

Chronic Fatigue Syndrome: Inflammation, Immune Function, and Neuroendocrine Interactions

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Investigations into the underlying cause of chronic fatigue syndrome have advanced the field considerably in the past year. Gene microarray data have led to a better understanding of pathogenesis. Recent research has evaluated genetic signatures, described biologic subgroups, and suggested potential targeted treatments. Acute viral infection studies found that initial infection severity was the single best predictor of persistent fatigue. Genomic studies showed that persistent cases express Epstein Barr virus-specific genes and demonstrate abnormalities of mitochondrial function. Studies of immune dysfunction extended observations of natural killer cytotoxic cell dysfunction of the cytotoxic T cell through quantitative evaluation of intracellular perforins and granzymes. Other research has focused on a subgroup of patients with reactivated viral infection. These advances should result in targeted therapies that impact immune function, hypothalamic-pituitary-adrenal axis regulation, and persistent viral reactivation.

Introduction

Chronic fatigue syndrome (CFS) is an illness characterized by unexplained fatigue lasting 6 months or more. The condition is not alleviated with rest and is accompanied by at least four of eight case-defining symptoms including sore throat, tender lymphadenopathy, impaired memory or concentration, myalgia, arthralgia, unrefreshing sleep, postexertional malaise, and headaches [1]. A diagnosis of CFS is made by excluding all other conditions that would cause similar symptoms. The study and clinical management of CFS is complicated by the lack of accepted biomarkers or pathogenomic signs for the illness.

CFS is characterized by a multifactorial pathogenesis. Endocrine, neuroendocrine, psychosocial, and immunologic factors mediate the physiologic response to CFS and the course of the illness. Although a consensus regarding the pathophysiology and etiology of CFS has yet to be developed, a large body of research supports a link between immune dysregulation and CFS.

A number of symptoms of CFS are linked to inflammatory processes (eg, lymphadenopathy, sore throat, myalgia, arthralgia), which has led many researchers to hypothesize that immune dysfunction causes the illness. CFS has been found to be associated with increased immune activation and inflammatory cytokine levels, with subgroups demonstrating viral reactivation and decreased cytotoxicity, alterations in lymphocyte function, activation, and subset distributions [2,3,4•,5••]. In addition, our expanded understanding of the genomics of CFS has reinforced the evidence that the illness is rooted in a biologic pathogenesis that involves cellular dysfunction and interactions between the physiologic stress response and inflammation. Progress in genetic research has provided new avenues for future study of immunomodulating therapies.

Immune Activation

Chronic immune activation has long been thought to be a component of CFS. In patients with CFS, T lymphocytes appear to be chronically activated. CD8 cells in CFS patients typically demonstrate an increase in activation markers (CD38, HLA-DR) and a reduction in CD8 suppressor cells. Levels of CD26, an ectoenzyme known to increase with cell activation, are also elevated in patients with CFS. CD26 is associated with the adenosine deaminase on T cells and plays a critical role in the immune response. Abnormal expression is also commonly seen in autoimmune diseases, HIV-related diseases, and cancer. Compared with controls, CFS patients also show significantly higher levels of CD26⁺ lymphocytes [4•].

The homeostasis between the cell-mediated or T helper (Th) 1 immune response and the humoral or Th2 immune response is disrupted in CFS. Th1 functions primarily by destroying infected human cells, whereas Th2 functions

through antibody production. Increased antibody production contributes to elevations in immune complexes, increased levels of antinuclear antibody production, and the increased prevalence of allergies among CFS patients [4•]. Some researchers have theorized that if infections can lead to an aberrant shift to an unremitting Th2 dominant response, then perhaps vaccines can cause the same reaction, because immunizations are designed to induce a persistent immunity to antigens. Although further investigation is needed, a recent study provides evidence that vaccines do not lead to CFS symptoms [6].

