REVIEW ARTICLE

Case definitions and diagnostic criteria for Myalgic Encephalomyelitis and Chronic fatigue Syndrome: from clinical-consensus to evidence-based case definitions

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Abstract

The symptom spectrum of Myalgic Encephalomyelitis (ME) was first detailed in 1959 and later operationalised into a diagnostic protocol (Melvin Ramsey). In 1988 the Holmes case definition coined the term chronic fatigue syndrome (CFS). Fukuda's Centers for Disease Control and Prevention criteria are very heterogeneous and comprise patients with milder symptoms than the Holmes case definition. The CDC Empirical Criteria for CFS lack sensitivity and/or specificity. Other CFS definitions, e.g. the Oxford criteria, delineate people with idiopathic fatigue. Some authors make the clinical CFS diagnosis when slightly increased self-rated fatigue scores are present. In 2011, Carruthers' International Consensus Criteria attempted to restore the focus on selecting people who suffer from ME. Cognitive bias in criteria construction, patient selection, data collection and interpretation has led to the current state of epistemological chaos with ME, CFS, CFS/ME and ME/CFS, and CF being used interchangeably. Moreover, none of the above mentioned classifications meet statistically based criteria for validation. Diagnostic criteria should be based on statistical methods rather than consensus declarations. Ongoing discussions about which case definition to employ miss the point that the criteria did not pass appropriate external validation. In 2012, Maes *et al* performed pattern recognition methods and concluded that CFS patients (according to Fukuda's criteria) should be divided into those with CFS or ME, on the basis that people with ME display a worsening of their illness following increases in physical or cognitive activity. Both ME and CFS are complex disorders that share neuro-immune disturbances, which are more severe in ME than in CFS. This paper expands on that strategy and details a range of objective tests, which confirm that a person with ME or CFS has a neuro-immune disease. By means of pattern recognition methods future research should refine the Maes' case definitions for ME and CFS by including well-scaled symptoms, staging characteristics and neuro-immune biomarkers, including immune-inflammatory assays, bioenergetic markers and brain imaging.

1. Introduction

Myalgic Encephalomyelitis (ME) may well have existed for centuries but the American neurologist, Dr. G. Beard (1839–1883), may well have been the first person to detect people suffering from ME when he described a neurological condition he termed neurasthenia. The characteristics consisted of a pronounced fatigue both mentally and physically, muscle weakness, depression, impotence, a feeling of malaise, loss of bodily functions, weakness in the back and spine, autonomic symptoms, muscle weakness, feeling of malaise, neuralgic pains, insomnia, anxiety, dizziness, tendency to fainting and severe headaches. Moreover, Beard thought the causes of neurasthenia could be explained by a depletion of power in the central nervous system. He also proposed that the condition was viral in origin.

Unfortunately the term neurasthenia was coopted and converted by Dr. Sigmund Freud to indicate a neurosis. Freud formed the belief that physical symptoms could somehow be caused by unresolved conflicts in the unconscious mind primarily sexual conflicts like masturbation and uncontrolled sexual urges. This belief spawned the psychoanalytical movement. Freud's most essential psychoanalytic concepts were based entirely on metaphors or erroneous out-of-date assumptions from 19th century biology (Sulloway 1991). Freud erected his psychoanalytic edifice on a kind of intellectual quicksand and the psychoanalytical perspective is totally unscientific (Sulloway 1991). Moreover the evidence base underpinning psychoanalytical beliefs consists of only six case studies based on misrepresentations, exaggerations and fraud (Ellenberger 1970; 1972; Hirschmuller 1978; Tolpin 1993; Sulloway 1991). Sadly, diagnostic terms stemming from the intellectual quicksand underpinning the psychoanalytic paradigm also persist to this day and are used as a device employed by practitioners for avoiding a confrontation with their own ignorance (Slater 1965; 1982).

In 1959, based on hundreds of sporadic cases and outbreaks of ME in several countries, Acheson defined ME as being characterized by myalgia, headache, paresis, mental symptoms, low or absent fever and no mortality (Acheson 1959). Ramsey later further operationalized the diagnostic criteria of ME (Ramsay 1981). This definition made the presence of neurological and autonomic symptoms mandatory, placed an emphasis on symptom exacerbation triggered by increase in activity and it was the presence of muscle fatigueability and not fatigue which was another mandatory requirement. The hallmark characteristic of ME is that sufferers experience a profound worsening of their symptoms or even a relapse of their disease following even trivial increases in cognitive or physical effort (Carruthers *et al* 2011; Morris & Maes 2012b).

Unfortunately for a number of reasons people who just suffer with chronic fatigue are now also given the label of ME, CFS/ME, ME/CFS and CFS (Booth *et al* 2012). This has confused research making any meaningful comparisons between studies very difficult. The adoption of the term CFS which is applied to patients whether they have a neuro-immune disease or not has had the effect of trivialising this devastating disease in the eyes of the general public and perhaps more importantly the medical profession.

This review aims to describe the steps which have been taken to arrive at the current position, the cognitive bias involved in generating the plethora of case definitions and the effect of cognitive biases in generating conflicting conclusions by different teams of researchers. The steps needed to restore the integrity of diagnostic criteria and end the current epistemological chaos using objective measurements are also discussed.

2. Case definitions and diagnostic criteria for CFS and ME

2.1. Earlier case definitions and an outbreak of ME in Incline Village Nevada 1984

Achelson described the following symptom complex associated with ME: a paralytic illness of worldwide distribution with neurological signs, a waxing and waning course and an acute or subacute onset. The symptoms encompass: severe fatigue, muscle pain, painful muscular spasms, myoclonus, headache, and neurocognitive, gastro-intestinal and upper respiratory symptoms, involvement of the cranial nerves and the bladder and lymph nodes and depressed mood. In a minority of patients, nystagmus, ophthalmoplegia, facial palsy, palatal paresis and extensor plantor responses may occur.

The Ramsay definition of ME (Ramsay 1986) described ME as an illness which developed following a virus infection and which had a sudden or gradual onset. In his considerable experience the disease affected every system in the body but was primarily neurological in nature. However impairments of cardiac and skeletal muscle as well as abnormalities of the organs of the neuroendocrine system were normally present. Ramsey also emphasized the unique presentation of ME namely the unpredictable state of nervous system exhaustion following mental or physical exertion often delayed and with an excessively long recovery time. He further described a state of cortisol axis hypofunction and dysfunction of the musculoskeletal system. Interestingly he noted that the latter abnormality was a result of the metabolic and autoimmune effects of prolonged viral infection. Finally he emphasized that the disease displayed a chronic but relapsing remitting course similar to multiple sclerosis (Ramsay 1986).

