Role of Infection and Neurologic Dysfunction in Chronic Fatigue Syndrome

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ABSTRACT

Chronic fatiguing illnesses following well-documented infections and acute “infectious-like” illnesses of uncertain cause have been reported for many decades. Chronic fatigue syndrome (CFS) was first formally defined in 1988. There is considerable evidence that CFS is associated with abnormalities of the central and autonomic nervous systems. There also is evidence linking several infectious agents with CFS, although no agent has been proven to be a cause of the illness. Most of the infectious agents that have been linked to CFS are able to produce a persistent, often life-long, infection and thus are a constant incitement to the immune system. Most also have been shown to be neuropathogens. The evidence is consistent with the hypothesis that CFS, in some cases, can be triggered and perpetuated by several chronic infections that directly or indirectly affect the nervous system, and that symptoms are a reflection of the immune response to the infection.

KEYWORDS: Chronic fatigue syndrome, neuroendocrine, magnetic resonance imaging, central nervous system, autonomic nervous system, depression, immune activation, mitochondrial dysfunction, Epstein-Barr virus, human herpesvirus 6, enterovirus

Chronic fatigue syndrome (CFS) is a chronic illness defined entirely by a constellation of symptoms, including profound fatigue, impaired memory and concentration, headaches, muscle and joint pain, and post-exertional malaise.1 Between 1 and 8 in 1000 adults in the United States meet the Centers for Disease Control and Prevention (CDC) criteria for the syndrome; it occurs in all age, ethnic, and socioeconomic groups. Patients with CFS report substantial functional impairment3 and cost the U.S. economy approximately $9 billion annually in lost productivity.4

There is no proof that any infectious agent causes CFS, yet there is considerable evidence linking infectious agents with CFS. There also is considerable evidence that the nervous system is involved in the pathogenesis of CFS, although there is no proof of this hypothesis. In this review, we will expand on both of these propositions.

CHRONIC FATIGUE SYNDROME AND THE NERVOUS SYSTEM

Evidence of Central Nervous System Involvement

In an illness characterized by fatigue, pain, and cognitive problems, it is reasonable to postulate that the central nervous system (CNS) is directly or indirectly involved.
Indeed, many studies of the CNS have compared patients with CFS to healthy controls and controls with other fatiguing illnesses.

**NEUROENDOCRINE STUDIES**

Multiple studies have demonstrated hypofunction of corticotropin-releasing (CRH) neurons in the hypothalamus, and hypocortisolism (distinct from Addison disease). This downregulation of the hypothalamic–pituitary–adrenal (HPA) axis in CFS stands in contrast to the upregulation seen in major depression. Serotonergic and noradrenergic hypothalamic pathways, and growth hormone secretion also are disrupted. One possible cause of hypothalamic dysfunction and fatigue is the production of cytokines produced in response to a chronic infection of the CNS.

**MAGNETIC RESONANCE IMAGING**

The preponderance of published studies have found areas of high signal on T2-weighted magnetic resonance imaging (MRI) in patients with CFS at a higher frequency than in age- and gender-matched healthy control volunteers. Most often, the areas of high signal are small and punctate, and are located in the subcortical white matter. These abnormalities may be more likely in CFS patients who have no concomitant psychiatric illness. Studies using MRI also have found enlarged ventricles and reduced gray matter volume. One group assessed MRI findings and functional capacity at the same point in time, and found a strong association between the two: CFS patients with more MRI abnormalities were also more functionally impaired, suggesting that the MRI findings had clinical relevance. These findings were not confirmed by other investigators, although the small number of patients made possible a type 2 error.

**FUNCTIONAL MRI (fMRI)**

Functional MRI (fMRI) of CFS patients compared with matched healthy control volunteers reportedly reveals abnormalities. When given motor and visual imagery tasks, patients with CFS demonstrated reduced striatal and ventral cingulate activation and greater visual system activation than control volunteers. Responsiveness of the auditory cortex to a task-independent stimulus (sound) was delayed and impaired in patients with CFS when engaged in a fatigue–inducing task (visual), and the degree of delay correlated with the patients’ report of fatigue severity.

