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Perspective

Myalgic Encephalomyelitis and Chronic Fatigue Syndrome: Current Insights Force up to a Paradigm Shift

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Abstract

Myalgic Encephalomyelitis (ME) and chronic fatigue syndrome (CFS) have been the subjects of controversy: from diagnosis and cause to therapies.

The disagreement with regard to the diagnosis relates to various case criteria (ME, CFS, ME/CFS, chronic fatigue) and the assessment of symptoms. While the case criteria for ME and CFS define two distinct, partially overlapping clinical entities, many researchers conceive ME and CFS to be 'similar disorders'. Symptoms are almost always assessed by subjective measures, sensitive to bias and other effects and incomparable between patients and over time. For that reason objective tests should be employed to assess the severity of the symptoms.

The controversy relating to the cause and treatment of ME and CFS originates from two contradictory paradigms: the (bio) psychosocial model(s) for 'incapacitating fatigue' and the biomedical explanatory model(s) for ME/CFS. The (bio) psychosocial models for 'CFS', biased towards psychological explanations, are invalid and lack to explain the organic abnormalities in 'ME/CFS'. CBT and GET have shown to have no objective effect at all. Moreover CBT and GET are potentially harmful. Biomedical researchers have observed various immunological, neurological, mitochondrial and other abnormalities, both in rest as in response to exertion. A clear-cut etiologic model is still lacking. Some studies suggest that rituximab and rintalomid are effective in a (large) CFS patient subgroup.

Looking at the evidence, it is time to leave the (bio)psychosocial framework(s) behind us and to investigate the abnormalities observed in 'ME/CFS' in ME patients and (symptomatic) CFS patient subgroups, in order to develop effective therapies.

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CONTEXT

Myalgic Encephalomyelitis (ME) [1-3], and chronic fatigue syndrome (CFS) [4], have been subjects of controversy for decades [5-7]. The dispute relates to all aspects of the diseases: from diagnosis and cause (the origin of symptoms) to therapies [8].

The disagreement with regard to the diagnosis relates to the mixture of diagnostic categories ME [1-3], CFS [4], and chronic fatigue (CF) [9], and the assessment of characteristic symptoms. Many authors consider ME and CFS to be similar disorders [10], while others pose that ME [1-3], and CFS [4], are distinct, partially overlapping diagnostic entities [11]. Even more, a subgroup of researchers consider CFS [4], to be equivalent to (a severe variant of) CF [9]. Next to mixture of various clinical labels [12], diagnosis is further complicated by the use of subjective measures based on questionnaires to assess symptoms, e.g. 'fatigue'. Some authors have argued that diagnosis [13], and the effects of therapies [14], should rely on objective measures.

The controversy with regard to the cause and treatment of ME and CFS originates from two contradictory paradigms: the (bio) psychosocial model(s) for 'incapacitating fatigue' ('CFS/CF') and the biomedical explanatory model(s) for ME and CFS [15]. The common idea behind (bio) psychosocial model(s) [16-18], is the trichotomy based on a distinction between initiating factors (e.g. infections), predisposing factors (e.g. genetic predisposition) and perpetuating factors (e.g. somatization and avoidance behaviour). The illness-perpetuating factors, almost exclusively psychosocial factors, are considered to be fully independent of the initiating factors, e.g. infections [19]. The (bio)psychosocial explanatory model justifies two interconnected therapies: cognitive behavioral therapy (CBT), targeting 'illness-perpetuating cognitions', and graded exercise therapy (GET), aimed at 'avoidance behaviour' and 'deconditioning', the proposed origin of 'fatigue' and other symptoms, e.g. disrupted sleep [20,21].

The general notion behind medical explanatory models is that, although clear-cut etiological models are still lacking, ME and CFS are like any other organic disease: "illness results from a specific pathological defect in physiological functioning, mediated at organ, tissue, cellular and/or molecular level" [15]. Although the methodological shortcomings, including the use of various diagnostic criteria and the large variation in experimental methods, have hampered progress, various typical 'abnormalities have been found repetitively in the 'ME/CFS' patient group or specific subgroups there of [11,22]. According to a recent study [23], describing the outcomes of a workshop sponsored by the National Institutes of Health (NIH) in the US: "Strong evidence indicates that immunologic and inflammatory pathologic conditions, neurotransmitter signaling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities are potentially important for the definition and treatment of ME/CFS.". Although some pharmaceuticals, e.g. rituximab [24], and rintatolimod [25], seem to be promising, curative therapies for ME and CFS are lacking. Symptomatic therapies can bring relief for patients [26,27].

