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Chronic fatigue syndrome: neurological findings may be related to blood–brain barrier permeability

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Summary Despite volumes of international research, the etiology of chronic fatigue syndrome (CFS) remains elusive. There is, however, considerable evidence that CFS is a disorder involving the central nervous system (CNS). It is our hypothesis that altered permeability of the blood–brain barrier (BBB) may contribute to ongoing signs and symptoms found in CFS. To support this hypothesis we have examined agents that can increase the blood–brain barrier permeability (BBBP) and those that may be involved in CFS. The factors which can compromise the normal BBBP in CFS include viruses, cytokines, 5-hydroxytryptamine, peroxynitrite, nitric oxide, stress, glutathione depletion, essential fatty acid deficiency, and N-methyl-D-aspartate overactivity. It is possible that breakdown of normal BBBP leads to CNS cellular dysfunction and disruptions of neuronal transmission in CFS. Abnormal changes in BBBP have been linked to a number of disorders involving the CNS; based on review of the literature we conclude that the BBB integrity in CFS warrants investigation. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Chronic fatigue syndrome (CFS) is an illness characterized by the primary complaint of persisting or relapsing fatigue, and is often accompanied by numerous neurological symptoms. These symptoms can include impaired cognition, sleep disturbances, headaches, visual disturbances, parasthesias, and gait abnormalities (1,2). Although the etiology of CFS remains unclear, there is mounting evidence which points to central nervous system (CNS) involvement in the pathogenesis of CFS (3,4).

The blood–brain barrier (BBB) protects the neural tissue of the (CNS) by way of endothelial cells that form tight junctions with one another. These occluding junctions are non-fenestrated and form a highly protective barrier to the diffusion of substances from the blood to the brain. Large organic molecules and plasma proteins are almost completely excluded, while small lipid soluble materials can freely move through the barrier (5). In addition to restricting non-specific permeation from circulation to the brain, the BBB removes xenobiotics from the brain by way of an active efflux transport system (*6*). This specialized microvascular system is necessary to maintain the stability of the CNS.

It is our contention that the integrity of the BBB may be compromised in CFS, contributing to the development of CNS symptoms. We will review the literature related to those factors that can lead to abnormally increased blood–brain barrier permeability (BBBP) and discuss coexisting factors in CFS to support our hypothesis.

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CFS AND THE CENTRAL NERVOUS SYSTEM

There are numerous studies that indicate that CFS is a disorder involving the CNS. Investigators using MRI have shown that CFS patients have white matter abnormalities present more often than healthy volunteers (*7–9*). Subcortical areas of the frontal lobes can be involved and it is

reported that these MRI abnormalities may represent areas of edema or demyelination of the white matter (7,8). These lesions of the CNS observed on MRI may account for the cognitive difficulties observed in CFS patients (9).

Single photon emission computed tomography (SPECT) has been used in several studies and has shown abnormalities among CFS patients. Research shows that CFS patients have abnormal perfusion in several brain regions, including the brain stem (10–13). Investigators conclude that the CNS dysfunction could be due to primary CNS damage or secondary systemic factors (13). The abnormalities appear to be related to cerebral hypoperfusion or CNS cellular dysfunction (10).

Various studies have found evidence of hormonal and neurotransmitter abnormalities in CFS patients. Researchers have found alterations in norepinephrine (14,15) and serotonin levels (14,16–19). Lower levels of arginine-vasopressin have been reported (20) as well as a mild, centrally induced adrenal insufficiency (21).

Nonspecific dysequilibrium is another common complaint among CFS patients. Two separate studies have examined vestibular function to determine the type of balance dysfunction. In both studies, the researchers concluded that the vestibular function test anomalies found in CFS patients are suggestive of CNS deficits (22,23).

An additional indicator of CNS involvement comes from the alterations in gait which have been observed in CFS patients. Alterations of hip angle, knee flexion, and various spatial and temporal parameters of gait have been found (24,25). Recent research has shown that the gait abnormalities are present before rapid increasing fatigue becomes a factor, thus pointing to direct CNS involvement (25).

