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CHRONIC FATIGUE SYNDROME:

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ABSTRACT

Chronic fatigue syndrome (CFS) is a common, enigmatic medical condition comprising mental and physical fatigue, diagnosed after exclusion of possible medical causes. The prominence of post-exertional exacerbation of fatigue is highlighted by the recently suggested re-naming as Syndrome of Exertional Intolerance Disease (SEID). Diagnosis is syndromic. No clinical test can confirm the presence of CFS. Treatment is supportive with no specific therapy shown to be reproducibly effective. There are several categories of hypotheses regarding CFS aetiology including infections, immune, mitochondrial, neurobehavioural or stress system (HPA axis and sympathetic nervous system) disorders. Recently, fatigue disorders have been popularly referred to as "adrenal fatigue." Although CFS and the syndromically related fibromyalgia have been shown to have lower HPA axis function especially reduced cortisol, when analysed compared to controls in aggregate, and in some cases excessive sympathetic nervous system usually sympathoneural system responses, these findings overlap with controls and such testing is not diagnostic. Moreover, augmentation of cortisol levels with glucocorticoids has not been shown to be clinically useful. The stress system abnormalities may represent epiphenomena of the disease process rather than pathogenic abnormalities of importance to the symptomatology. Recent studies have pointed to new pathological associations and small treatment trials exist which hold some promise but require replication before practical application.

CLINICAL DEFINITION

Fatigue is a state of extreme tiredness resulting from mental or physical exertion or illness. Persistent fatigue, without adequate environmental or medical explanation, has been recognized as the hallmark of a frequent and enigmatic clinical syndrome. Although difficult to precisely define and measure, primary fatigue may be appreciated centrally with reduced concentration, memory and motivation, or appreciated peripherally, where symptoms are often referred to the muscles.

Chronic Fatigue Syndrome (CFS) is a term that was chosen and defined by Holmes et al in 1988 to describe a combination of non-specific symptoms including profound fatigue,

weakness, malaise and cognitive impairment with a remarkable lack of objective physical or laboratory abnormalities (1).

This syndrome had previously been known as myalgic encephalomyelitis, Royal Free Disease or chronic Epstein Barr virus infection. The terminology CFS was widely accepted because it implies no aetiology or specific pathological process. The diagnosis of CFS is based on the characteristic symptoms and exclusion of causative medical or psychiatric disorders. Several definitions of CFS have been developed, primarily to standardize research (2, 3). All definitions require exclusion of potentially causative medical or mental illness.

The 1994 US Centres for Disease Control and Prevention (CDC) Fukuda criteria for chronic fatigue syndrome comprise the following (2):

1. Clinically evaluated, unexplained, persistent or relapsing fatigue lasting at least 6 months. The fatigue is not the result of ongoing physical exertion, and resting, sleeping, or downgrading activity is non-restorative. The fatigue causes significant impairment in personal, social, and/or occupational domains and represents a substantial reduction in premorbid levels of activity and functional capacity.
2. The concurrent presence of at least 4 of the 8 following symptoms over a 6-month period: Impaired short-term memory or concentration, sore throat, tender lymph nodes/glands, muscular pain, joint pain in multiple areas, new-onset headaches, unrefreshing sleep, and post-exertional fatigue/malaise lasting longer than 24 hours.

The Canadian ME/CFS Case criteria (2003) specifies: (4)

1. Post-exertional malaise must occur with rapid muscle or cognitive fatigability, taking 24 hours or longer to recover.
2. Unrefreshing sleep, myalgia and arthralgia must be reported.
3. Two or more neurological/cognitive manifestations must be present.
4. At least one of autonomic, neuroendocrine, immune manifestations must be present.

Recently an international panel of researchers, clinicians, and patient advocates have challenged the narrow definition of chronic fatigue syndrome and instead have proposed returning to the diagnostic label of myalgic encephalomyelitis (4). The resulting consensus criteria no longer required the 6-month symptomatic period before diagnosis, have less emphasis on fatigue and refer to a broader consideration of symptom clusters. The proposed myalgic encephalomyelitis ME/ICC diagnostic criteria are:

1. Post-exertional neuroimmune exhaustion characterized by marked, rapid physical and/or cognitive fatigability in response to exertion; post-exertional symptom exacerbation; post-exertional exhaustion; prolonged recovery period; and/or low threshold of physical and mental fatigability resulting in a substantial reduction in pre-illness activity levels.

2. Neurological impairments (at least 1 symptom from 3 of the following symptom categories): (a) neurocognitive impairments (difficulty processing information; short-term memory loss); (b) pain (headaches; non-inflammatory somatic pain); (c) sleep disturbance (disturbed sleep patterns; unrefreshing sleep); and (d) neurosensory, perceptual, and motor disturbances (inability to focus; sensory defensiveness; muscle weakness).
3. Immune, gastrointestinal, and genitourinary impairments (at least 1 symptom from the following 5 symptom categories): (a) recurrent or chronic flu-like symptoms that worsen with exertion; (b) susceptibility to viral infections with prolonged recovery periods; (c) gastrointestinal tract difficulties; (d) genitourinary problems; and (e) sensitivities to food, medications, odours, or chemicals.
4. Energy production/transportation symptoms (at least 1 symptom from the following): (a) cardiovascular intolerance; (b) respiratory difficulties; (c) loss of thermostatic stability; and (d) intolerance of extreme temperature.

The US Institute of Medicine (IOM) proposed new diagnostic criteria in 2015 for chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) (5). These clinical diagnostic criteria followed a comprehensive analysis of the literature and expert consultation. The term 'systemic exertion intolerance disease' (SEID) was recommended to replace CFS/ME.