Functional Immune Defects

Essential fatty acids, zinc levels, T cells, and inflammation

In a series of articles by Maes et al. [7–9] cellular levels of various minerals and fatty acids were correlated with immune dysfunction. Maes et al. [7] documented significantly lower serum zinc levels in patients with CFS compared with controls and found evidence that low levels of serum zinc are related to increased signs of inflammation and defects in the early T-cell activation pathways. The results of this study showed a negative correlation between serum zinc, the severity of CFS symptoms, and the subjective experience of infection. Serum zinc was also found to be negatively correlated to increases in the $\alpha 2$ protein fraction. Levels of serum zinc showed a positive correlation with decreases in the expression of a T-cell activation marker (CD69) on CD3 and CD8 T cells. Zinc is a strong antioxidant, and diminished levels in CFS support findings that the illness is accompanied by increased oxidative stress [7].

They also documented a significant positive relationship between lowered serum zinc levels, the omega 3/omega 6 ratio, and lowered mitogen-stimulated CD69 expression on CD3⁺, CD3⁺CD4⁺, and CD3⁺CD8⁺ T cells indicating abnormal early T-cell activation. Omega 3/omega 6 and eicosapentaenoic acid/arachidonic acid ratios were significantly reduced in patients with CFS, with a significant increase in proportionate omega 6 levels. Lowered levels of omega 3 or elevated levels of omega 6 contribute to inflammation and may contribute to CFS symptoms [8].

In a later study the Maes group [9] found an immunoglobulin (Ig) M-related immune response in CFS patients directed against disrupted lipid membrane components, by-products of lipid membrane elements, by-products of lipid peroxidation, S-farnesyl-L-cysteine and nitric oxide-modified amino acids. These neoepitopes normally go undetected by the immune system but appear to become immunogenic after undergoing oxidative and nitrosative damages. This study found a significant positive correlation between serum IgM levels directed at fatty acids and the severity of illness [9].

The role of long-chain polyunsaturated fatty acids (PUFA) biosynthesis in the pathophysiology of CFS is an

important area of research. A large body of evidence links CFS to a persistent viral infection. Additional evidence suggests that such an infection may play a role in adversely affecting cell membrane structure and the functioning and production of eicosanoids by affecting the biosynthesis of PUFAs. In light of this finding, treatment with long-chain PUFAs may be an area of future promise [10].

Estrogen and immune modulation

Grans et al. [11•] showed reduced levels of estrogen receptor B mRNA in a cohort of patients with CFS. Estrogen is an important steroid hormone that plays a critical physiologic role in various processes including sexual development and the reproductive cycle. CFS prevalence rates are estimated to be two to four times higher in women. A number of autoimmune diseases including rheumatoid arthritis and multiple sclerosis also disproportionately affect females and are thought to have a hormone-related pathogenesis. Estrogen is a potential immunomodulator that functions by binding to the two estrogen receptors, ER α and ER β . These two receptors have unique and overlapping roles. Grans et al. [11•] found that among a study sample of 30 patients with CFS, lower levels of ER β cx mRNA were found in patients with a shorter course of illness. These results should be viewed as preliminary due to the small sample size in this study. However, the role of ER β wt protein levels and cellular effects are interesting candidates for future study.

Inflammatory cytokines

Suboptimal functioning of the hypothalamic-pituitary-adrenal (HPA) axis in CFS has been well documented [12,13]. Hypofunctioning of the HPA axis could lead to an exaggerated stress response and a subsequently excessive release of proinflammatory cytokines. Long-term stress increases levels of glucocorticoids and catecholamines, which over time suppress immune function.

A recent study investigated potential immunologic changes in severely fatigued adolescent girls with symptoms similar to patients with CFS and with a symptom constellation of sickness behavior [14]. The immunologic changes under investigation were the levels of mitogen-induced T-cell proliferation and T-cell mitogen- or lipopolysaccharide (LPS)-induced pro- and anti-inflammatory cytokine production. Among the three cohorts studied (severely fatigued adolescent girls, CFS patients, and nonfatigued individuals), the severely fatigued participants reported higher levels of depression, anxiety, fatigue, reduced sleep quality, somatic and CFS-related symptoms. In addition, seasonal variations in cytokine and leukocyte subset distributions were observed among the severely fatigued individuals. No immunologic differences were seen between nonfatigued and fatigued individuals. However, CFS patients exhibited a distinct immune profile compared with severely fatigued and nonfatigued individuals. These patients displayed increased anti-inflammatory cytokines

(interleukin [IL]-10, decreased interferon (IFN)- γ /IL-10 ratio) and reductions in proinflammatory cytokines (IL-6, tumor necrosis factor- α).

