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Pathogenesis of Chronic Fatigue Syndrome, a Multisystem Hypothesis

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ABSTRACT. Fatigue is a very common complaint with a number of meanings. If the fatigue lasts for more than 6 months, it fulfills the definition of "chronic." The Center for Disease Control (CDC) has established specific criteria for the diagnosis of CFS. This is characterized by a persistent or relapsing debilitating fatigue for at least 6 months in the absence of a medical diagnosis that would otherwise explain the clinical presentation. CFS represents a heterogeneous group of patients that manifest symptom complexes with varying degrees of fatigue, limited exertional reserve and cognitive dysfunction. This treatise explores the pathogenesis of CFS as it relates to a complex multidimensional systemic process and offers a hypothesis for the disease processes. In particular, an up-regulated immune system, affecting mitochondrial dysfunction is described. These pathophysiologic mechanisms impact and in turn are being impacted by the neuroendocrine system and the HPA axis. In addition, the cardiovascular system involving blood pressure and heart rate anomalies along with neurocognitive pathology is characterized.

KEYWORDS. Fatigue, chronic fatigue syndrome, CFS

INTRODUCTION

Chronic Fatigue Syndrome (CFS) is an enigmatic, potentially disabling, process. The manifestations of this entity probably represents the end product of a several heterogeneous populations, most likely involving complex interplays of multiple systems. This treatise has been developed through search of the literature and directed by participation in state of the art workshops, such as those sponsored by the NIH and the American Association for Chronic Fatigue Syndrome.

DEFINITIONS

Fatigue is a very common complaint with a number of meanings. These include exhaustion; perceived decrease in mental or physical functioning; delay in recovery after demanding physical or mental activity; weariness or unrefreshing sleep. If the fatigue lasts for more than 6 months, it fulfills the definition of "chronic." The Center for Disease Control has established specific criteria for the diagnosis of CFS (1,2). This is characterized by a persistent or relapsing debilitating fatigue for at least 6 months in the absence of a medical diagnosis that would otherwise explain the clinical presentation.

The prevalence of the illness among patients seeking primary medical care for any reason has been estimated to be as low as 1 in 100 (3). While in the general community, prevalence has been estimated at -1 in 1,000 (4), other reports suggest greater than half a million US citizens are likely to have typical CFS. A significantly higher proportion of the population has unexplained chronic fatigue that may share the pathogenesis of CFS (5).

CFS probably represents a heterogeneous group of patients that manifest symptom complexes with varying degrees of fatigue, limited exertional reserve and cognitive dysfunction. Other common symptoms related to this entity include arthralgias, myalgias, headaches, lymphadenopathy and sleep disturbances. The present "State of the Art" regarding the pathogenesis of CFSis that of a complex, multidimensional systemic process.

In particular, the literature supports an up-regulation of the immune system (6-15), that is probably triggered by some stress (16,17), in susceptible individuals (18). That stress, in the majority of cases, usually follows either a viral or bacterial infection (16,19). In the vast majority of cases, this is felt not to represent an ongoing infectious process (6). Other stresses such as surgery or motor vehicle accidents, in susceptible individuals, may initiate this process (16,19). Not only is the immune system involved, but also neuroendocrine functions manifesting as an aberration of the HPA axis is seen (20-26). In addition, the cardiovascular system involving blood pressure and heart rate anomalies, with an increased incidence of dysautonomias has been identified (27,29). In addition, there are abnormalities of neurocognition manifesting as disorders in, memory, calculation and word finding (30-36), as is often described by patients as "brain fog."

ETIOLOGY

Remaining unclear, the majority of individuals affected' (-60-80%) have historically undergone some "viral like" process, classically described by patients as "I got the flu with aches and pains and I have never been the same since" (16,19). Different infectious agents have been described in the literature to be associated with CFS, such as EBV, HHV -6, other herpes viruses, *Borrelia* (Lyme) and *Mycoplasma.* But there has been no consistent cause and effect relationship established (37). Although on occasion, occult active infections with agents such as *Borrelia* and Hepatitis C may present with "CFS like" symptoms, the presence of these entities by definition, rules out the diagnosis of CFS. In addition, reported during the 2003 6th International Conference on CFS and related diseases, Peterson described a small cohort of individuals who had been categorized as having, out who subsequently were found to have clinical HHV -6A infection (38). However, this needs to be tempered with the consistent finding that the majority of cases of CFS are felt to be noninfectious. In essence, although there is an infectious process that often initiates the syndrome in the majority of cases, the ongoing symptom complex is presumably being perpetuated by an as yet to be defined "chronic process." This review explores the interplay of some possible mechanisms.

