CHRONIC FATIGUE SYNDROME

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ABSTRACT

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is an enigmatic medical condition that has growing prevalence across the globe, often diagnosed after exclusion of other medical or mental illnesses. As there is no clinical test to confirm the presence of this condition, the diagnosis is syndromic based on different clinical definitions. There was mixed evidence to support the use of a specific therapy that provides palliative effect. Pathophysiological hypotheses can be categorized into infection, immune, mitochondrial, neurobehavioral, or stress system (HPA axis and sympathetic nervous system) disorders. The prognosis of ME/CFS is mixed but recovery does occur in many cases, over time. All-cause mortality rate is not increased.

CLINICAL DEFINITION

Fatigue is a term used to describe unexplained subjective, chronic, pervasive tiredness or weakness physically, mentally, or a combination of both. The term “myalgic encephalomyelitis” was first described in the United Kingdom after an outbreak of serious infection at the Royal Free Hospital in 1955 (1). The US originated term Chronic Fatigue Syndrome (CFS) was introduced by Holmes et al in 1988 (2). Several definitions of CFS have been developed, primarily to standardize research (3,4). The key symptoms expected in this condition was later refined in 1994 and named after Dr Fukada (3). However, it was particularly challenging to reach a consensus on a name for this condition as its etiology and pathology are unexplained. An important milestone was achieved on October 1, 2022 with the update to International Coding Disease (ICD-10-CM) that include a specific diagnostic code for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME) (5). Prior to this, chronic fatigue syndrome was categorized in the “chronic fatigue, unspecified”, which could limit epidemiologic studies.

The 1994 US Centers for Disease Control and Prevention (CDC) Fukuda criteria for chronic fatigue syndrome comprise the following (3):

1. Primary symptoms that are 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.
- myalgia.
- multiple-joint pain without swelling or redness.
- headache of new type, pattern, or severity.
- unrefreshing sleep.
- post-exertional fatigue/malaise lasting longer than 24 hours.

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

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

This is a stricter criterion, compared to the Fukada Criteria and it is mainly used as case definition in research. Adults are diagnosed after 6 months of symptoms while pediatric cases were diagnosed after 3 months.

Nearly two decades after Fukada Criteria was introduced, the US Institute of Medicine (IOM), now known as National Academy of Medicine (NAM) 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 as below.

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.

As a large group of patients remain stigmatized with the term ‘chronic fatigue syndrome’ (CFS), renaming the condition to 'systemic exertion intolerance disease' (SEID) was recommended to overcome the old stereotypes as CFS is more associated to a mental disorder rather than an organic 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. However, the new IOM criteria could increase the prevalence rate of this condition compared to the use of previous Fukada criteria due to the lack of specifying exclusionary illnesses (5).

DIAGNOSTIC APPROACH

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) with an algorithm provided in Figure 1 (6). 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 from major depression. Hypersomnolence and sleep disorder suggests a need to exclude obstructive sleep apnea, particularly in groups at risk such as the obese.

Limited laboratory screening investigations are directed towards the discovery of subtle medical disorders. Unfortunately, there was no test with adequate sensitivity and specificity to 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. For example, sleep study may be considered in patients who have features of obstructive sleep apnea, while a morning cortisol concentration or a more definitive ACTH stimulation test may be considered for patients who have clinical features suggestive of adrenal insufficiency.

Although patients with CFS/ME tend to have more abnormalities on magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT), the significance of these findings are unclear, hence routine neuroimaging is not recommended in the diagnostic process (7,8).

Some recent studies have suggested reduced circulatory and myocardial function in CFS, although the utility of routine cardiac assessment is not established (9,10).

Table 1. Clinical Working Case Definition of ME/CFS, published in 2000 (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 dyspnea. (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 anemia, 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 apnea; 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, odors, and/or mixed sensory modalities.