In 1984 in Incline village Nevada, USA, many people succumbed to an illness with the typical symptom profile of ME. The patients reported severe debilitating fatigue or easy fatigueability unrelieved by bedrest and a host of other symptoms (Holmes *et al* 1988). These symptoms include fever or chills, painful lymph nodes, sore throat, generalized muscle weakness and myalgia, generalized headaches of a novel pattern, migratory arthralgia,

neurocognitive dysfunction, confusion, irritability, photophobia, transient scotoma and depression. Unfortunately this illness was incorrectly diagnosed as chronic mononucleosis and over time it became clear that the serological association with other viruses found infecting sufferers of the illness such as cytomegalovirus was stronger than the serological association with Epstein Barr (Holmes *et al* 1988).

2.2. Holmes case definition

In 1988 by a committee under the auspices of the Centers for Disease Control and Prevention (CDC) (Holmes *et al* 1988) in an effort to avoid naming one pathogen as the cause of the illness coined the term Chronic Fatigue Syndrome (CFS) to describe the symptoms reported by groups of patients who became ill at Incline Village. Although the intention may have been to create a restrictive definition of the illness the execution of this intention appears to have been somewhat wanting. Holmes *et al* (1988) suggested that the term CFS only referred to a particular symptom cluster and not necessarily to any specific disease. Nevertheless, we will use terminology devised elsewhere to describe the illness suffered by the people in Incline Village namely ME/CFS.

2.3. Dilution of original definition increasing population heterogeneity and diminishing symptom severity

In 1994, a committee once again under the auspices of the CDC developed the so called Fukuda criteria for classifying people as suffering from Chronic Fatigue Syndrome (CFS) (Fukuda *et al* 1994). This instrument stripped away 4 of the 8 symptoms which were mandatory in the earlier Holmes criteria, including the presentation which differentiates people with ME from other groups of patients. That symptom involves the worsening of the illness following an increase in mental or cognitive effort (Carruthers *et al* 2011). Applying Fukuda's CDC criteria may detect individuals with psychosocial stress or other psychiatric causes for the chronic fatigue. Application of this criteria selects patients with less severe symptoms than the original criteria and produced an entirely different symptom phenotype including more people with primary psychiatric conditions and with greatly increased clinical heterogeneity (De Becker *et al* 2001; Jason *et al* 1997a). Broadening the CFS definition enabled more people with psychiatric diseases to be (erroneously) classified as CFS. Abbey, a psychiatrist and member of the CDC Review Committee, said, "It is clear to my psychiatrist's eye that they (some participants) do not have CFS, but rather primary psychiatric disorder which has been misdiagnosed", yet they were being classified as having CFS (Jason *et al* 1997a). The inclusion of these misdiagnosed individuals in study samples diagnosed using Fukuda's CDC criteria has likely had serious detrimental effects on research into the causes and ultimately developing cures for people with the various illnesses subsumed under the CFS level and has likely led to the waste of scare research resources (Jason *et al* 2008; 2012). For example, patients with major depressive disorder have overlapping symptoms with CFS and therefore could be classified as suffering from CFS (Maes 2011). Fatigue, neurocognitive symptoms, sleep disorders, a flu-like malaise, autonomic symptoms and hyperalgesia occur in both depression and CFS (Maes 2011). This is perhaps hardly surprising given that there are biological abnormalities shared by people with ME/CFS and depression (Maes 2011) as indeed they are shared with people with all other diseases such as multiple sclerosis.

Using the original CFS case definition it was found that the prevalence rate of CFS was 0.0074% (Price *et al* 1992). Using Fukuda's CDC criteria in a primary health care setting, Wessely *et al* (1997) showed that 2.6% suffered from CFS. The effect of diluting the selection criteria qualitatively and quantitatively in creating population heterogeneity is obvious from this data. We will describe populations classified by these criteria as suffering from CFS while acknowledging that they will not suffer from a unitary illness.

2.4. CFS homonyms

In 1991 (Sharpe *et al* 1991), a small group of British psychosocial psychiatrists created guidelines to facilitate their research into fatiguing conditions once subsumed under the label of neurasthenia but later incorporated into such phenotypic classifications as anxiety and depression (Wessely 1995). Despite the fact that these guidelines were not intended to investigate ME or any other neuro-immune disease (Sharpe *et al* 1991; White *et al* 2011) and in essence identified people with idiopathic chronic fatigue (Twisk & Maes 2009; David 1991), they chose to use the term 'CFS' to describe the group of conditions which were the subject of their interest. We will ascribe the label "CF Oxford" to populations of patients selected by the use of this semi-structured questionnaire. The inclusion of patients with even less specific criteria, based on the presence or absence of fatigue as the only mandatory symptom, makes the inclusion of patients with primary psychiatric disorders in trial cohorts labeled with CFS even more of a problem (Jason *et al* 2012; Carruthers *et al* 2011; Morris & Maes 2012b).

A group of experienced physicians and scientists produced diagnostic criteria with a heavy emphasis on a range of neurological and endocrine symptoms in an attempt to create homogenous trial cohorts needed to further research (Carruthers *et al* 2003). A group of doctors employed by the CDC however later proposed a fatigue-based classification system based on accounts received during a survey of chronically unwell people in Witchita in 2003 (Reeves *et al* 2003). This decision tree was described as the CDC empiric criteria (Reeves *et al* 2005). This will henceforth be described as "CF CDC".

2.5. Cognitive and researcher biases

Constructing diagnostic criteria is very difficult without recourse to objective measurements (Lloyd 1998). In the

absence of empirical measurements, the resultant criteria are very prone to the cognitive biases of the group developing them (van der Meer & Lloyd 2012). If the criteria are intended for scientific research into causation or treatment, sensitivity and specificity are paramount, i.e. do the selection criteria reliably identify subjects with the disease and exclude those without (van der Meer & Lloyd 2012). We will now illustrate these points beginning with the so called CF Oxford criteria (Sharpe *et al* 1991). The authors of this instrument seem to provide a good example of cognitive bias as to the cause of the fatiguing conditions that they purport to investigate and this appears manifest in the construction of these criteria and the patients identified. We will consider the effect of various cognitive biases on the production of the White *et al* (2011) trial data and conclusions which were atypical when compared with the results of trials using internationally agreed criteria (Nunez *et al* 2011; Twisk & Maes 2009) and even studies focusing on fatigue of unknown origin (Ridsdale *et al* 2012; Wearden *et al* 2010). We will then turn our attention to the inaccuracies in diagnosis caused by sole reliance on patient accounts and the use of scales of various types.

