

## Resolution in order to make cohorts less heterogeneous

Here Myalgic Encephalomyelitis (ME) is understood as the disease that Melvin Ramsay described and the clinical criteria in the Canadian consensus document 2003.

Research into CFS (Chronic Fatigue Syndrome) and ME (Myalgic Encephalomyelitis) has been blurred through many decades due to heterogeneous patient populations (cohorts). One problem is that researchers, as well as clinicians, have different interpretations of what is CFS.

Some researchers/clinicians would (incorrectly) not set a CDC CFS diagnosis if post-exertional malaise is not present, although the CDC CFS definition does not require post-exertional malaise.

### What is the problem for the CDC CFS cohort?

- The CDC CFS cohort is highly heterogeneous, therefore there is an interest in reducing the level of heterogeneity, and thus making research more efficient. Also, it is problematic to find a treatment that fits all in a heterogeneous group.
- In some cases patients are selected with genuine ME (that is with e.g. post-exertional malaise) for a study, but are reported to have been selected according to the CDC CFS criteria. In that case the patients are not randomly selected and do not represent CDC CFS as a whole, and therefore the results are not applicable to the CDC CFS population as a whole.
- The ME-patients act as a noise (disturbance) on the statistic data.

### What is the problem for the people with ME?

- As long as the CDC CFS definition is used for study of ME, no real progress can be made. In some studies the majority of patients selected have ME, but in others ME patients are in minority. It is impossible to compare results between studies as required for the scientific approach.
- The ME-patients are submerged in the statistic data collected by the CDC CFS criteria.

### What can be done?

The solution is actually very simple and straightforward in order to resolve the problems. The solution is to incorporate ME as an exclusionary condition in the CDC CFS definition. Nothing else has to be done!

## Modified Version of CDC CFS criteria

Below is a modified version of CDC CFS definition ([link](#)). The modification is underlined and marked with yellow. Myalgic Encephalomyelitis is added as an exclusionary condition for CFS. The reason is that the CFS group will be less heterogeneous, if the disease myalgic encephalomyelitis is excluded, and that research and clinical trials on CFS will be more efficient if the cohort is less heterogeneous.

### Guidelines for the Evaluation and Study of CFS

A thorough medical history, physical examination, mental status examination, and laboratory tests (diagram) must be conducted to identify underlying or contributing conditions that require treatment. Diagnosis or classification cannot be made without such an evaluation. Clinically

evaluated, unexplained chronic fatigue cases can be classified as chronic fatigue syndrome if the patient meets both the following criteria:

Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

1. The concurrent occurrence of four or more of the following symptoms: substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain; multi-joint pain without swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours. These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

### **Conditions that Exclude a Diagnosis of CFS**

1. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea and narcolepsy, **myalgic encephalomyelitis** and iatrogenic conditions such as side effects of medication.
2. Some diagnosable illnesses may relapse or may not have completely resolved during treatment. If the persistence of such a condition could explain the presence of chronic fatigue, and if it cannot be clearly established that the original condition has completely resolved with treatment, then such patients should not be classified as having CFS. Examples of illnesses that can present such a picture include some types of malignancies and chronic cases of hepatitis B or C virus infection.
3. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features;
  - o bipolar affective disorders
  - o schizophrenia of any subtype
  - o delusional disorders of any subtype
  - o dementias of any subtype
  - o anorexia nervosa
  - o or bulimia nervosa
4. Alcohol or other substance abuse, occurring within 2 years of the onset of chronic fatigue and any time afterwards.
5. Severe obesity as defined by a body mass index [body mass index = weight in kilograms ÷ (height in meters)<sup>2</sup>] equal to or greater than 45. [Note: body mass index values vary considerably among different age groups and populations. No "normal" or "average" range of values can be suggested in a fashion that is meaningful. The range of 45 or greater was selected because it clearly falls within the range of severe obesity.]

Any unexplained abnormality detected on examination or other testing that strongly suggests an exclusionary condition must be resolved before attempting further classification.