GENETIC PREDISPOSITION

Buchwald et al. have performed twin studies (17), with the conclusion that supports familial aggregation of fatigue. Her impressions were, that genes might playa role in the etiology of chronic fatigue syndrome (17). In this study, characterizing different groups of fatigued individuals, the concordance rate for chronic fatigue in general, was found to be greater in monozygotic, as opposed to dizogotic twins. This was statistically significant when evaluating those with idiopathic chronic fatigue not explained by the medical or psychiatric criteria ($p = 0.042$). Their assessment suggested that the relative rate of genetic influence, in the setting of "Chronic Fatigue Not Due to Medical or Psychiatric Exclusions" (i.e., CFS), was ~51 %.

ENVIRONMENTAL EXPOSURE

Post Infectious

Recent reviews have noted the onset of CDC defined CFS were clearly temporally related to several well-identified infections (39). In particular, CFS has been noted to follow acute infectious mononucleosis. Whereas early in the categorization of this process, there were many in the field that felt this could represent a "chronic EBV" infection, the current general consensus is that this more probably reflects a state of chronic immune deregulation (39). Post Lyme disease CFS has also been identified (18,40,41). Repeated cases of CDC defined CFS have been noted to evolve after a clear clinical diagnosis of Lyme's disease, with appropriate serologic confirmation and after appropriate, IV antibiotics. Marmion et al. have described a post Q fever protracted fatiguing illness (42). Human Herpesvirus-6 (HHV -6) is reactivated more frequently in

patients with CFS compared with controls (43-46). However, like EBV, infection with HHV -6 is ubiquitous, and it is possible that the reactivation of HHV -6 in patients with CFS is a secondary event, reflecting immune deregulation (39). Alternatively, with respect to HHV-6 type A infection, Dan Peterson, during the 2003 6th International AACFS conference described a series of 135 CFS patients with profound neurologic symptomatology who underwent CSF analysis. In this cohort of 135, 27 were found to be PCR positive for HHV-6A. This group subsequently underwent antiviral therapy (primarily IV Foscarnet) and according to Dr. Peterson, "they all returned to work" (38). This "subgroup" would then need to be removed from the CFS category and defined specifically as clinically having chronic HHV -6A infection. This thus would represent an exclusionary feature to the diagnosis of CFS (i.e., "other chronically fatiguing illnesses").

Borna disease virus (BDV) is a newly classified virus that has been implicated with CFS (47,48). However, these are early studies have not been corroborated by others (49). In an attempt to better clarify this issue, Salit retrospectively investigated precipitating factors in 134 CFS patients and 35 controls through the use of a questionnaire, interview, clinical examination and serology for infecting agents (19). Serological analysis assessed the following agents: CMV and respiratory viruses (complement fixation), Epstein-Barr Virus (VCA, EA and EBNA), Lyme disease (ELISA and immunoblot) and enteroviruses (Coxsackie and Echovirus by neutralization). Definite infections were those with a four-fold change in titer, isolation of the infecting agent or where the clinical syndrome was diagnostic (e.g., dermatomal *Herpes zoster).* Probable infections had high, but stable serologic titers and a compatible clinical illness or there was an infectious syndrome (e.g., pneumonia, aseptic meningitis, etc.) but there was no proof as to the etiology. A definite infection was identified in only 7 of these 96 (7%). These included EBV in 2, *Borrelia burgdorferi* in 2, *Brucella abortus* in 1, Influenza in 1, *Herpes simplex* in 1 and *Herpes zoster* in 1. The general presentation of these "post infectious" patients involved symptoms of low grade fever, malaise, headache, generalized aches and some respiratory symptoms ("flu-like illness"). Other symptoms in some patients included nausea, vomiting and diarrhea. Some degree of fatigue was present even during the acute illness. However, the fatigue generally became more pronounced or more apparent, when the flu-like illness dissipated and the patients tried to return to normal activities.

