.g. physical functioning. Due to their nature subjective measures are incomparable over time and between patients. Moreover subjective measures introduce a significant risk of bias, for example due to researcher allegiance, the Hawthorne effect, and buy-in effects. Despite the fact that ME and CFS (subtypes) lack a clear etiological explanation (yet), the symptoms can and should be assessed by objective test measures, since subjective measures are ambiguous, incomparable and introduce the risk of bias. Objective test measures can also confirm the seriousness of both ME and CFS.

To resolve the diagnostic issues in research studies and clinical practice, a clear distinction between ME and CFS (not ME), based on the original criteria, is crucial.

Although the use of objective test methods is more expensive and time-consuming and severe cases cannot be subjected to these tests, considering the (scientific) confusion originating from the use of subjective measures it is essential to assess the symptoms of patients objectively both in clinical practice and research settings.

Keywords: Diagnosis; Myalgic encephalomyelitis; Chronic fatigue syndrome; Symptoms assessment; Criteria; Methods

Introduction

There is a fierce debate with relation to the diagnosis of ME and CFS, the nature and severity of characteristic symptoms, e.g. muscle weakness, cognitive impairment, day-night reversal, and post-exertional 'malaise', and the effectiveness of behavorial therapies, including cognitive behavioral therapy and/or graded exercise therapy. A lot of debate and confusion originates from the use of various (symptom-based) case definitions and the use of ambiguous subjective measures, e.g. fatigue and physical functioning scores, to determine the severity and frequency of symptoms.

This article reviews the current situation with regard to diagnostic criteria for ME and/or CFS and the assessment of the symptoms using subjective measures, and outlines a 'new' approach to resolve the diagnostic and scientific impasse, after which the necessity of this alternative approach and its limitations are discussed.

The current situation

ME and CFS: A diagnostic mess

ME (Ramsay criteria)

ME, an neuro-muscular illness resembling poliomyelitis [1-3], has been described in the medical literature since 1938 [3], often on account of outbreaks [4,5]. Typical features of ME [2,5-7] include muscular symptoms, especially an unique form of muscle fatiguability (muscle weakness and pain after minor exertion lasting for days) and muscle tenderness, neurological symptoms, implicating cerebral dysfunction, e.g. impairment of memory and concentration, day-night reversal, and emotional liability, and symptoms indicating circulatory impairment, e.g. cold extremities, hypersensitivity to climatic change and orthostatic tachycardia.

ME was recognized as a new clinical entity in the late 1950's [3,4,8,9] and in 1978 researchers at a Royal Society of Medicine conference agreed that the symptoms described as ME made up a distinct nosological entity [10]. ME has been classified as a

neurological disease by the World Health Organisation since 1969 [11,12].

CFS (Fukuda criteria)

Much of the current confusion originates from the introduction of the concept CFS. The only mandatory feature of CFS, introduced in 1988 [13] and redefined in 1994 [14], is (unexplained) chronic fatigue. The main problem with the diagnosis CFS [14] is that its definition is solely based on symptoms that are highly subjective and ambiguous and are also experienced in other medical and psychic disorders, e.g. fatigue, non-refreshing sleep, headaches, and muscle and joint pain. None of the characteristic features of ME [2,5-7] is mandatory to meet the diagnosis CFS, e.g. muscle weakness and cognitive impairment, while patients can meet the diagnostic criteria for CFS [14], and not experiencing any of the typical features of ME [15].

For that reason, the diagnostic criteria of ME and CFS define two distinct, partially overlapping, clinical entities (Figure 1). That's not a matter of preference, as suggested by the Institute of Medicine (IOM) [16], but a matter of definition.

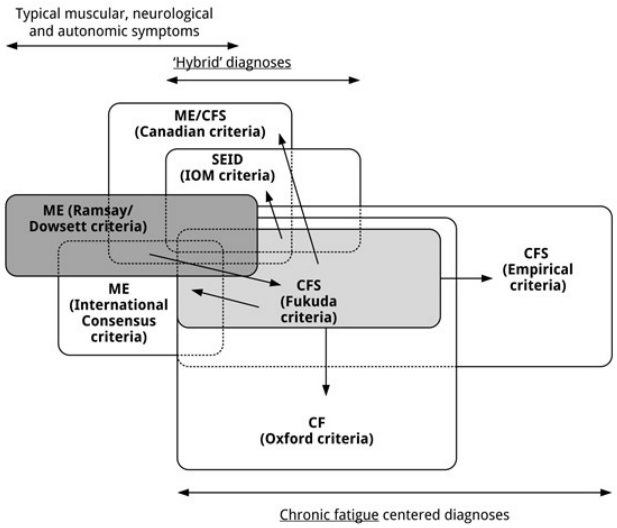

Figure 1: Diagnostic criteria for ME, CFS, ME/CFS and CF.

