Chronic fatigue syndrome (myalgic encephalopathy): A review

Chronic fatigue syndrome remains a longstanding medical mystery.

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Chronic fatigue syndrome (CFS) has a long history of medical interest. Over the years it has had numerous names including chronic Epstein-Barr virus (EBV) syndrome, chronic mononucleosis syndrome, post-viral fatigue syndrome, epidemic myalgic encephalomyelitis and most recently (derisively) the "yuppie flu." Even the father of ancient Greek medicine, Hippocrates, recognized the muscular fatigue associated with deconditioning. In 1869 Dr. George Miller Beard recognized that nervous energy can become exhausted and proposed the term "neurasthenia."

Definition debuts

Every century brought in new symptoms, names and diagnostic criteria for this debilitating illness, but it still remains with an unknown etiology and pathogenesis. In 1988 the case definition of CFS was first introduced by the Centers for Disease Control (CDC) in Atlanta, Ga. Since

then, there have been numerous attempts to better define CFS all over the world, especially in Australia and Great Britain.

Most recently the CDC, the NIH and the International Chronic Fatigue Syndrome Study Group proposed new diagnostic criteria, shown in Table 1.

Majority middle class

CFS is a disorder which is characterized by the sudden onset of debilitating fatigue. It is accompanied by symptoms such as fever, sore throat, painful lymph nodes, weakness, muscle aches, headaches, depression, sleep disturbance, memory difficulties and confusion. These symptoms can persist from six months to many years and can dramatically reduce the quality of a person's life. Since the primary symptoms are muscular fatigue and pain, along with symptoms of encephalopathy (lethargy and cognitive difficulties,) it has been recently proposed that CFS be renamed "myalgic encephalopathy."

CFS affects mainly young and middle-aged adults. The most common age for it to start is between 20 and 40 years. The female to male ratio of occurrence is 3:1. The mean time to recovery is about two years but many individuals end up suffering much longer. All socioeconomic groups are represented and the majority of patients are middle class. The incidence of CFS is approximately one percent in the United States, but our studies suggest the incidence may be significantly higher. Several pathogenetic hypotheses have been advanced to explain this illness: viral, immunologic, psychiatric and neurologic.

Much emphasis has been placed on a viral etiology for CFS. The finding that CFS occasionally follows an episode of infectious mononucleosis, coupled with evidence of high titers of antibodies to EBV antigen, led to suggestions that EBV infection is the cause of CFS. Controlled studies of seroepidemiology and

Electron microscopic photomicrograph of a muscle mitochondria from a CFS patient which demonstrates pleomphism and compartmentalization of the inner mitochondrial membrane. The biopsy was obtained using a Tru-Cut (Baxter) percutaneous biopsy needle from the right vastus lateralis muscle. The muscle mitochondria is markedly irregular in shape. The inner mitochondrial membrane is convoluted into small concentric circles. The interlacing myosin fibrils and muscle Z-bands are evident. Magnification: 96,000X.

antiviral therapy have shown that EBV infection cannot be the sole explanation for most CFS cases. No correlation has been found between serologic parameters of EBV activity and the severity of CFS or its clinical course. Other viruses have also been investigated as possible causative agents in CFS. Those including human T lymphotropic viruses I (HTLV-I) and II (HTLV-II), entoviruses, and human herpes viruses (HHV-6, HSV, CMV). However, antibody titers to these viruses in CFS patients do not differ significantly from controls. HHV-6 and EBV may be ubiquitous viruses, that are reactivated in outbreaks, but do not appear to be etiologic factors.

Most recently "stealth viruses" have been proposed to be a pathogenic cause of CFS. These viruses are felt to have significant DNA homologies to CMV and have been isolated repeatedly from one patient with CFS. However, it appears that a wide range of neurologic and psychiatric disorders, in addition to a large percentage of normal individuals, may harbor these viruses. It may be that the "stealth virus" is simply a DNA polymorphism that has been incorporated, with variations, into the human genome.