DIAGNOSIS

ME [1-3], and CFS [4], unjustly conceived as synonyms, are two distinct, partially overlapping clinical entities [11]. ME [1-3], qualified as 'atypical poliomyelitis' in the scientific literature in the first decades, is a neuromuscular disease. Long-lasting muscle weakness (and myalgia) after minor exertion and neurological symptoms, most likely due to cerebral dysfunction, are hallmark features of ME [1-3]. CFS [4], on the other hand is defined as (unexplained) chronic fatigue, accompanied by at least four out of eight 'additional symptoms', e.g. headaches, un refreshing sleep, tender lymph nodes and joint pain. Patients can meet the diagnosis ME [1-3], while not meeting the case criteria for CFS [4], while other patients can fulfill the diagnosis CFS [4] without experiencing any of the distinctive ME [1-3] symptoms [28].

Since the case criteria for ME [1-3] and CFS [4] define two distinct clinical entities, ME [1-3], and CFS [4], cannot be replaced by the 'hybrid diagnosis' Systemic Exertion Intolerance Disease (SEID) [28], as recently proposed by the US Institute of Medicine [10]. Contrary to what is posed by advocates of the (bio) psychosocial explanatory model [29-31], CFS [4], let alone ME [1-3], are not equivalent to or a variant of CF. Whether the recently proposed International Consensus criteria for ME [22] can adequate replace the original criteria for ME [1-3], remains to be investigated.

Another diagnostic problem relates to the way in which symptoms are assessed. In addition to the improper use and mixture of various diagnostic labels, including ME[1-3], CFS[4], CF[16], ME/CFS [27]and systemic exertion intolerance disease (SEID) [10], the assessment of the presence and severity of the symptoms often solely rely on self-report (subjective measures, e.g. 'fatigue scores', based on questionnaires). However many characteristic symptoms of ME [1-3], and CFS [4], e.g. 'fatigue', post-exertional 'malaise', cognitive deficits, and un refreshing sleep, are vague concepts. For that reason and because various ill-defined symptoms are also experienced by patients with other conditions, e.g. Lupus, MS and Major Depressive Disorder [32], it's crucial to assess the symptoms with objective test methods [13]. The negative effects of exertion on physical and cognitive functioning, discriminating ME and CFS from other conditions, for example can be assessed by performance indicators at two cardiopulmonary exercise tests with 24 hours in-between [33] respectively by scores during fatiguing cognitive tests or cognitive test scores after exertion [34].

CAUSE

The common idea behind the various (bio)psychosocial models is that psychosocial factors, e.g. 'illness beliefs', 'physical attribution'/somatization and 'kinesiophobia'/ inactivity, perpetuate the illness, irrespective of the initiating factors. However all (bio) psychosocial model(s) have shown to be incorrect. For example the model of Vercoulen et al. [18], in which 'fatigue' and 'impairment' are the direct or indirect consequence of 'physical attribution', focusing on symptoms, lack of control, and inactivity/reconditioning, has proven to be invalid by other researchers [35-37], and by findings of the research group promoting the model, for example "Physical deconditioning does not seem a perpetuating factor in CFS" [38], and "[C]hanges in physical activity were not related to changes in fatigue" after CBT/GET [39]. The 'boom-and-burst activity' model of Harvey and Wessely [17], is invalid and fully lacks to explain all biological abnormalities observed in ME and CFS repetitively [40]. This also applies to the (bio) psychosocial 'model' outlined by Sharpe and colleagues [16]. All in all, the (bio) psychosocial models for 'CFS', biased towards psychological and social factors only, have shown to be invalid and are lacking to explain the biological abnormalities observed, and. As the IOM [10], concludes: "Seeking and receiving a diagnosis can be a frustrating process for several reasons, including skepticism of health care providers about the serious nature of ME/CFS and the misconception that it is a psychogenic illness or even a figment of the patient's imagination."

Although contradicted by some studies, various abnormalities have been observed repetitively in the CFS [4] patient population or specific CFS patient subgroups, for example inflammation/ (Th2 predominant) immune activation [41-46], immune dysfunction [47-49], infections [50,51], gastro-intestinal abnormalities [52-55], elevated oxidative and nitrosative stress [56-59], mitochondrial dysfunction [60-62], disturbed metabolic pathways (hypometabolism) [63-66], cardiovascular dysfunction [67-70], neurological abnormalities [71-74], including gray [75-77] and white [75-78] matter reduction and abnormal brain perfusion [79-81], and (prolonged) deviant biological responses to exertion [82-86], and orthostatic stress [87,88]. Distinctive abnormalities (inflammation and immune dysfunction, mitochondrial dysfunction, oxidative and nitrosative stress) have been confirmed by differential gene expression [89-93]. Several authors have proposed (bio)medical explanatory models for 'ME/CFS' [94-99], but a clear-cut etiologic model is still lacking, also due to the fact that most research studies in the last decades relate to CFS [4], CFS, due to its definition, is a heterogeneous disorder [100], and CFS and ME are distinct, partially overlapping, clinical entities. To unravel the etiology and to develop effective therapies for ME and CFS patients it is essential to make a clear distinction between ME [1-3], and CFS [4], and to investigate immunological, mitochondrial, neurological

and other abnormalities in ME and specific (symptomatic) CFS patient subgroups.