A diagnosis of (SEID) is based on the three central symptoms and supplementary symptoms:

1. Substantial reduction/impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months, is accompanied by fatigue that is often profound, is of new or definite onset, is not the result of ongoing excessive exertion, and is not substantially alleviated by rest
2. Post-exertional malaise (PEM)
3. Unrefreshing sleep.
4. In addition, patients are required to have at least one of the following two symptoms:

- Cognitive impairment
- Orthostatic intolerance.

Symptoms must be present at least half of the time and have moderate, substantial, or severe intensity.

It was considered that the SEID nomenclature can help overcome old stereotypes. The name describes the practical consequences of the illness (5). SEID highlights the somewhat unique feature of exertion intolerance, and consequent impaired functional capacity. SEID criteria may help with the treatment by increased diagnosis and awareness, calling attention to the major disabling symptoms, and by validating the major symptoms as real and debilitating.

The term myalgic encephalomyelitis was considered inappropriate because there was a lack of evidence for encephalomyelitis in ME/CFS patients, and myalgia is not a core symptom of the disease.

The IOM criteria were not evaluated with data sets of patients and controls, after excluding non SEID disorders. The SEID criteria identified 88% of participants in the samples analysed, which is comparable to the 92% that met the Fukuda criteria (5).

The clinical diagnosis of CFS/ME is based on a constellation of symptoms where post-exertional malaise and fatigue are prominent; these are described in some definitions (Table 1). A thorough clinical assessment is necessary to exclude alternative medical and psychiatric diagnoses requiring specific treatment. For example, it is important to differentiate fatigue from weakness, which suggests a neuromuscular disease, and anhedonia which is suggestive of major depression. Hypersomnolence and sleep disorder suggests a need to exclude obstructive sleep apnoea, particularly in groups at risk such as the obese.

Limited laboratory screening investigations are directed towards the discovery of subtle medical disorders. No laboratory investigation can verify the diagnosis of CFS/ME. The protean manifestations of CFS/ME suggest diverse causes, hence it is unlikely a single diagnostic test for CFS/ME will be developed. Routine laboratory investigations include a complete blood examination, erythrocyte sedimentation rate (ESR), calcium, phosphate, magnesium, blood glucose, serum electrolytes, thyroid stimulating hormone and free thyroxine levels, protein electrophoresis screen, C-reactive protein (CRP), ferritin, creatinine, rheumatoid factor, antinuclear antibody, creatine kinase and liver function, and routine urinalysis. Any other investigations should be carefully chosen on an individual basis depending on the clinical assessment and risk factors for other conditions

Some recent studies have suggested reduced circulatory and myocardial function in CFS (6, 7), although the utility of routine cardiac assessment is not established.

Table 1. Clinical Working Case Definition of ME/CFS (3,4)

A patient with ME/CFS will meet the criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain; have two or more neurological/cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations; and adhere to item.
1. Fatigue: The patient must have a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.
2. Post-Exertional Malaise and/or Fatigue: There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period – usually 24 hours or longer.

3. Sleep Dysfunction:* There is unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.
4. Pain:* There is a significant degree of myalgia. Pain can be experienced in the muscles and/or joints, and is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity.
5. Neurological/Cognitive Manifestations: Two or more of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances – e.g., spatial instability and disorientation and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory – e.g., photophobia and hypersensitivity to noise – and/or emotional overload, which may lead to “crash” periods and/or anxiety.
6. At least one symptom from two of the following categories: (i) Autonomic Manifestations: orthostatic intolerance – neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural hypotension; lightheadedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnoea. (ii) Neuroendocrine Manifestations: loss of thermostatic stability – subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change – anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress. (iii) Immune Manifestations: tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.
7. The illness persists for at least six months. It usually has a distinct onset,** although it may be gradual. Preliminary diagnosis may be possible earlier. Three months is appropriate for children.
To be included, the symptoms must have begun or have been significantly altered after the onset of this illness. It is unlikely that a patient will suffer from all symptoms in criteria 5 and 6. The disturbances tend to form symptom clusters that may fluctuate and change over time. Children often have numerous prominent symptoms but their order of severity tends to vary from day to day. *There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset. **Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset.
Exclusions: Exclude active disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. It is essential to exclude certain diseases, which would be tragic to miss: Addison’s disease, Cushing’s syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of

anaemia, iron overload syndrome, diabetes mellitus, and cancer. It is also essential to exclude treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnoea; rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease, etc.; primary psychiatric disorders and substance abuse. Exclusion of other diagnoses, which cannot be reasonably excluded by the patient's history and physical examination, is achieved by laboratory testing and imaging. if a potentially confounding medical condition is under control, then the diagnosis of cfs can be entertained if patients meet the criteria otherwise.
Co-Morbid Entities: Fibromyalgia Syndrome (FMS), Myofascial Pain Syndrome (MPS), Temporo- mandibular Joint Syndrome (TMJ), Irritable Bowel Syndrome (IBS), Interstitial Cystitis, Irritable Bladder Syndrome, Raynaud's Phenomenon, Prolapsed Mitral Valve, Depression, Migraine, Allergies, Multiple Chemical Sensitivities (MCS), Hashimoto's thyroiditis, Sicca Syndrome, etc. Such comorbid entities may occur in the setting of CFS. Others such as IBS may precede the development of CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. CFS and FMS often closely connect and should be considered to be "overlap syndromes."
Overload phenomena affect sensory modalities where the patient may be hypersensitive to light, sound, vibration, speed, odours, and/or mixed sensory modalities.

