Chronic Fatigue Syndrome (Myalgic Encephalopathy)

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ABSTRACT: Chronic fatigue syndrome is associated with many misconceptions. In this review, we attempt to summarize various pathogenic hypotheses for this disease and discuss new lines of insight into causes and treatments of this baffling and most frustrating condition.

CHRONIC FATIGUE SYNDROME (CFS) has a long history of medical interest. Over the years it has had numerous other names, including chronic Epstein-Barr virus syndrome, chronic mononucleosis syndrome, postviral fatigue syndrome, epidemic myalgic encephalomyelitis, and most recently, "yuppie flu." Even Hippocrates recognized the muscular fatigue associated with deconditioning. In 1869, Beard[1] noted that nervous energy can become exhausted and proposed the term "neurasthenia." Every century brought in new symptoms, names, and diagnostic criteria for this debilitating illness, but its etiology and pathogenesis remain unknown. In 1988 the case definition of CFS was first introduced by the Centers for Disease Control (CDC) in Atlanta, Georgia.[2] Since then there have been numerous attempts to better define CFS, especially in Australia and Great Britain.[3,4] Most recently the CDC, the National Institutes of Health (NIH), and the International Chronic Fatigue Syndrome Study Group proposed new diagnostic criteria.[5] The 1988 CDC criteria for the diagnosis of CFS are presented in Table 1, and the 1994 revised criteria are shown in Table 2. The medical illnesses in the differential diagnosis of CFS are listed in Table 3.[6]

Chronic fatigue syndrome is characterized by the sudden onset of debilitating fatigue together with symptoms such as fever, sore throat, painful lymph nodes, weakness, muscle aches, headache, depression, sleep disturbance, memory difficulties, and confusion. These symptoms can persist from 6 months to many years and can dramatically reduce the quality of 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.

The most common age for onset of CFS is between 20 and 40 years. The female-male ratio is 3:1. The mean time to recovery is about 2 years, but many individuals have CFS for many years. All socioeconomic groups are represented, though the majority of patients are middle class. The incidence of CFS may be as high as 0.3% in the United States,[7] but recent epidemiologic studies being conducted in the Chicago area (studies in which this Center is actively involved) suggest that the incidence may be significantly higher.[8] Several pathogenetic hypotheses have been advanced to explain this illness: viral, immunologic, psychiatric, and neurologic.

VIRAL HYPOTHESIS

Much emphasis has been placed on a viral etiology for CFS. The finding that CFS occasionally follows an episode of infectious mononucleosis and evidence of high titers of antibodies to Epstein-Barr virus (EBV) antigen led to suggestions that EBV infection is the cause of CFS. Atypical profiles of antibody responses to EBV were found in many cases.[9-12] Controlled studies of seroepidemiology[12-15] and antiviral therapy[16] have shown that EBV infection cannot be the sole explanation for most cases of CFS. No correlation has been found between serologic parameters of EBV activity

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and the incidence of CFS.[15] More recently, however, EBV titers have been shown to correlate with disease severity: higher titers were seen in patients with more severe forms of the disease.[17] Other viruses have also been investigated as possible causative agents in CFS, including human T-cell lymphotropic viruses I (HTLV-I) and II (HTLV-II), enteroviruses, and human herpes viruses (HHV-6, HSV, CMV).[18] However, antibody titers to these viruses in patients with CFS do not differ significantly from titers in control subjects. HHV-6 and EBV may be ubiquitous viruses that are reactivated in isolated cases or in outbreaks of CFS, but they do not appear to be etiologic factors.

Most recently "stealth viruses"[19] have been proposed to be a pathogenic cause of CFS. These viruses are thought to have significant DNA homologies to CMV and have been isolated repeatedly from one patient with CFS.[19] However, it appears that patients with 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.

