



Aetiology and pathogenesis of chronic fatigue syndrome: a review

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Abstract

Chronic fatigue syndrome (CFS) is a debilitating disease of uncertain aetiology that is characterised by unexplained, severe fatigue associated with a number of typical symptoms. This paper reviews the scientific literature related to current theories about the aetiology and pathogenesis of CFS by focussing on what appear to be the four most significant aspects in the development and perpetuation of this disease: the role of infectious agents as well as immunological, neuroendocrine, and psychiatric factors. A multifactorial model for the aetiology of CFS, which includes and draws together these four aspects, is proposed; and suggestions are offered regarding approaches to the diagnosis and treatment of this disease.

Chronic fatigue syndrome (CFS) is a debilitating disease of uncertain aetiology that is characterised by unexplained, persistent or relapsing, severe fatigue associated with muscle aches, weakness, pharyngitis, lymphadenopathy, headache, depression, sleep disturbance, memory difficulties, and confusion.^{1,2}

Over the years, many different hypotheses have been proposed with regards to the aetiology and pathogenesis of this condition. The criteria used for the diagnosis of CFS were uncertain and inconsistent for a long time, but were standardised by an international study group of the US Centers for Disease Control (CDC) in 1994.

According to this CDC definition, which is now used everywhere in the world, CFS is a disease characterised by medically unexplained severe fatigue that persists or relapses for 6 months or more and is associated with at least 4 out of 8 distinctive physical symptoms.³ The CDC criteria for the diagnosis of CFS are summarised in Table 1 (adapted from *ibid*).

Possible medical explanations that need to be considered before CFS can be diagnosed include untreated hypothyroidism, sleep apnoea, narcolepsy, malignancies, unresolved hepatitis B or C infection, iatrogenic conditions such as side effects of medication, various psychiatric conditions, alcohol or substance abuse, and severe obesity (*ibid*). The CDC exclusion criteria for the diagnosis of CFS are summarised in Table 2 (adapted from *ibid*).

All of these, and various other conditions, are thus considered differential diagnoses of CFS.⁴ By far the most commonly mentioned differential diagnoses of CFS, however, are fibromyalgia (FM) and infectious mononucleosis. The clinical features of CFS, FM, and IM are very similar and include fatigue, muscle pain, reduced exercise tolerance, depressive complaints, and sleep disturbances.^{4,5}

Table 1. US Centers for Disease Control (CDC) criteria for the diagnosis of chronic fatigue syndrome (CFS)

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| <p>Main criteria:</p> <ul style="list-style-type: none">• Severe fatigue that persists or relapses for at least 6 months.• Medical explanations are excluded. <p>The condition will be classified as CFS if fatigue is sufficiently severe, of new or definite onset, not alleviated by rest, and results in substantial reduction in previous levels of activities and if 4 or more of the following symptoms exist:</p> <ul style="list-style-type: none">• Impaired memory or concentration capacity.• Recurrent sore throat.• Tender cervical or axillary lymph nodes.• Mild muscle pain.• Arthralgia.• New types of headache.• Sleep that is not refreshing.• Post-exertional malaise. <p>The condition will be classified as idiopathic chronic fatigue if fatigue severity or symptom criteria for CFS are not met.</p> |
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Table 2. CDC exclusion criteria for the diagnosis of CFS

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| <ul style="list-style-type: none">• Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnoea, and narcolepsy, and iatrogenic conditions such as side effects of medication.• Any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness. Such conditions may include previously treated malignancies and unresolved cases of hepatitis B or C virus infection.• Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; or bulimia nervosa.• Alcohol or other substance abuse within 2 years before the onset of the chronic fatigue and at any time afterward.• Severe obesity as defined by a body mass index equal to or greater than 45. |
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Although fatigue is one of the most commonly reported non-specific clinical symptoms, the prevalence of CFS does not appear to be particularly high. Studies using the CDC definition of CFS have generally reported a prevalence of the syndrome of 0.1–0.7%.⁶ A random digit dialling study conducted in Chicago found an increased prevalence of CFS among women, minority groups, and persons with lower levels of education and occupational status.⁷

This paper reviews the scientific literature related to current theories about the aetiology and pathogenesis of CFS. In doing so, it focuses on what currently appear to be the four most significant aspects in the development and perpetuation of this disease: the role of infectious agents, immunological, neuroendocrine, and psychiatric factors.