Although patients with CFS performed comparably to matched control volunteers on tasks of verbal working memory, fMRI revealed considerably greater activation of working memory networks in the CFS patients. As the intensity of the cognitive challenge increased, the difference between cases and controls was amplified. Similar findings with a different cognitive challenge have been reported by others.

**IN VIVO MAGNETIC RESONANCE SPECTROSCOPY OF BRAIN**

Proton magnetic resonance spectroscopy (MRS) has revealed significantly reduced concentration of N-acetylaspartate in the hippocampus of patients with CFS, compared with healthy control volunteers, a result thought likely to reflect reduced metabolism of neurons or glial cells. Using the same technology, other investigators have found a highly significant increase in the spectra from choline-containing compounds in CFS patients. This result may be due to higher cell membrane turnover secondary to injury.

**SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY**

Studies comparing patients with CFS to age- and gender-matched healthy control volunteers have found single photon emission computed tomography (SPECT) abnormalities that could represent either hypoperfusion in the microcirculation and/or metabolic dysfunction of neuronal and glial cells. Other investigators have not reported similar findings. Similar abnormalities have been reported in patients with CFS using positron emission tomography (PET), findings not present in a comparison group with major depression. PET also has revealed reduction of serotonin transporters in the anterior cingulate and hippocampus.

**ELECTROENCEPHALOGRAPHY**

Motor cortex excitability has been reported in chronic fatigue syndrome. Spectral analysis of EEG electroencephalography (EEG) data has been reported to produce a pattern that distinguishes patients with CFS from healthy and depressed control volunteers. Other investigators have identified several significant differences during motor performance in spectrum analysis and motor activity-related cortical potentials.

**SPINAL FLUID STUDIES**

A small study found that patients with CFS were significantly more likely than healthy control volunteers to have elevated levels of protein or pleocytosis. Nuclear magnetic spectroscopy has revealed increased lactate levels in ventricular spinal fluid in patients with CFS, compared with healthy control volunteers and control volunteers with generalized anxiety disorder and major depression. The results of the study, including patients with major depression, did not reach statistical significance, but the number of study participants was small. Finally, a study employing liquid chromatography, mass spectrometry, and peptide sequencing of spinal fluid from patients with CFS...
found a group of proteins (“a proteomic signature” of CFS) that distinguished patients with CFS from healthy control volunteers. The findings were replicated in a small independent second cohort of patients with CFS.

PAIN
Mechanisms of pain have not been studied extensively in CFS, but they have been in a very similar syndrome, fibromyalgia. The hyperalgesia and allodynia that are so frequently reported by patients with CFS and fibromyalgia may be due to central sensitization or augmented sensory processing.

COGNITION
Neuropsychological testing of cognition has revealed abnormalities in patients with CFS, abnormalities not explained by a coexisting depression. A recent meta-analysis of 50 eligible studies found deficits primarily in attention, memory and reaction time, and not in fine motor speed, vocabulary, or reasoning. Another recent study directly compared cognitive function in 25 patients with CFS, 25 with major depression and 25 healthy control volunteers. Patients with CFS were found to have impairments in attention and visual and verbal episodic memory; these deficits were not found in the comparison groups.

Evidence of Autonomic Involvement
Abnormalities of autonomic function in adults and children have been reported by multiple investigators. A consensus panel of autonomic experts concluded that the literature provided strong evidence for exaggerated venous pooling, diminished red cell mass, reduced plasma volume, disordered sympathetic activity, impaired baroreflex function, and reduced cerebral perfusion. The most frequently observed disorders on autonomic testing are postural orthostatic tachycardia syndrome, neurally mediated hypotension, and heart rate variability during head-up tilt testing. Investigators have reported a strong correlation between symptoms of autonomic dysfunction, as assessed by the Composite Autonomic Symptom Scale (COMPASS), and fatigue, as assessed by a validated instrument, the Fatigue Impact Scale.