Simon Wessely, who was instrumental in creating the CF Oxford criteria wrote the following about people with ME: "The description given by a leading gastroenterologist at the Mayo Clinic remains accurate: The average doctor will see they are neurotic and he will often be disgusted with them" (Wessely 1990). "Functional somatic syndromes refer to groups of symptoms lacking demonstrable abnormalities of structure. They include chronic fatigue syndrome" (Cho & Wessely 2005). It seems hardly surprising then that the CF Oxford case definition (Sharpe *et al* 1991) includes patients with psychiatric axis I and axis II morbidities. Shortly after publication of the CF Oxford criteria Anthony David wrote: "British investigators have put forward an alternative, less strict, operational definition which is essentially chronic fatigue in the absence of neurological signs (but) with psychiatric symptoms as common associated features" (David 1991). Criteria selected for people with idiopathic chronic fatigue (whose cause is not revealed by rudimentary testing) or fatigue overtly of psychological origin produces study cohorts where almost none of the patients actually have a neuro-immune disease (Morris & Maes 2012b; Twisk & Maes 2009). In a letter to the editor of the Lancet it is stated: "The PACE trial paper refers to chronic fatigue syndrome (CFS) which is operationally defined; it does not purport to be studying CFS/ME" (Hooper 2011).

Cognitive biases come in many shapes and forms and are not only involved in criteria construction, but patient recruitment and measuring the effects of treatment. It is well known that different cognitive biases can influence patient selection, the design of trial studies, the accuracy of the data collected and the conclusions presented by the authors of a study. Cognitive biases can grossly impede a clinician's ability to make an objective diagnosis. These biases lead to classifications driven by beliefs and preconceptions held in cognitive structures within the brain about the nature of the illness presented by a patient, such as assuming that physiological symptoms are psychological in origin (Garb 1998; Wood *et al* 2003; Eva *et al* 2003; Ashcraft 2002; Haverkamp 1993; Oskamp 1965; Tversky & Kahneman 2004; Friedlander & Phillips 1984; Silverman 1992; Scheinbaum 1979). For example, biases can creep into trial results as a consequence of creating artificial end points which lack any ecological validity to measure positive responders or the use of scales not fit for their intended purpose. An example would be the choice of arbitrary measures to indicate normal function and recovery in the PACE trial, which uses the Short Form (36) Health Survey (SF-36), a measure of physical and mental health status and quality of life (White *et al* 2011). The SF-36 scores to denote recovery in the PACE trial were predetermined and bear no relationship whatsoever to any state which a physician would call recovery. In addition, normative values for bad or good values do not really exist because the SF-36 values are very personal (Ware & Sherbourne 1992). Psychologists describe such measures as lacking in ecological validity. This term is also used now in epistemology. In other words, the SF-36 scores which qualified as recovery were plucked out of the air. Self reported data on physical functions can be very unreliable (Shephard 2003) and are particularly prone to confirmation bias (Kaptchuk 2003). In order to avoid or minimize confirmation bias trials should be designed so that the researchers are attempting to challenge their favored hypothesis rather than trying to confirm it (Mynatt *et al* 1977).

2.6. Chalder Fatigue Scale: Low ceiling effect

This scale purports to measure the severity of self reported tiredness using verbal reports of physical fatigue (7 items) and mental fatigue (4 items) (Chalder *et al* 1993). The results may be reported bimodally or using a Likert approach (Goudsmit *et al* 2008). Jason *et al* (1997) (Jason *et al* 1997b) reported that the Chalder Fatigue Scale was able to distinguish people diagnosed with CFS according to Fukuda's CDC criteria from healthy controls but was unable to differentiate people carrying a diagnosis of CFS from patients with Lupus or multiple sclerosis. Perhaps more importantly, the Chalder fatigue scale is incapable of differentiating people with CFS from people diagnosed with primary depression (Friedberg & Jason 2002). Concern has also been expressed about the effects of the low ceiling level built into the Chalder instrument and the overlap in fatigue scores between people who assessed themselves to be moderately sick and those who viewed their illness as being severe (Goudsmit *et al* 2008). The authors reported that nearly 90% of their patients received maximal scores for physical fatigue on likert and bimodal measures. Morriss *et al* (1998) and Stouten (2005) reported almost identical findings. Goudsmit and others (Goudsmit *et al* 2008) were of the opinion that this scale should not be used in clinical trials because so many people on maximal scores, despite being only moderately ill, would not be able to have

any worsening of fatigue as a result of any intervention. This is particularly important in trials involving the use of graded exercise therapy where the weight of evidence indicates that this approach is not only ineffective but potentially dangerous (Twisk & Maes 2009). The use of the Chadler scale may partly explain the atypical results reported in White *et al* (2011) report indicating a slight improvement in fatigue scores in people diagnosed with chronic fatigue syndrome using the unvalidated Sharpe *et al* (1991) criteria. It is also worth noting that the so called CF Oxford classification approach selects for people with idiopathic chronic fatigue or fatigue of a psychological origin (Twisk & Maes 2009; Morris & Maes 2012b).

2.7. The CDC Empirical Criteria for CFS: lack of sensitivity and specificity

The CDC has presented an empirical assessment of CFS symptoms, employing the CDC Symptom Inventory (SI) (Wagner *et al* 2005); disability, employing the Medical Outcomes Survey Short Form-36 (SF-36) (Ware *et al* 2000); and fatigue, employing the Multidimensional Fatigue Inventory (MFI) (Smets *et al* 1995; Reeves *et al* 2005). The SF-36 scale allows investigators to measure various dimensions, including physical, social and emotional functioning. A patient can meet the disability criterion when one of these dimensions is impaired. People with clinical depression would easily meet the disability threshold because impairment in emotional functioning is all that is required (Ware *et al* 2000). In fact Jason *et al* (2010) reported that the use of the empirical case definition produced a cohort of patients where 38% of patients suffered from depression. The fatigue criteria can be met by a score of 13 which compares to a score of 19 recorded by patients with CFS as diagnosed by more restrictive criteria. There is also an issue whereby people with clinical depression could easily agree to such questions as, "I get little done" and thus meet the fatigue criteria as well. To compound the felony the symptom inventory investigates the presence or absence of symptoms over a month. Thus a patient would meet the symptom threshold with only two ever present symptoms, only one of which need be severe according to the cutoff criteria of the symptom inventory.

Jason *et al* (2010) reported that they were able to detect with a high sensitivity (95%) those with CFS employing either the General Fatigue or Reduced Activity criteria. The specificity, however, was very low, i.e. 27% indicating that very few people without CFS were correctly diagnosed. The diagnostic performance data for the SI instrument were also extremely low: sensitivity was only 59% indicating that this instrument has major defects when it comes to identifying real cases of CFS. Using the SF-36 also yielded unacceptable results, i.e. sensitivity at 96%, but specificity was woefully inadequate at 17%. Also combining the three criteria (symptoms, fatigue and disability) resulted in an unacceptably low sensitivity (65%). All in all, the diagnostic performance of the Reeves *et al* (2005) criteria show that this instrument may not be used as a diagnostic tool for selecting CFS cases from the general population.

