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EXPERT OPINION

Diagnosis of myalgic encephalomyelitis: where are we now?

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Introduction: The World Health Organization has classified myalgic encephalomyelitis (ME) as a neurological disease since 1969 considering chronic fatigue syndrome (CFS) as a synonym used interchangeably for ME since 1969. ME and CFS are considered to be neuro-immune disorders, characterized by specific symptom profiles and a neuro-immune pathophysiology. However, there is controversy as to which criteria should be used to classify patients with "chronic fatigue syndrome."
Areas covered: The Centers for Disease Control and Prevention (CDC) criteria consider chronic fatigue (CF) to be distinctive for CFS, whereas the International Consensus Criteria (ICC) stresses the presence of post-exertion malaise (PEM) as the hallmark feature of ME. These case definitions have not been subjected to rigorous external validation methods, for example, pattern recognition analyses, instead being based on clinical insights and consensus.
Expert opinion: Pattern recognition methods showed the existence of three qualitatively different categories: (a) CF, where CF evident, but not satisfying full CDC syndrome criteria. (b) CFS, satisfying CDC criteria but without PEM. (c) ME, where PEM is evident in CFS. Future research on this "chronic fatigue spectrum" should, therefore, use the abovementioned validated categories and novel tailored algorithms to classify patients into ME, CFS, or CF.

Keywords: case definition, chronic fatigue, chronic fatigue syndrome, diagnosis, immune, inflammation, myalgic encepahlomyelitis

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1. Introduction

The World Health Organization (WHO) classifies myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) as a nervous system disease. Some authors [1,2] consider ME/CFS to be a neuro-immune disorder characterized by both a specific symptom profile and a neuro-immune pathophysiology [1,2]. The symptoms comprise fatigue, fatigability, hyperalgesia, sleep disorders, as well as inflammatory, neurological, neurocognitive, and autonomic and gastrointestinal symptoms. Fatigue, muscle weakness, and hyperalgesia are often exacerbated by minor physical or mental activities. ME/CFS is accompanied by many neuro-immune abnormalities, including immuno-inflammatory processes, oxidative and nitrosative stress (O&NS), damage to lipids, proteins, and DNA by O&NS, decreased natural killer cell activity, autoimmune responses directed against neuronal and other substances, for example, neurotransmitters and anchorage molecules, and mitochondrial defects and lowered ATP production, and neurological abnormalities, for example, brain metabolic dysfunction and reduced blood flow [1-6]. It is hypothesized that a complex interplay between these pathways may underpin the neuro-immune pathophysiology of ME/CFS [1,2]. Science Watch (Thomson Reuters) regards ME/CFS and the O&NS processes in that illness, as a new emerging research front in the neurosciences and behavioral sciences [7].

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Table 1. CDC CFS diagnostic criteria [8].

Persistent or relapsing CF for more than 6 months
Not due to other medical conditions
Interferes with daily activities
Four or more of the following secondary symptoms
Impairment in short-term memory or concentration
Sore throat
Tender cervical or axillary lymph nodes
Muscle pain
Multi-joint pain without joint swelling or redness
Headaches of a new type, pattern, or severity
Unrefreshing sleep
PEM lasting more than 24 h

Table 2. The ICC for myalgic encephalomyelitis [10].

Compulsory criterion
Post-exertion neuro-immune exhaustion, a pathological inability to produce sufficient energy on demand characterized by neuro-immune symptoms, such as physical–neurocognitive symptoms, flu-like symptoms, pain, and so on, and usually taking 24 h or longer
Neurological impairments
At least one symptom from the following symptom categories:
Difficulty processing information/short-term memory loss
Pain, including headaches/muscle, joint, and abdominal chest
Sleep disturbance, including disturbed sleep patterns/unrefreshing sleep
Neurosensory, perceptual, and motor disturbances
Immune, gastro-intestinal, and genitourinary impairments
At least one symptom from the following symptom categories:
Flu-like symptoms, including sore throat/tender lymph nodes
Susceptibility to viral infections with prolonged recovery periods
Gastro-intestinal tract, including irritable bowel syndrome
Genitourinary, including urinary urgency/nocturia
Sensitivities to food, medications, odors, or chemicals
Energy production impairments
At least one symptom of the following symptom categories:
Cardiovascular, including autonomic symptoms
Respiratory, including air hunger/fatigue of chest wall muscles
Loss of thermostatic stability, including feverishness and cold extremities
Intolerance of extremes of temperature

Since the 1930s, attempts have been made to use various symptom patterns in the chronic fatigue spectrum for diagnostic classification purposes. Various labels were given to ME/CFS, for example, epidemic neuromyasthenia and atypical poliomyelitis. In 1969, the WHO classified ME as a neurological disease with a chronic or remitting–relapsing course and characterized by neurocognitive and autonomic symptoms and post-exertion malaise (PEM) [8].