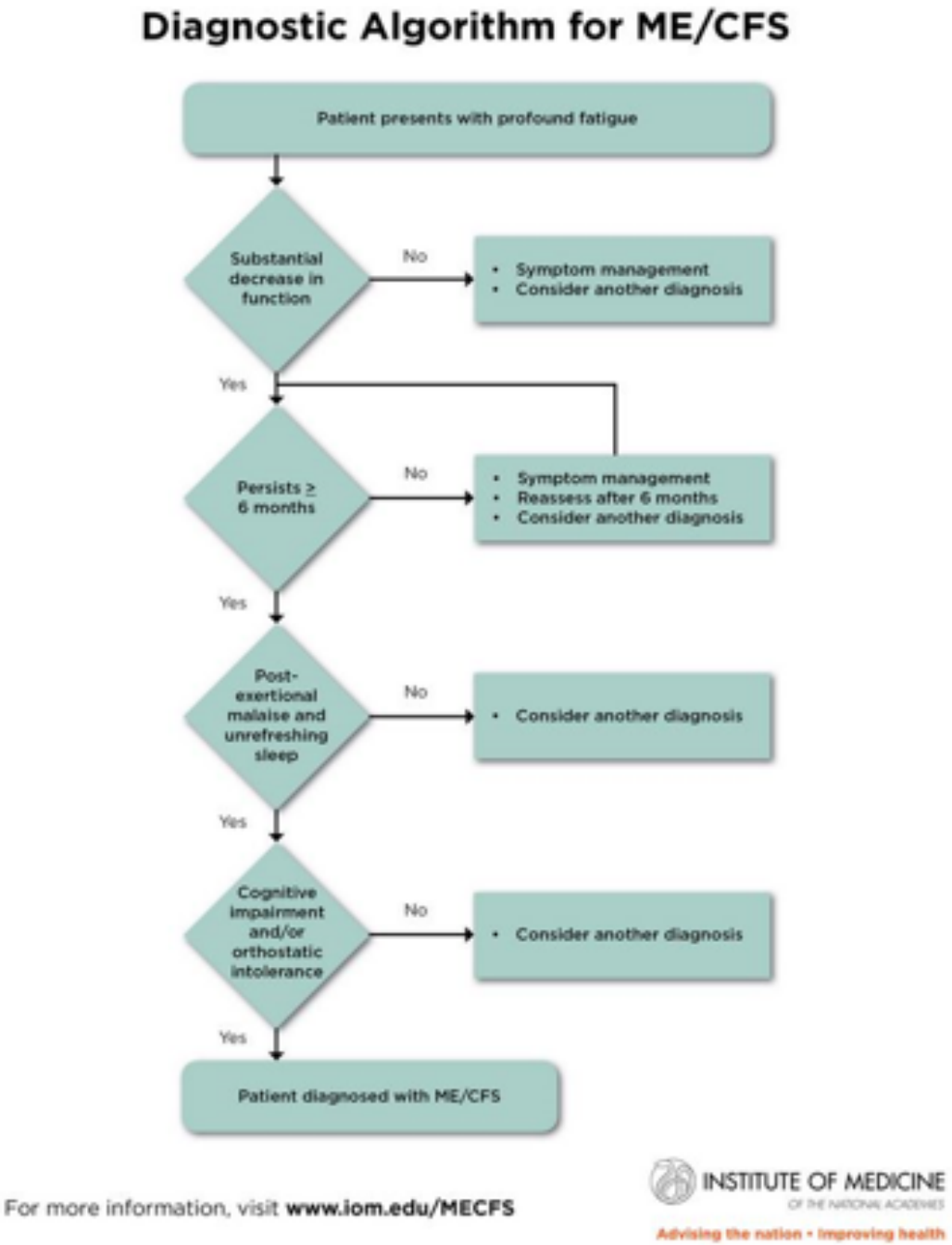

Figure 1. Diagnostic algorithm adapted from IOM (6).

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 (11,12). Another study suggested the global prevalence of CFS ranges from 0.4% and 2.5% (13).

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 (11, 14). Geographic location has not been shown to influence the prevalence of CFS but more recent study showed the condition is more common in certain countries such as the UK, Australia, and the USA (12, 14). Twin studies suggest that genetic factors play an important role (16). Population studies also associate elevated premorbid stress and childhood trauma, especially if complicated by psychopathology, with an increased risk of CFS (17,18).

An Australian sociodemographic cross-sectional study of patients diagnosed with CFS by their primary care physician was conducted over 2 years (2013-2015) (19). 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 who were obese or overweight, (41.3% and 43.3% respectively) and were unemployed or on a disability pension. The results of this study may not be representative of all CFS/ME patients in the general population due to sample recruitment bias.

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 titers to specific, but varying, infectious agents (20). 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 etiological agents of CFS (21). However, to date, there has been no consistent evidence that CFS results from a specific infection (22). 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 (20,23).

Recent study has examined the characteristics of cell function and receptors in CFS patients (24). 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 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 (25). This suggests that that atopy might increase the risk of CFS/SEID.

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 (26).

Neuropsychiatric Hypotheses

Chronic fatigue syndrome has been suspected to be a neuropsychiatric disorder, or a type of depression (28). 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 (28). Cognitive-behavioral models of CFS emphasize the importance of the interactions between cognitive, behavioral and biological variables in attempting to explain the genesis and maintenance of CFS. It may be that while organic factors may precipitate CFS, cognitive-behavioral factors may perpetuate the illness (28). 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, demoralization 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 (29). 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 (29). 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 (28). 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 (30). 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” (30).

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) (32-36, 40-41). 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 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 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, concomitant hypotension and/or orthostasis, 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 (28). Moreover, hypocortisolism is a trait shared with other chronic idiopathic disorders, including post-traumatic stress disorder, fibromyalgia, and inflammatory disorders such as rheumatoid arthritis and asthma (18). 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, (42). 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 acute stress system responses 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 2). 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 normoglycemia 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 synchronization of the CRH and AVP pulsations in the hypophyseal portal system markedly increases, resulting in increases of ACTH and cortisol secretory episodes (43). 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 (44).

Cortisol action is mediated by ubiquitous cytosolic corticosteroid receptors and (45). 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 (45). 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 (46).

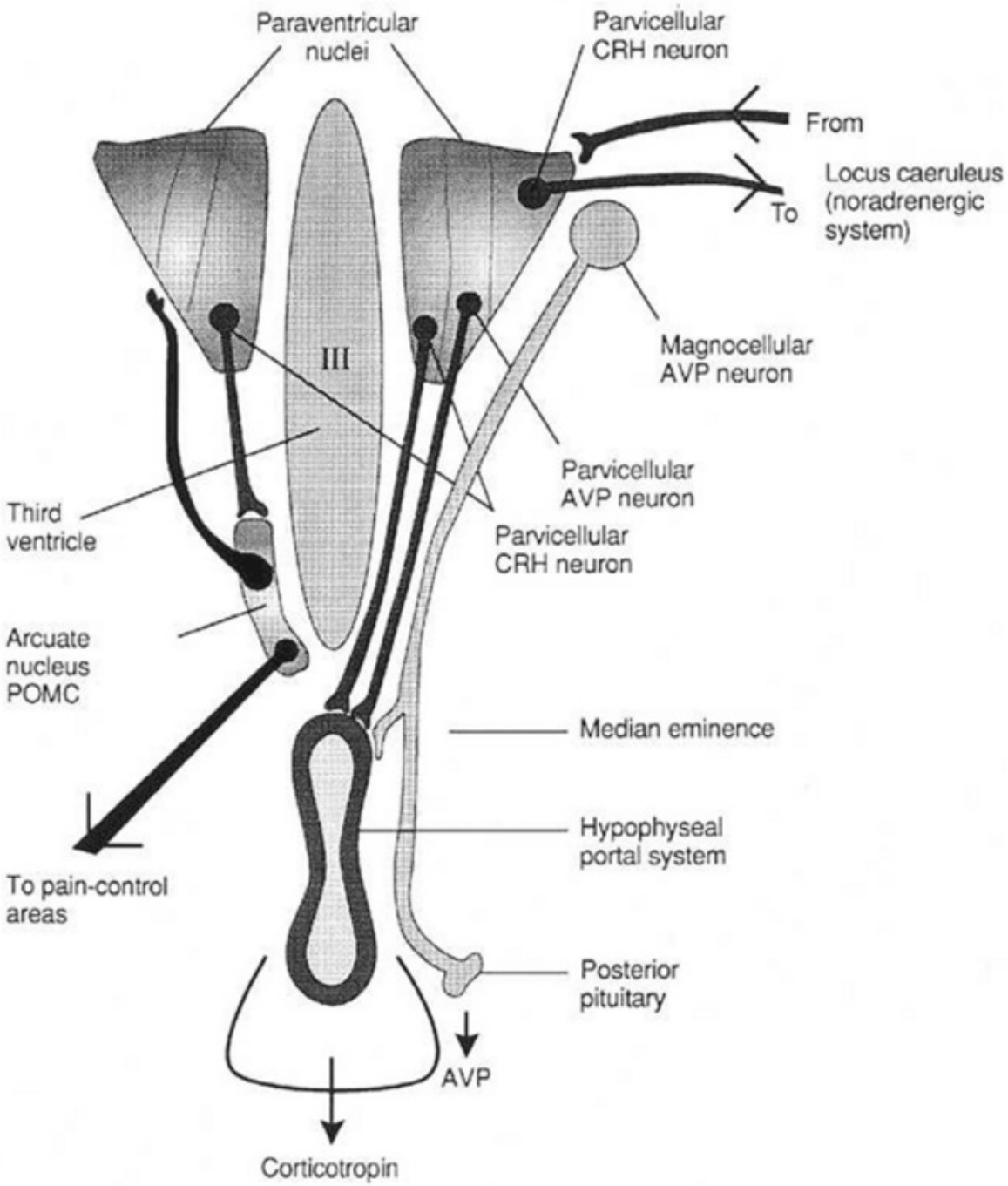
Paraventricular nuclei
Parvicellular CRH neuron
From
Locus caeruleus (noradrenergic system)
To
III
Magnocellular AVP neuron
Parvicellular AVP neuron
Parvicellular CRH neuron
Third ventricle
Arcuate nucleus POMC
Median eminence
Hypophyseal portal system
To pain-control areas
Posterior pituitary
AVP
Corticotropin