EPIDEMIOLOGY

The frequency of CFS has been assessed in two large-scale US community-based studies and a prevalence of 0.23-0.42% has been suggested (8,9). CFS is at least twice as common in women as in men, occurs more frequently in minority groups, and in those with lower levels of education and occupational status (8). Geographic location has not been shown to influence the prevalence of CFS (10) Twin studies suggest that genetic factors play an important role (11). Population studies also associate elevated premorbid stress and childhood trauma, especially if complicated by psychopathology, with an increased risk of CFS (12, 13).

An Australian sociodemographic cross sectional study of patients diagnosed with CFS by their primary care physician was conducted over 2 years (2013-2015) (14). Participants were classified according to Fukuda criteria and international consensus ME/ICC criteria. CFS was most prevalent between 45-55 years, with a peak onset between 25-35 years with a high proportion of females affected (78.6%). Patients were predominantly Caucasian and highly educated. Of a total of 535 patients, only 30% met the Fukuda criteria and 32% met both Fukuda and International consensus ME/ICC criteria. 15% did not meet the criteria and 23% had exclusionary conditions. There was higher proportion of participants obese or overweight, (41.3% and 43.3% respectively) and unemployed or on a disability pension. The results of this study may not be

representative of all CFS/ME patients in the general population given that the sample was not from a research cohort. Patients were recruited from CFS community support networks across Australia, as well as a public advertisements.

PATHOPHYSIOLOGY OF CHRONIC FATIGUE SYNDROME

Viral/Immune Hypotheses

For many years CFS was suspected to arise from a persistent response to an infection. Abrupt onset of symptoms and the presence of post-infectious fatigue after infections suggest this theory. There were also reports of a high frequency of antibody titres to specific, but varying, infectious agents (15). Epstein-Barr virus, human herpes virus 6, group B Coxsackie virus, human T-cell lymphotrophic virus II, hepatitis C, enteroviruses, and retroviruses, have all been proposed as aetiological agents of CFS (16). However, to date, there has been no consistent evidence that CFS results from a specific infection (17). Moreover, there is data to indicate that global increases in humoral immune responses are seen in chronic stress states and that neurohormonal changes may account for these and other immune aberrations (15,18).

Recent study has examined the characteristics of cell function and receptors in CFS patients(19). Participants between 20 and 65 years old were recruited, by using the Fukuda criteria. Patient were classified as moderate (mobile) or severely affected (housebound). Blood was collected from all participants between 8am and 11am, and sent for lytic protein analysis, cell activity analysis, respiratory burst analysis and natural killer cell receptors analysis. The study demonstrated that there was significant decrease in natural killer cell cytotoxic activity in CFS patients and there is correlation between low natural killer cells cytotoxic activity and severity of CFS illness. CFS patients have alterations in Natural Killer receptors, adhesion markers and receptors on CD4, and CD8.

A prospective population based cohort of 42,558 atopic patients and 170,232 controls without atopy were recruited between 2005-2007, with follow up until 2011. These 2 groups were similar in sex and age distributions, with a mean age of 47 years. The result of the study revealed that atopy might be related to increase risk of CFS/SEID. The overall incidence rate for CFS in the atopy cohort (1.37 per 1000 person-year) was higher than in the non-atopy cohort (0.87 per 1000 person-year (20).

Mitochondrial Hypotheses

Since mitochondria provide cellular energy, hypotheses of impaired mitochondrial function have been suggested to underlie CFS. Early studies have shown some associations between mitochondrial proteins and CFS but these require confirmation (21).

Neuropsychiatric Hypotheses

Chronic fatigue syndrome has been suspected to be a neuropsychiatric disorder, or a type of depression (22). Although depression is frequent in CFS, most patients do not

exhibit the characteristic self-reproach or biological features of endogenous depression. The depression often seen in CFS appears to be reactive and associated with marked frustration. However, the symptoms of depression can overlap with those of CFS. Profound fatigue is more commonly reported amongst CFS patients, than those with depression (22). Cognitive-behavioural models of CFS emphasise the importance of the interactions between cognitive, behavioural and biological variables in attempting to explain the genesis and maintenance of CFS. It may be that while organic factors may precipitate CFS, cognitive-behavioural factors may perpetuate the illness (23). Specifically, when individuals resume normal activity levels following an acute illness, it is common to experience symptoms of physical deconditioning. If individuals attribute these symptoms to signs of ongoing disease rather than deconditioning, they may resort to rest and inactivity in an attempt to "cure" the symptoms. A cycle of avoidance and symptom experience develops, which can lead to loss of control, demoralisation and possible depression and anxiety. These psychological states can further perpetuate the illness through generating more symptoms.

The cognitive-behavioral model has been expanded to include personality as predisposing factors (24). This model proposes that predisposed people are highly achievement orientated perfectionists and base their self-esteem and the respect from others on their ability to live up to certain high standards (24). When such people are faced with factors that affect their ability to perform, such as a combination of excessive stress and an acute illness, their initial reaction is to persist and to attempt to maintain usual coping strategies. This behavior leads to exhaustion. In making sense of the situation a physical attribution for the exhaustion is made, which protects an individual's self-esteem by avoiding the suggestion that their inability to cope is a sign of personal weakness. The bias may lead to a focus on somatic rather than emotional aspects of the illness, and favors physical rather than psychological explanation. However, this model remains to be fully evaluated and it is poorly integrated with physiological aspects of CFS. There have been few systematic studies undertaken on the relationship between personality and CFS (23). However, a personality trait characterized by "perfectionism, high standards for work performance, responsibility and personal conduct and marked achievement orientation" was reported in interviews with individuals with CFS (25). Interviewees referred to a desire for accomplishment and success, aiming to achieve perfection. These desires were associated with the belief that “failure to meet these standards would indicate failure as a person, or unacceptability to others” (25).

