Chronic Fatigue Syndrome: A Working Case Definition

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The chronic Epstein-Barr virus syndrome is a poorly defined symptom complex characterized primarily by chronic or recurrent debilitating fatigue and various combinations of other symptoms, including sore throat, lymph node pain and tenderness, headache, myalgia, and arthralgias. Although the syndrome has received recent attention, and has been diagnosed in many patients, the chronic Epstein-Barr virus syndrome has not been defined consistently. Despite the name of the syndrome, both the diagnostic value of Epstein-Barr virus serologic tests and the proposed causal relationship between Epstein-Barr virus infection and patients who have been diagnosed with the chronic Epstein-Barr virus syndrome remain doubtful. We propose a new name for the chronic Epstein-Barr virus syndrome—the chronic fatigue syndrome—that more accurately describes this symptom complex as a syndrome of unknown cause characterized primarily by chronic fatigue. We also present a working definition for the chronic fatigue syndrome designed to improve the comparability and reproducibility of clinical research and epidemiologic studies, and to provide a rational basis for evaluating patients who have chronic fatigue of undetermined cause.

[**MeSH Terms: axilla; chronic disease; depression; Epstein-Barr virus; fatigue; fever; lymph nodes; memory disorders; neck; pharyngitis.** Other indexing terms: chronic Epstein-Barr virus syndrome; chronic fatigue syndrome; sore throat]

THE CHRONIC EPSTEIN-BARR virus syndrome, also known as chronic mononucleosis or chronic mononucleosis-like syndrome, is a syndrome of unknown cause that has been the subject of interest in both medical and popular literature, particularly since 1985. As it was described (1-4) in four groups of patients, the syndrome consists of a combination of nonspecific symptoms—severe fatigue, weakness, malaise, subjective fever, sore throat, painful lymph nodes, decreased memory, confusion, depression, decreased ability to concentrate on tasks, and various other complaints—with a remarkable absence of objective physical or laboratory abnormalities. The syndrome was linked in these and other reports to Epstein-Barr virus, because many, but not all, of the patients had Epstein-Barr virus antibody profiles that suggested reactivation of latent infection.

Reference laboratories soon began to advertise Epstein-Barr virus serologic tests for use in the diagnosis of the chronic Epstein-Barr virus syndrome (5). Although reliable data are not available, indications are that the syndrome has been diagnosed commonly by physicians, often on the basis of poorly defined diagnostic criteria. Since late 1985, the Division of Viral Diseases, Centers for Disease Control, has responded to several thousand telephone and mail requests for information about the chronic Epstein-Barr virus syndrome, both from physicians and from patients in whom the syndrome has been diagnosed. Judging from the inquiries received, many physicians appear to have based their diagnoses on little more than the presence of detectable serum Epstein-Barr virus antibody titers.

More recent studies (6, 7) have cast doubt on the diagnostic value of positive Epstein-Barr virus serologic results and on the proposed relationship between Epstein-Barr virus infection and patients who have been diagnosed with the chronic Epstein-Barr virus syndrome. Although some statistically significant associations between positive Epstein-Barr virus serologic tests and illnesses diagnosed as the chronic Epstein-Barr virus syndrome were identified in one study using age-, sex-, and race-matched controls (6), the serologic associations between the syndrome and cytomegalovirus, herpes simplex virus types 1 and 2, and measles virus were as strong as or stronger than the association with Epstein-Barr virus. Epstein-Barr virus serologic results in this study were also found to be poorly reproducible, both within and among laboratories, leading to the conclusion that the results of these tests are not directly comparable unless they have been done in parallel.

With the apparent lack of correlation between serum Epstein-Barr virus titers and the presence of chronic fatigue symptoms, it is premature to focus research and diagnostic efforts on Epstein-Barr virus alone. Many public health officials and clinicians are concerned that a di-

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agnosis of the chronic Epstein-Barr virus syndrome may not be appropriate for persons with chronic fatigue who have positive Epstein-Barr virus serologic tests, and that definable occult diseases may actually be the cause of symptoms such as fatigue, weakness, and fever. It is also inappropriate to use a name for the syndrome that implies a specific causal agent. We, therefore, propose a new name—the chronic fatigue syndrome—that describes the most striking clinical characteristic of the chronic Epstein-Barr virus syndrome without implying a causal relationship with Epstein-Barr virus.

Because of the nonspecific nature of the symptoms and the lack of a diagnostic test, researchers have had difficulty devising a case definition for the chronic Epstein-Barr virus syndrome. When definitions have been described, they have differed greatly among the various published studies, making direct comparisons of the study results difficult. We have organized an informal working group of public health epidemiologists, academic researchers, and clinicians, to develop a consensus on the salient clinical characteristics of the chronic Epstein-Barr virus syndrome and to devise a definition for the chronic fatigue syndrome that will be the basis for conducting future epidemiologic and clinical studies. Because the syndrome has no diagnostic test, the definition at present is based on signs and symptoms only. This definition is intentionally restrictive, to maximize the chances that research studies will detect significant associations if such associations truly exist. It identifies persons whose illnesses are most compatible with a possibly unique clinical entity; persons who may have less severe forms of the syndrome or who have less characteristic clinical features may be excluded by the new definition.