In the 1980s, the label CFS was introduced. In contrast to the previous case definitions which focused on ME/CFS as a neurological disorder, these new case definitions focused on chronic fatigue (CF). The most commonly used case definition for CFS was published in 1994 by the Centers for Disease Control and Prevention (CDC), known as CDC criteria [9]. **Table 1** shows the case definition of CFS according to CDC criteria. Nevertheless, multivariate statistical analyses failed to validate CFS as a homogeneous diagnostic group as different subcategories were detected [10].

In 2011, an Expert Group published the International Consensus criteria (ICC) for ME in which PEM is a compulsory criterion [11]. **Table 2** shows the ICC criteria for ME. The consensus panel proposed to abandon the CF criterion and the label CFS. They stressed that the term ME is more appropriate as it refers to the underlying immuno-inflammatory and multi-systemic neuropathology. CFS and ME thus pinpoint different, albeit overlapping, diagnostic categories stressing CF versus PEM, respectively, as key characteristics [10]. Most research studies have employed CDC criteria for the CFS case definition, although in recent years there was a trend to label patients with CFS as ME/CFS [10]. The actual status is that ME, ME/CFS, CFS, and CF are used interchangeably. Some authors employ CF criteria even when subclinical symptoms are present, whereas others adopt much more strict (ME) criteria. In addition, some authors make the diagnosis of CFS only when invalidating CF or slightly increased scores on self-questionnaires for fatigue are present. Needless to say, those differences in case definitions have both obfuscated research and evidence-based practice.

The abovementioned case definitions were largely based on clinical viewpoints [9] or consensus between clinicians and basic scientists [11] rather than the results of adequate statistical analyses, such as pattern recognition methods [10,12,13]. The latter are statistical methods, including (a) supervised learning techniques, which are used to classify objects into categories, validate categories, which are known in advance, make new classification rules, and externally validate the categories; and (b) unsupervised learning techniques which are used to detect and delineate new categories in a dataset [10,12,13]. Therefore, none of these case definitions (CDC or ICC) has passed robust external validation, a serious limitation that hinders advances in classification and the pursuit of biomarkers. In our view, supervised learning techniques [12,13] should be employed to validate or reject any "a priori" knowledge of category membership, such as a clinical diagnosis based on a consensus. Unsupervised learning techniques, for example, cluster analysis, should be used to detect new classes in large clinical datasets [12,13]. In addition, biomarkers should be used as external validating criteria to validate the clinically delineated symptom clusters [14]. Thus, ongoing arguments about which definition to use or which illness CFS or ME is the real illness miss the point that none of the definitions meet empirically based criteria for validation.

A first pattern recognition study in ME/CFS was published in 2012 [10]. Using supervised learned techniques, it was concluded that CFS (according to CDC criteria), divided into those with PEM (labeled ME) and without PEM (labeled CFS) and CF (CF not fulfilling CDC criteria, CF) were each qualitatively distinct categories and thus should therefore be regarded as different case definitions. ME patients are characterized by PEM, a profound exacerbation of global symptomatology following trivial increases in mental or physical

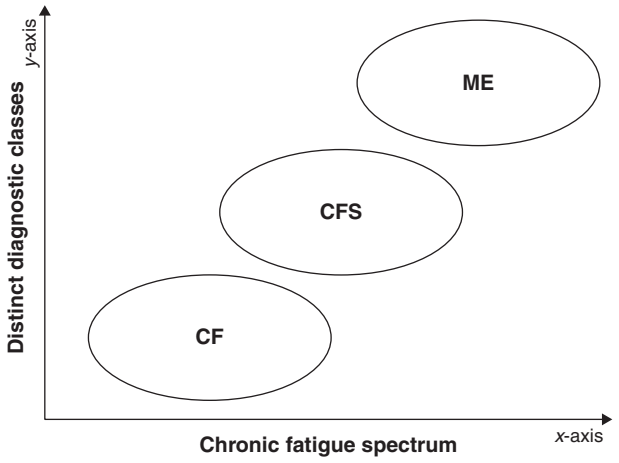

Figure 1. Three distinct diagnostic groups, that is, ME, CFS, and CF ranging along a continuum of illness severity (*x*-axis), which are well separated on the *y*-axis using discriminatory symptoms, for example, neurocognitive and inflammatory symptoms and PEM [10].