2.8. The Canadian Consensus Criteria: The return of ME

The Canadian Consensus Criteria when compared with the Fukuda approach selects patients with more neurological and neuropsychiatric symptoms but less psychiatric comorbidity. It also selects patients with considerably greater functional impairment and weakness. This pattern of neurological and neuropsychiatric symptoms is typically found in other neurological diseases such as multiple sclerosis and Parkinson's Disease (Thone & Kessler 2008; Diaz-Olavarrieta *et al* 1999; Figved *et al* 2005; Aarsland *et al* 2007; 2009). This pattern combined with the ability to select patients with severe functional impediments related to muscle weakness together with the reduction in misdiagnosis of people with primary psychological illnesses means that this approach shows great promise. However very little research has been carried out using these criteria and we are left in a position where there are studies purportedly investigating some aspects of ME/CFS where 90% (Jason *et al* 2010) or more (White *et al* 2011) of the patients in the trial do not have the illness ME.

The authors of the recent International Consensus Criteria (ICC) for ME (Carruthers *et al* 2011) have suggested a strategy to move research forward by eliminating the heterogeneity in cohorts produced by the Fukuda, Empiric CDC and the Sharpe *et al* criteria (Morris & Maes 2012b) and end the epistemological chaos that now exists which is preventing meaningful research towards discovering a cause and formulating treatments.

The ICC has produced a description that focuses on the hallmark phenotype of ME, namely, "a pathological low threshold of fatigability that is characterized by an inability to produce sufficient energy on demand." The authors of these criteria also emphasize the effect of an increase in cognitive effort also leading to a profound worsening of symptoms or even a full blown relapse (Carruthers *et al* 2011). In these criteria the term PEM and Post Exertion Fatigue is replaced by the encompassing term Post Exertional Neuro-immune Exhaustion (PENE). In order for research to proceed the creation of a homogenous cohort is essential hence the logical way to proceed would be to separate people with ME from those who have a range of fatiguing illnesses subsumed under the CFS label.

The members of the ICC panel stress that ME should be the only name given to people meeting the ICC criteria and those patients who do not have a neuroimmune disease should remain classified within the CFS umbrella. The aim of this approach is to introduce clarity and use the distinctive features of ME to provide homogenous cohorts, which ideally don't contain any patients suffering from any of the illnesses subsumed under the CFS umbrella.

This is in stark contrast with a strategy proposed by Jason *et al* (2011). These workers proposed to split ME

into level 1 and level 2 diagnostic ratings and proposed that a diagnosis could be made using nothing but self report questionnaires. They also proposed a further subdivision into ME-infectious non-viral, ME-viral and ME-other was also proposed. It would appear that this approach is unnecessarily complicated and could reinstate the problem of heterogeneous cohorts which the ICC aims to eliminate, especially as under this proposal anxiety and depression would not be exclusion criteria.

There are however major weaknesses in the execution of the decision tree of the ICC criteria. First, using the ICC criteria a patient could suffer from sleep disorders, hyperalgesia and neurosensory disturbance but not from neurocognitive disorders (Jason *et al* 2012) one of the key symptoms of ME (Maes *et al* 2012a). Second, PENE is an umbrella term which describes PEM or post exertional fatigue (Van Oosterwijck *et al* 2010), which was a mandatory requirement in the Canadian consensus criteria (Carruthers *et al* 2003). The problem arises because there are now many different phenotypes which can be described by the PEM label and that the number of people reporting PEM can range from 40% to 90% depending on the way a question is phrased (Jason *et al* 2012). There are also populations of patients other than those with ME/CFS which report PEM after exercise. They include people in emotional distress (Jason *et al* 2011) and major and melancholic depression (Jason *et al* 2002; 2012). A third and major flaw of the ICC criteria is that the ICC abandoned the requirement for the presence of severe incapacitating fatigue. A pathological level of chronic fatigue appears no longer to be a criterion to make the diagnosis of ME. Likewise, the large number of symptoms without CF required by the ICC criteria rather than identifying the new diagnostic group "ME" may select for another existing psychiatric diagnosis, i.e. "somatization" (disorder). Fourth, as will be discussed below this case definition did not pass external validation and therefore there is no evidence that this new category would exist.

2.9. Different definitions of PEM

Table 1 lists different definitions of PEM. The unpublished Report from the National Task Force on CFS, Post Viral Fatigue Syndrome (PVFS) and ME (National Task Force 1994) suggested that exercise-induced fatigue should be interpreted with respect to the patient's baseline exercise tolerance. This parameter is obviously very difficult if not impossible to measure objectively. The Nightingale criteria states that PEM can be caused by physical as well as mental activity. Goudsmit *et al* (Goudsmit *et al* 2009) in an article examining whether ME was in fact a clinical entity describes PEM as abnormally increased muscle fatigueability during the 24 to 48 hours and precipitated by minor activities. Another definition of PEM is unusual post exertional fatigue (Reeves *et al* 2005). One can see immediately that if the authors of a study merely stated that their patients suffered from PEM this can mean objectively very different patient populations.

To fulfill the criteria for a diagnosis of ME under the ICC guidelines a person's activity level must be 50% of their pre illness level or less. This is clearly unquantifiable. The authors of the ICC also seem to envisage that the diagnosis of ME will be via a self report questionnaire (Broderick 2012). This is likely to be highly problematic for all the reasons discussed above. The strategy of separating patients with ME from patients with fatiguing illnesses existing under the CFS umbrella appears logical however and without such an approach it is difficult to see how research into causation and the development of treatments can move forward. We now turn to methods of implementing this strategy without the use of self report questionnaires with their inherent inaccuracies, but focusing on empirical measurements to counter the effects of cognitive bias.

3. The way forward.

3.1. The way forward: use of pattern recognition methods

All abovementioned diagnostic classifications of CFS and ME have been developed based on a consensus between clinicians and basic scientists (e.g. Carruthers *et al* 2011) and on clinical viewpoints (e.g. Fukuda *et al* 1994). None of the abovementioned case definitions for CFS or ME has employed statistical analyses to validate the existence of the diagnostic categories that were developed. Previously we have discussed that pattern recognition methods should be used to validate clinical diagnoses, which are based on clinical views or a consensus (Maes *et al* 2012a). In general, results of pattern recognitions methods, i.e. supervised learning techniques, should be used to reject or accept "a priori" knowledge of case definitions (e.g. definition made based on clinical views or consensus). Moreover, research should also delineate clusters of patients in large-scaled patient samples in order to detect subgroups of patients with similar characteristics. The generated subclasses should be externally validated using biomarkers or other illness characteristics (Ramsay 1986). Consequently, none of the above mentioned definitions of CFS or ME, including the CDC and ICC criteria, meet empirically based criteria for validation. As discussed this is a major limitation that hinders advances in classification and the development of biomarkers (Matsuda *et al* 1994; Maes *et al* 2013).