Neurological hypothesis

CFS as a primary brain disorder has been studied with neuroimaging including Magnetic resonance imaging MRI, Single-photon emission computed tomography (SPECT) ,Electroencephalogram (EEG), quantitative electroencephalogram (qEEG), and positron emission tomography (PET) (27-31, 34-36). A variety of abnormalities associated with CFS have been reported but the diagnostic or potential pathogenic implications of these findings are unknown.

Neuroendocrine Hypotheses

In recent years, there have been a number of reports indicating neuroendocrine hypofunction, probably of hypothalamic origin, in chronic fatigue states. A tendency to hypocortisolism, has been identified, albeit inconsistently, in CFS patients. Relative hypocortisolism may reflect the primary abnormality in many CFS patients, such as a disorder of the brain regulation, or peripheral elements, of the stress system. Moreover, hypocortisolism may contribute to conceivably CFS symptomatology.

However, neuroendocrine studies in CFS have often led to contradictory results. Smaller studies may be confounded by differences between subgroups of CFS patients, such as duration of fatigue, presence of concomitant hypotension and/or orthostasis, presence of depression, familial occurrence and other factors. Although melancholic major depression is associated with mild hypercortisolism, the hypocortisolism of CFS seems to persist in at least some patients with co-morbid depression (23). Moreover, hypocortisolism is a trait shared with a number of other chronic idiopathic disorders, including post-traumatic stress disorder, fibromyalgia and inflammatory disorders such as rheumatoid arthritis and asthma (13). Wyller et al. studied 120 CFS patients and 68 healthy controls, aged 12-18 years. CFS patients had higher levels of plasma norepinephrine, plasma epinephrine and FT4, with lower urine cortisol/creatinine ratios, (37). This accords with previous studies of attenuation of cortisol secretion and enhancement of the sympathetic nervous system activity in CFS.

The Stress System and CFS/SEID

Stress is defined as threat to homeostasis. It is generally accepted that these processes are adaptive, designed to re-establish homeostasis. However excessive and/or prolonged activation of the stress system can disturb normal physiology. The stress system comprises the hypothalamic-pituitary-adrenal (HPA) axis of which cortisol is the major mediator, and the sympathoadrenal system which produces the catecholamines epinephrine and the sympathoneural system producing norepinephrine. Both glucocorticoids and catecholamines act widely to mediate the stress response.

Stress results in stimulation of parvicellular neurons of the paraventricular nucleus (PVN) of the hypothalamus and the release of the neuropeptides corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal blood system (Figure 1). The combined action of CRH and AVP on the anterior pituitary corticotropes stimulates secretion of adrenocorticotropin hormone (ACTH). Circulating ACTH acts on the zona fasciculata of the adrenal cortex to stimulate cortisol synthesis. Basal (unstressed) cortisol acts to prevent arterial hypotension by augmenting the effects of catecholamines, and maintain normoglycaemia through insulin counter-regulation.

ACTH secretion is influenced by stress, a light-entrained circadian rhythm, and negative feedback at the hypothalamus. During acute stress, the amplitude and synchronisation of the CRH and AVP pulsations in the hypophyseal portal system markedly increases, resulting in increases of ACTH and cortisol secretory episodes (38). Stress-induced cortisol secretion activates the central nervous system, increases blood pressure, elevates blood glucose and suppresses the inflammatory/immune response to prevent tissue damage (39).

Cortisol action is mediated by ubiquitous cytosolic glucocorticoid receptors (40). Free cortisol, unbound to corticosteroid binding globulin (3-10%), diffuses through cell membranes and binds to the carboxy-terminal end of the cytosolic glucocorticoid receptor. On cortisol binding, the ligand-receptor complex translocates into the nucleus, where it interacts with specific glucocorticoid responsive elements (GREs) within DNA to activate gene transcription (40). The activated receptors also inhibit other transcription factors, such as c-jun/c-fos and NF-kB, which are positive regulators of the transcription of genes involved in the activation and growth of immune and other cells (41).