Figure 2. The neurohormonal connections of 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 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 (47). However, fatigue as an isolated symptom has been described in a 55-year-old woman with glucocorticoid resistance (48). 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 (49).

Further to this, recent studies of glucocorticoid receptor polymorphisms have found an association between certain haplotypes and CFS (50). Although speculative, polymorphisms may result in altered receptor sensitivity to cortisol, and thus, impaired tissue-effect of cortisol, resulting in relative hypocortisolism.

CORTICOSTERIOD BINDING GLOBULIN ABNORMALITIES AND CHRONIC FATIGUE

Corticosteroid-binding globulin (CBG), also known as transcortin, is the high-affinity plasma transport glycoprotein for cortisol (51). 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 (51). 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 (51). 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 (52). High-affinity cortisol binding is saturated beyond cortisol levels of 500nmol/L, hence free cortisol levels rise exponentially at high cortisol concentrations (53). Under conditions of stress, elevated cortisol levels saturate available CBG and increase the free cortisol to above 20% (53).

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 neurons and it also inhibits CBG gene transcription thereby increasing the free cortisol fraction and thus, circulating glucocorticoid activity (54,55). 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 (56,57). Similar falls in circulating CBG concentrations are seen in septic shock and low CBG concentrations have been shown to be an independent predictor of mortality in ICU patients (58). 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 anti-inflammatory glucocorticoid doses (57). 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 (59).

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 (60). 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 (61). One other kindred member was a homozygote, the rest were heterozygotes, all were normotensive and none experienced fatigue.

In 2001, a 39-member Italian-Australian family was reported, including 21 heterozygotes and 3 homozygotes with a novel complete loss-of-function (null) CBG gene mutation involving exon 2 (62). 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 (63- 65). 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 (66).

PITUITARY-ADRENAL HORMONE ABNORMALITIES IN CHRONIC FATIGUE SYNDROME

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 (67). Many studies 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 (68-71). Plasma morning and late evening cortisol has been shown to be reduced in CFS/ME, but this finding has not been consistently reproduced, particularly when frequent plasma cortisol sampling has been performed (69,71). 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 waking (72-75). 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 (76). 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 (77). 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 (78).

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 patients revealed a trend towards lower cortisol responses – which became statistically significant if ACTH responses were analyzed as a covariate (79). ACTH responses to CRH may also be blunted in CFS (80). 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 (81).

Insulin hypoglycemia 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 hypoglycemia (82). 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 (83). Other studies of CFS patients have a normal ACTH and cortisol response to naloxone (81).

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 (82).

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 hypocortisolemic disorders, such as post-traumatic stress disorder, and has recently been reported in a small study of CFS patients (85).

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 (86).

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 (87,88).

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 (89). 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. However, another trial of hydrocortisone treatment in CFS, have subsequently shown no real benefit of treatment. The trial which included 70 patients, treated with hydrocortisone (16mg/m2 daily in 2 divided doses) for 3 months reported some improvement in symptom scales (90). 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 (90).

Blockmans et al., reported six month randomized, placebo-controlled, double-blind, crossover study of hydrocortisone (5mg/day) and fludrocortisone in 100 patients fulfilling the CDC criteria for CFS (91). There was no benefit of treatment on self-reported fatigue or well-being.

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 (92).

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. Overall, 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, but may be used to rule out adrenal insufficiency.

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 behavioral therapy is reduced in those with lower urine free cortisol or an attenuated diurnal rhythm (93).

The COVID-19 pandemic has led to a variety of symptoms after acute illness recovery. The recovery process from COVID-19 varies between individuals, depending on factors such as the illness severity, age, and underlying comorbidities. Despite not having a widely accepted definition, Centers for Disease and Prevention and the World Health Organization (WHO) has agreed the acute symptoms of COVID can last up to four weeks following the onset of the illness (94,95). Various terminologies such as “long COVID’, “post-acute sequalae of SARS-CoV-2 infection”, “post-acute COVID-19” have been used to describe the prolonged symptoms following COVID-19. In this article, we will use Long COVID to describe the condition.