Maes *et al* (2012a) were the first to report on results of pattern recognition methods used to confirm or reject Fukuda's CDC CFS criteria and the PEM criterion used to delineate the new diagnostic class ME. They reported that the CDC Fukuda criteria were adequate to differentiate people with CFS from those with chronic fatigue, but that people diagnosed with CFS according to Fukuda's criteria should be differentiated into those with PEM (labeled ME) and without PEM (labeled CFS). Moreover, these authors used specific supervised learning techniques and showed that those three subgroups (ME, CFS, CF) were mutually exclu-

Tab. 1. Various terms are used in conjunction with different versions of PEM, such as, ‚exertion', ‚inappropriate', ‚pathological'. These terms however are not defined and will result in different interpretations from one study to the next.

	Symptom(s) increased	Activity level given as inducing the feature	Severity	Recovery	Possibility of delayed reaction	Criteria
PEM 1	Fatigue	Holmes - Exercise previously tolerated CCC - Exertion ICC - Any	Holmes - General fatigue CCC - Inappropriate ICC - Pathological	Holmes - 24 hrs or longer CCC - Slow recovery ICC - No duration required	N/A	Holmes/CCC/ ICC
PEM 2	Pain	Exertion	Inappropriate	Slow recovery	N/A	CCC
PEM 3	Malaise	Fukuda - Exertion CCC - Exertion	Fukuda - N/A CCC - Inappropriate	Fukuda - 24 hrs or longer CCC - Slow recovery	N/A	Fukuda/CCC
PEM 4	Fatigue	Anything which is not an excessively demanding schedule	Exhaustion	N/A	N/A	Fukuda (but described in Reeves et al., 2003) *
PEM5	Global increase in symptoms	Minimal activity	Abnormal	24 hrs or longer	May be delayed by 24 to 48 hrs	Morris and Maes, (2012a)

A) N/A - Not applicable.
B) Oxford: No version of PEM is included in the criteria.
C) Fukuda: PEM is not required for this diagnosis, but can be included as a minor symptom.
D) *Fukuda: The Reeves et al. (2003) definition of PEM may be used instead of the version originally described in Fukuda et al. (1994).
E) CCC: Only one version of PEM (PEM 1, 2 or 3) from the table above is required for a diagnosis, but it must include inappropriate loss of stamina and fatigability.
F) ICC: Characteristics are listed for PEM (PENE), but it is unclear if all of these characteristics, if any, are required for a diagnosis.

sive and qualitatively distinct categories. ME patients are discriminated from those with CFS on the basis of PEM, neurocognitive symptoms and subjective feelings of infection or a flu-like malaise and higher overall severity of illness. These three classes lie in a categorical continuum of increasing severity of illness (from CF to CFS to ME) whereby new symptoms emerge with increasing severity (eg. neurocognitive symptoms, a subjective feeling of infection and PEM) thereby shaping distinct symptom profiles. Therefore for clinical diagnostic purposes and future research the abovementioned algorithms should be used to classify patients into three mutually exclusive and distinct classes, i.e. ME, CFS or CF.

The supervised learning techniques also showed that Fukuda's CDC CFS classification defines a heterogeneous patient sample because around 50% of CFS individuals should be diagnosed as suffering from ME. In accordance with the ICC criteria it was found that PEM is a significant discriminatory symptom. The pattern recognition methods validated operational case definitions characterized by CF and PEM. The question that arises is then whether ME according to the ICC criteria (Carruthers *et al* 2011) exists and whether it is different from ME defined by Maes *et al* (2012a).

The above unresolved issues show that the new diagnostic criteria for ME (and CFS) should be refined in order to develop more evidence-based case definitions and diagnostic criteria to reliably classify individuals with chronic fatigue, PEM, and autonomic, gastrointestinal and neurological symptoms. Toward this end, future research should use large study samples applying pattern recognition methods on well scaled illness characteristics to examine which classes can be retrieved in the data set (using unsupervised techniques) and developing more accurate classification rules to discriminate the existing (ME, CFS) or newly generated case definitions (using supervised learning techniques). Recently, we discussed these techniques and their application in ME/CFS research in more detail somewhere else (Maes 2011).

3.2. The way forward: Objective criteria

It is clear that the Fukuda criteria select patient populations which are clinically heterogeneous compared to the original Holmes criteria and the newer ICC and Maes criteria. The Fukuda criteria probably select markedly more patients with primary depression and anxiety and people with far milder symptoms. This is hardly surprising considering that a diagnosis of CFS can be made when patients present with idiopathic chronic fatigue and four minor non specific symptoms. The situation using the CDC CF and Oxford CF criteria is even worse and it is entirely likely that trial cohorts selected using these criteria may not contain patients with a neuro-immune disease. The ICC and Maes ME criteria do emphasize the importance of exercise or activity intolerance provoked by physical or cogni-

tive effort and indeed a diagnosis of ME under this approach cannot be made without a patient presenting with this phenomenon. Unfortunately, it is entirely possible to diagnose a patient with ME using ICC diagnostic criteria without the patient displaying any neurological symptoms whatsoever. These patients would be highly unlikely to suffer from a neuro-immune disease. Pattern recognition methods show that ME patients according to Maes *et al* criteria display neurological symptoms, including neurocognitive and autonomic symptoms (Maes 2011).

Therefore on balance the criteria recommended to the primary care physician would be the ME and CFS Criteria as defined by Maes *et al* (2012a) as this approach would produce the greatest chance of producing a correct diagnosis in inexperienced hands and of course produce the greatest number of patients with ME in a trial cohort if used as a preliminary screening instrument. While the use the Maes criteria affords a reasonable pathway to a useful diagnosis all methodology relying solely on patient accounts may be prone to high levels of inaccuracy. We therefore move to discuss the external validation methodology (Maes *et al* 1990) which, by using biomarkers, can both confirm that a patient has a neuro-immune disease and whose pathology is underpinned by inflammatory pathways, bioenergetic failure and brain disorders (Carruthers *et al* 2011; Morris & Maes 2012a).