Noninfectious

The corollary to this 77% "post infectious" category, is the group of thirty-eight (23%), that had no apparent infectious onset. This is supported by McDonald et al. who also found that 28% did not have a clearly defined illness at onset (16). Salit found 15/38 (40% of this group) had specific noninfectious precipitants (trauma-usually motor vehicle accidents, allergy, surgery). There was no apparent precipitating event in 23/38 (61% of this group). Immunization (with hepatitis B, tetanus, influenza, DTP, Polio or Rubella) did not appear to be a significant precipitant. Stressful events were very common in the year preceding the onset of CFS (114/134 or 85% of the total group). This level of stress exposure was compared to only 2/35 (6%) of the healthy controls ($p < .0001$).

Cellular Insult

Pall has described what he terms "The Peroxynitrite Hypothesis," which describes a cellular mechanism of oxidative stress that can conceivably be playing a role in the genesis and perpetuation of CFS (50). Peroxynitrite is a powerful oxidant formed from the reaction of two relatively nonreactive free radicals, nitric oxide and superoxide. A specific isozyme of peroxynitrite has been shown to be highly induced in response to four different inflammatory cytokines: interferon-y (IFNy), interleukin-l_ (IL-lbeta), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) (51,52). These are also induced by viral infection or the presence of bacterial antigens (53). In essence, the presence of infections or remnants of infections by virtue of activation of the immune system, can induce elevated levels of the highly reactive oxidant peroxynitite. One potential mechanism by which this phenomenon can be responsible for symptoms related to CFS is the impact on inactivating several of the enzymes in mitochondria, so that mitochondrial and energy metabolism

dysfunction occur (54,55). Pall then proposes several feedback mechanisms by which peroxynitrite levels are magnified and perpetuated, impacting on such systems as the HPA axis (50).

MULTISYSTEM INVOLVEMENT

Immune System

As already alluded, there is much support in the literature regarding the relationship between the immunologic system and chronic fatigue syndrome. The best validated work and most consistent findings demonstrate decreased function of natural killer cells (8-10) and reduced responses of T cells to mitogens and other specific antigens. NK cell activation is regulated by cytokines, including interleukin-2(IL-2) and interferons (IFNs). In addition, increased serum levels of IL-6 and IL-l-alpha have been reported (12). Interleukin-6 exerts its fatigue-enhancing effects via numerous endocrine and metabolic pathways (13). This includes stimulation of HPA axis activity and growth hormone secretion and the inhibition of thyroid stimulating hormone. These findings lend support to a multisystem relationship.

Treatment with IL-l can often be associated with symptoms of CFS, such as low-grade fevers, arthralgias and malaise (14). Whereas improved cytokine balance is associated with an improved sense of well being. Note that the commonly described cyclic nature of CFS symptoms may be due to the changing production of these cytokines. Whiteside and Friberg (59) have identified a "cyclic rather than persistent" decrease in NK cell activity in some patients. This potentially supports the "cyclic" nature of CFS symptoms. Numerous reports in the literature identify an association of NK cell activity and stress (15,48,56,57). Especially activated NK cells are capable of crossing the blood-brain barrier and are present in the brain in certain pathologic states (58). A possible mechanism for an Immune/CNS interaction may in part relate to altered vascular permeability caused by cytokines (including IL-2) that are secreted by activated NK and T cells. Some of these activated NK cells may cause local damage to the CNS cells (59). This pathophysiology could potentially explain the neuroendocrine and neurocognitive dysfunction described below.