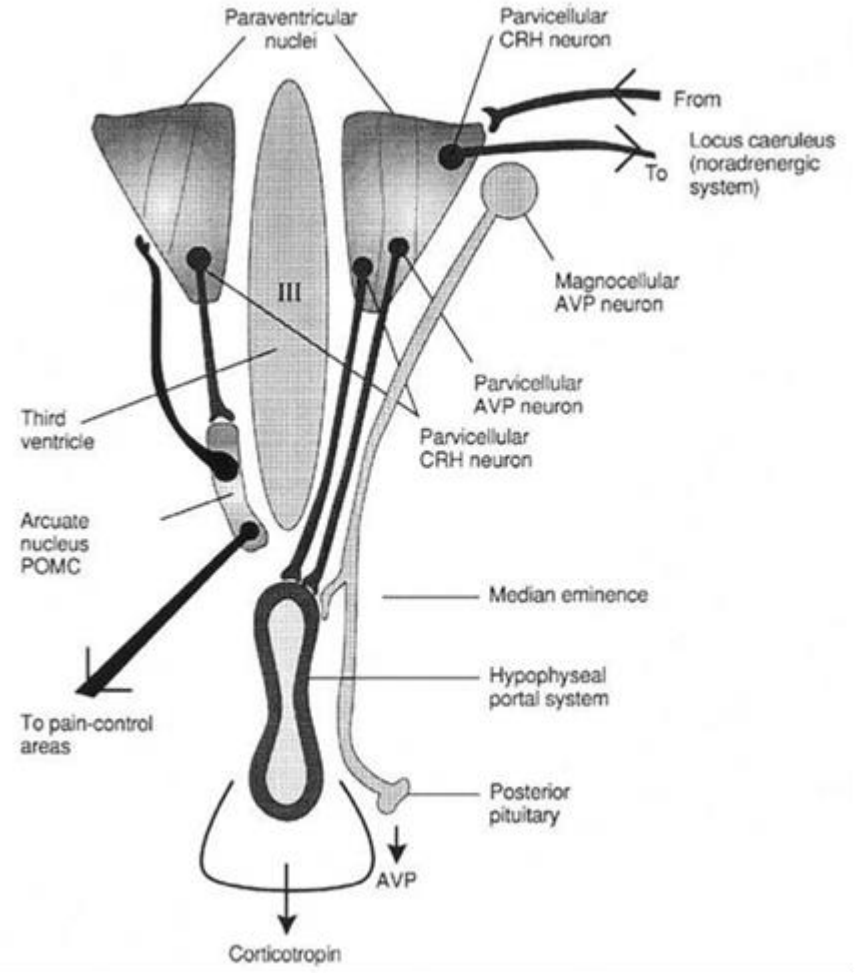

Figure 1. The stress system.

Several complementary sets of studies have examined basal and stimulated pituitary-adrenal gland function in CFS.

Two different types of heritable disorders of this axis have been described, where fatigue is the principal symptom. These include glucocorticoid resistance due to glucocorticoid receptor abnormalities, and mutations of the corticosteroid-binding globulin gene, the chief cortisol transport protein. These disorders are probably rare, but reinforce the notion that primary pituitary-adrenal abnormalities may produce chronic fatigue. Studies in the broader CFS patient group have generally detected relative hypocortisolism and altered dynamic responses, providing indirect evidence of a central nervous system under-stimulation of pituitary-adrenal function.

Familial glucocorticoid resistance is a rare syndrome characterized by diminished tissue effect of cortisol as a result of a glucocorticoid receptor defect. Glucocorticoid resistance is generally due to a loss of function mutation of the glucocorticoid receptor gene, although the genetic defect has not been identified in all cases. Decreased sensitivity to cortisol results in activation of the HPA axis, with increased ACTH and cortisol levels. In most cases, elevated cortisol levels sufficiently compensate to overcome the hormone resistance, thus these patients do not clinically manifest either cortisol excess or deficiency. Increased ACTH secretion also results in elevated mineralocorticoid and androgen levels resulting in hypertension and hirsutism (42). However, fatigue as an isolated symptom has been described in a 55 year old woman with glucocorticoid resistance (43). Fatigue in this patient was intermittent, but blood pressure was constantly in the low-normal range, with no postural hypotension. Fatigue was sufficient to prohibit full-time work. Urinary cortisol was elevated (400-800nmol/24h; Range <300nmol/24h), as were plasma cortisol levels. A thermolabile glucocorticoid receptor was noted, specifically a temperature-induced reduction in dexamethasone binding, although a specific glucocorticoid receptor mutation was not reported. It has been proposed that fatigue in such cases is a result of insufficient overproduction of cortisol (44).

Further to this, recent studies of glucocorticoid receptor polymorphisms have found an association between certain haplotypes and CFS (45). Although speculative, polymorphisms may result in altered receptor sensitivity to cortisol, and thus, impaired tissue-effect of cortisol, resulting in relative hypocortisolism.

Corticosteroid-Binding Globulin abnormalities and Chronic Fatigue

Corticosteroid-binding globulin (CBG), also known as transcortin, is the high-affinity plasma transport glycoprotein for cortisol (46). It is secreted by hepatocytes as a 383-amino acid polypeptide, after cleavage of a 22-amino acid signal peptide. Each CBG molecule contains a single high-affinity steroid binding site (46). Under circadian conditions, 80% of circulating cortisol is bound to CBG, 10-15% is bound to low-affinity albumin and 5-8% of circulating cortisol is unbound or free (46). Currently, only the free fraction is thought to be biologically active. CBG levels are generally stable. CBG is

traditionally thought to function primarily as a carrier molecule for cortisol, but it may also serve as a buffer and as a reservoir, during secretory surges, or during times of reduced cortisol secretion, respectively. CBG may also have a specific-tissue cortisol delivery role, in particular enabling cortisol to act in an immunomodulatory capacity (47). High-affinity cortisol binding is saturated beyond cortisol levels of 500nmol/L, hence free cortisol levels rise exponentially at high cortisol concentrations (48). Under conditions of stress, elevated cortisol levels saturate available CBG and increase the free cortisol to above 20% (48).

CBG is involved in the stress response. Immune activation releases interleukin-6 (IL-6) which increases circulating free cortisol levels by two mechanisms. IL-6 stimulates cortisol secretion through activation of hypothalamic CRH neurones and it also inhibits CBG gene transcription thereby increasing the free cortisol fraction and thus, circulating glucocorticoid activity (49,50). In vivo, exogenous IL-6 results in a 50% reduction in CBG levels in humans. Severe illness, such as sepsis and burns, are associated with similar reductions in CBG levels, in conjunction with a similar rise in endogenous IL-6 (51,52). Stress-induced falls in circulating CBG concentrations may also relate to cortisol elevations, as low CBG levels are seen in Cushing's syndrome or after antiinflammatory glucocorticoid doses (52). This effect is probably mediated through the glucocorticoid receptor as glucocorticoid receptor knockout mice exhibit increased hepatic CBG expression and 50% increased plasma CBG levels (53).