Is Chronic Fatigue Syndrome a Psychiatric Illness?
Depression may be the most common cause of the presenting complaint of fatigue. Thus, the role of psychiatric illness in CFS has been debated. Most studies have found that in 30 to 50% of patients with CFS there is no co-existing psychiatric disorder, and that most of those with a psychiatric disorder developed the disorder only after becoming ill with CFS. In addition, a controlled trial of fluoxetine showed no improvement in fatigue in patients with CFS, including those with a concomitant major depression. Clauw notes the evolution of thinking on this issue: “Investigators who once staunchly viewed CFS as a psychiatric condition have significantly tempered their views, now acknowledging that these conditions are clearly separable from, and often occur independently of, psychiatric disorders.”

CHRONIC FATIGUE SYNDROME AND INFECTION

Epidemiologic Studies
Postinfectious fatigue syndromes have been described in the literature over the past 70 years. Sometimes these syndromes have followed well-documented specific acute viral and bacterial infections, and sometimes they have followed acute syndromes with symptoms suggesting infection, such as fever, myalgias, respiratory, and gastroenterologic symptoms. Hickie and colleagues reported a prospective observational study that confirmed the existence of a postinfectious fatigue syndrome. The study was conducted in a small, rural Australian town. Virtually all medical care in the community was provided by a small number of health professionals and facilities. This meticulously conducted study identified all cases of acute infection with Epstein-Barr virus (a DNA virus), Ross River virus (an RNA virus), and Coxiella burnetii (the intracellular bacterium that causes Q fever) during a predefined window of time. Of the 253 patients in the study, 12% of patients developed a postinfectious fatigue syndrome 6 months after their acute infection. Virtually all the patients met the CDC criteria for CFS. The progression and regression of symptoms was quite similar regardless of the infectious agent. Chronic fatigue syndrome was more likely to develop in patients with more severe acute infectious symptoms, and was not more likely to occur in those with premorbid psychological problems. The presence of more severe acute infectious symptoms was correlated with increased production of proinflammatory cytokines in blood. This increased production of cytokines did not persist 6 to 12 months later, when cytokine levels were comparable between the patients who developed CFS and those who did not, suggesting that infection may have initiated the disease process but may not be perpetuating it.

Immunologic Studies
Although not all published studies concur, the preponderance of the published literature indicates that patients...
with CFS have increased numbers of CD8+ cytotoxic T cells that bear antigenic markers of activation on their cell surface.101

Most published studies have found an increased production of various proinflammatory cytokines15–17,102–106 and type 2 cytokine–producing cells107 in the blood. A recent analysis of cytokine networks in patients with CFS, compared with healthy control volunteers, found an enhanced T\(_{H2}\) milieu.108 Proinflammatory cytokines can produce symptoms characteristic of CFS—fatigue, fevers, adenopathy, myalgias, arthralgias, sleep disorders, cognitive impairment, and mood disorders—whether produced in the periphery (and penetrating a porous blood–brain barrier) or produced by an inflammatory process in the CNS. There have been few studies on cerebrospinal fluid (CSF) to pursue this possibility.

Additionally, an important arm of the antiviral immune response, function of natural killer cells, is impaired in patients with CFS.108–113 These observations are similar to those seen in patients with well-documented latent viral infections.108

The 2–5A synthetase/ RNase L enzymatic pathway in lymphocytes (the 2–5A pathway), which is induced by viral infection, is activated in CFS, and a characteristic low–molecular-weight form of RNase L is produced.114–116

Finally, gene expression studies using microarray technology from different laboratories, studying different groups of patients, find changes indicating a state of chronic activation of the immune system.117–122 Collectively, these studies suggest, but do not prove, that there may be an underlying chronic infectious process in some patients with CFS.

Evidence of Mitochondrial Dysfunction, Oxidative and Nitrosative Stress

Several studies of muscle mitochondria have found what appear to be acquired abnormalities in patients with CFS.123–126 Gene expression studies have also found altered expression of genes involved in mitochondrial function in cases of postinfectious fatigue caused by Epstein–Barr virus.127