Alternatively, Ottaway and Husband have shown a direct response of the sympathetic nervous system on lymphoid tissue (60). Specific behavioral challenges affecting the sympathetic nervous system were then found to have impact on lymphoid tissue and lymphocytes (60). Thus there appears to be an interplay in both immune system affects to the central nervous system, and vice versa. According to Hurwitz et al., there is support in the literature to suggest a link between IL-l and TNF activation and cardiovascular dysfunction (14). IL-l induces prostaglandin synthesis (e.g., PGI2) by the endothelium and smooth muscle (61-63); and PGI2, a potent vasodilator used in the treatment of pulmonary hypertension, reduces both peripheral and coronary vascular resistance. IL-l and TNF also have been shown to inhibit j3-adrenergic agonist-mediated cardiac myocyte contractility in cultures (64). These phenomenon can thus be extrapolated to play a role in the pathophysiology of the dysautonomias described.

Sleep Disturbances

Krupp et al. evaluated the prevalence of sleep disturbances in 72 patients with CFS, comparing them with 57 patients having the diagnosis of multiple sclerosis and 40 healthy controls. They concluded that subjective sleep disturbance is common in CFS. In addition, specific sleep disorders were also ultimately identified (65). For example, in response to specific items on a questionnaire, sleep in CFS was much more disrupted than in controls. CFS patients reported sleeping "lightly" in 37% of cases (25/68) compared with 10% of controls (2110) ($p < 0.01$) and "badly" in 15% (10/68) vs. 5% (1120) ($p < 0.001$) in controls.

To further clarify the significance of these complaints, the most severely described sleep disturbances were evaluated by formal polysomnography. Of the 16 CFS patients undergoing this procedure, 2 were found to have obstructive sleep apnea (one responding to CP AP) and one with narcolepsy responding to pharmacotherapy (66). Thus two individuals who had otherwise represented CDC defined CFS, polysomnography ultimately recategorized them to these respective sleep disturbances.

Mullington et al. described a complex relationship between the immune system and sleep (67). The

interaction of TNF-a and IL-6 with sleep was noted to potentially either enhance or disrupt sleep, depending upon the dose. Gupta et al. found that spontaneous IL-6 production by isolated monocytes and lymphocyte spontaneous production of TNF-a were higher in patients with CFS (21). Borish et al. replicated the finding of increased IL-6 and TNF-a and decreased IL-l 0 seen in spontaneous production of isolated cells (68). Extrapolating from this information, it is conceivable but yet unproven, that these cytokines have the capacity to play an integral role in the aforementioned sleep disturbance. In essence, depending upon the degree and type of cytokine production, sleep may either be enhanced or diminished.

