

The Case Definition of Chronic Fatigue Syndrome

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The 1994 case definition of chronic fatigue syndrome is widely used not only for diagnosis but also for clinical and laboratory-based observations of this clinical entity. The criteria for the 1994 case definition are based primarily on symptoms and not on physical signs or chemical or immunological tests. This situation has resulted in conflicting clinical and laboratory observations that in all likelihood is due to different populations of patients being studied in different centers. Based on some of the recent publications, there appears to be an emerging picture of this disease entity that we propose could be used to subgroup chronic fatigue syndrome into four different subclasses. These subclasses would consist of chronic fatigue with primarily nervous system disorders such as impaired memory or concentration and headache, chronic fatigue with primarily endocrine system disorders such as unrefreshing sleep and postexertional malaise, chronic fatigue with musculoskeletal system disorders such as muscle pain and joint pain, and chronic fatigue with immune system/infectious disorders such as sore throat and tender lymph nodes. It is suggested that if clinical and laboratory-based studies on chronic fatigue syndrome were conducted on more homogeneous subgroups of patients, the data from one center to the other might not be as conflicting and more insights can be shed on the nature of this clinical condition.

KEY WORDS: Chronic fatigue syndrome; chronic fatigue syndrome subgroups.

INTRODUCTION

Chronic fatigue syndrome (CFS) has been defined as a disabling systemic illness characterized by severe fatigue and a combination of symptoms among which are impairment in thought concentration and short-term memory, sleep disturbance, musculoskeletal pain, sore throat, and cervical or axillary lymphadenopathy (1–4). Because severe fatigue can be a manifestation of a number of other illnesses, the diagnosis of CFS as a

distinct clinical entity can be made only after alternative medical and psychiatric causes of fatigue have been excluded. An important issue in CFS was stated in the consensus report from the International Chronic Fatigue Syndrome Study Group (1). It states that the problem in CFS research is to determine “whether the chronic fatigue syndrome or any subset of it is a pathologically discrete entity, as opposed to a debilitating but non-specific condition shared by many different entities.” It goes on to state that “resolution of this issue depends on whether clinical, epidemiological and pathophysiologic features convincingly distinguish the chronic fatigue syndrome from other illnesses.”

The acknowledged standard guidelines for case definition of CFS in the United States and one that also is widely used in other countries is the 1994 case definition (1) which is abstracted in Table I. This definition of CFS was a revision and updating of previous guidelines published in 1988, and (2) involved a group of 25 participants constituting an International Chronic Fatigue Syndrome Study Group, which convened at a meeting called by the Centers for Disease Control and Prevention (CDC). The study group included principals who were involved in CFS case definitions in UK (3) and in Australia (4) and the 1994 case definition has the imprimatur of international consensus and is not a unilateral position promoted by US physicians.

The 1994 case definition was developed by consensus of the study group based on the anecdotal experience of the participants. In this respect, it is different from the process used to derive certain other case definitions or disease classifications such as that for systemic lupus erythematosus (5), which like CFS is a multisystem disease. In the case of systemic lupus erythematosus (SLE), a subcommittee of the American College of Rheumatology (formerly American Rheumatism Association) by consensus arrived at 30 individual variables consisting of physical signs and laboratory tests associated with SLE. This list of 30 variables was put in the form of a questionnaire and sent to 18 medical centers

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Table I. Abstract of the 1994 Case Definition for Chronic Fatigue Syndrome^{a,b}

Criteria	Definition
Major	Chronic or relapsing severe fatigue for ≥ 6 months Exclude other medically diagnosed illnesses that may explain fatigue such as hypothyroidism, malignancy, viral hepatitis, psychotic or major depression disorder, alcohol or substance abuse
Minor	1. Impaired memory or concentration 2. Sore throat 3. Tender cervical or axillary lymph nodes 4. Muscle pain 5. Multijoint pain 6. New headaches 7. Unrefreshing sleep 8. Postexertional malaise

^aAbstracted from K. Fukuda *et al.*, *Ann. Int. Med.* 121: 953–959, 1994 (1).

^bThe major and four or more of the minor criteria are required for case definition.

with recognized competence and interest in SLE and each center was asked to complete the questionnaire for 10 SLE patients and 10 age- and sex-matched rheumatology control patients without SLE. The data from this exploratory set were examined using cluster analysis of the variables and other multivariate techniques and sensitivity and specificity of individual variables as well as clusters were analyzed for clinical and statistical differences using chi-square contingency tables. Combinations of individual and aggregated variables were then examined as potential criteria sets. Tests of potential criteria sets were performed on the exploratory set of patients and controls and validated on other sets of patient data, both SLE and non-SLE rheumatic diseases that had been collected for other studies. The final SLE classification guidelines were narrowed down to 11 criteria based on organ system involvement and 4 or more criteria were required for case definition of SLE.