THERAPIES

CBT and GET are justified by (bio) psychosocial model(s) for 'unexplained fatigue' [21]. CBT and GET are aimed at the so-called 'illness-perpetuating factors' [16]. CBT is directed at 'cognitive responses' [20], e.g. 'catastrophic' misinterpretation of symptoms [16], somatic attributions [21], and fear of movement [101]. GET targets 'behavioural responses '[20], e.g. "avoidance behaviour toward physical activity" [101] and aims at gradually increasing activity levels [20]. CBT and GET, inextricably linked [21], are declared to be effective [102,103] and safe [104,105], interventions for CFS. Some studies claim that CBT/GET results into clinical improvement in CFS patients subgroups [21], while according to other studies even full recovery from CFS by CBT and GET is possible, with recovery rates ranging from 30% [104], to 69% [106]. However, the moderate or negligible effects of CBT and GET on subjective measures [20,21,106-108] are by far insufficient to achieve 'normal levels' for 'fatigue', disability et cetera [106,109]. A re-analysis [110], of the data of the PACE trial into CBT, GET and specialist medical care (SMC) [20], showed that when the original criteria for recovery [109], were employed, "recovery rates in the GET and CBT groups were low, not significantly higher than in the control group (4%, 7% and 3%, respectively)" and comparable with rates of natural recovery [111,112]. When looking at the effect on objective measures [113], e.g. activity levels [39], cognitive test scores [114], number of meters walked in 6 minutes [20], physical fitness [115], re-employment rates [116], disability benefits [116], medication usage [116], etc. the controversial PACE trail [117-120], affirms that CBT and GET have no real effect at all [121,122]. Moreover the safety claim posed by advocates of the (bio)psychosocial model and CBT and GET therapy [104,105] is contradicted by (large) patients surveys showing negative effects of CBT and GET in large 'ME/CFS' patient subgroups [123,124], a Spanish trial [125], observing a negative effect on physical functioning and bodily pain, and a trial [126,127], which observed that CBT, GET and other interventions have a negative effect on physical functioning in a CFS [4], subgroup (48% of the patients) which is characterized by immune activation.

Although research into pharmaceutical and other medical therapies is scarce, some therapies have shown to be promising for specific subsets of CFS [4], patients, e.g. valganciclovir for patients with elevated IgG antibody titers against Human herpes virus 6 (HHV-6) and Epstein-Barr virus (EBV) [128], and valacyclovir for patients with elevated EBV serum IgM antibodies to viral capsid antigen and/or EBV early antigen [129]. Several studies [25,130,131], suggest Ampligen (rintalolimod) to have positive effects on symptoms and exercise tolerance. Trials into the effect of the monoclonal anti-CD20 antibody rituximab [24,132-135], suggest that a CFS [4] patient subgroup responds to rituximab (500 mg/m2) two infusions two weeks apart (18/28), that a part of that patient subgroup (7/18) relapses after improvement initially, that maintenance rituximab infusions after 3, 6, 10 and 15 months can increase the success rate, and that a CFS patient subgroup (10/28) doesn't respond to rituximab. These findings illustrate the assertion that, due to the heterogeneous nature of CFS [4], one etiologic model and one-size-fits all treatment for CFS will never be found.

CONCLUSION

The controversy about ME [1-3], and CFS [4], incorrectly conceived as synonyms, have been lasting for decades. The (bio) psychosocial model(s), in which 'chronic fatigue' ('CFS') is fully explained by psychosocial factors (cognitions and behavior) are biased and invalid and fail to explain the various typical organic abnormalities in 'ME/CFS'. The therapies based on this paradigm, CBT and GET, have shown to have a no effect or a very modest effect on subjective measures, and no effect on objective measures at all. Moreover research studies and patient surveys suggest that CBT and GET have detrimental effects in substantial 'ME/CFS' patient subgroups [134]. Despite these observations the (bio) psychosocial paradigm dominates the debate.

A paradigm shift is unavoidable. "ME/CFS is a serious, chronic, complex systemic disease that often can profoundly affect the lives of patients" [10]. ME/CFS is "a medical -not a psychiatric or psychological- illness". As Green and others conclude: "Both society and the medical profession have contributed to the disrespect and rejection experienced by patients with ME/CFS." [23]. In order to unravel the etiology and to develop effective treatments for 'ME/CFS' it's time to leave the (bio) psychosocial framework definitely behind us and to acknowledge that, although clear-cut etiologic models are still lacking, ME [1-3], and CFS [4], are like any other organic disease. In order to improve research into causes and therapies, immunological, mitochondrial, neurological and other abnormalities should be investigated in ME [1-3], and (symptomatic) CFS [4], patient subgroups.

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