Studies of blood and muscle demonstrate increased oxidative stress, as evidenced by increased levels of isoprostanes and oxidized LDL cholesterol,128 reduced levels of antioxidants,129 increased levels of peroxides and superoxides,130 and decreased levels of \( \alpha \)-tocopherol.131 A study employing in vivo proton MR spectroscopy found evidence of cerebral oxidative stress.132 Longitudinal studies suggest that oxidative stress is greatest at times of clinical exacerbation.133 Similarly, increased levels of nitric oxide, nitrate, and peroxynitrite demonstrated in patients with CFS is evidence of increased nitrosative stress.134 Strikingly increased lactate levels in CSF indicate increased anaerobic metabolism in the CNS, consistent with mitochondrial dysfunction.50,51 Finally, increased production of iNOS, COX-2, and of NFκB have been reported in the blood of patients with CFS.135,136

Several studies have found that exercise precipitates oxidative stress in patients with CFS, in contrast to healthy and disease control groups. Nitric oxide metabolism production in blood reportedly rises nearly fivefold in patients, but does not rise in controls.137 One group compared patients with CFS to healthy control volunteers following a sustained moderate exercise task. Patients with CFS had much higher expression of genes for receptors important in sensing metabolites that mediate muscle fatigue and pain than the control volunteers.138 A controlled study comparing patients with CFS to sedentary healthy control volunteers during two types of controlled exercise (submaximal, and self-paced physiologically limited) found that pain thresholds following exercise increased in controls, but decreased in patients with CFS.139 These studies suggest, but do not prove, a physiologic basis for the postexertional malaise reported by a high fraction of patients with CFS.

An intriguing model has been proposed by Maes135,136 and others, and is summarized in Fig. 1. In patients with CFS, a series of vicious metabolic cycles may exist involving inflammation, oxidative and nitrosative stress, mitochondrial dysfunction, and possibly cell death; the inflammation is triggered by mitochondrial fragments entering the circulation.140 At the core of these vicious cycles are mitochondrial dysfunction and increased production of NFκB—both of which are commonly caused by infection. Oxidative damage is prominent in viral infections of the nervous system.141 However, when it comes to incrementing infectious agents in CFS, this is all no more than circumstantial evidence.

Studies of Specific Infectious Agents

EPSTEIN-BARR VIRUS

Fatigue states following acute infectious mononucleosis, an illness typically caused by Epstein–Barr virus (EBV), have been reported for over 60 years,142 and recently have been well documented.143,144 Interest in CFS became resurgent in the mid-1980s due to several publications linking high titers of antibodies to EBV with a chronic, fatiguing illness.145,146 Subsequent studies have often, but not always, found higher titers of two EBV antibodies—viral capsid antigen–IgG and early antigen–IgG. However, over 90% of adults in the United States are chronically infected with EBV, and therefore seropositive. Higher levels of antibodies to EBV could be a secondary reflection of subtle primary immune dysfunction in CFS, and do not necessarily indicate an etiologic role for EBV in CFS.
First discovered in 1986 in the laboratory of Robert Gallo, the virus now called human herpesvirus-6 (HHV-6) also has been linked with CFS. Like its cousin herpesvirus EBV, HHV-6 permanently infects nearly 90% of the human race. Thus, as with EBV, most people are seropositive.

Unlike EBV, the evidence linking HHV-6 to CFS does not rely on antibody levels to viral antigens. The first large study to suggest a link included 259 patients with a CFS-like illness (the case definition had not yet been developed). Primary culture of lymphocytes showed active replication of HHV-6 in 70% of the patients in contrast to 20% of the age- and gender-matched healthy control volunteers ($p < 10^{-5}$). Many studies that have employed assays that can detect active infection—polymerase chain reaction (PCR) of serum or plasma, IgM early antigen antibodies, and primary cell culture—have found an association between CFS and active HHV-6 infection. Several other studies have not demonstrated this association. The greater frequency of reactivated infection with HHV-6 more often in patients with CFS in comparison to healthy control volunteers does not prove an etiologic role for this virus. As with EBV, a primary condition that led to subtle immune dysfunction could encourage reactivation of latent HHV-6 infection.

