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Viewpoint

Myalgic Encephalomyelitis, Chronic Fatigue Syndrome, and Systemic Exertion Intolerance Disease: Three Distinct Clinical Entities

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Received: 16 March 2018; Accepted: 11 April 2018; Published: 13 April 2018

Abstract: Many researchers consider chronic fatigue syndrome (CFS) to be a synonym of Myalgic Encephalomyelitis (ME). However, the case criteria of ME and CFS define two distinct clinical entities. Although some patients will meet both case criteria, other patients can meet the diagnosis of ME and not fulfil the case criteria for CFS, while the diagnosis of CFS is largely insufficient to be qualified as a ME patient. ME is a neuromuscular disease with distinctive muscular symptoms, including prolonged muscle weakness after exertion, and neurological signs implicating cerebral dysfunction, including cognitive impairment and sensory symptoms. The only mandatory symptom of CFS is chronic fatigue. Chronic fatigue must be accompanied by at least four out of eight nonspecific symptoms: substantial impairment in short-term memory or concentration, a sore throat, tender lymph nodes, muscle pain, multijoint pain, a new type of headaches, unrefreshing sleep, and postexertional "malaise" lasting more than 24 h. So, regardless whether the name ME is appropriate or not, ME is not synonymous to CFS. That is not a matter of opinion, but a matter of definition. Due to the definitions of ME and CFS, "ME/CFS" does not exist and cannot be replaced by a new clinical entity (SEID: Systemic Exertion Intolerance Disease), as recently suggested.

Keywords: myalgic encephalomyelitis; chronic fatigue syndrome; systemic exertion intolerance disease; diagnosis; nosology; neurology; muscular disease

1. Introduction

Many researchers consider ME [1] and CFS [2] to be "conditions with similar symptoms" [3]. However, considering the case criteria defining the clinical entities, this position is incorrect. While ME [1] is defined as a "polio-like" neuromuscular disease with distinctive features, CFS [2] is a heterogeneous condition characterized by chronic fatigue, accompanied by four out of eight "additional symptoms". SEID [3], suggested to replace ME and CFS in the future, is defined by fatigue, postexertional "malaise", unrefreshing sleep, and at least one of two other symptoms.

1.1. ME

ME has been described in the medical literature under various names, including "atypical poliomyelitis" and "epidemic neuromyasthenia" since 1936 [4], often on account of outbreaks [5–7]. In the late 1950s, the name "Myalgic Encephalomyelitis" was proposed in a Lancet editorial to describe a "syndrome characterized by (1) symptoms and signs of damage to the brain and spinal cord, in a lesser or greater degree; (2) protracted muscle pain with paresis and cramp; (3) emotional disturbances in convalescence; (4) normal cerebrospinal fluid; (5) involvement, in some variants, of the reticuloendothelial system; (6) a protracted course with relapses in severe cases; (7) a relatively benign outcome." [8]. ME has been classified as a neurological disease by the World Health Organization

since 1969 [9]. One of the most recent definitions of ME originates from 1990: "a syndrome commonly initiated by respiratory and/or gastrointestinal infection but an insidious or more dramatic onset following neurological, cardiac or endocrine disability occurs. The pathognomonic features are: a complaint of general or local muscular fatigue following minimal exertion with prolonged recovery time; neurological disturbance, especially of cognitive, autonomic and sensory functions; variable involvement of cardiac and other systems; and a prolonged relapsing course." [3]. Although the different case criteria differ slightly from each other, typical muscular and neurological symptoms are a constant in the definition of ME over time [10,11].

1.2. CFS

In 1988, the clinical entity of CFS was introduced as "a new name for the chronic Epstein–Barr virus syndrome . . . that more accurately describes this symptom complex as a syndrome of unknown cause characterized primarily by chronic fatigue." [12]. The distinctive feature of CFS is (unexplained) chronic fatigue. According to the case criteria for CFS from 1994 [2], most commonly used in CFS research in the last decades, "persistent or relapsing chronic fatigue" (lasting more than six months) must be accompanied by at least four out of eight symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, new headaches, unrefreshing sleep, and postexertional "malaise".

Due to the polythetic nature of its definition [13], the case criteria of CFS [2] define a heterogeneous population of patients [14] with chronic fatigue as the principle symptom; for example, patients with postviral fatigue states triggered by Epstein–Barr virus [15], Ross River virus [16], and Coxiella burnetii [16] infections; patients with CFS induced by noninfectious triggers (trauma, allergy, and surgery) [17]; patients with severe psychosocial stress [18]; and patients with (undiagnosed) Addison disease [19].