While Long COVID and chronic fatigue syndrome/myalgia encephalitis (CFS/ME) are distinct conditions, they do share some similarities in terms

of symptoms and impact on individual's lives. Both conditions are characterized by persistent and debilitating fatigue. It is worth noting that CFS/ME is diagnosed after fatigue present for at least six months, which is not relieved by rest while fatigue experienced in Long COVID can last for weeks, months or longer. The accompanying symptoms of Long COVID syndrome are broad and can affect multiple organ systems including respiratory and cardiac symptoms, which does not typically present in CFS/ME (94- 97). While the triggering event of long COVID is attributed to COVID itself, the triggering event of CFS/ME is not fully understood. Patients with long COVID syndrome may have symptoms consistent with and meet diagnostic criteria of CFS/ME where similar assessment and management strategy can be employed.

MANAGEMENT

Generally, all treatment for CFS/ME must be individualized aiming to address the most debilitating symptom first. No specific treatment is known to be successful for CFS as the current evidence for pharmacological or non-pharmacological interventions was heterogenous and inconclusive (98). However, diagnosis may help patients by providing a basis for prognostic advice and validating their need for assistance in their personal lives and workplace.

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 ME/CFS although their efficacy has not been the subject of a long-term trial. Developing good sleep hygiene to provide sufficient rest is often part of the management strategy. The latest NICE guideline also suggested dietary strategies including adequate hydration, referral to dietician for patients at risk of weight gain or malnutrition, as well as vitamin D repletion for vitamin D deficiency. It is important to explain to patients with ME/CFS that there is insufficient evidence to support routine vitamin supplementations as treatment for the condition (NICE) (98). Patients with significant cognitive decline should be referred for further neurocognitive evaluation.

Cognitive behavioral 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. It is important for clinicians to establish a rapport as patients may be mistrustful due to prior negative health care experiences (99). In randomized-controlled trials comparing CBT to control conditions, the intervention has been shown to have a positive overall effect (21). Graded-exercise therapy may also be of benefit (22).

No pharmacological agent has been reproducibly shown to be effective in the treatment of chronic fatigue syndrome.

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. A systemic review suggested some evidence that Rinatotolimod may improve symptoms of ME/CFS (100). Another double blind, randomized, placebo-controlled clinical trial showed statistically significant improvements in primary endpoints in phase II and phase III trials. About 30-40% of ME/CFS patients can be expected to respond beneficially to Rintatolimod (101). Previous double-blind, randomized clinical trial of Rintatolimod showed an improvement in exercise

tolerance and improvement of medication usage for CFS/ME-related symptoms (102). However, the application to the US Food and Drug Administration (FDA) was rejected in 2009 as the previous RCTs that failed to provide credible evidence of efficacy (103). At present, Rintatolimod is only approved for use in Argentina. Therefore, some authorities suggest Rintatolimod should be considered an experimental drug until confirmatory studies are available (32).

Rituximab is an anti-CD20 monoclonal antibody. There may be some benefits shown in a small double-blind, placebo-controlled trials involving 30 patients, particularly in patients with self-reported fatigue, but a subsequent, larger study showed no difference in the treated group and the control group after 24 months of treatment (104,105).

A small trial revealed significant improvement in ME/CFS patients who received CoQ10 plus NADH supplementation, but a larger study is warranted to verify its beneficial effect in ME/CFS patients (106).

There is a list of therapies that have been trailed in the past, with no proven benefit over placebo. These therapies include acyclovir, antibiotics, cytokine inhibitors, galantamine, glucocorticoids, mofadanil, and methylphenidate (107-113).

PROGNOSIS

Overall, full recovery from untreated ME/CFS is rare but improvement of symptoms in long term is slightly more optimistic (114-116). However, the prognosis of ME/CFS also varies widely among individuals. The reported improvement rates range from 0 to 8% (117-122). Broad range improvement rate is reported at 17-64% (117,120,122,123). A study suggested although most patients with this condition improve, a significant proportion remain functionally impaired over time (118). Another study that was conducted using a questionnaire, reported 73% of patients remain functionally impaired at six weeks to six months but this improved to 33% at two to four years (115).

A systematic review showed the median full recovery only happened in 5% of patients (122). Another retrospective study that includes patients with unexplained debilitating fatigue lasting for more than six months but does not fulfil the criteria of ME/CFS showed complete resolution of symptoms only occurred in 2% of these patients (119).

As there was lack of operationalized criteria for recovery and improvement, the studies yielded contradictory results in terms of factors that predict the likelihood of recovery. Some studies suggested that old age is associated with poorer outcome while others did not support this hypothesis (118,119,124,125). There has been mixed evidence that shorter duration of illness to be a predictor of better improvement (118,121). Mixed evidence was demonstrated across studies with regards to a worse prognosis in patients with comorbid fibromyalgia (125-127). There may be an increased risk of suicide (128).

ME/CFS has not been associated with increased mortality rate. Treatment is supportive and a defined pathogenesis has not been identified, despite a syndromic definition that is quite frequent and stable across individuals and populations.

CONCLUSION

Many diagnostic criteria exist for MF/ CFS 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 etiology of ME/CFS is unknown and the mechanism of altered stress system function is uncertain. Several other pathogenetic mechanisms are proposed. Currently, some treatment trials have been promising and confirmation of their effect is awaited.

