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CHRONIC FATIGUE AND IMMUNE DYSFUNCTION

One of the most common symptoms presented to the primary care physician is fatigue. Unfortunately, because fatigue may be due to a wide variety of conditions, it is also one of the most nonspecific symptoms. The concept that chronic fatigue, variously named chronic Epstein-Barr virus infection, chronic mononucleosis, and, more recently, chronic fatigue immune dysfunction syndrome (CFIDS), is itself a specific disease entity has been popularized. In fact, because the working definition of CFIDS is broad, the syndrome surely represents many disorders. Recent advances in our understanding have allowed a rational approach to diagnosis and treatment of subsets of fatigue patients.

No current laboratory test is specific for CFIDS. The working criteria established by the Centers for Disease Control in 1988 serve as a useful guide but have yet to be validated. Clinically, the disease most often occurs in middle-aged females and has onset within hours to days. A viral prodrome is frequently followed by acute symptoms from which the patient never recovers. The dominant symptom is profound fatigue which interferes with activity and life-style and which is often exacerbated by minimal exertion. Other symptoms include persistent or recurrent low-grade fever, pharyngitis, painful but rarely palpable lymph nodes, arthralgias, myalgias, new onset of headaches, disordered sleep, and difficulty with concentration, memory, or both. The physical examination may reveal low-grade fever, nonexudative pharyngitis, tender lymph nodes and muscular tender points.

CFIDS AND FIBROMYALGIA

Fibromyalgia and CFIDS are similar clinical syndromes. Fifty patients with fibromyalgia were analyzed to determine the prevalence of chronic fatigue symptoms. As in patients with CFIDS, recurrent pharyngitis (54%), rash (47%), cough (40%), adenopathy (33%), and intermittent low-grade fever (28%) characterized this population. In addition, the majority also experienced disordered sleep, myalgias,

joint pain, anxiety, and depression. Other studies of fibromyalgia and CFIDS patient populations have compared and contrasted signs and symptoms. Sleep disturbance, morning stiffness, and manually palpated tender points were common in CFIDS patients with myalgias; however, fibromyalgia patients tended to have more tender points and were less bothered by fatigue.

In addition, these syndromes share some common physiologic muscle dysfunction. Low muscle-oxygen tension, reduced perfusion, and abnormal phosphate metabolism have been described in both. In addition, disordered sleep which can be due to anxiety and depression is a prominent feature in both fibromyalgia and CFIDS and may provide a common pathoetiology in some subsets.

PSYCHOLOGICAL FACTORS

The diagnosis of depression, as with CFIDS, depends on consensus definitions and comprises heterogeneous sets of symptoms. From 62% to 82% of patients with major depression present with fatigue. Therefore, some cases of CFIDS possibly represent misdiagnosed depressive illness. However, until the relationship between CFIDS and depression is clarified, using one to exclude the other is unwise. In some cases, depressive signs and symptoms may occur either as an organic effective syndrome (perhaps due to immune dysfunction or chronic viral infection) or as a psychological consequence of prolonged periods of inactivity and disability. Other patients may indeed suffer from both conditions.

Certain features help to differentiate CFIDS from depression. Symptoms such as self-criticism, inappropriate guilt, pessimism, feelings of worthlessness, suicidal thoughts and delusions, and the presence of severe psychomotor retardation or agitation are prominent in depression but not in primary organic disease. On the other hand, somatic preoccupation in depression is often expressed as headache, musculoskeletal pain, and gastrointestinal distress, whereas night sweats, lymphadenopathy, and recurrent pharyngitis are not commonly observed in depression and signify an organic cause.

ETIOPATHOGENESIS AND IMMUNOLOGIC FACTORS

CFIDS is a highly heterogeneous condition which is unlikely to be explained by a single etiologic agent. Although viral sequences have been detected in the lymphocytes of CFIDS patients, it is unclear whether they are cause, effect, or epiphenomena. While Epstein-Barr virus, *Candida* sp, *Brucella* sp, human herpes virus 6, retroviruses, and enteroviruses have all been implicated, the role of an infectious agent is at present obscure.

The immune abnormalities in CFIDS reflect abnormalities of baseline regulation. Circulating interleukin-2 levels can be elevated, as can the number of lymphocytes, particularly CD8, bearing activation markers including HLA-DR. Despite apparent increased activation, when challenged, the CFIDS immune system responds inadequately. Delayed hypersensitivity and in vitro mononuclear proliferation are depressed when a patient's lymphocytes are exposed to pokeweed mitogen or phytohemagglutinin. Natural killer cells are also frequently suppressed, a defect only partially corrected by the addition of interleukin-2.

All of this information is preliminary and requires confirmation in studies using appropriate disease controls (ie, patients with depression, fibromyalgia, and atopy). At the same time, the activated state of the immune system provides some evidence that many of the symptoms experienced by CFIDS patients have a physiologic basis.

DIAGNOSIS AND TREATMENT

As already implied, fibromyalgia and depression must be excluded as the primary causes of symptoms. Other conditions which must be considered and would require specific treatment include endocrine disorders such as hypothyroidism, and autoimmune diseases such as Sjögren's syndrome.

Experimental therapies for CFIDS, including intravenous immunoglobulin and immunomodulating agents such as polyribonucleotide (Ampligen), have yet to be demonstrated unequivocally effective. At present, treatment is directed at symptoms. A graduated program of frequent, moderate-intensity exercises may help to relieve fatigue. Sleep disturbance may be treated with tricyclic antidepressant drugs, and myalgias and arthralgias with nonnarcotic anti-inflammatory medications. Most importantly, patients must be helped to understand that, in general, long-term prognosis is good and that their symptoms are not due to a more serious disease.

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SUGGESTED READING

Abbey SE, Garfinkel FE. Chronic fatigue syndrome and depression: cause, effect, or covariate. *Rev Infect Dis* 1991; 13(Suppl):573-583.

Calabrese L, Danao T, Camara E, Wilke W. The chronic fatigue immune dysfunction syndrome. *Am Fam Physician*. In press.

Goldenberg DL, Simms RW, Geiger A, Komaroff AL. High frequency of fibromyalgia in patients with chronic fatigue seen in a primary care practice. *Arthritis Rheum* 1990; 33:381-387.

Holmes GP, Kaplan JE, Grantz NM, et al. Chronic fatigue syndrome; a working case definition. *Ann Intern Med* 1988; 108:387-388.

Landay AL, Jessop C, Lennette ET, Levy IA. Chronic fatigue syndrome: clinical condition associated with immune activation. *Lancet* 1991; 338:701-712.

ASSESSING NEW TECHNIQUES
IN CORONARY ANGIOPLASTY

The number of angioplasties performed in the United States has continued to grow with the introduction of improved catheters and the increasing realization that angioplasty is indeed a viable option for many patients. New techniques are being designed to meet the many treatment challenges. But the recent proliferation of newer technologies has been daunting for many interventional cardiologists. Clinicians need to know the benefits and drawbacks of the new modalities before recommending them or using them in daily practice.

The following brief discussion relates our experience with two of these new techniques over the last 3 years at Boston's Beth Israel Hospital and offers suggestions for integrating these devices into everyday practice.

BALLOON-EXPANDABLE STENTING

Stents serve as internal scaffolds of coronary arteries and provide predictable results and excellent luminal