The vast majority of research studies of "ME/CFS" [20] in the last two decades used CFS case criteria to select patients. However, the diagnostic criteria for CFS [2] define a heterogeneous group of patients with chronic fatigue as principle complaint. For that reason, it is not very surprising that the outcomes of these studies are often contradictive. Moreover, since the case criteria for ME [1] and CFS [2] define two different sets of patients, the outcomes of these studies do not apply to ME [1].

The current confusion originating from the introduction of the diagnostic entity CFS [2] was forecasted by a prominent ME researcher from the beginning [21]: "Other fatigue states lacking the cardinal clinical and laboratory features of ME may follow influenza, measles, and chickenpox, for example, or accompany herpesvirus infections such as infectious mononucleosis. The introduction of 'chronic fatigue syndrome' to designate ME does nothing to indicate the unique epidemiological, geographical, clinical, and laboratory findings in ME and can only add to the confusion surrounding the diagnosis, therapy, and prognosis of the condition."

1.3. SEID

To resolve the diagnostic confusion, the Institute of Medicine (IOM, now the National Academies of Medicine, NAM) proposed a new clinical entity to replace "ME/CFS": SEID [3]. SEID is defined by chronic fatigue, postexertional "malaise", and unrefreshing sleep; and orthostatic intolerance and/or cognitive impairment. However, the case criteria for ME [1] and CFS [2] define two different conditions. So, a new clinical entity simply cannot replace ME and CFS [22]. That is not a matter of opinion or preference, as suggested [3], but a matter of definition. In addition to the theoretical impossibility of replacing two different definitions by a new definition, the SEID case criteria do not do justice to either ME [1] or CFS [2]. Furthermore, the SEID case criteria are also applicable to subsets of people with other diseases, for example, Multiple Sclerosis (MS) and lupus; and psychological conditions, for example, major depression; while only a subset of people with the diagnosis of CFS meet the diagnosis of SEID [23]. In conclusion, the introduction of SEID does not resolve the impasse, but rather increases the "diagnostic confusion".

1.4. ME, CFS, and SEID: Three Distinct Entities

As can be seen in Table 1, the case criteria for ME [1], CFS [2], and SEID [3] define three different nosological entities with partial overlap (as illustrated in Figure 1).

Table 1. Diagnostic criteria defining ME, CFS, and SEID.

	ME (Ramsay) [1]	**CFS (Fukuda) [2]**	**SEID (IOM/NAM) [3]**
Name and definition	1957–1990	1994 (1988)	2015
Onset	Illness commonly initiated by respiratory and/or gastrointestinal infection, but an insidious or more dramatic onset following neurological, cardiac, or endocrine disability occurs.	Unspecified	Unspecified
Definition (distinctive symptoms)	Muscular symptoms, including prolonged postexertional muscle weakness (mandatory), myalgia, and muscle tenderness (often). Neurological symptoms, including cognitive impairment, day–night reversal, sensory dysfunction, and emotional lability.	Chronic fatigue (mandatory) and at least four of the following eight symptoms: Substantial impairment in short-term memory or concentration, a sore throat, tender lymph nodes, muscle pain, multijoint pain, headaches (of a new type, pattern, or severity), unrefreshing sleep, and postexertional "malaise".	Chronic fatigue (not lifelong, not due to ongoing excessive exertion, and not alleviated by rest), postexertional "malaise", unrefreshing sleep, and cognitive impairment and/or orthostatic intolerance.
Other common symptoms	Cardiovascular impairment, and Autonomic dysfunction		