CBG Lyon refers to a CBG gene mutation that was first described in a 43 year old Moroccan woman presenting with chronic fatigue, depressed mood and low blood pressure, suggesting adrenal insufficiency (54). She had very low plasma cortisol levels, but normal ACTH levels. She was found to be homozygous for a point mutation in exon 5, leading to an Asp-Asn substitution, and a 4-fold reduction in CBG-cortisol binding affinity. Immunoreactive-CBG levels were 50% of the lower limit of normal, suggesting that the mutation affects CBG secretion or degradation. The proband's four children were heterozygous for the mutation. A 10-member Brazilian kindred with the same genetic mutation and reduced CBG-binding affinity has also been described, having been discovered after low cortisol levels were detected in the proband, a homozygote, who presented with fatigue (55). One other kindred member was a homozygote, the rest were heterozygotes, all were normotensive and none experienced fatigue.

In 2001, Torpy et al., reported a 39-member Italian-Australian family, including 21 heterozygotes and 3 homozygotes with a novel complete loss-of-function (null) CBG gene mutation involving exon 2 (56). The null mutation is a point mutation leading to a premature stop codon corresponding to residue -12 (tryptophan) of the pro-CBG molecule. It resulted in a 50% reduction of or undetectable CBG levels in heterozygotes or homozygotes, respectively. The proband was investigated because of unexplained fatigue and low blood pressure, suggesting glucocorticoid deficiency, and the finding of low plasma but normal urine cortisol levels, suggesting CBG deficiency. Amongst kindred members who were homozygous or heterozygous for the mutation, there was a high prevalence of chronic fatigue and low blood pressure. Surprisingly, five members had the previously reported CBG Lyon mutation.

Hence, CBG gene mutations are associated, albeit, inconsistently, with fatigue. Amongst CFS patients, the Lyon and Null mutations have not been detected (57,58,59).

To date several CBG mutations were identified following investigations of patients presenting with low plasma cortisol in variety of medical conditions such as chronic fatigue (Table 2) (60).

Table 2: CBG variants detected in humans with clinical implications

CBG variant	Nucleotide change	Discovery	CBG affect	Biochemical findings	Clinical features
CBG Leuven L93H [84, 91, 96]	T>A	Isolated in 3 unrelated individuals from a population study; subsequently detected in one out of 22 patients from a septic cohort	3 fold reduction in CBG-cortisol binding affinity	• Normal CBG levels	N/A
CBG Lyon D367N [85, 87, 88, 97-99]	G>A	Isolated from at least 5 pedigrees and an isolated (de novo) case.	4 fold reduction in CBG-cortisol binding affinity	• Low TC • Normal FC • Increased %FC • Normal ACTH and 24 hour UFC • Low CBG	• Chronic fatigue • Weakness • Depression • Hypotension
CBG Null/Adelaide Trp11Stop [88, 99]	G>A Premature stop codon	Isolated from a large Italian-Australian kindred and in pedigrees from the Italian village of origin. Some also carried CBG Lyon	Complete loss of CBG synthesis	• Normal 24 hour UFC • Low TC • Elevated FC • Increased %FC	• Hypotension • Chronic fatigue • Chronic pain

		Some also carried CBG Lyon D37N.		• Increased %FC • 50% reduction in CBG in heterozygotes • Undetectable CBG in homozygotes	
CBG A224S [91, 92]	G>T	Found with increased frequency from a candidate gene study in an Australian chronic fatigue cohort; also seen in conjunction with other CBG mutations [87, 89, 91]	No apparent affect on binding affinity or production	• Increased plasma CBG • Trend to low TC and FC	• Chronic fatigue
CBG G237V [86]	G>T	Isolated from a single kindred	Complete loss of CBG-cortisol binding affinity	• Very low TC • Normal FC • Low CBG • Increased % FC • Increased cortisol pulsatility	• Hypotension • Fatigue
CBG Santiago Leu5CysfsX26 [89]	Single base deletion → frameshift Premature stop codon	Isolated from a 9 year old Spanish male, also heterozygous for A224S	Decreased CBG synthesis	• Low TC • 50% reduction in CBG • Normal ACTH	• Chronic fatigue • Weakness • Headaches
CBG A51V [90, 100]	C>T	CBG polymorphism screening study in Han Chinese, prevalence 1:35 frequency	Decreased synthesis and/or secretion of CBG *in vitro* in CHO cells	• 30-50% reduction in CBG in heterozygotes • Higher female-to-male live birth rate	NA
CBG E102G [90]	A>G	CBG polymorphism screening study in Han Chinese	Reduced CBG-cortisol binding capacity *in vitro* in CHO cells	NA	NA
CBG Athens W371S [87]	G>C	Isolated from a single Greek kindred, also heterozygous for CBG Lyon D367N and CBG A224S	Complete loss of CBG-cortisol binding affinity	• Normal CBG levels • Low TC • Normal FC • Increased %FC • Normal 24 hour UFC	• Obesity

N/A – not available; UFC – urine free cortisol; TC – total cortisol; FC – free cortisol; %FC – percentage free cortisol; CHO – Chinese hamster ovary

Recent interest in the role of the HPA axis in CFS has arisen from the observation that conditions in which there is low circulating cortisol are characterized by debilitating fatigue. Addison's disease, glucocorticoid withdrawal and bilateral adrenalectomy are all associated with fatigue and with other symptoms also seen in CFS, including arthralgia, myalgia, disturbed sleep and mood (61). The literature consists of many studies which provide inconsistent data on HPA axis function in patients with CFS, in part because of methodological differences, but also reflecting perhaps, individual variation in HPA axis activity.