Viral reactivation

Some of the most robust data exploring the link between immune dysregulation and CFS has been garnered through the investigation of postinfective states. Since the illness was first described, researchers have been interested in the potential role of reactivated viruses, especially after the discovery of human herpes virus (HHV)-6 in the blood sample of a CFS patient [15]. CFS often has an acute postviral onset, and two longitudinal studies observed postinfectious chronic fatigue following Epstein-Barr virus (EBV) infection [5••,16].

In a recent study Hickie et al. [5••] demonstrated that CFS is a fairly common sequel of several types of viral and nonviral infections including EBV, Q fever, and Ross River virus. The investigators conducted a prospective observational study in one rural township in Australia, which confirmed the presence of a postinfective fatigue syndrome linked to these three infections. Among 253 patients, 12% experienced a postinfective fatigue that was present 6 months after acute infection. The best predictor of prolonged fatigue was the severity of the acute infection. Premorbid mood disorders and other potential psychiatric risks were not predictive of risk for prolonged fatigue. This work confirms previous findings that the severity of the acute illness rather than the infective pathogen appeared to be the critical determinant of postinfective fatigue syndrome [16].

Chapenko et al. [17] recently found a significantly higher prevalence of persistent/latent HHV-6 infections and dual HHV-6 and HHV-7 infections among patients with CFS. The study compared levels and characteristics of viral infection using nested polymerase chain reaction, restriction endonuclease analysis, and flow cytometry in 17 patients with CFS, 12 patients with unexplained chronic fatigue, and 20 healthy controls. Researchers found active HHV-6 and dual HHV-6 and HHV-7 infections only in CFS patients, and these infections were present in 40% of those tested. Based on these findings, the researchers concluded that HHV-6 and HHV-7 may be involved in the pathogenesis of CFS and that reactivation of both viruses could cause changes in circulating lymphocytes and a state of chronic immune activation [17].

Petersen et al. [18•] recently published prevalence figures for fatigue post-EBV infection. Their study found an immediate link between EBV infection and fatigue, but also found that the median duration of fatigue was 8 weeks and the majority of the patients recovered within 1 year. Only one of the 10 patients studied had an additional record of fatigue. Based on these findings, the authors concluded that acute fatigue after EBV infection and CFS may share some risk factors but most likely do not share the same etiology [18•].

Enteroviral infections can cause acute respiratory and gastrointestinal infections with tropisms for the heart, muscles, and central nervous system. Enteroviruses have been evaluated in several studies, with early data from Gow et al. [19] initially suggesting muscle infection; however, the same group failed to find levels higher than those in controls in later studies. Maes et al. [20] found elevated serum levels of IgA and IgM against the LPS of gram-negative enterobacteria in a group of CFS patients, indicating increased gut permeability and an anti-LPS immune response. Researchers noted that the intestinal barrier may be weakened by factors that have been shown to trigger CFS such as psychologic stress, strenuous exercise, allergies, surgery, and trauma. These same factors may induce inflammation, immune activation, and oxidative stress. Inflammation may then increase the permeability of the gastrointestinal barrier, and they suggested this may lead to autoimmunity or increased inflammation in patients with an existing fatigue syndrome. Based on these findings, the authors suggested that patients with CFS and other forms of chronic fatigue should be assessed for the presence of increased gut permeability through the measurement of IgA/IgM against the LPS of gram-negative bacteria. The authors also recommend using certain antioxidants to treat patients with increased gut permeability [20].