REFERENCES

1. Crownley N, Nelson M, Stovin S. Epidemiological aspects of an outbreak of encephalomyelitis at the Royal Free Hospital, London, in the summer of 1955. J Hyg (Lond). 1957 Mar;55(1):102-22.
2. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic Fatigue Syndrome: A Working Case Definition. Ann Intern Med. 1988; 108: 387-9.
3. Fukuda K, Straus SE, Hickie I, et al, and the International Chronic Fatigue Syndrome Study Group. Chronic Fatigue Syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121:953-9.
4. Carruthers BM, Jain AK, De Meirleir KL, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. J Chronic Fatigue Syndr 2003;11(1):7-115.
5. Jason LA, Sunnquist M, Brown A, Newton JL, Strand EB, Vernon SD. Chronic Fatigue Syndrome versus Systemic Exertion Intolerance Disease. 2015;3(3):127-4
6. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Centre for Disease Control and Prevention (CDC). Updated April, 2021. Accessed June 2023. https://www.cdc.gov/me-cfs/healthcare-providers/diagnosis/iom-2015-diagnostic-criteria.html
7. Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolesz FA, Holman BL. Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. AJR Am J Roentgenol. 1994 Apr;162(4):935-41. doi: 10.2214/ajr.162.4.8141020.
8. Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, Kikinis R, Jolesz FA, Folks T, Balachandran N, Peter JB, Gallo RC, Komaroff AL. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. Ann Intern Med. 1992 Jan 15;116(2):103-13.
9. Newton JL, Finkelmeyer A, Petrides G, Frith J, Hodgson T, Maclachlan L, et al. reduced Cardiac volumes in chronic fatigue syndrome associate with plasma volume but not length of disease: a cohort study. Open Heart. 2016;3(1):e000381
10. Olimulder MA, Galjee MA, Wagenaar LJ, van Es J, van der Palen J, Visser FC, et al. Chronic fatigue syndrome in women assessed with combined cardiac magnetic resonance imaging. Neth Heart J. 2016;24(12):709-16
11. Reyes M, Nisenbaum R, Hoaglin DC, et al. Prevalence and Incidence of Chronic Fatigue Syndrome in Wichita, Kansas. Arch Intern Med 2003;163:1530-6.
12. Jason LA, Richman JA, Rademaker AW, et al. A Community-Based Study of Chronic Fatigue Syndrome. Arch Intern Med 1999;159:2129-37.
13. Twisk FNM. A critical analysis of the proposal of the Institute of Medicine to replace myalgic encephalomyelitis and chronic fatigue syndrome by a new diagnostic entity called systemic exertion intolerance disease. Current Medical Research and Opinion 2015;31:1333–47.
14. Steele L, Dobbins JG, Fukada K, et al. The epidemiology of chronic fatigue in San Fracisco. Am J Med. 1998; 105 (3A): 83S-90S.
15. Bakken I,Tveito K,Gunness, et al.Two age peaks in the incidence of chronic fatigue syndrome/Myalgic encephalomyelitis:a population-based registry study from Norway 2008-2012.BMC Med 2014 Oct1:12(1):167
16. Reeves WC, Jones JF, Maloney E, et al. Prevalence of Chronic Fatigue Syndrome in Metropolitan, Urban and Rural Georgia. Pop Health Metr 2007;5:5.
17. Kato K, Sullivan PF, Evengård B, et al. Premorbid Predictors of Chronic Fatigue. Arch Gen Psych 2006;63:1267-72.

18. Heim C, Wagner D, Maloney E, et al. Early Adverse Experience and Risk for Chronic Fatigue Syndrome. Results From a Population-Based Study. Arch Gen Psych 2006;63:1258-66.

19. Johnston SC, Staines DR, Marshall-Gradisnik SM. Epidemiological characteristics of chronic fatigue syndrome/myalgic encephalomyelitis in Australian patients. Clinical Epidemiology 2016;8:97-107

20. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4:134-53

21. Whiting P, Bagnall A-M, Sowden AJ, et al. Interventions for the treatment and management of Chronic Fatigue Syndrome. JAMA 2001;286:1360-8

22. White PD, Thomas JM, Amessis J, et al. The existence of a fatigue syndrome after glandular fever. Psychol Med 1995;25:907-16.

23. Smith WR, Noonan C, Buchwald D. Mortality in a cohort of chronically fatigued patients. Psychol Med 2006;36:1301-6

24. Hardcastle SL, Brenu EW, Johnston S, Nguyen T, Huth T, Wong N, et al. Characterisation of cell functions and receptors in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). BMC Immunol. 2015;16:35

25. Yang TY, Kuo HT, Chen HJ, Chen CS, Lin WM, Tsai SY, et al. Increased Risk of Chronic Fatigue Syndrome Following Atopy: A Population-Based Study. Medicine (Baltimore). 2015;94(29):e1211

26. Ciregia F, Kollipara L, Giusti L, Zahedi RP, Giacomelli C, Mazzoni MR et al. Proteomics suggests an association between differential expression of mitochondrial proteins and chronic fatigue syndrome. Transl Psychiatry. 2016;6(9):e904

27. Komaroff AL, Fagioli LR, Geiger AM, et al. An examination of the working case definition of chronic fatigue syndrome. Am J Med 1996;100:56-64.

28. Wessely S, Butler S, Chalder T, et al. The cognitive behavioral management of the post-viral fatigue syndrome. In R. Jenkins and J. Mowbrey (Eds.), Postviral fatigue syndrome (pp.305-334). Chichester: John Wiley and Sons.

29. Surawy C, Hackmann A, Hawton K, et al. Chronic fatigue syndrome: a cognitive approach. Behaviour Research Therapy 1995;33:535-44.

30. White C, Schwitzer R. The role of personality in the development and perpetuation of chronic fatigue syndrome. J Psychosomatic Med 2000;48:515-24.

31. Rasouli O, Fors EA, Borchgrevink PC, Ohberg F, Stensdotter AK. Gross and fine motor function in fibromyalgia and chronic fatigue syndrome. J Pain Res. 2017;10:303-9

32. Gluckman SJ. Treatment of systemic exertion intolerance disease (chronic fatigue syndrome). In: Aronson MD, Mitty J, editors. UpToDate. Waltham, MA: UpToDate; 2017

33. Wu T, Qi X, Su Y, Teng J, Xu X. Electroencephalogram characteristics in patients with chronic fatigue syndrome. Neuropsychiatr Dis Treat. 2016;12:241-9.

34. Tuller, David (2014-11-24), "Brains of People With Chronic Fatigue Syndrome Offer Clues About Disorder", NY Times.

35. Zeineh, Michael M; Kang, James; Atlas, Scott W; et al. (2014-10-29), "Right Arcuate Fasciculus Abnormality in Chronic Fatigue Syndrome", Radiology, 274 (2): 517–526, doi:10.1148/radiol.14141079.

36. Goldman, Bruce (2014-10-28), "Study finds brain abnormalities in chronic fatigue patients", Stanford Medicine News Center.

37. Shan, ZY; Kwiatek, R; Burnet, R; Del Fante, P; Staines, DR; Marshall-Gradisnik, SM; Barnden, LR (2016-04-28), "Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study", Journal of magnetic resonance imaging: JMRI, PMID 27123773, doi:10.1002/jmri.25283.