TABLE 1. Criteria for Diagnosis of Chronic Fatigue Syndrome (CFS) According to the CDC[2]

A case of CFS must fulfill major criteria 1 and 2, plus the minor criteria: 6 or more of the 11 symptom criteria and 2 or more of the 3 physical criteria; or 8 or more of 11 symptom criteria. (These criteria are currently under revision.)

Major Criteria

1. Persistent or relapsing fatigue or easy fatigability that
   (a) does not resolve with bed rest
   (b) is severe enough to reduce average daily activity by >50%.
2. Other chronic clinical conditions have been satisfactorily excluded, including preexisting psychiatric disease.

Minor Criteria

Symptomatic or historical criteria (persistent or recurring symptoms lasting >6 months):

1. Mild fever (oral temperature of 37.5°C to 38.6°C if documented by the patient) or chills
2. Sore throat
3. Lymph node pain in anterior or posterior cervical or axillary chains
4. Unexplained generalized muscle weakness
5. Muscle discomfort
6. Prolonged (>24 hr) generalized fatigue after previously tolerable levels of exercise
7. New, generalized headaches
8. Migratory noninflammatory arthralgia
9. Neuropsychologic symptoms
   (a) photophobia
   (b) transient visual scotomata
   (c) forgetfulness
   (d) excessive irritability
   (e) confusion
   (f) difficulty thinking
   (g) inability to concentrate
   (h) depression
10. Sleep disturbance
11. Patient's description of initial onset of symptoms as acute or subacute

Physical Criteria

Documented by a physician on at least two occasions, at least 1 month apart:

1. Low-grade fever (37.6°C to 38.6°C oral or 37.8°C to 38.8°C rectal temperature)
2. Nonexudative pharyngitis
3. Palpable or tender anterior or posterior cervical or axillary lymph nodes (<2 cm in diameter)

IMMUNOLOGIC HYPOTHESIS

Immunologic causes have been hypothesized as 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.[20] Immunologic disorders seen in viral infections and described in CFS are decreased function in natural killer (NK) cells and macrophages, reduced mitogenic response of lymphocytes, and B-cell subset changes and activation of CD8 cells.[21-24] There have also been reports of IgG subclass deficiencies, the presence of circulating immune complexes, decreased complement, and the presence of anticardiolipin and antiphospholipid antibodies.[25] However, the reported immunologic abnormalities vary between studies.[26] There is no correlation between the immunologic findings in CFS and any viral serology.[20] One recent study has shown evidence that individuals with two or more CD8 cell subset alterations (increased CD11b-, CD38, and HLA-DR) have a high probability (90%) of having active CFS.[20] 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.[27] Several studies have shown significant differences in the levels of gamma interferon, interleukin-1, interleukin-2, interleukin-6, and tumor necrosis factor in CFS patients,[28-31] but others have not.[32]

Most recently, investigators have reported clusters of cytokine abnormalities in patients with CFS.[33] 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,

TABLE 2. Revised Criteria for the Diagnosis of CFS (From CDC, NIH, and International Chronic Fatigue Syndrome Study Group[5])

A case of CFS must fulfill all the major criteria, plus 4 or more of the minor criteria. Each minor criterion must have persisted or recurred during 6 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 given a diagnosis of 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, educational, 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

TABLE 3. Differential Diagnosis of Chronic Fatigue Syndrome (Modified From Komaroff[6])

- Endocrinologic
  - Hypothyroidism
  - Diabetes
  - Addison's disease
  - Cushing's disease
- Rheumatologic
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Fibromyalgia
  - Sjögren's syndrome
  - Polymyalgia rheumatica
  - Polymyositis
- Neurologic
  - Sleep disorders
  - Multiple sclerosis
  - Myasthenia gravis
- Infectious
  - Lyme disease
  - Human immunodeficiency virus infection
  - Chronic hepatitis B and C infection
  - Fungal disease
  - Tuberculosis
  - Subacute bacterial endocarditis
- Hematologic
  - Anemia
  - Lymphoma
- Metabolic
  - Hypokalemia
  - Hypomagnesemia
  - Hyponatremia
  - Hypercalcemia
- Psychiatric
  - Depression
  - Psychosis
- Other
  - Chronic illness (cardiac, hepatic, pulmonary, renal)
  - Chronic pain
  - Medication side effects (eg, beta blockers)
  - Alcohol or other substance abuse
  - Heavy-metal toxicity
  - Occult malignancy
  - Sarcoidosis

