CHRONIC FATIGUE SYNDROME

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Fatigue in General Medical Practice

Everyone experiences fatigue. Furthermore, nearly everyone occasionally experiences a fatigue which is felt to be "unnatural", not clearly explained by the mental, emotional and physical stresses of the previous days. Usually, such fatigue is transient.

Chronic fatigue accounts for 10-15 million office visits per year in the USA. It is generally agreed that primary psychiatric disorders, particularly depression and anxiety, along with overwork, are the cause of most cases of chronic fatigue in a general medical practice. On occasion various "organic" conditions also can produce fatigue -- for example, occult malignancies, anemia, thyroid disorders, etc.

Chronic Fatigue Syndrome

In recent years, there has been growing discussion of another illness that many believe may have an "organic" basis: chronic fatigue syndrome (CFS). This illness is controversial because no causal agent and no diagnostic laboratory test have been identified. In some cases, CFS follows in the wake of a well-defined acute infectious illness, including acute infectious mononucleosis and Lyme disease (despite adequate antibacterial therapy and the resolution of Lyme disease-specific symptoms).

Symptoms. A formal case definition of the illness has been developed by the Centers for Disease Control (Figure 1). The illness is characterized by at least six months of exceptional fatigue, with several associated chronic symptoms. Patients may be of any age, either sex, and from all walks of life: the typical patient is a 35-year old white woman. Typically, the onset is sudden, often following an acute "viral" syndrome. Some patients appear to be completely disabled by the fatigue, cognitive impairment, muscular weakness and pain.

A few of the patients that we have been following have had transient acute neurologic events: primary seizures (7%), acute, profound ataxia (6%), focal weakness (5%), transient blindness (4%), and unilateral paresthesias (not in a dermatomal distribution). The clinical and laboratory findings in these relatively few patients with dramatic neurologic events are very similar to those of the larger group of patients with chronic fatigue, except for the neurologic events themselves.

Past medical history is notable primarily for a high frequency of atopic or allergic illness (in approximately 50%-80%).

Physical examination is notable for posterior cervical adenopathy; and abnormal tests of balance (Romberg and tandem gait).

Laboratory Tests. No single laboratory test has been identified which has both high sensitivity and specificity for CFS; hence, there is as yet no diagnostic test for CFS. However, a growing literature reports a number of laboratory findings that clearly distinguish patients with CFS from healthy control subjects (and, in some cases, from

comparison group patients with various fatiguing psychiatric and organic diseases). In our experience, several findings are seen more often in patients with CFS: low levels of circulating immune complexes, elevated total complement (CH50), elevated IgG, atypical lymphocytosis, elevated alkaline phosphatase, low lactic dehydrogenase, elevated total cholesterol, and low levels of ANA. A variety of other immunologic abnormalities have been reported, especially impaired function of natural killer cells and T lymphocytes, along with increased numbers of lymphocytes bearing antigens indicating that they are in an activated state (particularly activated CD8+ T cells); all these tests must be regarded as research tools only, at this time.

Neuroendocrine Findings. One study has found that patients with CFS, in comparison with healthy control subjects, have reduced hypothalamic production of corticotropin releasing hormone, leading to diminished pituitary release of ACTH, leading to basal hypocortisolism. Interestingly, this axis abnormality is the opposite of what is seen in patients hospitalized for major depression. Several other studies have examined other aspects of the hypothalamic-pituitary axes, and found abnormalities.

Neuroimaging. Several different groups have reported that magnetic resonance imaging (MRI) reveals punctate areas of high signal in the white matter, particularly in the subcortical areas, more frequently than in age and gender-matched healthy control subjects. Nevertheless, these findings are neither very sensitive nor specific. MRI is not recommended for the diagnosis of CFS, although it can be useful in pursuing the diagnosis of multiple sclerosis. MS is sometimes in the differential diagnosis, since patients with MS often present with prominent fatigue, paresthesias, visual blurring, and other symptoms suggestive of CFS, and since some patients with CFS have had a transient focal neurologic deficit.

Single photon emission tomography (SPECT) also reveals defects of perfusion and/or metabolism much more often in patients with CFS than in healthy control subjects. Depression also produces SPECT scan abnormalities; however, most studies indicate that SPECT abnormalities occur more often in CFS than in depression. SPECT is not recommended for the diagnosis of CFS.