CFS patients commonly report sleep dysfunction. According to one study, approximately 70% of CFS patients complain of problems with sleep (26). Researchers have found evidence of objective sleep dysfunction among CFS patients including alpha rhythm intrusion, resulting in absence of deep sleep, periodic movement disorder and sleep apnea (27,28). The sleep disturbances of CFS appear to be secondary to the illness as frank treatment of sleep disorder does not lead to complete resolution (28).

Further evidence of CNS involvement in CFS comes from a number of studies that have demonstrated that cognitive deficits exist in this population. Findings include memory and learning impairments (29,30), psychomotor slowing, decreased attention and impaired visual recall (31). Impaired information processing also appears to be a significant deficit among CFS patients (32–34). Researchers have also found evidence of significant prolongation of central motor conduction time by recordings of motor evoked potentials in CFS (35).

Thus there is substantial supporting evidence in the literature connecting CNS deficits to CFS. Despite this evidence, the etiology or mechanism of CNS dysfunction remains unclear. In order to support our hypothesis that the integrity of the BBB is compromised in CFS, it is necessary to examine those factors related to CFS that can increase BBBP.

BBB, CFS, AND IMMUNE RESPONSE TO VIRAL INFECTION

It has been found that viral replication in cerebral endothelial cells can increase BBBP through both direct and immune-mediated damage (36). Cytokines produced during the viral immune response have been implicated in directly increasing BBBP in animal models (37). Specific cytokines, TNFα and IL-6 have been shown to increase BBBP in experimental acute pancreatitis (38). Cytokines can induce nitric oxide (NO), which can increase BBBP through a number of mechanisms including histamine production (39) and through increased peroxynitrite levels (NO reacts with superoxide to form the potent oxidant peroxynitrite) (40). Increased peroxynitrite (ONOO-) levels can lead not only to increased BBBP but also CNS demyelination in animals (41). The potent ONOO-scavenger, uric acid, is capable of lowering ONOO-levels which in turn lowers the abnormally increased blood–CNS barrier in animals (42).

Damage to the BBB has been found to be associated with HIV induced CNS symptoms (43). Recent findings indicate that this BBB dysfunction in HIV infection is correlated with increased cerebrospinal fluid and serum nitrite and nitrate levels. Researchers conclude that CNS related symptoms in HIV are associated with NO and ONOO- mediated damage to the BBB (44).

Over the last 15 years, investigators have examined the role of a number of viruses as an etiological agent of CFS. Although no singular virus has been found to be uniformly present, specific viruses have been implicated, including Epstein–Barr (45), Human Herpes Virus #6 (7) and enteroviruses (46). Perhaps one, or a combination of these viruses, can influence the BBBP of a susceptible individual under stress, either directly or through the immune response.

Elevated cytokines have been found in CFS including INFα, TGFβ, IL-6, IL-1α and TNFα (47–51). These cytokines are capable of increasing NO/ONOO-levels, and if sustained, may account for many of the symptoms of CFS (52). It is quite possible that cytokine and NO/ONOO-mediated BBB dysfunction can occur in CFS.

BBB, CFS AND SEROTONIN

In animal models there is evidence that 5-hydroxytryptamine (5-HT) plays an important role in the breakdown of normal BBBP. Under stressful conditions such as summer

heat and forced swimming, a correlation was found between increased plasma and brain 5-HT levels and increases in BBBP (53–55). Furthermore, when blood serotonin levels were increased in animals not under stress, investigators found increased BBBP and resultant desynchronization of spontaneous cerebral cortical activity. This increased BBBP was prevented when cyproheptadine, a serotonin antagonist, was administered. Researchers conclude that increased 5-HT in blood can induce abnormal neuronal function via increased BBBP (56).