interleukin-1α, interleukin-4, soluble interleukin-2 receptor, and interleukin-1 receptor antagonist. However, specific explanations for these clusterings of cytokine abnormalities are 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, results of thorough immunologic studies of patients with CFS have been entirely normal except for elevations in neopterin levels. Other studies have reported similar results.[30] Neopterin is an enzyme produced by macrophages and is elevated in the serum when the immune system is activated. Our investigations of neopterin are ongoing.

PSYCHIATRIC HYPOTHESIS

A psychiatric explanation for CFS symptoms has been proposed. The similarity between CFS and affective illness has been noted in several studies.[34,35] In addition to chronic fatigue, depressed patients have a cluster of nonspecific symptoms, such as arthralgias, weakness, malaise, myalgias, decreased memory, and confusion, with few or no physical findings. Patients with CFS are in the 60th percentile of psychiatric patients in the Global Symptoms Index, their highest overall scores being in depression (67th percentile) and somatization (65th percentile).[15] A recent study of CFS patients has suggested that those nonspecific symptoms have a heterogeneous cause.[36] Neuropsychologic complaints such as sleep disorders, anxiety, mood instability, 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.[34,37-39] Thus, these complaints should not exclude the diagnosis of CFS.[40] The pattern of event-related brain potential (ERP) activity in patients with CFS and depression differs substantially from ERP activity in patients with major depressive disorders.[41] ERP abnormalities indicating cognitive impairment are found in CFS, but not in patients with depression, who frequently have concentration and memory problems.[42-44] These results suggest that although depression is a prevalent feature of CFS, it arises from an entirely different neural mechanism than

major depression. Furthermore, 25% to 40% of CFS patients, well into the course of their illness, do not have depression or any other psychiatric disorder.[34,37-39]

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

NEUROLOGIC HYPOTHESIS

Fatigue can be a prominent symptom in many central nervous system (CNS) diseases, such as multiple sclerosis, Parkinson's disease, and postencephalitic syndromes. These same patients, besides having debilitating fatigue, can have symptoms of headache, sleep disorder, cognitive impairment, and mood instability—symptoms that are common to CFS.[45] 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. Lines of evidence for a neurologic abnormality in CFS will be discussed in the following sections dealing with neuroimmunology, neurotransmitters, neurovirology, neuroendocrinology, neuropsychology, MRI abnormalities, evoked potential abnormalities, and muscle abnormalities.

Neuroimmunology

Abnormalities in immune system activity in CFS have already been discussed. Chronic immune system activation is accompanied by increased concentrations of cytokines.[30,45] Several studies of patients with CFS have reported increased levels of interferon and interleukins. Interferons (α and β) have neuronal cytoskeletal effects by increasing the immunohistochemical expression of neurofilament proteins[46] and by acting as neuronal growth factors.[47] Thus CNS neurons appear to have functioning interferon receptors and may have receptors for other cytokines.[27] Administration of interferon to patients with chronic hepatitis B can produce symptoms of fatigue, lethargy, and myalgia—symptoms identical to those of CFS, again indicating direct CNS effects of the cytokines.[48] Furthermore, the cytokines, including tumor necrosis factor, may be instrumental in producing the CNS manifestations of cerebral malaria.[49] In this case the cytokine effect may not be a direct neuronal one, but rather one mediated by the endothelial cells of the cerebral microvasculature.[27] The CNS effects of the cytokines 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,[50] suggesting that this fatigue may be mediated by neurotransmitters. Many HIV-positive patients also have fatigue symptoms. These patients have been reported to have decreased tryptophan levels and increased tryptophan catabolites (kynurenic and quinolinic acids) suggesting that their fatigue and cognitive impairment may be due to changes in tryptophan metabolism. In vitro, interferon-γ induces the degradation of tryptophan.[51] It is possible that activation of cell-mediated immunity in CFS is associated with increased production of interferon-γ, and this in turn may alter tryptophan metabolism.