A recent study evaluated the presence of chronic enterovirus infections in patients with CFS experiencing chronic gastrointestinal complaints [21••]. The study took stomach biopsy specimens from 165 patients with CFS; 82% of CFS patients tested positive for the presence of viral capsid protein 1 within parietal cells compared with only 20% of controls. In addition, enterovirus RNA and noncytopathic viruses were also detected in a subsample of subjects tested. Based on these results, investigators concluded that a significant subset of CFS patients may have a chronic, noncytolytic, potentially disseminated enteroviral infection, which could be diagnosed through stomach biopsy. The investigators noted the tropism with brain and muscle and suggested that the neuroinflammation seen in neuroimaging studies of a subgroup of CFS patients may result from enteroviral infection.

Genomics and Proteomics

Gene expression microarray data has become a highly productive tool in better understanding CFS research. A group of research studies supported by the US Centers for Disease Control and Prevention led to a series of 14 articles published in a dedicated issue of *Pharmacogenomics* in April 2006. These publications were the result of a multidisciplinary endeavor among an international cadre of 20 molecular biologists, epidemiologists, mathematicians, engineers, and other scientists, who independently analyzed genomic, laboratory, and clinical data collected from 227 study participants. During a 2-day hospital stay, the study participants underwent a comprehensive battery of tests that included measurements

of cognitive function, sleep physiology, autonomic nervous system function, and blood analyses of the sequencing and expression of over 20,000 genes. Mitochondrial and ion channel regulatory genes were dysregulated. Microarray data also showed upregulation of proinflammatory cytokine pathways, and subgroup analyses linked different patterns of endocrine, immune, and metabolic dysregulation that identified as many as six subgroups of CFS. Although the investigators could not identify a definitive genetic marker for CFS, they were able to identify 28 single nucleotide polymorphisms to predict with 76% accuracy whether an individual had CFS.

These investigators also found that patients with CFS and control patients demonstrated different levels of gene expression for genes affecting the HPA axis and the sympathetic nervous system. Genes that modulate physiologic response to chemical messengers like hormones released as part of a normal stress response were altered in the CFS group. These data from gene arrays and single nucleotide polymorphisms are consistent with the studies of Jerjes et al. [22••] and others that have shown an enhanced sensitivity of the HPA axis to negative feedback in CFS, as demonstrated using the prednisolone suppression test. Abnormal stress responses in patients with CFS and the link between the deregulation of immune function and abnormalities in HPA axis activity have been investigated in several studies. Another study, published this year by Rajeevan et al. [23] identified sequence variations in the glucocorticoid receptor gene (*NR3C1*) in patients with CFS. *NR3C1* is a key effector of the HPA axis. The study demonstrated that *NR3C1* is a potential mediator of CFS, and further study into variations in this area may broaden our understanding of how CFS manifests [23].

Recent studies using microarray technology have suggested that infectious agents may trigger and perpetuate CFS symptoms. A study by Vernon et al. [24••] found evidence of mitochondrial dysfunction in cases of postinfective fatigue caused by EBV. The investigators compared subjects with acute mononucleosis who developed postinfective fatigue of more than 6 months' duration to HLA-matched subjects who recovered within 3 months. The gene expression profiles of subjects who displayed a postinfective fatigue response lasting more than 6 months differed from those of the controls. Six genes known to be activated during EBV infection were differentially displayed in the postinfective fatigue cases. A number of these differentially expressed genes are known to affect mitochondrial functions, including fatty acid metabolism and the cell cycle [24••].

Immunology Dysregulation and Treatment Modalities

Immune dysregulation has been described by many groups, with evidence of cellular dysfunction and chronic immune activation described in early articles on CFS [25,26]. Studies of the mechanisms of immune dysfunction attempt to

discover targets for immune-based therapies. Research into treatments that target humoral immune response and viral loads are important areas of investigation.