Electroencephalography. A study by our group compared a large number of patients with CFS to a disease comparison group with major depression and to healthy control subjects, of similar age and gender. Using computer algorithms to objectively score abnormalities, a much higher frequency of sharp waves and spike waves was noted in the patients with CFS.

Autonomic Nervous System Testing. Studies from Johns Hopkins and Harvard find evidence of both sympathetic and parasympathetic neuropathy in patients with CFS. Clinically, many patients meet criteria for neurally-mediated hypotension and postural tachycardia syndromes.

Studies of Infectious Agents. No infectious agent has been convincingly shown to be a cause of CFS. Nevertheless, there is evidence from controlled studies of the reactivation of several chronic viral infections in CFS. The evidence is strongest for human herpesvirus-6, a neurotropic and immunotropic virus.

Diagnostic Workup. A patient with a debilitating chronic condition, as described above, should have the following diagnostic tests: CBC, manual differential WBC, ESR, chemistry panel, TSH, ANA, RF (if arthralgias), urinalysis. These tests can help identify well-recognized organic diseases and, as indicated above, may provide clues regarding the diagnosis of CFS.

Treatment. Treatment with low-dose tricyclics (e.g. amitriptyline, 10-20mg q.h.s.) has been proven efficacious in a randomized trial of a closely related condition (fibromyalgia), and is widely used in CFS. This treatment improves an objectively documented sleep disorder (alpha intrusion into delta wave sleep) seen in these conditions. Several recent trials of cognitive behavioral therapy demonstrated improvement; the generalizability of this therapist-dependent treatment remains to be demonstrated.

Model for CFS. At this time, most investigators studying CFS believe that the illness involves abnormalities of the limbic system of the brain, abnormal regulation of the immune system (possibly as a result of limbic system abnormalities), and (in some cases) reactivation of latent viruses (including enteroviruses, human herpesvirus-6, and occasionally Epstein-Barr virus and cytomegalovirus). A single cause seems unlikely; multiple different triggering agents (viruses, toxins, stress) could be involved in different cases. A past history of depression is seen in about 30% of patients with CFS, and some investigators think the CFS may be a form of atypical depression.

Psychiatric Issues. Probably only a small fraction of patients who seek medical care for fatigue have CFS; most fatigued patients probably suffer from depression or overwork. Of the few patients with chronic fatigue who meet criteria for CFS, most become depressed and anxious after the onset of the illness, and this depression and anxiety need to be recognized and treated, when present. Most patients with CFS have no prior history of significant psychiatric disease, according to several careful studies, but there is a higher lifetime history (including before and after the onset of CFS) of psychoneurotic disorders. One randomized, placebo-controlled, double-blind trial of fluoxetine therapy in patients with CFS found no evidence of benefit.

FIGURE 1: REVISED (1994) CASE DEFINITION OF CHRONIC FATIGUE SYNDROME AND IDIOPATHIC CHRONIC FATIGUE: AN ALGORITHM FOR EVALUATION

Severe fatigue that persists or relapses for ≥ 6 months.

→ Exclude if patient found to have:

1. Active medical condition that may explain the chronic fatigue, such as untreated hypothyroidism, sleep apnea, narcolepsy;

2. Previously diagnosed medical conditions that have not clearly fully resolved, such as previously treated malignancies or unresolved cases of hepatitis B or C virus infection;

3. Any past or current major depressive disorder with psychotic or melancholic features; bipolar affective disorders, schizophrenia, delusional disorders, dementias, anorexia nervosa, or bulimia nervosa;

4. Alcohol or other substance abuse within two years before the onset of chronic fatigue and at any time afterward.

→ Classify as **chronic fatigue syndrome** if:

Sufficiently severe: of new or definite onset (not lifelong) not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social or personal activities; **and**

Four or more of the following symptoms are concurrently present for ≥ 6 months:

1. Impaired memory or concentration
2. Sore throat
3. Tender cervical or axillary lymph nodes
4. Muscle pain
5. Multi-joint pain
6. New headaches
7. Unrefreshing sleep
8. Post-exertional malaise

→ Classify as **idiopathic chronic fatigue** if fatigue severity or symptom criteria for chronic fatigue syndrome are not met.

Taken from: Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff AL, International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med. 1994;121:953-959.