3.3. The way forward: inflammatory biomarkers as an aid to diagnosis

There are many aberrations in immuno-inflammatory markers in ME/CFS. For example, there is growing evidence that ME/CFS is accompanied by elevated levels of proinflammatory cytokines (Maes *et al* 2012a;b;c;d; Brenu *et al* 2011; 2012). Maes and fellow workers have reported elevated levels of serum neopterin in ME/CFS (Maes *et al* 2012a;c;d). An abnormal level of serum neopterin has also been detected in previous studies (Matsuda *et al* 1994). Increased translocation of gram negative bacteria with a subsequent increased load of bacterial LPS in the systemic circulation and inflammation derived from the gut has been described in ME/CFS (Maes *et al* 2008). There is also evidence for abnormalities in the pathways culminating in activation of T cells and natural killer cells (Mihaylova *et al* 2007). The majority of patients with ME/CFS display signs of autoimmunity, which include, among other things, elevated antibody titers directed against microtubule-associated proteone and ssDNA, microtubule-associated proteome, gangliosides, serotonin, antilamine phospholipids, and anti-68/48kd proteone (Bassi *et al* 2008). Many patients with ME/CFS display increased IgM-related immune responses towards a) disrupted lipid membrane components (e.g. oleic, palmitic and myristic acid); b) the major anchorage molecules (palmitic and myristic acid, phosphatidylinositol, S-farnesyl-L-cysteine); c) nitric oxide (NO)-adducts (e.g. NO-tyrosine, NO-tryptophan, NO-phenylalanine) and d) by-products of lipid peroxidation (e.g. azelaic acid and malondialdehyde). These molecules have been corrupted undergoing major conformational change because of continual attack by high levels of oxidative and nitrosative stress (O&NS) have thus lost their immune tolerance. The levels of these damaged entities correlate significantly and positively with the severity of the symptoms experienced by patients (Maes *et al* 2006).

Importantly, we have reviewed elsewhere that those immuno-inflammatory, O&NS and autoimmune pathways are well established causes of ME and CFS symptoms, such as fatigue, hyperalgesia, neurocognitive and autonomic symptoms, sleep disorders, PEM, etc (Morris & Maes 2012a). Maes *et al* (2012a) pioneered a diagnostic approach using raised levels of neopterin, lysozyme, IL-1 and TNFα as external validating criteria for their clinical diagnosis into ME and CFS. It may therefore be concluded that their operational case definitions based on specific ME and CFS symptoms and including neurological symptoms and validated by immuno-inflammatory biomarkers delineate diagnostic classes which have a neuro-immune origin (Maes *et al* 2012a). Testing for elevated levels of neopterin and elastase would be an elegant approach to detect inflammation and activated cell mediated immunity. Neopterin is produced by monocytes/macrophages following activation by interferon-(IFN)γ and therefore measurement of neopterin is a marker of cell-mediated immunity and Th1 activation (Murr *et al* 2002). A number of antibody measurements would also be useful such as IgM antibodies to lipid and protein components damaged by raised O&NS and antibodies to gangliosides and serotonin as described above. Neutrophil elastase, is an innate immunity effector molecule (Sonawane *et al* 2006) with antimicrobial activity against bacteria, spirochaetes and fungi (Tkalcevic *et al* 2000).

3.4. The way forward: bioenergetic biomarkers as an aid to diagnosis

There are a number of approaches which could objectively measure impaired bioenergetic function and which could be used as external validation criteria. The simplest of all approaches is the so called ATP test (Myhill *et al* 2009). Interestingly the vast majority of patients in studies trailing this test met the ICC criteria for ME (Booth *et al* 2012). The ATP test measures ATP availability in neurtrophils, the efficiency of oxidative phosphorylation in mitochondria leading to a mitochondrial energy score, etc. (Myhill *et al* 2009; Booth *et al* 2012). The results of this test, reflecting mitochondrial dysfunction, are highly significantly associated with the severity of illness ($r=0.80$, $p<0.001$). This test could be a valuable tool in the quest to separate people with ME from people with a range of fatiguing conditions subsumed under the CF or Fukuda's CFS banner.

Patients with ME/CFS reach exhaustion at a much earlier time point than healthy controls. They display

increased lactate and diminished ATP production compared to healthy controls, which is even more evident upon repeat exercise testing in the brain and striated muscle. Impairments in oxidative metabolism result in a marked acceleration of glycolysis in striated muscle and a prolonged recovery time needed to restore pre exercise level of ATP (Vermeulen *et al* 2010). Exercise intolerance in patients with ME/CFS is associated with gross immune abnormalities consistent with a channelopathy involving O&NS-related toxicity (VanNess *et al* 20100). This can be illustrated in a study by VanNess and fellow workers (VanNess *et al* 2010). In this study 85% of controls recovered completely within 24 hours, whereas none of ME/CFS had recovered. This pattern is comparable to that found in patients with classical mitochondrial disease where even trivial exercise produces a rapid increase in disabling fatigue (Taivassalo *et al* 2002; 2003). Many such patients have trouble in meeting the energy costs of normal living (Taivassalo *et al* 2003). In Mitochondial disease $V0_2$ max is limited.

Exercise testing (bicycle and treadmill ergometry) is used as a diagnostic tool for mitochondrial myopathies showing increased lactate levels and reduced lactate clearance (Tarnopolsky 2004). This test approach requires specialized equipment and patients with ME are often unable to engage with this testing approach (Booth *et al* 2012).

Forearm exercise testing would appear to be a viable alternative which should suit a wide range of disabilities. Forearm exercise testing and measurements of venous oxygen saturation (observing "arterialized" venous blood) are often performed in patients suffering from mitochondrial diseases (Garrabou *et al* 2006). The forearm test is a simple procedure and any problems are usually associated with catheter placement (Taivassalo *et al* 2003). The test is based on a measure of partial pressure (pO2) and oxygen saturation at rest and during exercise. In normal healthy people the level of oxygen in venous blood decreases dramatically because mitochondria in muscle cells extract oxygen at a greater rate to match the increase in oxidative phosphorylation. When oxidative phosphorylation is impaired however the rate of oxygen extraction by mitochondria falls. This means that the level of oxygen saturation in venous blood in a person exercising with mitochondrial dysfunction is far higher than would be expected in an age-sex matched healthy person (Meulemans *et al* 2007). A number of different forearm tests have been used ranging from ischaemic, non ischaemic and aerobic (van Adel & Tarnopolsky 2009).

^{31}P-Magnetic resonance spectroscopy (MRS) may be used to measure high-energy phosphate (HEP) levels, the bioenergetic state of a tissue (Befroy & Shullman 2011) and the metabolism of skeletal muscles (Schmitz *et al* 2008). This technique enables rate of ATP synthesis in muscle to be measured non invasively in vivo (Mintzopoulos *et al* 2009). This technique is able to measure ATP changes in exercising human forearm flexor muscle (Wu *et al* 2007; Blei *et al*1993)). In fact this technique can determine the free energy of ATP hydrolysis and ADP and AMP levels in human muscle and brain tissues (Jung *et al* 1997). We refer the readers to comprehensive reviews on these methods (Befroy & Shullman 2011).