Cardiovascular System

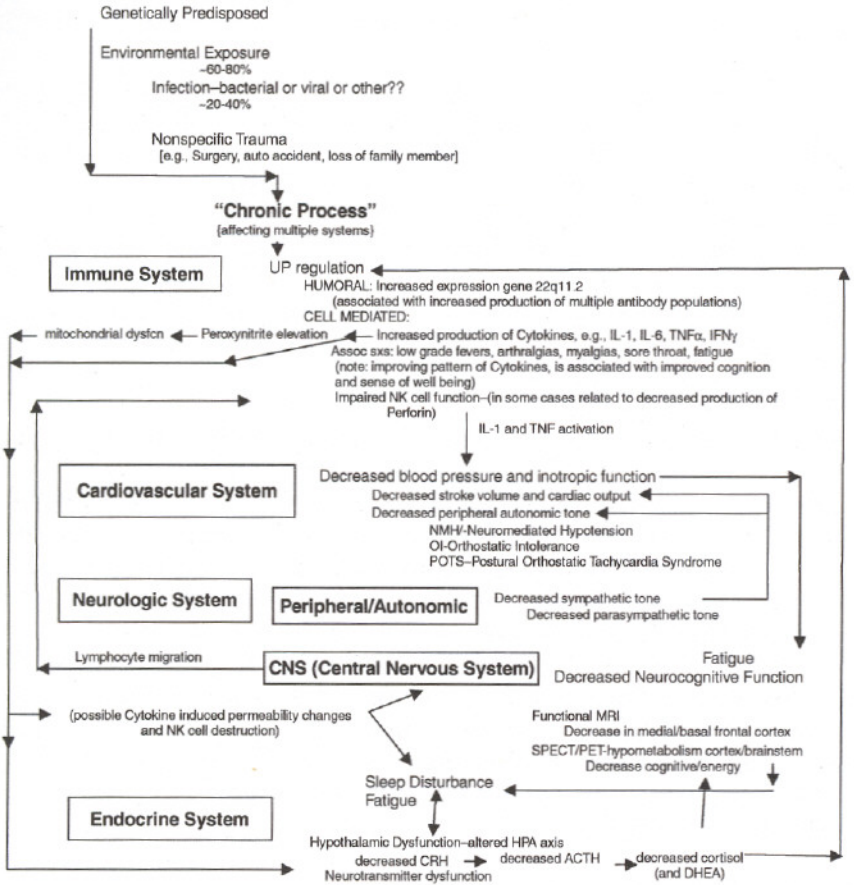
A substantial body of clinical evidence now supports an association between various forms of hypotension and both idiopathic chronic fatigue and CFS (69). Patients with CFS have a higher than normal prevalence of Neuromediated Hypotension and other forms of dysautonomia including "NeuroCardiogenic Syncope" or "Neurally Mediated Hypotension" (NMH), "Orthostatic Intolerance" (01), "Postural Tachycardia Syndrome" (POTS) (69). In addition, Freeman and Komaroff were able to show that CFS patients showed alterations in measures of sympathetic and parasympathetic nervous system function (27). These alterations were manifested as an increase in baseline and maximum heart rate on standing and tilting (both $p < 0.0001$). Tests of parasympathetic nervous system function (the expiratory inspiratory ratio, $p < 0.005$; maximum minus minimum HR difference, $p < 0.05$), were significantly less in the CFS group. Other sympathetic nervous system function measures included systolic blood pressure decrease with tilting ($p < 0.01$), diastolic blood pressure decrease with tilting ($p < 0.05$) and the systolic blood pressure decrease during phase II of a Valsalva maneuver ($p < 0.05$). In this setting, it was their contention, that the aforementioned dysautonomia could be explained by cardiovascular deconditioning, a postviral idiopathic autonomic neuropathy, or both. It is generally felt that the pathophysiology of dysautonomias includes a central hypovolemia (depleted intravascular volume, exaggerated venous pooling). In POTS, exaggerated tachycardia and vasoconstriction develop in response to this relative hypovolemia. Impaired vasoconstriction and minor abnormalities of cardiovascular autonomic function have been noted in some studies (28). Although cognitive stresses should elicit peripheral vasoconstriction, over half of subjects with neurally mediated syncope in a study by Manyari and colleagues (29) had an inappropriate vasoconstriction response when asked to perform mental arithmetic tasks. Such inappropriate venous responses could provoke orthostatic intolerance in response to common, everyday cognitive stresses, and provide an explanation for the cognitive deterioration noted in patients with CFS (69). In essence, these dysautonomias can potentially manifest as cognitive impairment and fatigue, associated with abnormal cerebral perfusion even without abnormalities in blood pressure. Thus, the interplay between the autonomic nervous system, cardiovascular and neurocognitive systems (see Figure 1).

Neuroendocrine Systems

Primary glucocorticoid deficiency states and affective disorders putatively associated with a deficiency of the arousal-producing neuropeptide corticotropin releasing hormone (CRH) can be associated with similar symptoms. Demitrack et al. reported a mild glucocorticoid deficiency in CFS (70). Compared with normal controls, patients demonstrated significantly reduced basal evening glucocorticoid levels, and low 24 hour urinary free cortisol excretion, but elevated basal evening ACTH concentrations. In addition, there was increased adrenocortical sensitivity to ACTH, but a reduced maximal response. Interpretation of these findings was most consistent with "a mild central adrenal insufficiency secondary to either a deficiency of CRH or some other central stimulus to the pituitary-adrenal axis" *(70).* Reevaluating the CRH activation of this axis in CFS patients free from concurrent psychiatric illness, Scott et at. reported similar HP A axis dysfunction *(20).* A sample of 14 patients with CDC defined CFS were compared with 14 healthy volunteers. ACTH and cortisol responses were measured following the administration of 100 mg ovine CRH. Basal ACTH and cortisol values did

FIGURE 1. CFS (Chronic Fatigue Syndrome)