CF (Oxford criteria)

In the beginning of the 1990's researchers in the UK start using their own definition of 'CFS', the so-called Oxford definition [17,18]. However 'CFS' defined by the Oxford criteria should best be labeled CF, since in contrast with CFS, the only symptom required to meet the diagnosis 'CFS' is severe and disabling fatigue of definite onset. A common interpretation of the Oxford definition, i.e. a cut-off score on the Chalder Fatigue Scale [19], is used in studies into Cognitive Behavorial Therapy (CBT) and/or Graded Exercise Therapy (GET) to select patients and to define 'recovery' [20-22].

Since its introduction, the Oxford case criteria have endured much criticism, since they don't select patients with CFS, let alone ME, but patient with chronic fatigue.

Medical authorities in the US recently took a firm stand with regard to the Oxford criteria [17]: ''[T]he multiple case definitions for ME/CFS have hindered progress. In particular, continuing to use the Oxford definition may impair progress and cause harm. .. [W]e recommend that this definition be retired [..]". [23] and "[W]e recommended in our report that future intervention studies use a single agreed upon case definition, other than the Oxford (Sharpe, 1991) case definition." [24].

CFS (Empirical criteria)

In an attempt to resolve the shortcomings related to nature of the definition of CFS, researchers [25] proposed an 'operationalized' definition of CFS: cut-off scores on questionnaires for functional impairment, fatigue, and other symptoms. However, these 'operationalized criteria' for CFS lack sensitivity and specificity [26], which is illustrated by the observations that these new criteria misclassified 38% of patients with Major Depressive Disorder [27] and that the prevalence of 'CFS' (2,54%) [28] is more than 10 times as high as the prevalence of CFS (0,19%) [29]. The 'operationalized criteria' for 'CFS' have only been used in some studies.

ME/CFS (Canadian criteria)

In order to "reflect ME/CFS as a distinct entity and distinguish it from other clinical entities that have overlapping symptoms" as "fatigue is an integral part of many illnesses", a panel of specialists proposed criteria for ME/CFS (Canadian consensus criteria: CCC) [30]. To meet the diagnosis ME/CFS a patient must experience 'fatigue', post-exertional 'malaise' (prolonged worsening of symptoms after minor exertion), sleep dysfunction, (muscle and/or joint) pain, two or more neurological/ cognitive symptoms, and at least one symptom from two of three categories: autonomic, neuroendocrine and immunological symptoms. Although the ME/CFS criteria have more overlap with ME than with CFS, there are still fatigue-oriented criteria.

ME (International Consensus criteria)

In 2011 an expert group proposed new criteria for ME (International Consensus Criteria: ICC) [31] and recommended to abandon the label CFS and its diagnostic criteria. To meet the diagnosis ME/ICC a patient must experience post-exertional "malaise" (neuro-immune exhaustion), at least one symptom from three of four symptom categories (neurocognitive symptoms, pain, sleep disturbance, and neurosensory, perceptual and motor disturbances), at least one symptom from three of five immune, gastro-intestinal and genitourinary symptom categories (flu-like symptoms, susceptibility to viral infections, gastro-intestinal abnormalities, genitourinary symptoms, and sensitivities to food, medications, odours or chemicals), and at least one symptom indicating energy production/ transportation impairment (cardiovascular symptoms, respiratory symptoms, loss of thermostatic stability, and intolerance of extremes of temperature). Note that chronic fatigue, the core of various CFS [13,14,25] /CF [17] criteria, isn't mandatory. Although the ICC criteria show the most resemblance with the original criteria, there are also relevant differences between ME/ICC [31] and ME as described in the literature [2,5-7].

SEID (IOM criteria)

To resolve the diagnostic impasse, mainly caused by the introduction of CFS, the IOM, commissioned by the US medical authorities, conducted a review to develop new criteria for 'ME/CFS' [16]. The IOM proposed to replace 'ME/CFS' by Systematic Exertion Intolerance Disease (SEID). To meet the diagnosis SEID the patient

must experience 'fatigue', post-exertional 'malaise', non-refreshing sleep.

In addition the patient must also report cognitive deficits and/or orthostatic intolerance [16]. However, since the premise of the review that ME and CFS are similar disorders is invalid, the criteria [16], largely based on a review of research into CFS [14], define a 'hybrid disease'. If the original criteria of ME [2,5-7] would have been taken into consideration and research into ME would have been involved in the review, the IOM most likely would have come to the conclusion that a new diagnostic entity cannot replace two distinct clinical entities with different definitions [15,32].