Immunologic hypothesis

Immunologic etiologies have been hypothesized to be pathogenetic in CFS. The presence of subtle abnormalities in cell-mediated and humoral immunity led to speculation that in CFS there may be a disordered immune system response resulting from exposure to an infectious agent. Immunologic disorders seen in viral infections have been described in CFS: Decreased function in natural killer (NK) cells and microphages—reduced mitogenic response of lymphocytes, B-cell subset changes and activation of CD8 cells. There have also been reports of IgG subclass deficiencies, the presence of circulating immune complexes, decreased complement and the presence of anti-cardiolipin and antiphospholipid antibodies.

However, the reported immunologic abnormalities vary between different studies. There is no correlation between the immunologic findings in CFS and any viral serologies. One recent study has shown evidence that individuals with two or more CD8 cell subset alterations (increased CDllb-, CD38 and HLA-DR) have a high probability (90 percent) of having active

CFS. If there is a continuing immune response against a pathogenic virus in CFS, part of the symptomatology may be due to the production of immunologic mediators (interferons, interleukins and other cytokines) which may produce central nervous system (CNS) or muscle symptoms. Several studies have found significant differences in the levels of gamma interferon, interleukin-1, interleukin-2, interleukin-6 and tumor necrosis factor in CFS patients, but others have not.

Most recently, investigators have reported clusters of cytokine abnormalities in CFS patients. One cluster of abnormalities includes tumor necrosis factor receptor type 1, soluble interleukin-6 receptor and beta-2-microglobulin. The other cluster of abnormalities includes tumor necrosis factor alpha, interleukin-1-alpha, interleukin-4, soluble interleukin-2 receptor and interleukin-1 receptor antagonist. However, specific explanations for these clusterings of cytokine abnormalities is not known, and from the large battery of analyzed data sets, nonsignificant statistical findings may occur. Further, verification of these clusterings of cytokine abnormalities is necessary.

Thus far, in our own experience, thorough immunologic studies of CFS patients have been entirely normal except for elevations in neopterin levels, a finding that other researchers have noted. Neopterin is an enzyme produced by activated macrophages and is seen in elevated serum levels when the immune system is activated.

Psychiatric hypothesis

A psychiatric explanation for CFS symptoms has been proposed. The similarity between CFS and affective illness has been noted in several studies. In addition to chronic fatigue, depressed patients have a cluster of nonspecific symptoms, such as arthralgias, weakness, malaise, myalgias, decreased memory and confusion with little or no physical findings. Patients with CFS are in the 60th percentile of psychiatric patients in the Global Symptoms Index, with their highest overall scores in depression (67th percentile) and somatization (65th percentile.) Recent studies of CFS patients have suggested that these nonspecific symptoms have a heterogeneous cause. Neuropsychologic complaints such as sleep disorders, mood instability, anxiety, depression and impairment of higher cognitive functions in CFS patients arise after the onset of fatigue and thus may be features of CFS or, most likely, reactions to CFS. These complaints should not exclude the diagnosis of CFS. The pattern of event-related brain potential (ERP) activity in CFS patients with depression differs substantially from ERP activity in patients with major depressive disorders. ERP abnormalities indicating cognitive impairment are found in CFS but not in patients with depression where concentration and memory problems are frequently present. These results suggest that, although depression is a prevalent feature of CFS, it arises from an entirely

Table 1—Criteria for the diagnosis of CFS

A case of CFS must fulfill all the major criteria, plus four or more of the minor criteria. Each minor criteria must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue. A patient who does not fully meet the CFS criteria may be diagnosed as having idiopathic chronic fatigue.

Major criteria

1. Unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (not lifelong).
2. Fatigue is not due to ongoing exertion.
3. Fatigue is not substantially alleviated by rest.
4. Fatigue results in substantial reduction in previous levels of occupational, education, social or personal activities.