38. Jaime S (2016-05-05), "Progressive Brain Changes in Patients with Chronic Fatigue Syndrome: Are our Brains Starved of Oxygen?", #MEAction

39. Zinn, Marcie L; Zinn, Mark A; Jason, Leonard A (2016), "qEEG / LORETA in Assessment of Neurocognitive Impairment in a Patient with Chronic Fatigue Syndrome: A Case Report", Clinical Research: Open Access (ISSN 2469-6714), 2 (1), ISSN 2469-6714, doi:10.16966/2469-6714.110.

40. Nakatomi, Yasuhito; Mizuno, Kei; Ishii, Akira; et al. (2014-03-24), "Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C-(R)-PK11195 PET Study", Journal of Nuclear Medicine, 2014 Jun;55(6): 945-50, PMID 24665088, doi:10.2967/jnumed.113.131045.

41. Puri, BK; Jakeman, PM; Agour, M; Gunatilake, KDR; Fernando, KAC; Gurusinghe, AI; Treasaden, IH; Waldman, AD; Gishen, P (2012), "Regional grey and white matter volumetric changes in

myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3 T MRI study", British Journal of Radiology, 85 (1015): e270-3, doi:10.1259/bjr/93889091.

42. Wyller VB, Vitelli V, Sulheim D, Fagermoen E, Winger A, Godang K, et al. Altered neuroendocrine control and association to clinical symptoms in adolescent chronic fatigue syndrome: a cross-sectional study. J Transl Med. 2016;14(1):121.

43. Tsigos C, Chrousos GP. Physiology of the hypothalamic-pituitary-adrenal axis in health and dysregulation in psychiatric and autoimmune disorders. Endocrinol Metab Clin Nth Am 1994;23:451-66.

44. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to physiological actions. Endocr Rev 1984;5:25-44.

45. Pratt WB. Glucocorticoid receptor structure and the initial events in signal transduction. Prog Clin Biol Res 1990;322:119-32.

46. Scheinman RI, Gualberto A, Jewell CM, et al. Characterisation of mechanisms involved in transrepression of NF-KB by activated glucocorticoid receptors. Mol Cell Biol 1995;15:943-53.

47. van Rossum EFC and Lamberts SWJ. Glucocorticoid resistance syndrome: a diagnostic and therapeutic approach. Best Pract Res Clin Endocrinol Metab 2006;20:611-26.

48. Bronnegard M, Werner S, Gustafsson JA. Primary cortisol resistance associated with a thermolabile glucocorticoid receptor in a patient with fatigue as the only symptom. J Clin Invest 1989;78:1270-8.

49. Huizenga N, De Lange P, Koper JW, et al. Five Patients with Biochemical and/or Clinical Generalised Glucocorticoid Resistance without Alterations in the Glucocorticoid Receptor Gene. J Clin Endocrinol Metab 2000;85:2076-81.

50. Rajeevan MS, Smith AK, Dimulescu I, et al. Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome. Genes, Brain and Behav 2007;6:167-76.

51. Hammond GL. Molecular properties of corticosteroid binding globulin and the sex-steroid binding proteins. Endocr Rev 1990;11:65-79.

52. Hammond GL, Smith CL, Paterson NA, et al. A role for corticosteroid-binding globulin in delivery of cortisol to activated neutrophils. J Clin Endocrinol Metab 1990;71:34-9.

53. Ballard PL. Delivery and transport of glucocorticoids to target cells. Monographs on Endocrinology 1979;12:25-48.

54. Papanicolaou DA, Wilder RL, Manolagas SC, et al. The pathophysiologic roles of interleukin-6 in human disease. Ann Intern Med 1998;128:127-37.

55. Tsigos C, Kyrou I, Chrousos GP, et al. Prolonged suppression of corticosteroid-binding globulin by recombinant human interleukin-6 in man. J Clin Endocrinol Metab 1998;83:3379.

56. Ho JT, Al-Musalhi H, Chapman MJ, et al. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. J Clin Endocrinol Metab 2006;91:105-14.

57. Bernier J, Jobin N, Emptoz-Bonneton A, et al. Decreased corticosteroid-binding globulin in burn patients: relationship with interleukin-6 and fat in nutritional support. Crit Care Med 1998;26:452-60.

58. Meyer EJ, Nenke MA, Davies ML, et al. Corticosteroid-Binding Globulin Deficiency Indepednently Predicts Mortaility in Septic Shock. J Clin Endocrinol Metab. 2022; 107:1636-1646.

59. Cole TJ, Harris HJ, Hoong I, et al. The glucocorticoid receptor is essential for maintaining basal and dexamethasone-induced repression of the murine corticosteroid-binding globulin gene. Mol Cell Endocrinol 1999;154:29-36.

60. Emptoz-Bonneton A, Cousin P, Seguchi K, et al. Novel human corticosteroid-binding globulin variant with low cortisol-binding affinity. J Clin Endocrinol Metab 2000;85:361-7.

61. Brunner E, Baima J, Vieira TC, et al. Hereditary corticosteroid-binding globulin deficiency due to a missense mutation (Asp367Asn, CBG Lyon) in a Brazilian kindred. Clin Endocrinol 2003;58:756-62.

62. Torpy DJ, Bachmann AW, Grice JE, et al. Familial Corticosteroid-Binding Globulin Deficiency Due to a Novel Null Mutation: Association with Fatigue and Relative Hypotension. J Clin Endocrinol Metab 2001;86:3692-700.

63. Torpy DJ, Bachmann AW, Gartside M, et al. Association between chronic fatigue syndrome and the corticosteroid-binding globulin gene ALA SER224 polymorphism. Endocr Res 2004;30:417-29.

64. Smith CL, Power SG and Hammond GL. A Leu-His substitution at residue 93 in human corticosteroid binding globulin results in reduced affinity for cortisol. J Steroid Biochem Mol Biol 1992;42:671-6.

65. Torpy DJ and Ho JT. Corticosteroid-binding globulin gene polymorphisms: clinical implications and links to idiopathic chronic fatigue disorders. Clin Endocrinol 2007 Aug;67(2):161-7.