3.5. The way forward: brain imaging as an aid to diagnosis

MRS also provides information on brain functions, such as alterations in N-acetyl aspartate (NAA) signaling and lactate accumulation in the brain (Detre *et al* 1991). Decreases in NAA are interpreted to indicate neuronal dysfunctions as observed in neurodegenerative and metabolic brain disease (Urenjak *et al* 1993). MRS may detect metabolic abnormalities in brain areas that are normal on MR images (Bianchi *et al* 2003). The use of proton MRS has revealed abnormally high levels of cerebral lactate in patients with ME/CFS (Murrough *et al* 2010). Brooks *et al* (2000) examined a cohort of ME/CFS using magnetic resonance imaging (MRI) and MRS. The latter showed significant reductions in NAA measurements in the right hippocampus of ME/CFS patients. Chaudhuri *et al* (Chaudhuri *et al* 2003; Puri *et al* 2002) using the same technique demonstrated abnormalities in choline signaling in the basal ganglia of ME/CFS patients.

Voxel based morphometry (VBM), a fully automated technique used to assess the density of brain tissues at a voxel level, has consistently revealed abnormalities consistent with grey matter volume reduction in patients with ME/CFS (Barnden *et al* 2011). VBM is an observer independent method and hence is not subject to the vaugries of manual analysis and the cognitive biases of a radiologist (Brenneis *et al* 2004; Prinster *et al* 2010; Whitwell 2009). This approach seems robust and we would suggest it as part of a routine workup of ME/CFS patients and would urge physicians to retest patients who revealed no prior MRI abnormalities using this technique.

Finally, Positron Emission Topography is a form of neuroimaging which can reveal the presence of neuroinflammation and glucose hypometabolism which is a characteristic feature of neuro-immune disease (Henkel *et al* 2004; Gerhard *et al* 2006; Cagnin *et al* 2001). Neuroinflammation is an active process driven by activated microglia (Streit *et al* 2004). Activation of microglia may be the mechanism by which systemic bacterial endotoxins influence the course of diseases like multiple sclerosis, Parkinson's disease and depression (Hannestad *et al* 2012). FDG-PET imaging may reveal metabolic defects and regional cerebral hypometabolism in the brain (Mosconi 2005; Bakshi *et al* 1998). Brain white matter loss and glucose hypometabolism can often precede clinical symptoms in neurological disease (Ciarmiello *et al* 2006). The use of FDG PET in ME/CFS has revealed glucose hypometabolism in various areas of the brain (Siessmeier *et al* 2003). Studies examining the presence of activated microglia in the brain and spinal cord appear sorely needed, not least eradicate arbitrary and distracting debates as to whether ME is a scientific description of the disease.

4. Biomarkers as external validating criteria or diagnostic criteria

Future research should employ the abovementioned immuno-inflammatory, bioenergetic and brain imaging markers as external validating criteria to confirm the case definitions of ME (Carruthers *et al* 2011; Maes *et al* 2012a) and CFS (Maes *et al* 2012a). This will further allow to establish ME and CFS as neuro-immune disorders and to confirm the case definitions ME and CFS. Apart from developing new and better case definitions which are externally validated by biomarkers, another holy grail of ME/CFS research should be to define biomarkers of sufficient diagnostic performance which define the underlying pathophysiology and guide research and treatment. Those biomarkers should have good sensitivity, specificity and predictive values for positive and negative test results. However, until today, the diagnostic performance of most biomarkers is not sufficient to be used as diagnostic criteria. For example, the diagnostic performance of an adequate external validating biomarker, neopterin, is insufficient to allow neopterin to be used as a diagnostic criterion. Needless to say, that the different ME/CFS case definitions used in biomarker research have obfuscated results on the diagnostic performance of neuro-immune biomarkers. Nevertheless, pathologically increased levels of TNFα, elastase and neopterin, lowered ATP and brain aberrations as measured by brain imaging techniques in a patient with ME/CFS confirm the clinical diagnosis and reveal the neuro-immune pathophysiology of the illness the patient suffers from and should be used as a guide towards treatment.

In addition, not one of the abovementioned biomarkers is specific for ME and CFS because similar immuno-inflammatory, bioenergetic and brain disorders may be observed in many other illnesses including neuro-inflammatory/neurodegenerative disorders, autoimmune disorders, mitochondrial disorders and clinical depression (Morris & Maes 2012a;b). What is specific to ME and CFS is the combination of clustering symptoms, e.g. fatigue, PEM, neurocognitive and autonomic symptoms, the staging characteristics of ME and CFS (relapsing-remitting or chronic course) and their neuro-immune pathophysiology (Morris & Maes 2012a). Therefore, future research should develop new case definitions based on newly generated results of cluster analyses performed on large groups of ME/CFS/CF patients analyzing clinical, neuro-immune and staging characteristics. These methods will assemble groups of patients with clinical and neuro-immune similarities. The most adequate strategy would be to define new case definitions for ME and CFS that include biomarkers and course characteristics instead of definitions that rely solely on ME or CFS symptoms. This strategy using recognized biomarkers would also eliminate people with chronic fatigue resulting from other non-neuro-immune etiologies.

5. Conclusions

We have endeavored to convey the historical development of different case definitions purporting to select patients with ME/CFS. Table 2 gives an overview of the different case definitions for ME and CFS. The original case definition of the illness suffered by people in Incline Village was virtually identical to the operationalized descriptors published by Melvin Ramsey. The creation of criteria which purported to select patients with the same illness but in fact selected patients with idiopathic chronic fatigue have grossly impeded research into the causes of ME and CFS and led to the production of studies with conflicting results. In general, studies containing people with idiopathic chronic fatigue have been conducted by researchers adhering to a viewpoint that ME is somehow of psychological origin despite the plethora of studies demonstrating neuro-immune abnormalities. The effects of cognitive biases in criteria construction, patient selection and the conduct of trials was discussed. The ICC and Maes criteria were an attempt to overcome the cohort heterogeneity created by the adoption of the Fukuda criteria, which allows a diagnosis of CFS if a patient presents with unexplained fatigue and four minor non specific symptoms. The authors of the ICC criteria reintroduced the name of ME. Both Carruthers *et al* (Carruthers *et al* 2011) and Maes *et al* (Morris & Maes 2012b) suggested a strategy whereby patients with ME could be separated from those with chronically fatiguing syndromes which are now subsumed under the CFS or CF labels. We have discussed that biomarkers, e.g. neuro-immune and bioenergetic tests and brain imaging techniques should be used either as external validating criteria for existing case-definitions or as new diagnostic criteria. We suggest the use of the Maes criteria confirmed by objective measurements of immuno-inflammatory pathways, bioenergetic measurements and brain imaging techniques. Future research should define more refined case definitions for ME and CFS including specific symptoms profiles, biomarkers as well as staging characteristics. This task could be achieved using pattern recognition methods performed on large study samples with well-scaled symptoms, staging characteristics and biomarkers.

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Tab. 2. Overview of the different case definitions for ME and CFS.