Urinary free cortisol levels in CFS patients have been found to be significantly lower, or no different to, controls (62,63,64,65). Plasma morning and late evening cortisols have been shown to be reduced in CFS/SEID, but this finding has not been consistently reproduced, particularly when frequent plasma cortisol sampling has been performed (63,65). Salivary cortisol has emerged as a useful test to detect hypercortisolism because of its non-invasiveness and correlation with free blood cortisol levels. In CFS, salivary cortisol day-curves are blunted compared with controls, evening salivary cortisol levels are lower, and there is a blunted salivary cortisol rise in response to awakening (66,67,68,69). DHEA and its long half-life sulphated metabolite DHEA-S represent major adrenal gland products in terms of mass. They represent important contributors to circulating androgen activity, particularly in women. DHEA and DHEA-S levels were shown to be lower in 15 CFS patients relative to 11 controls; furthermore CFS patients did not display the usual decrease in DHEA:cortisol ratio with ACTH stimulation (70). A preliminary study in eight selected CFS patients with a subnormal 1µg ACTH stimulation test showed a 50% reduction in adrenal gland volume on CT scan (71). This finding might indicate that the hypocortisolism of CFS is due to a lack of ACTH stimulation or a primary adrenal abnormality. In a recent study however, DHEA levels were higher in CFS patients and were correlated with higher disability scores (72).

To further examine the endocrine axes, stimulation testing is a classic endocrine paradigm, where subtle hypofunction may become more evident through the administration of stimulatory hormones or neuroactive agents. Nevertheless, as central control of endocrine axes cannot be directly assessed due to the lack of accessibility of the hypothalamic-pituitary circulation, the interpretation of the findings tends to be indirect. Often it is necessary to implicate underlying receptor up or down-regulation or secondary adrenal atrophy. Moreover, neuroactive agents often have incomplete specificity and the central neurotransmitter systems under study may in fact not be exclusively tested.

Dynamic endocrine testing with human CRH (pituitary stimulus) in CFS/SEID patients revealed a trend towards lower cortisol responses – which became statistically significant if ACTH responses were analysed as a covariate (73). ACTH responses to CRH may also be blunted in CFS (74). Other studies have found a normal ACTH and cortisol rise to CRH in CFS patients, which contradict the hypothesis, and previous data, suggesting that CFS is associated with a blunting of the HPA axis (75).

Insulin hypoglycaemia is a profound stimulus of ACTH and cortisol release, as it is likely to induce release of many hypothalamic ACTH secretagogues. Studies in CFS have revealed increased ACTH but normal cortisol responses after insulin hypoglycaemia

(76). This could be interpreted as indicating low CRH tone, with chronic CRH hyposecretion despite an intact CRH neuron, and secondary adrenal atrophy.

Naloxone is thought to stimulate ACTH and cortisol secretion by blocking tonic opioidergic inhibition of the CRH neuron. Naloxone mediated activation may be blunted in CFS suggesting it is the CRH neuron or pathways inhibitory to this neuron that lead to HPA axis hypofunction in CFS, rather than increased opioidergic tone (77). Other studies of CFS patients have shown a normal ACTH and cortisol response to naloxone (75).

The waking cortisol response, where cortisol levels rise 30-50% by 30 mins after waking compared to levels immediately on waking, is attenuated in chronic fatigue syndrome as a result of both higher waking and lower 30 min salivary cortisol levels, as documented in 75 CFS patients versus controls (78).

Another explanation for the hypocortisolism of CFS is increased glucocorticoid sensitivity, particularly in relation to the cerebral structures involved in glucocorticoid feedback such as the hypothalamic-paraventricular nucleus, the site of CRH neurons, and the anterior pituitary and hippocampus. Increased glucocorticoid sensitivity has been described in other stress-related hypocortisolaemic disorders, such as post-traumatic stress disorder, and has recently been reported in a small study of CFS patients (79).

Finally, it is not known if the hypocortisolism of CFS is a response to chronic deconditioning since exercise is a potent stimulator of HPA axis function. Experimental acute exercise deprivation led to some symptoms relating to pain, fatigue and mood as well as lower cortisol in a subset of healthy individuals (80).

CFS is associated with prominent features of autonomic dysregulation such as postural hypotension, disturbances in temperature regulation and altered skin microcirculation. The other arm of the stress system, the sympathetic nervous system with its outflow components, the sympathoneural and sympathoadrenal limbs have been less studied than cortisol in CFS. However, studies of both norepinephrine levels and a variety of tests of autonomic function suggest hyperactivity of the SNS, perhaps as a response to inadequate HPA axis responsivity (81,82).