Natural killer cell and cytotoxic T-cell dysfunction: interferon β use

Natural killer cells are versatile lymphocytes, which—in healthy individuals—can destroy infected cells. Patients with CFS often have reduced natural killer cell cytotoxic activity [27,28,29•]. Maher et al. [4•] found that the natural killer cells of patients with CFS had abnormally low levels of perforin, which natural killer cells use to penetrate infected cells and inject cytotoxic granzymes. Perforin plays a critical role in immune surveillance and immunomodulation; therefore, a decrease in perforin levels may play a role in the pathogenesis of CFS. This study was the first to examine cytotoxic T cells in CFS. The authors describe a decrease in perforin and granzyme content of the cytotoxic T cells equal to that seen in natural killer cells. The clinical implications are consistent with an immune system that may allow viral reactivation and raises a concern for tumor surveillance as well.

Some researchers have proposed that natural killer cell activity (NKCA) could be used as an immunological subgroup marker in CFS. Siegel et al. [29•] found that relative to CFS patients with normal NKCA, patients with low NKCA levels reported more cognitive dysfunction, more daytime impairment, and less vigor. These patients also scored lower on objective measures of cognitive function relative to patients with normal NKCA levels. Immunomodulatory therapies that target natural killer cell and cytotoxic T-cell function would seem reasonable, using functional and quantitative flow to identify the appropriate subgroup [30•].

One such therapy is postulated by Kerr et al. [30•]. IFN- β , a licensed treatment for multiple sclerosis, may hold some hope for patients with CFS. To date, no trials have tested the efficacy of IFN- β on patients with CFS, but the theoretical support for such a trial is compelling. Much like CFS, the pathogenesis of fatigue in multiple sclerosis is thought to be cytokine mediated. IFN- β is known to regulate humoral immune responses and response to viral infection. IFN- β increases the activity of natural killer cells and the expression of human leukocyte class 1 antigens while blocking the expression of human leukocyte class 2 antigens. In addition, it can selectively inhibit the expression of several genes implicated in genomic studies of patients with CFS. Based on gene expression data, studies are planned to explore CFS treatment with IFN- β . A clinical trial of IFN- β is expected to begin at St. George's University in London.

Antiviral treatments

At the 2007 International Association of Chronic Fatigue Syndrome meeting, investigators presented two phase 1 studies of valganciclovir in CFS patients with evidence of HHV-6 or EBV infection. Kogelnik et al. [31•] found

evidence of clinical improvement in 20 of 23 subjects with acute onset CFS and high EBV and/or HHV-6 antibody titers. Lerner et al. [32•] presented data from an open-label phase 1 trial supporting EBV reactivation affecting cardiac function in profoundly ill CFS patients. The study, which was a follow-up to his previously published study of 19 CFS patients with cardiac wall motility abnormalities, showed a favorable clinical response from most of the 60 patients to 6 months of oral valganciclovir. Both investigators cautioned that the drug had a significant risk of bone marrow suppression and renal toxicity, and phase 2 placebo control studies are underway.

In an open-label study of folic acid, authors reported a high incidence of chronic reactivated EBV infection accompanied by B-cell immunodeficiency in patients with CFS. A significant proportion of these patients experienced a marked improvement in symptoms after treatment with folic acid [33].

A retrospective study measuring the response of patients with CFS to azithromycin found that 58 of the 99 participants reported a decrease in symptom severity [34]. The responders improved to an estimated maximum of 80% of their premorbid level. Those patients who responded to the treatment had lower levels of plasma acetylcarnitine. The investigators theorize that the efficacy of the azithromycin could be attributed to the modulating effect on the chronically primed immune glia-cells in the brain or in the activated immune system of the patients with CFS.

Conclusions

The preponderance of available research confirms that immune dysregulation is a primary characteristic of CFS. New research has further elucidated our understanding of the genomics of the illness and the role of viral infection and reactivation in the pathogenesis. Advances in the field should result in targeted therapies to impact immune function, HPA axis regulation, and persistent viral reactivation in CFS patients. Future research investigating these important areas may lead to promising new discoveries and options for treating CFS.

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