Nevertheless, HHV-6 is a plausible candidate to cause some cases of CFS. A recent review summarizes the evidence suggesting that HHV-6 is a CNS pathogen associated with multiple sclerosis, mesial temporal lobe epilepsy, encephalitis in both immunosuppressed and immunocompetent individuals, and febrile seizures in children. The review also discusses the capacity of HHV-6 to infect multiple types of glial cells, and to induce potentially destructive immune responses. As a potent inducer of TNF-α and IL-1B, and IL-6, the virus could produce CNS infection directly following primary infection, and achieve latency there, or it could traverse the blood–brain barrier, leading to the production of inflammatory cytokines in the CNS.

XMRV AND POLYTROPIC MURINE LEUKEMIA VIRUSES

Xenotropic murine leukemia virus-related virus (XMRV) was first identified in prostate cancer specimens, although not all investigators have corroborated the initial finding. Recently, a multiinstitutional team reported a strong association of this virus with CFS. They detected viral nucleic acids by PCR in 67% of patients compared with 4% of healthy blood donors. These investigators also reported finding antibodies to the virus in serum, and viral antigens in peripheral mononuclear cells. Additionally, the virus was isolated from both the plasma and from peripheral mononuclear cells on co-cultivation with a reportedly infection-free
cell line (called LNCaP cells) known to permit XMRV infection. These additional studies were performed on only a small fraction of the total patients, however.

Another group of investigators reported that it had identified nucleic acids not from XMRV, but from a related family of viruses, the polytropic murine leukemia viruses (MLVs) in 87% of 37 CFS patients and 7% of 44 healthy blood-donor controls. By several measures, including a highly sensitive assay for mouse mitochondrial DNA, the team argued that the PCR results were not falsely positive due to contamination with mouse DNA.

However, as of the time of publication, many other groups have not been able to confirm the association, including in patients that previously had tested as positive for XMRV. Moreover, XMRV may be a contaminant of commercial reagents. Whether these murine viruses are associated with CFS remains uncertain. The National Institutes of Health has launched studies to develop sensitive and reproducible assays for these viruses, and a multicenter study to look for the viruses in patients with CFS, including patients previously found to be positive by the two laboratories. Hopefully, these studies will resolve the uncertainty as to whether mouse retroviruses are associated with CFS.

**ENTEROVIRAL INFECTION**

Several epidemics in different countries of an apparently infectious illness followed by months or years of fatigue were studied in the mid-20th century. Investigators initially suspected that they were atypical epidemics of poliovirus (an enterovirus). Because of their tropism for the nervous system, enteroviruses have long been suspected as etiologic agents in postinfectious fatigue syndromes. Several investigators have reported entervoiral involvement in some cases of CFS. The most provocative recent report involved 165 consecutive patients with CFS accompanied by prominent gastrointestinal symptoms. Each of them had biopsies of the gastric antrum, as did 34 control volunteers without CFS. The entervoiral antigen VP1 was found in 82% of the CFS patients versus 20% of the controls. Entervoiral RNA was found in 37% of the CFS patients versus 5% of controls. In five patient samples, transient growth of noncytopathic enteroviruses was noted. None of the samples from patients or controls were positive for antigens from a “control” enteric pathogen, cytomegalovirus. No report from another group attempting to replicate these findings has yet been reported. Some investigators have been unable to link entervoiruses to CFS through studies of blood and stool.

**PARVOVIRUS**

The development of CFS following well-documented acute infection with parvovirus B19 has been reported. One study involved 200 patients with CFS and 200 normal blood donor control volunteers. There were no differences in the frequency of IgG or IgM antibodies to structural proteins, but 42% of the CFS patients versus 7% of controls had IgG antibodies to the nonstructural protein, NS1, a marker associated with chronic and severe parvovirus infection.

**BACTERIAL INFECTIONS**

There are cases of a chronic fatiguing illness that develop in the wake of well-documented, and appropriately treated cases of Lyme disease, in which the cardinal manifestations of Lyme disease (e.g., arthritis, carditis) have resolved. However, even among patients with CFS who live in areas endemic for Lyme disease, this bacterial infection is an unusual cause of CFS.

A condition very similar to CFS has been described following Q fever, and is associated with the persistence of bacterial antigen. Cytokine dysregulation has been reported in these patients and could explain the symptoms.