Examination of the 1994 CFS case definition reveals that with the exception of tender cervical or axillary lymph nodes, the major criterion and seven of the eight minor criteria represent symptoms and not physical signs, and with many of the symptoms, grading or measurement of the mildness or severity of the symptoms is difficult to standardize with currently available health measure instruments. Furthermore, none of the criteria are based on objective chemical or immunological tests. There is therefore a disadvantage in the use of the 1994 CFS case definition when compared to the SLE criteria where several items in the latter are quantifiable in chemical and immunological tests and other criteria are objective physical signs. Lack of quantifiable measurements in the CFS case definition would likely give rise to differences in CFS patient populations from one

center to another or even from one individual physician to the next.

CLINICAL AND LABORATORY OBSERVATIONS IN CFS

Consideration has to be given to the possibility that at this stage in our understanding of CFS, a more precise definition of this condition is not feasible and that the 1994 case definition was the “state of the art.” Studies aimed at finding physiological and immunologic abnormalities have been pursued for many years and continue to be ongoing efforts by many investigators. It is becoming apparent from these studies that abnormalities or dysfunction in certain organ systems might be associated with CFS. These include symptoms that might be attributed to disorders of the nervous system, the endocrine system, the musculoskeletal system, and the immune system.

Impaired memory or concentration, often referred to as neurocognitive problems, is one of the major symptoms of CFS and appears to be coexpressed frequently with depression and anxiety (6). However, many studies show that CFS is not a reflection of a primary psychiatric disorder such as major depression, since in contrast to the latter where there is mild hypercortisolism, CFS patients have a down-regulation of the hypothalamic–pituitary–adrenal (HPA) axis resulting in mild hypocortisolism (7). Other studies have shown the presence of abnormalities in diagnostic brain imaging using magnetic resonance imaging and single-photon emission computed tomography (8, 9). The latter findings have been interpreted to represent subtle changes related to reduced small vessel blood flow or dysfunctional neuronal or glial cells, but hard evidence of such abnormalities is not available.

Studies that have reported abnormal findings related to the endocrine system appear to be connected to central nervous system function and frequently have been called neuroendocrine dysfunction. These abnormalities include hypofunction of the HPA axis and disturbances of the serotonergic and nonadrenergic pathways involving metabolism of 5-hydroxy-indoleacetic acid, arginine, vasopressin, 5-hydroxytryptamine, and prolactin (10–16). Recently orthostatic hypotension demonstrated as fall in blood pressure using tilt table tests have been reported in CFS (17–21).

Muscle and joint pains are two items included in the case definition of CFS and physicians specializing in CFS and fibromyalgia have reported large overlapping between patient populations identified as having either of the two conditions (22–24). Although figures as high as 70% overlap have been reported, these have come

primarily from two medical centers, and it would be of interest to know the extent of overlap in other medical centers, especially if strict criteria for diagnosis of fibromyalgia were applied. In one of the two centers, it was found that only 20% of CFS patients met the American College of Rheumatology criteria for fibromyalgia, although many more of the CFS patients had been told at some point in the course of their illness that they had fibromyalgia (25).

Infectious agents as a cause or trigger for CFS have been reported by many investigators. The infectious agents and related illnesses include Epstein–Barr virus and infectious mononucleosis (26, 27), *Borrelia burgdorferi* and Lyme disease (28), Q fever (29), human herpes virus type 6 (30, 31), and several others (32). If any of these infectious agents should have a relationship to CFS, they are not direct cause and effect, since only a small percentage of patients with such infections go on to develop symptoms fulfilling CFS criteria. It is in this context that the nature of the host response may be important in view of a number of different abnormal immune responses observed in CFS patients.