The data suggesting relative hypocortisolism in CFS, along with the co-existence of fatigue, low blood pressure and mood alterations in both Addison's disease and CFS, have led to trials of hydrocortisone therapy in CFS. A randomized crossover trial in 32 CFS patients, of low-dose hydrocortisone (5mg or 10mg) treatment compared with placebo showed a reduction in self-reported fatigue scores after 1 month of treatment (83). In 28% of patients taking hydrocortisone, fatigue scores reached a predefined cut-off value similar to the normal population score. Only 9% of patients taking placebo achieved this reduction in fatigue score. Two larger trials of hydrocortisone treatment in CFS, have subsequently shown no real benefit of treatment. The first trial, which included 70 patients, treated with hydrocortisone (16mg/m2 daily in 2 divided doses) for 3 months reported some improvement in symptom scales (84). It is of interest that those with the lowest cortisol levels and adrenal reserve were not the most symptomatic, nor were they more likely to respond to hydrocortisone treatment. Adverse effects including

weight gain, increased appetite and disturbed sleep, occurred in those taking hydrocortisone. Hydrocortisone treatment was also associated with significant adrenal suppression, on the basis of basal and ACTH-stimulated cortisol levels in 12 patients. The authors concluded that the risks of adrenal crisis outweighed any perceived benefit of treatment and therefore that systemic corticosteroids should not be used in the treatment of CFS (84).

Fludrocortisone (0.1-0.2mg) was tested in a placebo-controlled, double-blind crossover trial. No improvement in symptoms, treadmill exercise performance or reaction time was observed in the 20 CFS patients who completed the trial (85).

Blockmans et al., reported six month randomised, placebo-controlled, double-blind, crossover study of hydrocortisone (5mg/day) and fludrocortisone in 100 patients fulfilling the CDC criteria for CFS (86). There was no benefit of treatment on self-reported fatigue or well-being.

The available scientific data indicates that the symptomatic benefit achieved with hydrocortisone or fludrocortisone replacement is, at best, marginal, and importantly, may be associated with clinically significant adverse effects, including adrenal suppression or features of glucocorticoid excess. These adverse effects outweigh any perceived benefit of treatment. Thus hydrocortisone and fludrocortisone treatment in CFS patients is not justified. In addition, ACTH stimulation testing has no practical relevance in the routine assessment of CFS patients, and should not be used to formulate management decisions.

Although low cortisol may not be the chief source of disability in CFS, it may be a marker of therapeutic significance. For example, the response to cognitive behavioural therapy is reduced in those with lower urine free cortisol or an attenuated diurnal rhythm (87)

MANAGEMENT

No specific treatment is known to be successful for CFS/SEID. However diagnosis may help patients by providing a basis for prognostic advice and validating their need for assistance in their personal lives and workplace. Reassurance is justified as many patients eventually recover (16)

Cognitive behavioural therapy involves the provision of information and counselling to reduce the psychological impediments to recovery, as well as encouraging the patient to participate at an appropriate level of social and occupational activity. In randomized-controlled trials comparing CBT to control conditions, the intervention has been shown to have a positive overall effect (16). Graded-exercise therapy may also be of benefit (17).

Spontaneous recovery in cases of prolonged fatigue is high. A literature search of all published studies which included a follow-up of patients with chronic fatigue syndrome or chronic fatigue were performed. Of 26 studies identified, four studied fatigue in children, and found that 54-94% of children recovered over the periods of follow-up. Another five studies operationally defined chronic fatigue syndrome in adults and found

that < 10% of subjects return to pre-morbid levels of functioning, (16). After infectious mononucleosis (88) 41% of patients reported prominent fatigue during the acute illness, of these 71% had prolonged fatigue one month later, 43% at two months and 9% at six months. The prognosis for prolonged fatigue or CFS in children may be even better than in adults (16). Chronic fatigue syndrome is not thought to be associated with an increased overall mortality rate, or an increase in suicide rate(18).

Symptomatic treatments, such as non-steroidal anti-inflammatory drugs or non-opiate analgesics for pain and counselling or antidepressants for major depression, are commonly used in CFS although their values in condition have not been the subject of long scale trial.

No pharmacological agent has been reproducibly shown to be effective in the treatment of chronic fatigue syndrome. Two recent studies have shown some promise for therapy.

Rintatolimod is an antiviral, restricted Toll-like Receptor 3 (TLR3) agonist lacking activation of other primary cellular inducers of innate immunity. It also activates interferon-induced protein. Rintatolimod was associated with significant improvement (89). A recent study tested the efficacy of Rintatolimod in the treatment of CFS/SEID in randomized Phase I and Phase II double blind placebo controlled, multisite clinical trials. Rintatolimod was administered bi-weekly up to forty weeks. About 30-40% of CSF patients can be expected to respond beneficially to Rintatolimod (Mitchell et.al 2016). Rintatolimod has been approved for use in Europe and Canada. Some authorities suggest Rintatolimod should be considered an experimental drug until confirmatory studies are available (27).

Coenzyme Q10 and NADH are antioxidants which may improve mitochondrial function. A study enrolled 113 CFS patients, diagnosed according to the Fukuda criteria, in an 8 week randomized double blind placebo controlled trial of CoQ10 and NADH (90). 33 patients were excluded as they didn't meet the criteria, 73 patients were eligible for the study, randomized to CoQ10 plus NADH supplementation group or placebo group. The trial revealed significant improvement in CFS patients who received CoQ10 plus NADH supplementation, which can cause potential therapeutic benefits on fatigue and biochemical markers in CFS patients (90). This is an area for further study.

CONCLUSION

Many diagnostic criteria exist for CFS/SEID but the emphasis on exercise intolerance is thought to have significant specificity, although secondary features are also typical. The stress system has been shown to exhibit a reasonably consistent phenotypic pattern comprising relatively low cortisol and elevated sympathetic, particularly sympathoneural function. The aetiology of CFS/SEID is unknown and the mechanism of altered stress system function is uncertain. Several other pathogenetic mechanisms are proposed. Recently, some treatment trials have been promising and confirmation of their effect is awaited.

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