activity above individual norms that is often delayed by 24 or even 48 h. They additionally show higher ratings on overall severity of illness, neurocognitive symptoms, and feelings of inflammation–infection and a flu-like malaise. ME patients additionally displayed significantly higher levels of several immuno-inflammatory variables (including levels of pro-inflammatory cytokines and T cell activation markers), used as external validating criteria, than those with CFS and CF. It should be underscored, however, that in addition also CFS, but not CF, patients showed aberrations in immuno-inflammatory pathways. The conclusions of these studies [10] are:

1) In accordance with previous studies, CDC CFS case definition appeared to define a heterogeneous group of patients [15].
2) PEM is a highly distinctive symptom that parcels off patients with ME.
3) Around 50% of patients with CFS (defined by CDC criteria) should be classified as suffering from ME, with PEM, neurocognitive, and flu-like symptoms as distinctive features.
4) ME and CFS are two qualitatively distinct categories that should be differentiated from each other based on PEM and other symptoms.
5) Both ME and CFS are accompanied by activation of immuno-inflammatory pathways, being significantly more pronounced in ME than in CFS, which distinguishes both groups from each other as well as from CF.

2. Conclusions

The WHO regards ME/CFS as a neurological disease. Both ME and CFS are accompanied by neuro-immune aberrations. Different classification systems were proposed based on clinical expertise or consensus among clinicians and scientists. The most relevant being CDC and the ICC criteria, which delineate the diagnosis of CFS and ME, respectively, although the patient groups defined by these criteria are not mutually exclusive categories. The major flaw of both case definitions is that they have not been validated by pattern recognition methods. Diagnosis and case definitions should be empirically based on statistical analyses of symptom prevalence data and biomarkers rather than consensus declarations [10]. A recent multivariate statistical analysis showed the existence of qualitatively distinct and mutually exclusive classes. These analyses show that CDC criteria did not take into account that PEM is a significant discriminatory symptom that divides patients with ME/CFS into those with PEM (ME patients) and those without PEM (CFS patients). The ICC, however, define only one diagnostic group, characterized by PEM but without CF, while statistical analyses show the existence of diagnostic groups characterized by CFS with (ME) and without PEM (CFS). These resulting subgroups would hold the promise of more productive study of biological variables in ME and CFS [10].

3. Expert opinion

Scientific research on the "chronic fatigue spectrum" has used different case definitions, some very liberal and others more strict criteria, including ME/CFS, CFS, post-viral fatigue, subclinical "CF," and even CF based on self-report questionnaires. Therefore, there is a compelling need to develop and use an evidence-based diagnostic classification method and accurate diagnostic criteria to reliably classify sufferers with PEM, CF, neurological and autonomic symptoms, and so on. Pattern recognition analyses based on symptomatology have revealed different qualitatively distinct and mutually exclusive categories of patients with "CF" based on clinical symptoms. The algorithms derived from those statistical analyses show that CDC criteria may be used to make a distinction between CFS and CF and that patients with CFS should be subdivided into those with PEM (ME patients) and without PEM (CFS patients). This method yields three distinct classes, that is, CF, CFS, and ME, which lie in a continuum of severity of illness. However, when severity increases, that is, from CF to CFS to ME, specific symptoms arise, for example, neurocognitive symptoms, a flu-like malaise and PEM, which shape distinct symptom profiles, that is, CFS and ME. External validation with immuno-inflammatory biomarkers suggest that both ME and CFS are immune-inflammatory in origin and that ME patients present with more immuno-inflammatory aberrations than those with CFS.

Figure 1 shows that those three different diagnostic groups range along a continuum of illness severity (*x*-axis) but are well separated on the *y*-axis, reflecting the most significant discriminatory symptoms (including PEM, neurocognitive, and inflammatory symptoms). This shows quantitative

(dimensional) differences (*x*-axis) and qualitative (categorical) differences (*y*-axis) between ME, CFS, and CF.

Future biological research on this "chronic fatigue spectrum" should consider CDC [9] and ICC [12] criteria using the abovementioned algorithm to sub-classify patients into mutually exclusive categories, that is, ME, CFS, or CF. By inference, labels such as ME/CFS should be abandoned and replaced by the more specific and statistically validated case definitions of ME or CFS.

Future research should further refine the diagnostic criteria and discriminatory symptoms and biomarkers to delineate ME, CFS, and CF, including via the utilization of broader illness characteristics or other combinations of discriminatory characteristics. Toward this end, a comprehensive list of symptoms, objective measurements (including neurocognitive testing, repeated cardiopulmonary tests), staging characteristics (e.g., duration of illness, illness onset, number of relapses, precipitating factors), and biomarkers (e.g., bioenergetic status and gene expression after exercise [10,16]) should be applied and analyzed with pattern recognition methods [10,12-14]. This would better refine classification and subsequent treatment.

Declaration of interest

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