66. Meyer EJ, Spangenberg L, Rmirez MJ, et al Corticosteroid-Binding Globulin. J Endocr Soc. 2021 Jun 22; 5(9):bvab115.

67. Cleare AJ. The Neuroendocrinology of Chronic Fatigue Syndrome. Endocr Rev 2003;24:236-52.

68. Cleare AJ, Blair D, Chambers S, et al. Urinary free cortisol in Chronic Fatigue Syndrome. Am J Psych 2001;158:641-3.

69. Jerjes WK, Taylor NF, Peters TJ, et al. Urinary cortisol and cortisol metabolite excretion in chronic fatigue syndrome. Psychosom Med 2006;68:578-82.

70. Crofford, LJ, Young EA, Engleberg NC, et al. Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. Brain, Behav Immun 2004;18:314-25.

71. Jerjes WK, Peters TJ, Taylor NF, et al. Diurnal excretion of urinary cortisol, cortisone and cortisol metabolites in chronic fatigue syndrome. J Psychosom Res 2006;60:145-53.

72. Jerjes WK, Cleare AJ, Wessely S, et al. Diurnal patterns of salivary cortisol and cortisone output in chronic fatigue syndrome. J Affect Disord 2005;87:299-304.

73. Strickland P, Morriss R, Wearden A, et al. A comparison of salivary cortisol in chronic fatigue syndrome, community depression and healthy controls. J Affect Disord 1998;47:191-4.

74. Roberts ADL, Wessely S, Chalder T, et al. Salivary cortisol response to awakening in chronic fatigue syndrome. Br J Psych 2004;184:136-41.

75. Nater UM, Youngblood LS, Jones JF, Unger ER, Miller AH, Reeves WC, Heim C. Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome. Psychosom Med. 2008 Apr;70(3):298-305.

76. Scott LV, Salahuddin F, Cooney J, et al. Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health. J Affect Disord 1999;52:129-37.

77. Scott LV, The J, Reznek R, et al. Small adrenal glands in chronic fatigue syndrome: a preliminary computed tomography study. Psychoneuroendocrinology 1999;24:759-68.

78. Cleare AJ, O'Keane V, Miell JP. Levels of DHEA and DHEAS and responses to CRH stimulation and hydrocortisone treatment in chronic fatigue syndrome. Psychoneuroendocrinology 2004;29:724-32.

79. Cleare AJ, Miell J, Heap E, et al. Hypothalamo-Pituitary-Adrenal Axis Dysfunction in Chronic Fatigue Syndrome, and the Effects of Low-Dose Hydrocortisone Therapy. J Clin Endocrinol Metab 2001;86:3545-54.

80. Scott LV, Medbak S, Dinan TG. Blunted adrenocorticotropin and cortisol responses to corticotropin-releasing hormone stimulation in chronic fatigue syndrome. Acta Psychiatr Scand 1998;97:450-7.

81. Inder WJ, Prickett TCR, Mulder RT. Normal opioid tone and hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome despite marked functional impairment. Clin Endocrinol (Oxf) 2005;62:343-8.

82. Bearn J, Allain T, Coskeran P, et al. Neuroendocrine responses to d-fenfluramine and insulin-induced hypoglycemia in chronic fatigue syndrome. Biol Psychiatry 1995;37:245-52.

83. Scott LV, Burnett F, Medbaks S, et al. Naloxone-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome. Psychol Med 1998;28:285-93.

84. Nater UM, Maloney E, Boneva RS, Gurbaxani BM, Lin JM, Jones JF, Reeves WC, Heim C. Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls. J Clin Endocrinol Metab. 2008;93:703-9.

85. DiGiorgio A, Hudson M, Jerjes W, et al. 24-hour pituitary and adrenal hormone profiles in chronic fatigue syndrome. Psychosom Med 2005;67:433-40.

86. Jerjes WK, Taylor NF, Wood PJ, et al. Enhanced feedback sensitivity to prednisolone in chronic fatigue syndrome. Psychoneuroendocrinology 2007;32:192-8.

87. Wyller VB, Godang K, Mørkrid L, Saul JP, Thaulow E, Walløe L. Abnormal thermoregulatory responses in adolescents with chronic fatigue syndrome: relation to clinical symptoms. Pediatrics. 2007;120:e129-37.

88. Wyller VB, Saul JP, Amlie JP, Thaulow E. Sympathetic predominance of cardiovascular regulation during mild orthostatic stress in adolescents with chronic fatigue. Clin Physiol Funct Imaging. 2007;27:231-8.

89. Cleare AJ, Heap E, Malhi GS, et al. Low-dose hydrocortisone in chronic fatigue syndrome: a randomized crossover trial. Lancet 1999;353:455-8.

90. McKenzie R, O'Fallon A, Dale J, et al. Low-Dose Hydrocortisone for Treatment of Chronic Fatigue Syndrome. A randomized controlled trial. JAMA 1998;280:1061-6.

91. Blockmans D, Persoons P, Van Houdenhove B, et al. Combination Therapy with Hydrocortisone and Fludrocortisone Does Not Improve Symptoms in Chronic Fatigue Syndrome: A Randomised Placebo-Controlled, Double-blind Crossover Study. Am J Med 2003;114:736-41.

92. Peterson PK, Pheley A, Schroeppel J, et al. A preliminary placebo-controlled trial of fludrocortisone for chronic fatigue syndrome. Arch Intern Med 1998;158:908-14.

93. Roberts AD, Charler ML, Papadopoulos A, Wessely S, Chalder T, Cleare AJ. Does hypocortisolism predict a poor response to cognitive behavioral therapy in chronic fatigue syndrome? Psychol Med. 2010;40:515-22.

94. Centers for Disease Control and Prevention (CDC). COVID-19: Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Available at: http://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-managemnet-patients.html. Accessed on 9th July 2023.

95. 2. Soriano JB, Murthy S, Marshall JC, et al. WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. Lancet Infct Dis. 2022; 22(4)e102. Epub 2021.

96. 3. Townsend L, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. JAMA Network Open. 2021;4(3):e211641.

