Critique of the CDC Case Definitions

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1994 Definition and Overlap with Psychiatric Conditions

The 1994 U.S. Centers of Disease Control & Prevention (CDC) case definition for the Chronic Fatigue Syndrome (CFS) is flawed because the committee which designed and authored it (under the auspices of the CDC) was constituted by 3 different groups with opposing viewpoints concerning the nature of the illness.

The first group was made up of clinicians who had become experienced with the illness as a result of its recent outbreaks in different parts of the country in both its epidemic and endemic forms. These physicians had seen hundreds of patients with very similar, coherent illnesses of flu-like and neurological symptoms that seemed to follow no usual diagnostic pattern. Initial research had been undertaken that demonstrated immune system abnormalities and the presence of higher than normal levels of antibodies to viruses, as well as the viruses themselves, in the blood and tissues of patients.

The second group on the committee, mainly from the CDC, wished to lump this illness with many other "fatiguing illnesses"—the main symptom for diagnosis would be the extreme fatigue. Such a diagnostic scheme would allow for CFS and primary depression and even cancer to be identified as CFS.

The third group was made up of psychiatrists and others who believed CFS was a psychiatric illness, likely somatoform disorder, neurasthenia, "atypical depression", or somatization disorder.

Hence the 1994 definition was a "compromise by committee". It can diagnose CFS correctly, but could also diagnose a psychiatric disorder as CFS, because of the loose requirement of having only 4 of 7 symptoms to qualify—once the fatigue requirement is met. An individual can be diagnosed as having CFS by having only the following four symptoms:

1. unrefreshing sleep;
2. headaches of a new type;
3. neuropsychological complaints, including problems with short-term memory and concentration;
4. muscle pain, or multi-joint pain without swelling or redness.

Sleep and memory problems, headaches, and muscle pain, in addition to being a few of the common CFS symptoms, are also symptoms of a variety of other illnesses, including psychiatric illnesses such as depression and anxiety disorder. A strict observance of the Criteria differentiates CFS from Generalized Anxiety Disorder (DSM-IV 300.021); Major Depressive Disorder (DSM IV); and Somatoform Disorders (DSM-IV). (N.B. DSM-IV is the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.)

However, only a physician or psychiatrist thoroughly familiar with the necessary qualifying symptoms of each of the psychiatric disorders and of ME/CFS would be able to make the differential diagnoses. The fact that the four qualifying symptoms, above, for CFS can also represent important qualifying symptoms for psychiatric illness can lead to patients with psychiatric illness being erroneously diagnosed with CFS.

Moreover, the allowance of neurasthenia as a co-morbid illness in CFS diagnosis, as well as the fact that the DSM-IV requirements for neurasthenia provide for an overlap with five of the seven 1994 CFS criteria leads to utter confusion between the two illnesses —depending on whether the conditions' symptoms are interpreted "medically" or "psychiatrically."

Hence a doctor who interprets the patient's symptoms medically arrives at a diagnosis of CFS. But if the doctor interprets the symptoms psychiatrically, the diagnosis is neurasthenia.

It's obvious that many psychiatrists (who are familiar with the neurasthenia diagnosis) might be prone to interpreting CFS symptoms psychiatrically. In fact, the history of CFS has been one of confusion between the actual physical illness and various psychiatric illnesses. Some of this confusion was codified in the 1994 definition.

Need to improve the CDC Definitions

The 2003 Canadian definition is the most accurate definition so far—until one or more definitive diagnostic markers are found for ME/CFS. However, prior to the development of the Canadian definition, interest in improving the 1994 CDC definition was intense (for obvious reasons). Numbers of researchers are still working to improve the 1994 definition.

Because of the confusing and diagnostically porous nature of the 1994 Criteria, a number of the top international researchers most familiar with ME/CFS, decided to return to the earlier 1988 CDC CFS Criteria as a starting point for fashioning a suggested CFS symptom criteria with greater specificity in selecting CFS cases and in differentiating CFS from other fatiguing illness diagnoses.

There is no doubt that the 1988 (Holmes) CDC CFS Definition is more rigorous, selective and accurate in describing and defining the clusters of illness reported by various clinicians around the country than the 1994 CDC definition.

As it was more rigorous and selective, it was less open diagnostic confusion—the misdiagnosis of ME/CFS as another illness, and the diagnosis of other illnesses as ME/CFS. It should also be noted that, in many ways, the 1988 Criteria is a better guide to careful clinical investigation of the illness (except for the requirement that a diagnosis of CFS be excluded in the presence of anxiety disorder and some non-major mental illnesses).

Summary of the findings of a number of research efforts to improve the 1988 CDC Definition

What symptoms are the most discriminating in CFS?

In 1996, Komaroff *et al*. in a paper, "An Examination of the Working Case Definition of Chronic Fatigue Syndrome," published in the *American Journal of Medicine* (v. 100, Jan. 1996) conducted an exhaustive statistical analysis of the frequency of symptoms in CFS patients compared with the frequency of the same symptoms in samples of healthy control subjects, Multiple Sclerosis(MS) patients, and patients with major depression. The object was to determine which symptoms associated with CFS best discriminated CFS from the healthy controls and the patients in the two disease comparison groups.

Those symptoms which best discriminated CFS would be the basis for an improved case definition.

Of the symptom-criteria in the better 1988 definition "...the discriminating ability was clearest for myalgias, post-exertional malaise, headaches, and a group of infectious-type symptoms (i.e., fever/chills, sore throat, swollen neck glands, swollen arm glands). All these symptoms were found much more frequently...[in the CFS cases than] in either of the two comparison groups ($p<0.01$)"

However, patients with MS were just as likely to report the symptom of muscle weakness than those patients with CFS. In contrast, patients with major depression were less likely to report muscle weakness than those in the CFS and MS groups.