Summary

In summary, much of the confusion with regard to the neuromuscular disease ME [2,5-7] originates from the introduction of CFS [13,14], reinterpreted by some as CF [17]. 'Operationalization' criteria or replacing ME and CFS by a new clinical entity (SEID) won't resolve the fundamental issue that ME and CFS are distinct diseases.

Whether the ME/ICC can replace the original criteria for ME is not yet investigated. The diagnostic criteria for ME and/or CFS and their history are illustrated in Figure 1.

Assessment of symptoms based on questionnaires and subjective measures

A second important methodological issue concerning the diagnosis of ME and CFS relates to the way in which the symptoms are assessed. This is extremely relevant since, as long as satisfactory etiological explanations for ME and CFS are lacking, the diagnosis is symptom-based. The assessment of symptoms in clinical practice and research studies is almost always based on the outcomes of questionnaires, e.g. the DePaul Questionnaire [33] or Multidimensional Fatigue Inventory (MFI) [34]. Often the questionnaires used aren't related to the symptoms of CFS, but to general notions, like physical impairment, e.g. the Medical Outcomes Survey Short Form-36 (SF-36) - Physical Functioning subscale, and fatigue, e.g. Chalder Fatigue Scale [19].

Using questionnaires and varying cut-off scores for subjective and non-specific notions also experienced in other conditions, like fatigue and unrefreshing sleep, will not only result in incomparable outcomes (in-between patients, over time and between studies), but also introduces a risk of misdiagnosis [35]. In trials assessing the effect of proposedly effective therapies, e.g. CBT, GET and rituximab, the use of subjective outcomes (only) involves an important risk of bias, e.g. due to researcher allegiance [36], the Hawthorne effect [37], placebo effects [38] and buy-in effects [39], especially when subjective measures are combined with different cut-off scores for meeting the diagnosis CFS [21] and improvement or recovery [40].

A new direction: Back to the future

In order to resolve the diagnostic impasse related to ME and CFS and to enable more effective research, it is crucial to make a clear distinction between ME [2,5-7] and CFS [14], to use objective tests, e.g. repeated exercise tests [41,42], cognitive tests [43,44], tilt table tests [45,46], muscle power (endurance) tests [47,48], for diagnosing patients [49] and determining the effect of interventions [50], to find correlations between symptoms/subjective measures and objective test outcomes, and to define symptomatic subgroups of the ME and CFS patient population [51].

A clear distinction between ME and CFS

Most importantly, a clear distinction must be made between the neuromuscular disease ME, based on the original criteria [2,5-7]. and other diseases fulfilling the commonly used CFS criteria [14], because the case criteria define distinct diagnostic entities, which cannot be merged into a hybrid diagnosis ('ME/CFS'). Since the majority of research studies in the last decades have been investigated patients with CFS (or even CF), research into ME [2,5-7] has been scarce since the 1980's. However, to unravel the etiology and pathophysiology of ME and diseases currently meeting the 'umbrella diagnosis' CFS [52,53] making a distinction is unavoidable.

Using objective test methods to assess the symptoms, improvement and recovery

To establish the presence and severity of symptoms and to assess the health status of patients impartially objective test measures are indispensable [51]. Subjective measures solely based on questionnaires, e.g. fatigue and physical functioning scores, are inadequate to diagnose and to assess the health status of patients in research studies and clinical practice. Accepted objective test methods (Figure 2) should be used to make abstract notions, e.g. post-exertional malaise, tangible.