In CFS, investigators have found elevated levels of plasma 5-hydroxyindolacetic acid (5-HIAA, serotonin metabolite) (14). Recently, urinary levels of 5-HIAA have also been found to be elevated, indicating increased serotonergic activity (19). Other researchers have found evidence of increased 5-HT activity through buspirone challenge (17) and D-fenfluramine administration (16,18).

It is evident that serotonergic dysfunction can be a feature of CFS. In following the animal model, it is possible that the integrity of the BBB in CFS patients is compromised due to chronically elevated serotonin levels. Stress may be an important factor related to the serotonin mediated increases in BBBP among CFS patients.

BBB, CFS AND STRESS RESPONSE

Research indicates that major stressors play an important role in the onset and exacerbations of many human illnesses including infections and autoimmune disease (57,58). Of importance to our hypothesis is the research which has demonstrated that physical and psychological stress can compromise the integrity of the BBB in the animal model. The effects of stress on the BBB are thought to be moderated by catecholamines released during the stress response (59).

Studies have shown that under cold or isolation stress (60), summer heat stress (53,54,61) immobilization stress (62–64) and forced swimming exercises (55,65) the BBBP is increased. This increased BBBP under stress can allow for viral entrance to the CNS (60). Stress induced alterations of BBB can also lead to alterations of brain electroencephalogram readings (64). While most studies on the BBB have been performed on animals, there is evidence of increased BBBP in humans under stress. Researchers discovered that peripheral administration of pyridostigmine, an acetylcholinesterase inhibitor, in Israeli soldiers during the Gulf War resulted in a three-fold increase of CNS symptoms (66). These symptoms included headaches, sleep disturbances and cognitive difficulties. Pyridostigmine, when administered peripherally to healthy volunteers, resulted in only peripheral side-effects such as diarrhea, sweating and salivation (67,68). Pyridostigmine was then administered in lab animals under stress, and it was discovered that the dose required to inhibit brain acetylcholinesterase by 50% was 1/100th that required in non-stressed animals (68).

Stress appears to play a major role in onset and exacerbations of CFS. Some investigators have referred to CFS as a disorder of stress, noting the influence of physical and psychological stressors (69). Research into the influence of stress at onset of CFS has resulted in various findings. While Wood and colleagues found 33% of patients had a major stressful life event in the 6 months preceding fatigue onset (70), other investigators have reported higher numbers. In a much larger study, Salit found that 85% of CFS patients had stressful events in the year preceding CFS onset vs 6% of controls (71). In examining physical, behavioral, and psychological risk factors for CFS, Dobbins et al. found that 95% of patients reported increased levels of stress in the 5 years prior to illness vs 55% of controls. A relationship was also found between the number of sources of stress and risk of CFS. The highest risk was when three or more sources of physical and/or psychological stress were reported (72). Theorell and colleagues found an almost two-fold increase in prevalence of both infections and negative life events in the 3 months preceding the onset of CFS (73). The belief of many CFS patients is that a combination of infection and stress resulted in the illness (74). Investigators have also found that those who reported to a doctor with a viral infection were more likely to develop CFS if they were under psychological distress (75).

Recent literature has demonstrated the ability of emotional stress to exacerbate the symptoms of CFS. Researchers found that the severe environmental trauma of Hurricane Andrew worsened the symptoms of CFS, including the CNS related symptoms of headaches, sleep disturbances and cognitive complaints. There was a correlation between increased CFS exacerbations and closeness to the high impact areas of South Florida. The patients post-hurricane distress response was the single strongest predictor of the likelihood and severity of relapse (76).

As with many illnesses, stress appears to play a role in CFS onset and/or exacerbations. Researchers have shown that plasma levels of adrenaline are substantially higher among CFS patients (77). Catecholamines may, along with other factors discussed, play a role in BBBP changes in CFS. Future investigations could use brain imaging to determine if major stressors are related to increased abnormalities among CFS patients. In the case of multiple sclerosis, stressful life events appear not only to worsen the symptoms (78) but also cause the development of new brain lesions as observed through imaging (79).