Neurovirology

Much interest has recently arisen with the description of "stealth viruses."[19] 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 suggests 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 with normal subjects, patients with CFS have mild glucocorticoid deficiency.[52] This finding is compatible with central adrenal insufficiency due 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,[53,54] hypothyroidism, and seasonal affective disorder[55] show evidence of hypofunction in hypothalamic CRH neurons[52] and clinically have symptoms of lethargy, fatigue, and depressed mood. Deficiency of CRH function appears to be associated with the fatigue and lethargy seen in CFS.

TABLE 4. Final Diagnoses Among 75 Patients Referred to the Chronic Fatigue Syndrome Center, Mercy Hospital and Medical Center, Chicago

CFS		50
Neurologic Disorders		6
Multiple sclerosis	2	
Tension headaches	2	
Brain stem stroke	1	
Early Parkinson's disease	1	
Psychiatric Disorders		6
Depression	5	
Anorexia nervosa	1	
Sleep Disorders		4
Narcolepsy	1	
Restless legs syndrome	1	
Idiopathic hypersomnia	1	
Sleep apnea	1	
Other Diseases		5
Medication side effects	2	
Chronic allergic rhinitis	2	
Carnitine deficiency	1	
Incomplete Evaluation		4
Total diagnoses other than CFS		21

Neuropsychology

Impaired cognitive functioning is a frequent symptom in CFS. Many patients experience impaired memory and difficulty in concentrating, maintaining attention, problem solving, and abstract thinking.[6] These symptoms are present in 45% to 89% of CFS patients.[56] The most frequent cognitive deficits identified are memory and concentration difficulties, ranging from mild to severe.[57] In a recent well-controlled study of 12 patients with CFS,[56] significant impairments were detected in tests of complex concentration, thus substantiating the subjective patient symptoms.

MRI Abnormalities

Several investigators have reported that patients with CFS have subtle findings on magnetic resonance imaging (MRI) brain scans.[58-60] In a northern Nevada study,[59] all 15 patients with CFS had pathologic MRI abnormalities. The most common finding was multiple tiny punctate foci of increased signal intensity in the upper centrum semiovale and bilaterally in the high parasagittal convolutional white matter. The second most common pattern of abnormality was multiple bilateral patchy areas of abnormally increased signal intensity in the deep frontal white matter. In another investigation of 52 patients with CFS, 13% had similar MRI findings, 10% showed ventricular enlargement, and 4% had other lesions, whereas only one of 52 control subjects had an abnormality.[61] However, in our experience over the past year, none of 10 CFS patients who had MRI scans showed these abnormalities.

Evoked Potential Abnormalities

Cognitive evoked potential (CEP) abnormalities have been reported in CFS.[62] 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 patients with CFS.

Muscle Abnormalities

Profound muscle fatigue, precipitated by minimal physical activity, is one of the major symptoms in CFS patients.[63] There have been reports of excessive intramuscular acidification[64] and abnormal jitter shown by single fiber electromyography,[65] 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).[66] However, other investigators have not found abnormalities in muscle fatigability, membrane function, and excitation-contraction coupling.[63,67,68]

In vitro tests have shown depressed muscle mitochondrial respiration in CFS, and patients have shown reduced aerobic work capacity.[69] These results suggest a mitochondrial abnormality.

Recent investigations in Great Britain have shown that 70% of CFS patients have ultrastructurally abnormal muscle mitochondria (the energy-producing center in cells), and this may be a cause of fatigue.[70-73] These mitochondria have been found to have abnormal sizes and shapes and a peculiar "compartmentalization" of their internal structure. These structural abnormalities of mitochondria may be a cause of mitochondrial energy production deficits that may lead to fatigue.