Minor criteria

1. Self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities.
2. Sore throat.
3. Tender cervical or axillary Lymph nodes.
4. Muscle pain.
5. Multijoint pain without joint swelling or redness.
6. Headaches of a new type, pattern, or severity.
7. Unrefreshing sleep.
8. Postexertional malaise lasting more than 24 hours.

Source: Centers for Disease Control, National Institute of Health, and the International Chronic Fatigue Syndrome Study Group

different neural mechanism than major depression. Furthermore, 25-40 percent of CFS patients do not develop depression.

In our own experience, it has been possible to distinguish primary depression from reactive depression in CFS. Primary depression usually presents with an indolent onset and progression, along with prominent depressive symptomatology and significant clinical improvement with the use of antidepressants. In contrast, CFS patients have an acute onset with much later evolution of depressive symptomatology and minimal response to antidepressants.

Neurologic hypothesis

Fatigue can be a prominent symptom in many CNS diseases, such as multiple sclerosis, Parkinson's disease and postencephalitic syndromes. These same patients, besides having debilitating fatigue, can have symptoms of headaches, sleep disorders, cognitive impairment and mood instability—symptoms that are common to CFS. Since definite neurologic diseases can be accompanied by CFS-like symptoms, it is probable that the fatigue seen in CFS is primarily a manifestation of a neurologic disorder.

Neuroimmunology

Abnormalities in immune system activity in CFS were discussed above. Chronic immune system activation is accompanied by increased concentrations of cytokines. Several studies of CFS patients have reported increased interferon and interleukin levels. Alpha and beta interferon have neuronal cytoskeletal effects by regulating neurofilament proteins and by acting as neuronal growth factors. Thus, CNS neurons appear to have functioning interferon receptors and may have receptors for other cytokines. Administration of interferon to patients with chronic hepatitis B can produce symptoms of fatigue, lethargy and myalgia—symptoms identical to those seen in CFS, again indicating direct CNS effects of the cytokines. These effects may be mediated by producing CNS humoral factors, including endorphins and serotonin.

Neurotransmitters

A large proportion of patients with Lyme disease have CFS symptoms. In Lyme disease, altered CNS metabolism of tryptophan and serotonin has been reported suggesting that this fatigue may be mediated by neurotransmitters. Many HIV patients also have fatigue symptoms. These patients have been reported to have decreased tryptophan levels and increased tryptophan catabolites (kynurenin and quinolinic acids) suggesting that their fatigue and cognitive impairment may be due to changes in tryptophan metabolism. In vitro, gamma interferon induces the degradation of tryptophan. It is possible that activation of cell-mediated immunity in CFS is associated with increased production of gamma interferon and this in turn may alter tryptophan metabolism.

Neurovirology

Much interest has recently arisen in "stealth viruses." In one patient with CFS, this category of virus was isolated from the cerebrospinal fluid, in the absence of inflammatory spinal fluid changes. This result suggest that if the "stealth virus" is a cause of CFS, it is a neurotropic virus and that the primary site of action is the CNS.

Neuroendocrinology

Compared to normal subjects, patients with CFS have mild glucocorticoid deficiency. This finding is comparable with central adrenal insufficiency secondary to a deficiency of corticotropin-releasing-hormone (CRH) or some other central stimulus of the pituitary-adrenal axis (PAA). CRH is the main stimulus to the PAA and is a behaviorally active neuropeptide. Patients with Cushing's disease, hypothyroidism and seasonal affective disorder show evidence of hypofunction in hypothalamic CRH neurons and clinical have symptoms of lethargy, fatigue and depressed mood. Deficiency of CRH function appears to be associated with the fatigue and lethargy seen in CFS.

Neuropsychology

Impaired cognitive functioning is a frequent symptom in CFS symptoms include impaired memory and difficulties in concentrating, problem solving and abstract thinking. The most frequent cognitive deficits identified are memory and concentration difficulties, ranging from mild to severe. These symptoms are present in up to 90 percent of CFS patients. In a recent well controlled study, significant impairments were detected in tests of complex concentration thus substantiating the subjective patient symptoms.