The chronic fatigue syndrome is currently an operational concept designed for research purposes that physicians must recognize not necessarily as a single disease but as a syndrome—a complex of potentially related symptoms that tend to occur together—that may have several causes. Periodic reconsideration of conditions such as those listed under major criteria, part 2, should be standard practice in the long-term follow-up of these patients.

Case Definition for The Chronic Fatigue Syndrome

A case of the chronic fatigue syndrome must fulfill major criteria 1 and 2, and the following minor criteria: 6 or more of the 11 symptom criteria and 2 or more of the 3 physical criteria; or 8 or more of the 11 symptom criteria.

MAJOR CRITERIA

1. New onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms, that does not resolve with bedrest, and that is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level for a period of at least 6 months.

2. Other clinical conditions that may produce similar symptoms must be excluded by thorough evaluation, based on history, physical examination, and appropriate laboratory findings. These conditions include malignancy; autoimmune disease; localized infection (such as occult abscess); chronic or subacute bacterial disease (such as endocarditis, Lyme disease, or tuberculosis), fungal disease (such as histoplasmosis, blastomycosis, or coccidioidomycosis), and parasitic disease (such as toxoplasmosis, amebiasis, giardiasis, or helminthic infestation); disease related to human immunodeficiency virus (HIV) infection; chronic psychiatric disease, either newly diagnosed or by history (such as endogenous depression; hysterical personality disorder; anxiety neurosis; schizophrenia; or chronic use of major tranquilizers, lithium, or antidepressive medications); chronic inflammatory disease (such as sarcoidosis, Wegener granulomatosis, or chronic hepatitis); neuromuscular disease (such as multiple sclerosis or myasthenia gravis); endocrine disease (such as hypothyroidism, Addison disease, Cushing syndrome, or diabetes mellitus); drug dependency or abuse (such as alcohol, controlled prescription drugs, or illicit drugs); side effects of a chronic medication or other toxic agent (such as a chemical solvent, pesticide, or heavy metal); or other known or defined chronic pulmonary, cardiac, gastrointestinal, hepatic, renal, or hematologic disease.

Specific laboratory tests or clinical measurements are not required to satisfy the definition of the chronic fatigue syndrome, but the recommended evaluation includes serial weight measurements (weight change of more than 10% in the absence of dieting suggests other diagnoses); serial morning and afternoon temperature measurements; complete blood count and differential; serum electrolytes; glucose; creatinine, blood urea nitrogen; calcium, phosphorus; total bilirubin, alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase; creatine phosphokinase or aldolase; urinalysis; posteroanterior and lateral chest roentgenograms; detailed personal and family psychiatric history; erythrocyte sedimentation rate; antinuclear antibody; thyroid-stimulating hormone level; HIV antibody measurement; and intermediate-strength purified protein derivative (PPD) skin test with controls.

If any of the results from these tests are abnormal, the physician should search for other conditions that may cause such a result. If no such conditions are detected by a reasonable evaluation, this criterion is satisfied.

MINOR CRITERIA

Symptom Criteria

To fulfill a symptom criterion, a symptom must have begun at or after the time of onset of increased fatigability, and must have persisted or recurred over a period of at least 6 months (individual symptoms may or may not have occurred simultaneously). Symptoms include:

1. Mild fever—oral temperature between 37.5° C and 38.6° C, if measured by the patient—or chills. (Note: oral temperatures of greater than 38.6° C are less compatible with chronic fatigue syndrome and should prompt studies for other causes of illness.)

2. Sore throat.

3. Painful lymph nodes in the anterior or posterior cervical or axillary distribution.

4. Unexplained generalized muscle weakness.

5. Muscle discomfort or myalgia.

6. Prolonged (24 hours or greater) generalized fatigue after levels of exercise that would have been easily tolerated in the patient's premorbid state.

7. Generalized headaches (of a type, severity, or pattern that is different from headaches the patient may have had in the premorbid state).

8. Migratory arthralgia without joint swelling or redness.

9. Neuropsychologic complaints (one or more of the following: photophobia, transient visual scotomata, forgetfulness, excessive irritability, confusion, difficulty thinking, inability to concentrate, depression).

10. Sleep disturbance (hypersomnia or insomnia).

11. Description of the main symptom complex as initially developing over a few hours to a few days (this is not a true symptom, but may be considered as equivalent to the above symptoms in meeting the requirements of the case definition).

Physical Criteria

Physical criteria must be documented by a physician on at least two occasions, at least 1 month apart.

1. Low-grade fever—oral temperature between 37.6° C and 38.6° C, or rectal temperature between 37.8° C and 38.8° C. (*See* note under Symptom Criterion 1.)

2. Nonexudative pharyngitis.

3. Palpable or tender anterior or posterior cervical or axillary lymph nodes. (Note: lymph nodes greater than 2 cm in diameter suggest other causes. Further evaluation is warranted.)

ACKNOWLEDGMENTS: The authors thank Mrs. Josephine M. Lister for manuscript preparation.

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