**EVALUATION OF PATIENTS WITH POSSIBLE CFS**

Clinical evaluation of a patient with protracted and severe fatigue, who may have CFS, requires both assessing the possibility of other chronic, fatiguing illnesses—including multiple sclerosis, systemic lupus erythematosus, and many others—as well as verifying the presence of those symptoms that constitute the CDC case definition of CFS.

It is our clinical impression—not tested in a blinded, controlled study involving non-CFS control volunteers—that patients with CFS are more likely to have the following abnormalities on examination: posterior cervical and posterior auricular adenopathy, persistent tachycardia when moving from a recumbent to a standing position, impaired tandem gait, and abnormal Romberg test.

Although as summarized above, many laboratory and imaging tests have revealed abnormalities that are more common in patients with CFS than in various healthy control and disease comparison groups, none of these tests has sufficient specificity and sensitivity to constitute a diagnostic test. A panel convened at NIH recommended a small and inexpensive battery of laboratory tests in patients with protracted and severe fatigue, primarily to rule out other causes of fatigue: complete blood count with manual differential white blood cell count, erythrocyte sedimentation rate, chemistry panel, urinalysis, and thyroid function testing. Based on a case-control study that we conducted involving over 700 cases and controls over 10 years in two different geographic areas, the following test abnormalities may be found more often in patients with CFS:
atypical lymphocytosis, circulating immune complexes, elevated levels of IgG, and antinuclear antibodies. As patients with severe and prolonged fatigue who live in areas endemic for Lyme disease nevertheless rarely have positive serology, in the absence of Lyme-specific symptoms and signs, we do not recommend routine testing for Lyme disease.

**FUTURE DIRECTIONS FOR THE STUDY OF CFS**

The symptom constellation of fatigue, concentration/memory problems, headache, and generalized weakness is familiar to any neurologic practice. These symptoms are commonly seen in primary CNS diseases, such as multiple sclerosis; systemic diseases with secondary impact on the CNS, such as infectious mononucleosis; and in primary psychiatric diseases, such as depression. These symptoms may also occur independently of these diseases in CFS. A first step for the neurologist is to acknowledge that the syndrome of CFS can occur in the absence of psychiatric illness or malingering. The evidence suggests that objective changes occur in the CNS in the context of CFS and are distinct from depression alone. We recognize that many challenges remain in terms of defining the nature of the correlation (causality) and the specificity of the changes to CFS.

T2-weighted MRI changes and metabolic patterns on fMRI, MRS, and SPECT functional connectivity MRI may help clarify specific CNS abnormalities in CFS, help study the natural history of CFS, and provide tools for assessing response to treatment. Connecting these radiographic changes to underlying pathologic processes will remain a challenge, however, as the non-life-threatening severity of illness and lack of focal localization within the brain preclude routine studies of antemortem or postmortem brain tissue. Developments in molecular imaging may eventually help bridge this gap by allowing more specific imaging of affected brain tissue at the molecular and cellular level. The coupling of reporter molecules to cells, enzymes, or genes of interest could theoretically be applied to CFS to assess specific pathologic processes that alter brain function in CSF.

In addition to further refinement of neuroimaging, further technologic advances in virology, immunology, and genetics may elucidate the underlying mechanisms through which infection, immune response, and genetic predisposition converge in CSF. As described by Wilson and Tyler (this issue), MassTag PCR, DNA microarrays, and high-throughput DNA pyrosequencing may identify viral pathogens in encephalitis and other CNS syndromes where conventional technologies have failed.

Further research should incorporate formal neuropsychological testing, neuroimaging, and immunologic markers over longer periods to distinguish those changes that are specific to CFS as opposed to other evolving diagnoses, and to define which changes are dynamic. As with other diseases without a well-defined pathologic etiology, such as multiple sclerosis, there may be multiple underlying triggers of an inflammatory process, which in certain susceptible individuals leads to the clinical manifestations of CFS. By building on the evidence we have summarized here, our hope is that ongoing research will lead to a better understanding of CFS and thus to more effective treatment or even prevention of this debilitating disorder.

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ROLE OF INFECTION AND NEUROLOGIC DYSFUNCTION IN CHRONIC FATIGUE SYNDROME


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