Increased numbers of CD8+ cytotoxic T cells have been reported by several investigators as well as decreased numbers of natural killer (NK) cells (33–37). Elevation of transforming growth factor beta (TGF- β) has been reported (38), including conflicting reports of increased levels of interleukin-1 α (IL-1 α), IL-2, IL-6, interferon-alpha (IFN- α), and tumor necrosis factor-alpha and -beta (TNF- α and - β) (see ref. 37). In a blinded study, IL-6 produced by mononuclear cells from patients with CFS correlated with the symptoms of CFS (39). This study emphasized the importance of longitudinal studies in CFS and that physical fatigue was a poor marker of CFS. Elevated antinuclear antibodies (ANAs) have been reported consisting of increased incidence of generic ANAs (40, 41) and antibodies to the nuclear matrix protein lamin B1 (42). Other findings include elevated immune complexes (39, 42) and decreased complement C3 and C4 levels (43). However, in a study carried out by CDC investigators on a population of CFS patients in Atlanta (44), certain immunological findings such as immune complex, C3 and C4, and NK cell function were found to be no different between patients and age-, race- and sex-matched controls.

A PROPOSAL TO SUBSET THE 1994 CASE DEFINITION OF CFS

The 1982 lupus criteria (5) were categorized into organ system involvement with the first four criteria (malar rash, discoid rash, photosensitivity, and oral

Table II. Proposal to Subclassify the 1994 Case Definition^a

Major criterion	Fatigue of 6 months duration
Minor criteria	A. Nervous system
	1. Impaired memory or concentration
	2. Headache
	B. Endocrine system
	3. Unrefreshing sleep
	4. Postexertional malaise
	C. Musculoskeletal system
	5. Muscle pain
	6. Joint pain
	D. Immune system/Infection
	7. Sore throat
	8. Tender cervical or axillary lymph nodes

Classify CFS cases as CFS (A, B, C or D or combinations of A,B,C,D)

^aAs with the 1994 CFS Case Definition, CFS is defined as requiring fulfillment of the major criterion and four of the eight minor criteria, after certain illnesses associated with chronic fatigue have been excluded.

ulcers) related to involvement of the skin, but with each criterion standing on its own in terms of contributing independently to the case definition. Following these four criteria, the other seven were also grouped according to organ system involvement, including musculoskeletal, renal, nervous system, hematologic, and immune system disorders. In the brief analysis of the possible etiopathogenesis of CFS described above, the available evidence based on clinical and laboratory observations point to involvement of a number of different organ systems that we suggest could be grouped into disorders of the nervous system, the endocrine system, the musculoskeletal system, and the infectious/immune system. It is interesting to note that the 1994 CFS case definition that preceded many of the clinical and laboratory observations and therefore were not directly influenced by them seem to support the involvement of these four organ systems.

In the interest of promoting accuracy of the CFS case definition so that future clinical and laboratory studies can be carried out on more homogeneous groups of patients from one center to the next, we propose that the 1994 case definition could be subclassified into symptoms generally related to involvement of the four organ systems (Table II). In this proposed classification, CFS patients with neuroendocrine-type symptoms would be subclassified as CFS-A,B and patients with histories of acute viral type illnesses (with sore throat) and muscle and joint pains would be subclassified as CFS-C,D. Some patients might be classified in other ways, such as CFS-A,C or CFS-A,B,D and so on. In view of the fact that the 1994 case definition required only four of the eight minor criteria, it would seem reasonable to expect that some CFS patients would not have all of the eight

minor criteria and could therefore be subgrouped as proposed.

It might be anticipated that subclassification not only would lead to studies of more homogeneous subsets of patients from different centers that would allow for proper comparison of data but also to clarification of whether CFS is an illness with several etiopathogenic factors. If the latter were the case, CFS patients subclassified as CFS-A,B might show different immune disorders from CFS-C,D, perhaps explaining the conflicting observations reported from different centers that might be studying different subgroups and giving support to different disease-initiating events for the disorder described as CFS. Furthermore, subgroups of CFS patients could be analyzed comparatively with related organ systems disorders, such as CFS-A with patients with major depression, CFS-B with patients with untreated hypothyroidism, CFS-C with fibromyalgia, CFS-D with chronic infectious mononucleosis, and so on. In addition, subgroups of CFS patients could be analyzed against patients with allergic disorders (45) and functional somatic syndromes (46).

The subclassification of CFS proposed here is intended to encourage another look at the disorder from the perspective of another multisystem illness, albeit one with more distinctive clinical features such as is seen in SLE. There might be other ways of subclassifying CFS that could be brought to the table including different groupings of the minor criteria. The advantages of identifying more homogeneous subgroups would contribute significantly to future clinical and laboratory studies and hopefully bring better understanding to this disorder so that effective therapy could be designed. We also recommend that all laboratory investigations must be done in a longitudinal manner and correlated with the symptomatology.

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