MRI abnormalities

Several investigators have reported that CFS patients show subtle findings on magnetic resonance image (MRI) brain scans. In a Nevada study all 15 CFS patients had pathologic abnormalities. The most common finding was multiple, tiny punctuate foci of increased signal intensity in the upper centrum

semiovale and bilaterally in the high parasagital convolutional white-matter tracts. The second most common pattern of abnormality was multiple bilateral patchy areas of abnormally increased signal intensity in the white matter tracts of the brain, particularly in the deep frontal white matter. In another investigation of 52 CFS patients, 13 percent had similar MRI findings, 10 percent showed ventricular enlargement and four percent had other lesions. Only one of 52 controls had an abnormality. However, in our experience over the past year, out of eight CFS patients who had MRI scans performed, none demonstrated these abnormalities.

Evoked potential abnormalities

Cognitive evoked potential (CEP) abnormalities have been reported in CFS patients. Significant prolongation of the mean latencies of N2 and P3 were present and reaction time was prolonged. These abnormalities may correlate with attention deficits and slowed processing of information as part of the cognitive impairment seen in CFS patients.

Muscle abnormalities

Profound muscle fatigue, precipitated by minimal physical activity is one of the major symptoms in CFS patients. There have been reports of excessive intramuscular acidification and abnormal jitter using single fiber electromyography suggestive of abnormal muscle membrane function. A low-grade persistent intracellular infection and localized cytokine release may produce a generalized disorder of cell membranes (including muscle and CNS membranes). However, other investigators have not found abnormalities in muscle fatigability, membrane function and excitation-contraction coupling.

In addition to chronic fatigue, depressed patients have a cluster of nonspecific symptoms, such as arthralgias, weakness, malaise, myalgias, decreased memory and confusion with little or no physical findings.

In vitro tests have shown depressed muscle mitochondrial respiration and CFS patients have demonstrated reduced aerobic work capacity. These results suggest a mitochondrial abnormality.

Recent investigations in Great Britain have shown that 70 percent of CFS patients have ultrastructurally abnormal muscle mitochondria (the energy-producing center in cells) and this could be a cause of fatigue. These mitochondria have been found to have abnormal sizes, shapes and a very peculiar "compartmentalization" of their internal structure. These structural abnormalities of mitochondria may be a cause of mitochondrial energy production deficits that could lead to fatigue.

Thus, from a variety of different pathogenetic perspectives, CFS may be considered to be a primarily neurologic disorder. Given the prominent muscular and cognitive difficulties seen in this condition, renaming this disease "myalgic encephalopathy" is appropriate.

Elusive cure

The cause of this illness remains unclear and there is no known cure for CFS. Numerous treatments have been tried, but none of them have cured CFS. A number of medicines are available that can improve many of the symptoms that patients may have. These include analgesics, anti-inflammatory medications, antidepressants and immunotherapies. Cognitive-behavioral techniques have also been used with success in CFS patients. Counseling and support groups may help.

Research investigations are ongoing, trying to discover the cause of CFS. Currently we are investigating the possibility that the mitochondria, the energy factory in our cells, are abnormal in CFS patients. If we are able to reproduce the work of other researchers, these results could lead to an explanation for the fatigue seen in CFS.

One-year anniversary

One year ago, in August 1993, we opened the Chronic Fatigue Syndrome Center. During this first year, 75 patients were referred for evaluation. It is important to note that all of the patients seen had undergone extensive medical evaluations before seeing us. Yet, 28 percent of these presumed CFS patients had entirely different diseases that required different management. Also, four of our CFS patients had an additional significant medical disease which we diagnosed and which required a change in medical management. Two developed diabetes mellitus, one hypothyroidism and one hyperthyroidism. ■

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