	RAMSAY	MAES	ICC	CCC
Minimum duration of illness	NA	see Fukuda (6 months)	NA	6 Months
Onset type	Infectious or gradual	NA	Infectious or gradual	Distinct or gradual
Outbreaks and/ or sporadic cases	Outbreak & sporadic	NA	NA	NA
Lab tests used	Standard laboratory tests are usually negative	Neuro-immune biomarkers are used to externally validate the clinical diagnosis	None listed	Minimum battery of standard laboratory screening tests looking for known cause of fatigue
Exclusions	Psychologically induced phenomena and fatigue. Post-viral Epstein-Barr mononucleosis, influenza and other common fevers.	See Fukuda, but neuro-immune or autoimmune disorders should not be used as exclusionary criteria	Unless clinically indicated no additional tests are required to exclude other diagnosis. Primary psychiatric disorders, somatoform disorder and substance abuse are excluded.	Active disease processes that explain most of the major symptoms
Depression and anxiety	Excluded	Excluded in research but in clinical practice depression or anxiety should not be used as exclusion criteria	Not excluded, reactive depression is.	Not excluded
PEM	See Table 1	See Table 1	See Table 1	See Table 1
Fatigue (Subjectively perceived)	Extreme muscle fatigability (not fatigue), of excessively prolonged duration following minimal exercise, which is worsened by repeat exercise.	See Fukuda and based on a clinical interview	Fatigue is included under the term PENE (AKA PEM): A pathological (pathological is not explained) inability to produce sufficient energy on demand	Persistent, or recurrent fatigue that substantially reduces activity level.
Minor Symptoms (All are subjectively perceived)	Autonomic, cardiac, neurological, immune, neuroendocrine	Based on a clinical interview	1 symptom from each of the 3 symptom categories of pain, sleep disturbance and cognitive symptoms. 3 symptoms from a mix of immune and neuroendocrine/autonomic symptoms. 1 symptoms from autonomic symptoms. (Minimum of 7 symptoms)	Must have pain, sleep disturbance, 2 or more cognitive symptoms, and one symptom from 2 of these categories (autonomic, neuroendocrine and immune symptoms). (Minimum of 6 symptoms)
Pain	Headaches. Neck pain. Intermittent or chronic disabling pain.	Based on a clinical interview	Headaches. Non inflammatory muscle pain or joint pain. Abdomen or chest pain.	New Headaches. Myalgia. Pain in muscles and/ or joints.
Sleep disturbance symptoms	Reversal of sleep rhythm. Insomnia. Vivid dreams.	Based on a clinical interview	Sleep disturbance. Unrefreshing sleep.	Unrefreshed sleep. Rhythm disturbances.
Cognitive/ Neurological symptoms	Symptoms related to cognitive impairment. Muscle weakness. Fasciculations. Sensory overload. Emotional overload. Attacks of giddiness. Clumsiness.	Based on a clinical interview	Symptoms related to cognitive impairment. Perceptual and sensory disturbances. Ataxia. Muscle weakness. Fasciculations. Sensory overload.	Symptoms related to cognitive impairment. Perceptual and sensory disturbances. Ataxia. Muscle weakness. Fasciculations. Sensory overload. Emotional overload.
Autonomic symptoms	Visual disturbances. Vertigo. Syncope. Respiratory symptoms. Gastro-intestinal upset with nausea and vomiting. Poor temperature regulation. Low grade fever. Episodes of severe sweating. Paresthesia. Frequency of micturition or retention.	Based on a clinical interview	Symptoms related to blood pressure, gastric and urinary systems, cardiac involvement	Symptoms related to blood pressure, gastric and urinary systems, cardiac involvement
Neuroendocrine symptoms	Hypoglycemia. Hypothalamic/ pituitary/ adrenal response to stress is deficient.	Based on clinical interview	Symptoms related to temperature. Genitourinary symptoms.	Symptoms related to temperature and weight. Stress induced exacerbation
Immune symptoms	lymphadenopathy. Sore throat. Malaise. Flu like symptoms.	Based on a clinical interview	Symptoms such as painful lymph nodes, sore throat, flu like symptoms, sensitivities to food, medicine and/ or chemicals	Painful lymph nodes. Sore throat.Flu like symptoms. Sensitivities to food, medicine and/or chemicals.

Tab. 2 - *cont*. Overview of the different case definitions for ME and CFS.

	HOLMES	FUKUDA	REEVES 2005	OXFORD
Minimum duration of illness	6 Months	6 Months	NA	6 Months
Onset type	Distinct	New or definite	NA	Distinct
Outbreaks and/ or sporadic cases	Outbreak & sporadic	NA	NA	NA
Lab tests used	Minimum battery of standard laboratory screening tests looking for known cause of fatigue	Minimum battery of standard laboratory screening tests looking for known cause of fatigue	Routine analysis of blood and urine	None
Exclusions	Clinical conditions that would produce similar symptoms	Unless clinically indicated no additional tests are required to exlude other diagnosis. Findings, lab or imaging test suggesting the presence of a condition that MAY explain chronic fatigue must be RESOLVED (meaning is not clear) before further classification.	A list of permanent medical and psychiatric exclusions is given, as well as possible exclusions,	Medical conditions that cause chronic fatigue. Range of mental health disorders. Organic brain disease
Depression and anxiety	Not excluded	Not excluded, only major depressive disorder WITH psychotic OR melancholic feature is excluded	Not excluded, only major depressive disorder WITH psychotic OR melancholic feature is excluded for 5 years before onset of illness	Not excluded
PEM	See Table 1	See Table 1	See Table 1	NA
Fatigue (Subjectively perceived)	Debilitating fatigue or fatiguability	Persistent or relapsing chronic fatigue that is not the result of ongoing exertion, not substantially alleviated by rest, that substantially reduces activity level.	Fatigue is incorporated into the 3 self-report scales	Fatigue of psychiatric or idiopathic origin.
Minor Symptoms (All are subjectively perceived)	6 or more of the 11 symptom criteria and 2 or more of the 3 physical criteria; or 8 or more of the 11 symptoms listed. (Minimum of 6 to 8 symptoms)	4 or more of 8 symptoms listed.	NA	May be present.
Pain	New headaches. Muscle discomfort or myalgia. Migratory arthralgia without joint swelling or redness.	New headaches. Muscle pain. Multi joint pain without swelling or redness.	NA	NA
Sleep disturbance symptoms	Sleep disturbance	Unrefreshing sleep	NA	NA
Cognitive/ Neurological symptoms	Neuropsycholgocial complaints. Muscle weakness.	Symptoms related to cognitive impairment.	NA	NA
Autonomic symptoms	Fever (temp 37.5° C to 38.6) or chills	NA	NA	NA
Neuroendocrine symptoms	NA	NA	NA	NA
Immune symptoms	Painful lymph nodes, sore throat	Painful lymph nodes, sore throat	NA	NA

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