Interestingly, 84% of the CFS patients experienced sudden onset, while 0% of patients with major depression had a sudden onset.

Komaroff *et al*. also compared 31 other symptoms characteristic of CFS with their incidence in the control and disease comparison groups. These symptoms were in 5 categories: respiratory, gastrointestinal, neurologic, rheumatological, and miscellaneous.

Four of the 31 symptoms: poor appetite (anorexia), nausea, tingling sensations, and alcohol intolerance were reported significantly less often by patients in the disease comparison groups than by CFS patients.

As already discussed, the 1994 CDC Diagnostic Criteria is deficient in that it reduces, in comparison with the 1988 CDC definition, the number of qualifying physical symptoms—namely it omits fevers or chills, muscle weakness (often indicative of a neurological problem) and sudden onset. By doing so, the characteristic clinical picture of the illness is distorted and undermined.

Based on the Komaroff article, a careful clinician could confirm diagnosis of ME/CFS by the 2003 Canadian Criteria or by using the 1988 CDC definition criteria with the addition of poor appetite, nausea, tingling sensations and alcohol intolerance.

Komaroff *et al* also proposed eliminating the "Physical Criteria" from the 1988 definition, which require confirmation in the

physician's office. As it may be difficult, due to fluctuation of symptoms, to obtain the required temperature during a doctor's visit, the patient can keep a record of his/her own temperature fluctuations. It is probably reasonable to maintain swollen lymph nodes and nonexudative pharyngitis for physician examination.

Are the illnesses described by the 1988 and 1994 CDC definitions the same?

In 1998, at the AACFS Conference, Natelson *et al*. presented a poster entitled "Do the 1988 and 1994 CFS case definitions identify the same illness?"

The results were as follows: "When subjects who met the 1988 case criteria (n=45) were compared to those who met only the 1994 criteria (n=17), subjects in the 1988 group were found to suffer from a more severe form of the illness. Specifically, subjects in the 1988 group demonstrated more severe symptoms as well as a greater reduction in activity. The latter group also more frequently reported infectious-type symptoms..."

The conclusions were: "The 1988 and 1994 CFS case definition criteria appear to identify distinct patient groups. Given that the subjects of the 1988 group more frequently endorsed infectious symptoms and more frequently reported a sudden flu-like illness onset, an infectious etiology for this group is hypothesized."

Finally, in September of 2001, De Becker, McGregor, and De Meirleir published "A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome." The article was published in the *Journal of Internal Medicine*.

The article begins: "The Holmes [1988] and Fukuda [1994] criteria are widely used criteria all over the world...yet a specific European study regarding chronic fatigue syndrome (CFS) symtomatology has not been conducted...This study was performed to answer the need to assess the homogeneity of a large CFS population in relation to the Fukuda and Holmes definition...

"A total of 2073 consecutive patients with major complaints of prolonged fatigue participated in this study...Of the 2073 patients complaining of chronic fatigue (CF), 1578 CFS patients fulfilled the Fukuda criteria (100% of CFS group), and 951 (60.3% of the CFS group) fulfilled the Holmes criteria...The Holmes criteria was more strongly associated than the Fukuda definition with the symptoms that differentiated the CFS patients from the patients that did not comply with the CFS definitions. The inclusion of 10 additional symptoms were found to improve the sensitivity/specificity for the selection of CFS patients.

"Whilst the Fukuda and Holmes definition are very similar, the Fukuda definition is less stringent...and is likely to include a greater and more heterogeneous group of patients with profound fatigue...

"...[This] shows that the patients who were included under the CFS definition using the Fukuda criteria had less severe symptoms and an altered symptom prevalence distribution to those patients classified under the Holmes criteria.

"The different definition groups...were compared using standard discriminant function analysis with the Holmes profile with the addition of attention deficit, paralysis, new sensitivities to food/drugs, difficulties with words, urinary frequency, cold extremities, photophobia, muscle fasiculations, lightheadedness, exertional dyspnea, and gastrointestinal disturbance. The symptoms were chosen as they represented the 10 symptoms with the greatest prevalence differences between the Holmes and Fukuda criteria....

"Thus the addition of 10 extra symptoms to the Holmes criteria results in a small increase in definition sensitivity and a much larger increase in specificity and improves the accuracy of the definitions. [Emphasis added..]

"The study showed that the analysis of individual symptom severity and prevalence revealed that the Holmes criteria patients had increased symptom prevalence and severity of many of the symptoms that determine the difference between CFS patients and CF subjects compared with the Fukuda defined group...Thus, the addition of patients to the CFS definition by the Fukuda criteria has resulted in the selection of less severely affected patients. This has also resulted in the introduction of an increase in patient symptom heterogeneity." [I.e., less of a clearly defined illness entity].

Conclusions to draw

What are patients and physicians too make of all these different diagnostic criteria and important research suggestions for their modification?

First, when acceptable to the physician, diagnose using the 2003 Canadian definition.

Second, in order to confirm the diagnosis, the patient and physician may want to make a careful comparison with the Holmes criteria (disregarding the exclusion of non-major mental illness diagnoses) using the additional symptoms suggested by Komaroff *et al*. and De Meirleir *et al*.

Third, when a patient is applying for public or private sector disability and insurance programs, such diagnosis should also be specifically documented using the 1994 CDC criteria.