State of the Art Program



not differ between the two groups. The release of ACTH was significantly attenuated in the CFS group ($p < 0.005$), as was the release of cortisol ($p < 0.05$). They postulated that the blunted response of ACTH to exogenous CRH stimulation might be due to an abnormality in CRH levels with a resultant alteration in pituitary CRH receptor sensitivity. Or it may reflect a deregulation of vasopressin or other factors involved in HP A regulation. This may simply be due to a "stress" response that produces a down regulation of the CRH receptor at the anterior pituitary corticotropes. This then may fail to normalize following a reduction in CRH levels. A diminished output of neurotrophic ACTH could thus cause a reduced adrenocortical secretory reserve, suggesting a functional hypoplasia. In essence, this would represent an inadequately compensated adrenoceptor up regulation (71). Supportive evidence for this hypothesis rests in the finding that N infusion of ACTH results in an attenuation of the anticipated release' of dehydroepiandrosterone (DHEA), a major adrenal androgenic secretory product (21).

A possible explanation for the blunted adrenal cortisol response in CFS is an increased activation of corticotropic inhibitory factors (CIFs). These are peptides that are involved in the restraint of the pituitary-adrenal activity. One such peptide is atrial natriuretic factor (ANF), which has been shown by Kellner et al. to suppress HP A activation in normal humans (22).

Another possible explanation to this blunted adrenal cortisol response in CFS may be related to growth hormone. Growth hormone-releasing hormone (GHRH) and CRH have a reciprocal regulatory influence on sleep endocrine activity (72). Secretion of growth hormone (GH) from the pituitary is stimulated by GHRH and inhibited by somatostatin (SS). The pulsatile administration of GHRH suppresses HPA activity, and increases GH and slow wave sleep, the opposite effects occurring with CRH (71).

According to Scott et al. (20) a possible deregulation of GHRH/ CRH activity due to either excess GHRH, alterations in somatostatin tone or CRH levels may explain the blunted pituitary-adrenal responses in CFS and the significant disruption of sleep patterns described by these patients. Interestingly, Leese et al. demonstrated a disruption of the normal HPA response in short-term night-shift workers, such that the HP A abnormalities were indistinguishable from those of CFS patients (30). This then raises the question, is the HP A anomaly in CFS simply a secondary process to the sleep disorder, or are the sleep disorder and the HP A deregulation due to an underlying GHRH and/or somatostatin excess?

Taking this concept one step further, one can postulate that given the anti-inflammatory function of adrenocorticosteroids, a deficient response in this system might lead to an inadequately suppressed immune system (23). Hence, a possible explanation for the aforementioned up regulated immune response previously described in CFS. In addition, Demitrack postulates that a functional deficit in CRH, not only would adversely impact the downstream HP A axis, but also have bearing on the symptoms of fatigue itself. Support for this concept is the behaviorally active nature of CRH. In essence, this neurohormone, when centrally administered in animals, induces signs of physiological arousal (24). Thus, a relative or absolute deficiency of hypothalamic CRH could contribute to the profound lethargy and fatigue so clinically tied to the diagnosis of CFS (23).

Neurocognitive

Historically, clinicians have often interpreted a CFS patient's maladies as to simply "being depressed." DeLuca et al. report an analysis of this concept and conclude that "impaired cognition in CFS cannot be explained solely by the presence of a psychiatric condition" (74). In this study, patients were divided into two groups: Those without psychiatric disorder(s) in their lifetime or concurrent with the chronic fatigue syndrome (CFS-nonpsyche group) and those with a concurrent axis 1 psychiatric disorder (CFS-Psyche group). All patients were given a battery of standard neuropsyche testing. The results conclusively supported differences in cognitive performance in patients with CFS with and without comorbid psychiatric disorders. This does not mean to say that secondary depression does not often accompany any chronically disabling process, which it does. But rather that there are independent factors in CFS that contribute to the often disabling cognitive disturbance. These can manifest as word finding and calculating difficulties, along with memory loss. Other discrepancies include the finding that depression is associated with persisting and often overwhelming negative thoughts and feelings. This often goes along with anhedonia, or a lack of interest in improving. In CFS however, patients usual have fatigue, but are motivated to try to improve. Suhadolnik et al.