BBB, CFS AND GLUTATHIONE

Glutathione (GSH) depletion has been found to be related to increased BBBP in animals (80–82). Increased BBBP is

also associated with decreased levels of the antioxidant enzyme glutathione peroxidase (83,84). In one study administration of N-acetylcysteine, methionine and GSH were all found to be helpful in restoring GSH levels and preventing increased BBBP among GSH depleted animals (81).

GSH depletion is thought to be involved in the pathogenesis of CFS. Researchers have found that CFS patients have low levels of blood glutathione (85) and its precursor, cysteine (86). It is possible that immune system demand for GSH precursors may be so high in CFS that depletion can occur (87). An informal trial using weekly intramuscular injections of 1 cc GSH/ATP has shown promising results. Of 276 CFS patients treated over six months, 82% reported improvements in fatigue and 71% reported improvements in memory and concentration (88).

BBB, CFS AND ESSENTIAL FATTY ACIDS

Essential fatty acids are incorporated into and play an important role in normal BBB function (89). Researchers have found that essential fatty acid (EFA) deficiency in animals can alter the normal BBBP (90,91). One study showed that the BBBP was increased in EFA deficient animals with experimental allergic encephalomyelitis (animal model of multiple sclerosis), thus suggesting that EFA deficiency may play a role in multiple sclerosis (92).

EFA deficiency has been implicated in CFS, both through abnormalities of EFA metabolism (93) and through viral and immune induced deficiencies (94). The administration of EFAs, including combined gamma-linolenic, eicosapentaenoic and docosahexaenoic acids, has led to marked improvement in one study. Researchers found that 85% of those CFS patients treated with EFAs showed improvement vs 17% on placebo. Initially, the CFS patients showed low baseline plasma EFA levels and elevated monounsaturated/saturated fatty acid levels. These levels were normalized after the 3–T month trial (95). It is possible that a viral induced EFA deficiency, or a defect in EFA metabolism among certain CFS patients could affect the BBB integrity.

BBB, CFS AND NMDA RECEPTORS

It has been proposed that the CNS disturbances observed in CFS are a result of the N-methyl-D-aspartate (NMDA) overactivity (96). The NMDA receptor is an excitatory receptor that can lower the firing threshold of neurons and lead to CNS stimulation. Overactivity of the NMDA receptor can result in peroxynitrite formation (97,98) and neuronal loss (99). If, indeed, excessive stimulation of the NMDA receptors to excitatory amino acids such as glutamate and aspartate does occur in CFS, then increases in BBBP will likely follow. A number of investigators have found that NMDA overactivity in animals leads to excitotoxicity and associated inappropriate increases in BBBP (99–101).

DISCUSSION

Researchers have examined the role of disturbed BBBP in an effort to understand a number of medical conditions with CNS involvement. The conditions in which increased BBBP has been implicated as part of the pathophysiology include multiple sclerosis (40), Alzheimer's disease (102), systemic lupus erythematous (103), psychoses (104), and HIV infection (44). While there is substantial evidence that CFS is a disorder that involves the CNS, the mechanisms of this involvement remain unclear. The BBB provides protection and ensures the normal stability of the CNS. The integrity of the BBB could be compromised in CFS that may be a contributing factor in the onset or exacerbations of the illness.

We have reviewed the literature and found a strong connection between factors which can increase BBBP and which also may be present in CFS. We conclude that one, or more likely, a combination of factors may affect the BBB in CFS. These factors include viruses, cytokines, 5-HT, NO, ONOO-, GSH depletion, stress response, EFA deficiency and NMDA overactivity. With increased BBBP, potential neurotoxins can gain access to CNS tissue, causing cellular dysfunction and disruption of proper neuronal transmission. Neurotoxicity by way of increased BBBP is one mechanism that can account for the various CNS related signs and symptoms among CFS patients. Despite a large volume of research, the etiology and pathogenesis of CFS remains elusive, investigators should examine the BBB as its integrity could certainly play an important role in this debilitating illness.

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