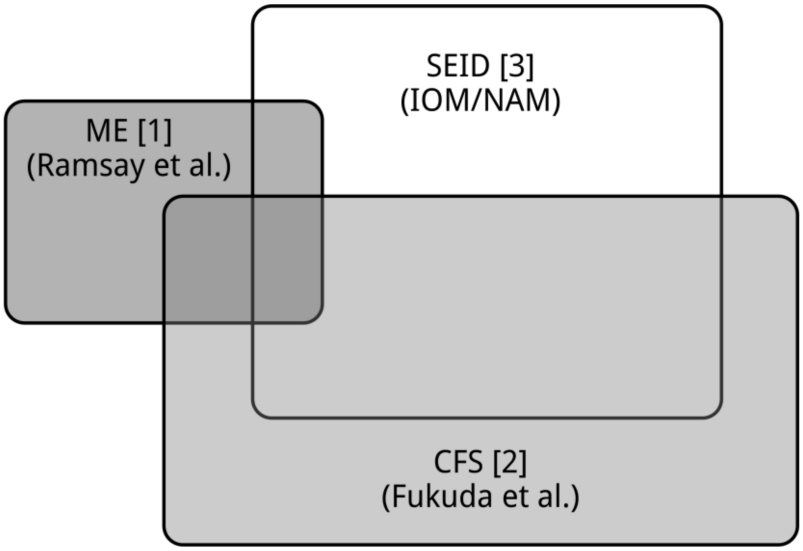

Figure 1. ME [1], CFS [2], and SEID [3]: three distinct clinical entities. Note: the sizes of the rectangles do not reflect absolute numbers, but the prevalence of CFS and SEID are most likely considerably higher than the prevalence of ME [23,24].

1.5. Diagnosis

As explained above, diagnoses should be based on the correct definitions (case criteria). ME, CFS, and SEID are three distinct clinical entities. In addition, the severity of the symptoms should be established by using objective tests, since various symptoms, for example, fatigue, postexertional "malaise", and unrefreshing sleep, are abstract and ambiguous notions. This results in missed diagnoses and misdiagnoses, as illustrated by a study of Jason et al. [23], which observed that a substantial subgroup of patients with other medical diseases, such as MS, lupus, and major depressive disorders,

also qualify as being SEID [3] patients. For that reason, and because ME [1], CFS [2], and SEID [3] are considered to be controversial disorders, characteristic symptoms of ME [1], CFS [2], and SEID [3] should be assessed objectively [25], both in research projects as well as in clinical practice.

Prolonged postexertional muscle weakness [26], for example, a hallmark symptom of ME [1], can be established by assessing muscle power at repeated muscle contraction tests using dynamometers. Postexertional "malaise" can be assessed objectively by comparing the results of two cardiopulmonary exercise tests (CPET) with a 24 h rest in-between [27] and by comparing the cognitive test results before and after a CPET [28]. Orthostatic intolerance, often reported by patients [29,30], can be established objectively by (long-lasting) tilt table tests; and cognitive deficits [31,32], for example, impairments in simple and complex information-processing speed, in tasks requiring working memory over a sustained period of time, and in tasks requiring interference control, can be assessed using the appropriate cognitive tests [33].

2. Conclusions

ME [1,10,34] is a neuromuscular disease with (a) distinctive muscular symptoms, including myalgia, prolonged muscle weakness after minor exertion, and muscle tenderness; (b) neurological symptoms implicating cerebral dysfunction, for example, day–night reversal, cognitive deficits, and autonomic dysfunction; and (c) a prolonged relapsing course. ME is commonly initiated by respiratory and/or gastrointestinal infection.

The only mandatory symptom of CFS [2] is chronic fatigue. Chronic fatigue must be accompanied by at least four out of eight nonspecific symptoms: substantial impairment in short-term memory or concentration, a sore throat, tender lymph nodes, muscle pain, multijoint pain, a new type of headache (in pattern or severity), unrefreshing sleep, and postexertional "malaise" lasting more than 24 h. Irrespective of whether the label ME is appropriate [35] or not [36], ME is not equivalent to CFS. That is not a matter of preference, but a consequence of the definitions (case criteria) [22].

For example, a patient experiencing chronic fatigue, a sore throat, headaches, tender lymph nodes, and unrefreshing sleep qualifies as a CFS [2] patient, but does not exhibit any of the distinctive features of ME [1]; while a patient reporting prolonged muscle weakness after minimal exertion, typical neurological symptoms, and symptoms related to circulatory impairment, distinctive for ME [1], cannot be qualified as a CFS [2] patient.

The case criteria for ME [1] and CFS [2] define two different patient populations, which partially overlap. Due to their different definitions, "ME/CFS" cannot be replaced by a new clinical entity (SEID) [22] as proposed by the Institute of Medicine in 2015 [3]. Moreover, patients with other medical and psychological conditions also meet the SEID criteria, while a CFS [2] patient subgroup does not meet the SEID criteria [23].

The diagnosis of ME [1], CFS [2], and/or SEID [3] in research and clinical practice should be based upon the correct criteria and objective test methods (if feasible). Future research should investigate ME [1] patient and (clinical) CFS [2] patient subgroups separately to unravel the pathogenesis and to develop treatments.

Conflicts of Interest: The author declares no conflict of interest.

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