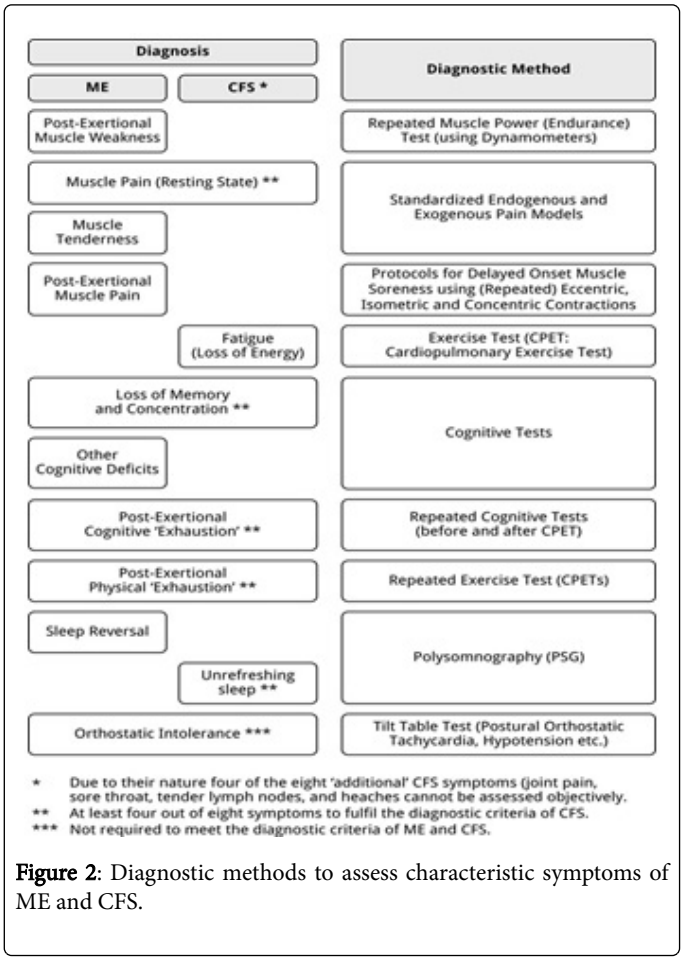

Figure 2: Diagnostic methods to assess characteristic symptoms of ME and CFS.

Finding correlations between symptoms and objective test measures

In order to distinguish ME and CFS patient subtypes and to re-evaluate the research into ME and CFS so far, it is important to establish correlations between symptoms (abstract notions) and objective measures, e.g. between post-exertional malaise and the effect of exercise on the exercise capacity [41] and cognitive test scores [54], between orthostatic intolerance and tilt table test results [55], and between cognitive deficits and cognitive test performance during orthostatic stress [56].

Using pattern recognition analysis to define ME and CFS patient subgroups

Based on the intercorrelation of symptoms, to be assessed objectively and stratified by duration of illness, ME and CFS patient subgroups should be investigated to unravel the relationship between specific symptoms and distinct abnormalities found in the last decades in the CFS patient group as a whole or in CFS subgroups. Promising area of interests are abnormalities related to post-exertional 'malaise', and (energy-related) aberrations associated with prolonged muscle weakness.

Discussion

The current situation with regard to the diagnosis of ME and CFS in clinical practice and research studies is characterized by diagnostic disorder and subjectivity. This approach results into confusion, discussion and fierce debates, e.g. with regard to the (assumed) positive effects of behavioral therapies, CBT and GET [21,22,38,40,57,58], and pharmaceutical therapies, including rituximab [59,60]. With regard to diagnosis, most researchers, including members of the IOM committee [16] urging for a new diagnostic entity (SEID), consider ME and CFS to be 'similar disorders'. However the (original) clinical diagnostic for ME [2,5-7] define a neuromuscular disease with distinctive muscular and neurological symptoms, while CFS [14] is primarily defined by (unexplained) chronic fatigue. The diagnostic criteria of ME [2,5-7] and CFS [14] define two distinct, partially overlapping, clinical entities (Figure 1). That's not just a matter of preference as suggested [16], but a matter of definition.

Next to the (unnecessary) confusion with regard to diagnostic criteria of ME and CFS, the use of subjective measures based on self-report by the patient is the cause of disorder and a heated debate. This is for example illustrated by the observation that researcher [21] reported that 30% in the CBT arm and 28% of the patients in the GET group were 'within normal ranges' for fatigue and physical functioning (versus 15% for standard medical care), while other researchers [57] using the original criteria for recovery as defined in the protocol [61] found that recovery rates in the GET and CBT groups were low and not significantly higher than in the control group (4%, 7% and 3%, respectively) and follow-up studies observed no improvement using objective measures, e.g. physical fitness and employment [58]. This example illustrates the need to use of objective measures to assess the health status of patients and the effects of proposed effective therapies impartially. Although the use of objective test methods is more expensive and time-consuming and severe cases cannot be subjected to these tests, it is essential to assess the symptoms of patients objectively both in clinical practice and research settings. It is very unlikely that all patients meeting specific diagnostic criteria will show abnormal results for all specific objective tests, e.g. repeated exercise tests [41,42], cognitive tests [43,44], tilt table tests [45,46], muscle power (endurance) tests [47,48], but it is essential to establish physiological and neurocognitive abnormalities in the individual patients impartially, both in clinical practice as in research studies.

To improve the quality of research (and to re-evaluate the results of prior research), it is also important to establish (potential) correlations between subjective and objective measures and to use pattern recognition analysis methods to objective measures and biological abnormalities to unravel ME and CFS patient subgroups.

Conclusion

Much of the diagnostic confusion with regard to ME [2,5-7], a neuromuscular disease (often) with an infectious onset, originates from the introduction of the ill-defined concept CFS [14]. To unravel the etiology of ME and other diseases currently diagnosed as CFS, it is crucial to make a clear distinction between ME and CFS, to assess symptoms objectively, to stratify patients by the duration of illness, to establish correlations between symptoms and objective test results and to use pattern recognition methods to symptoms to define ME and CFS patient subgroups.

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