Thus, from a variety of pathogenetic perspectives, CFS may be considered a primarily neurologic disorder. In keeping with our own evaluation of CFS, other clinicians have likewise hypothesized the primary disease site to be the central nervous system, in particular the limbic system.[74] Given the prominent muscular and cognitive difficulties seen in this condition, renaming this disease myalgic encephalopathy is appropriate.

The cause of CFS remains unclear and

there is no known cure. 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 CFS patients may have. These include analgesics, anti-inflammatory medications, antidepressants, and immunotherapeutic agents, among many other symptomatic medicine possibilities. Cognitive-behavioral techniques have also been used with success in some patients with CFS. Also, counseling and support groups may help patients cope with the symptoms and socioeconomic problems that often occur as a result of this illness.

CLINICAL EXPERIENCE

One year ago we opened the Chronic Fatigue Syndrome Center at Mercy Hospital and Medical Center in Chicago. During this first year, the number of patients referred for evaluation of CFS was 75. The final diagnoses in this group of patients are listed in Table 4. All of the patients seen had had extensive medical evaluations before seeing us, yet 28% of these patients presumed to have CFS 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 (diabetes mellitus in two, hypothyroidism in one, and hyperthyroidism in one). These results underscore the need for continued periodic reassessment of patients with CFS. A medical cause of fatigue may become apparent years after the onset of fatigue, and other illnessess can develop in addition to CSF.

Our results differ from those of a previous report in which 327 fatigued patients were evaluated in a medical clinic.[75] It is not clear whether the patients were referred for fatigue evaluation or were seen for primary medical care. Of these 327 patients, 76% had a psychiatric diagnosis explaining their fatigue (depression being the primary one) and only 4% had other medical diseases. Our patient population, in contrast, was a highly referred population that had had extensive previous medical testing. None of our patients were seen for the first time for fatigue-related symptoms. Also, 28% of patients in the other study had a history of substance abuse,[75] whereas in our experience the incidence of substance abuse was only 1%. Thus our results cannot be compared with those of the previous report.

RESEARCH EXPERIENCE

As part of our research efforts toward understanding the cause of CFS, we have investigated muscle mitochondria in CFS patients. We obtained percutaneous needle muscle biopsy specimens from the right vastus lateralis muscle using a Tru-Cut (Baxter) biopsy needle. The tissue was immediately fixed and subsequently processed for electron microscopic analysis. Our results are based on 15 CFS patients and controls. We performed a detailed analysis of muscle mitochondria analyzing previously published mitochondrial abnormalities[70-73]: Compartmentalization of the inner mitochondrial membrane, pleomorphic mitochondrial shapes, the size of the mitochondria, and the presence of intramyofibrillar and subsarcolemmal mitochondrial aggregates. There was no statistically significant difference in any of these parameters between the patients and the control subjects.[76] Thus, our results did not support the previously published reports[70-73] of ultrastructural mitochondrial abnormalities in CFS patients.

We are also investigating possible metabolic causes of CFS. L-Carnitine is essential for mitochondrial energy production. A decrease in acylcarnitine levels has been previously reported in CFS.[77] We determined the serum L-carnitine levels in 35 patients with CFS. As a population, our CFS patients had significantly lower L-carnitine levels (total, free, and acyl).[78] We also found a statistically significant correlation between serum L-carnitine levels and degree of fatigue as measured by the Fatigue Severity Scale and the CFS Impairment Index (lower carnitine levels correlated with worse symptoms).[78]

CLINICAL RESEARCH EXPERIENCE

We have enrolled 30 CFS patients into a crossover medication trial comparing the effectiveness of amantadine and L-carnitine. Our previous investigations have shown L-carnitine to be effective in treating the lethargy seen in a number of neurologic conditions.[79,80] Our preliminary results have shown that L-carnitine is of benefit in more than 50% of cases of CFS.[81]

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