97. 4. Perrin R, et al. Symptoms and signs of COVID-19: A systematic review and meta-analysis. BMJ Open. 2021;11(1):e044327.

98. National Institute for Health and Care Excellence. Myalgic encephalomyelitis (of encephalopathy)/chronic fatigue syndrome: diagnosis and management. NICE guideline. 2021.

99. Cluff LE. Medical aspects of delayed convalescence. Rev Infect Dis. 1991 Jan-Feb;13 Suppl 1:S138-40.

100. Smith ME, Haney E, McDonagh M, et al. Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A systematic Review for a National institutes of Health Pathways to Prevention Workship. Annals of Intern Med. 2015; 162 (12): 841-850.

101. Mitchell WM. Efficacy of rintatolimod in the treatment of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Expert Rev Clin Pharmacol 2016;9(6):755-70.

102. Strayer DR, Carter WA, Stouch BC, et al. A double-blind, placebo-controlled, randomized, clinical trial of the TLR-3 agonist rintatolimod in severe cases of chronic fatigue syndrome.PLoS One. 2012; 7 (3):e31334.

103. Castro-Marrero J, Saez-Francas N, Santillo D, et al. Treatment and management of chronic fatigue syndrome/myalgic encephalitis: all roads lead to Rome. Brit Jour of Pharm. 2017; 174: 345-69.

104. Fludge Ø, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS One. 2011; 6(10).

105. Fluge Ø, Rekeland IG, Lien K, et al. B-lymphocyte Depletion in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med. 2019 May 7;170(9):585-593.

106. Castro-Marrero J, Cordero MD, Segundo MJ, Saez-Francas N, Calvo N, Roman-Malo L, et al. Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome? Antioxid Redox Signal 2015;22(8):679-85.

107. Lightfoot RW Jr, Luft BJ, Rahn DW, et al. Empiric parenteral antibiotic treatment of patients with fibromyalgia and fatigue and a positive serologic result for Lyme disease. A cost-effectiveness analysis. Ann Intern Med 1993; 119:503.

108. Roerink ME, Bredie SJH, Heijnen M, et al. Cytokine Inhibition in Patients With Chronic Fatigue Syndrome: A Randomized Trial. Ann Intern Med 2017; 166:557.

109. Blacker CV, Greenwood DT, Wesnes KA, et al. Effect of galantamine hydrobromide in chronic fatigue syndrome: a randomized controlled trial. JAMA 2004; 292:1195.

110. McKenzie R, O'Fallon A, Dale J, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA 1998; 280:1061.

111. Cleare AJ, Heap E, Malhi GS, et al. Low-dose hydrocortisone in chronic fatigue syndrome: a randomized crossover trial. Lancet 1999; 353:455.

112. Blockmans D, Persoons P, Van Houdenhove B, Bobbaers H. Does methylphenidate reduce the symptoms of chronic fatigue syndrome? Am J Med 2006; 119:167.e23.

113. Randall DC, Cafferty FH, Shneerson JM, et al. Chronic treatment with modafinil may not be beneficial in patients

with chronic fatigue syndrome. J Psychopharmacol 2005; 19:647.

114. Ghali A, Lacout C, Fortrat JO, et al. Factors Influencing the Prognosis of Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Diagnostics (Basel). 2022 Oct 19;12(10):2540.

115. Sharpe M, Hawton K, Seagroatt Vet al. Follow up of patients presenting with fatigue to an infectious diseases clinic. BMJ. 1992 Jul 18;305(6846):147-52.

116. Straus SE, Dale JK, Tobi M, Lawley T, Preble O, Blaese RM, Hallahan C, Henle W. Acyclovir treatment of the chronic fatigue syndrome. Lack of efficacy in a placebo-controlled trial. N Engl J Med. 1988 Dec 29;319(26):1692-8.

117. Peterson P.K., Schenck C.H., Sherman R. Chronic Fatigue Syndrome in Minnesota. Minn. Med. 1991;74:21–26.

118. Wilson A, Hickie I, Lloyd A, et al. Longitudinal Study of Outcome of Chronic Fatigue Syndrome. BMJ. 1994;308:756–759.

119. Bombardier CH, Buchwald D. Outcome and Prognosis of Patients With Chronic Fatigue vs Chronic Fatigue Syndrome. Arch. Intern. Med. 1995;155:2105–2110.

120. Vercoulen JH, Swanink CM, Fennis JF, et al. Prognosis in Chronic Fatigue Syndrome: A Prospective Study on the Natural Course. J. Neurol. Neurosurg. Psychiatry. 1996;60:489–494.

121. van der Werf SP, de Vree B, Alberts M, et al. Natural Course and Predicting Self-Reported Improvement in Patients with Chronic Fatigue Syndrome with a Relatively Short Illness Duration. J. Psychosom. Res. 2002;53:749–753.

122. Cairns R, Hotopf M. A Systematic Review Describing the Prognosis of Chronic Fatigue Syndrome. Occup. Med. 2005;55:20–31.

123. Collin SM, Crawley E. Specialist Treatment of Chronic Fatigue Syndrome/ME: A Cohort Study among Adult Patients in England. BMC Health Serv. Res. 2017;17:488.

124. Clark MR, Katon W, Russo J, et al. Chronic Fatigue: Risk Factors for Symptom Persistence in a 2 1/2-Year Follow-up Study. Am. J. Med. 1995;98:187–195.

125. Tiersky LA, DeLuca J, Hill N, et al. Longitudinal Assessment of Neuropsychological Functioning, Psychiatric Status, Functional Disability and Employment Status in Chronic Fatigue Syndrome. Appl. Neuropsychol. 2001;8:41–50.

126. Ciccone D.S., Chandler H.K., Natelson B.H. Illness Trajectories in the Chronic Fatigue Syndrome: A Longitudinal Study of Improvers versus Non-Improvers. J. Nerv. Ment. Dis. 2010;198:486–493.

127. Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. Q J Med 1997;90:223-33.

128. Roberts E, Wessely S, Chalder T, et al. Mortality of people with chronic fatigue syndrome: a retrospective cohort study in England and Wales from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Clinical Record Interactive Search (CRIS) Register. Lancet. 2016 Apr 16;387(10028):1638-43.