have shown a statistically significant increase in the immune marker 37-kDa RNase L in patients with CFS as opposed to those with depression or healthy controls (75). In addition as indicated above, in CFS cortisol excretion is decreased. This is compared to depressed patients, where there is an elevation in the 24 hour cortisol excretion rate (31). Interestingly, in their small study, Scott and Dinan showed the subgroup of CFS patients with comorbid depression, retained the profile of cortisol secretion of that seen in the CFS alone group. Suggesting a possible different pathophysiological basis of depression in this subgroup (25). Other cognitive deficits have been identified, exemplified by the comment "I used to be a high level executive and now I can't even count the change at the cash register." Marshall et al. reported that compared with control subjects, CFS patients consistently scored lower on tests in which motor and cognitive processing speeds were a critical factor, e.g., reaction-time tasks. They also had more difficulty on working-memory tests in which rapid cognitive processing speed is also an important factor (73). According to them, the CFS patient's performances on neuorpsyche testing were typically approximately one standard deviation below the control group's performances. Joyce et al. supported these findings, concluding that patients with CFS have reduced attention capacity resulting in impaired performance on effortful tasks requiring planned or self ordered generation of responses from memory (26).

Recent studies have identified specific impairment of information processing (32). Impairments in learning and memory were described elsewhere, in a subset of patients (33,34). When CFS patients were compared to MS patients and depression, greater deficits were seen in the CFS patients in such tests as complex auditory information processing (35).

Neuroimaging

Static MRI for structural abnormalities has yielded inconsistent findings of "small nonspecific white matter abnormalities, occurring predominantly in the frontal lobes." These findings may be more prevalent in those patients with concurrent psychiatric comorbidity, the significance of which is unclear (36). Using more dynamic imaging with quantifiable regional cerebral blood flow (rCBF) via detection of Tc-99m hexamethylpopyleneamine oJdme distribution by single-photon emission computed tomography (SPECT), Costa et al. were able to find generalized cerebral hypoperfusion in CFS patients (76). Most of the marked abnormalities were manifested in the frontal lobes and brain stem, perhaps being associated with cognitive disturbance in the former and fatigue by way of the reticular activating system in the latter.

Using (18F) fluorine-deoxyglucose (18FDB) positron emission tomography (PET) scanning technology, Tirelli et al. were able to investi gate brain metabolism of patients affected by CFS (77). According to this study, which evaluated CFS patients without psychiatric comorbidity compared to clinically depressed patients and healthy controls. The CFS group showed a significant hypometabolism in right mediofrontal cortex ($p = 0.010$) and brains tern ($p = 0.013$), in comparison to healthy controls. Comparing CFS with depressed patients, the latter group showed a significant and severe hypometabolism of the medial and upper frontal regions bilateral ($p = 0.037$-0.001), whereas the metabolism of the brain stem was normal. These findings again suggest both cortical/cognitive and reticular activating system/energy involvement in CFS patients.

SUMMARY

Attempts have been made to provide plausible, complex intersystem relationships, to better explain the entity known as Chronic Fatigue Syndrome. Usually following what appears to be an infectious process, in susceptible individuals, this phenomenon most likely represents the culmination of the chronic, inadequately controlled interplay of several aberrant systems. In particular, abnormalities in the immune, cardiovascular and neuroendocrine systems, perhaps being perpetuated by peroxynitrite induced mitochondrial dysfunction, have been identified. Future goals to better understand and treat Chronic Fatigue Syndrome will require improved categorization. This will hopefully lend to better understanding of subpopulations. Perhaps classification of individuals

with Psychiatric comorbidity, or those that have clearly occurred acutely after an infectious process (perhaps even subclassing into which infection-post Lyme, post EBV, etc...) compared to a posttraumatic case, compared to a case that developed "spontaneously." Perhaps also categorizing into comorbidities such as a "dysautonomia," or fibromyalgia or perhaps, those with profound cognitive or sleep disturbances. Lastly, categories could be made on more cellular or immune levels such as by the level of NK cell activites. In so doing, it is our hope to better understand and manage these most complex, oftentimes disabling problems.

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