The role of infectious agents

Many CFS patients report an infectious-like onset of their illness, and much research has thus been conducted to identify a possible causative infectious agent for CFS. The fact that outbreaks of CFS have occurred in the past⁶—and the observation that there seems to be a higher rate of onset during the cold season^{8,9}—also supports the hypothesis that an infectious illness can trigger the onset of CFS.

In a review of the scientific literature published before the year 2002, Evengard and Klimas⁶ conclude that various infectious agents may trigger the onset of CFS. Epstein Barr virus (EBV), the causative agent of IM and *Borrelia burgdorferi* (the spirochete causing Lyme disease) were most commonly cited.

Both of these agents are polyclonal immunologic activators, and could thus trigger the disease through activation of the immune system. Other possible triggering agents suggested included cytomegalovirus (CMV), human herpesvirus (HHV) type 6 and 7, Borna Disease virus (BDV), various enteroviruses, as well as *Chlamydia* and *Mycoplasma* species. Evidence for a persistent chronic infection in CFS sufferers was only found for two agents, however, HHV-6 and possibly *Mycoplasma* species.

Several studies published after 2002 reported results that might shed some more light on the possible role of infectious agents in the pathogenesis of CFS

- A study involving 150 subjects with a history of IM found support for the existence of two discrete post IM chronic fatigue syndromes, one of which was still demonstrable 4 years after onset.¹⁰
- Lane et al¹¹ reported the detection of enterovirus sequences in muscle biopsy samples from 20.8% of CFS patients, but not in any of their control samples.
- Nicolson et al¹² found a high prevalence of mycoplasmal (52%), *Chlamydia pneumoniae* (7.5%), and active HHV-6 (30.5%) infections in 200 CFS patients. Parts of those findings were in agreement with a number of previous studies that had consistently found evidence of chronic mycoplasmal infection in about 50% of CFS sufferers.¹³
- Another study (including 22 monozygotic twin-pairs discordant for CFS), however, found no evidence of an increased prevalence of active HHV-6, HHV-7,

HHV-8, CTV, EBV, herpes simplex virus, varicella zoster virus, JC virus, BK virus, or parvovirus B19 infections in CFS sufferers.¹⁴

- Gustaw¹⁵ reported the development of CFS in as many as 71% of borreliosis patients and in 24% of subjects with a history of tick-borne encephalitis.

In summary, it thus appears that the presence of chronic mycoplasmal infections might play a role in the perpetuation and/or development of CFS, while several viruses and bacteria (especially *B. burgdorferi*) may trigger the onset of the disease, but do not seem to be consistently associated with its perpetuation.

Immunological factors

A significant number of studies have been conducted to investigate the possible presence of characteristic immunological abnormalities in CFS patients. Many of these studies have, however, produced results that were either inconclusive or in contradiction with previous findings.

A systematic review of the relevant literature published between 1966 and 2000 found no consistently present decisive differences between CFS patients and control groups in the quantity and function of T-cells, although the highest rating studies reviewed pointed to a possible increase in T-cell activity in CFS subjects.¹⁶ Clear differences could also not be demonstrated between CFS subjects and normal controls with regards to cytokine levels, B-cell quantity and function, and immunoglobulin levels. Overall, this review concluded that no consistent evidence exists for an aetiological role of immune dysfunction in CFS.

Several studies published after 2000 found additional immunological differences between CFS subjects and control groups:

- Skowera et al,¹⁷ for example, found evidence for an effector memory cell bias towards type 2 responsiveness, as well as ongoing type 0 immune activation in unstimulated cultures of peripheral blood cells, while Brunet et al.¹⁸ reported the detection of delayed-type hypersensitive responses to certain common environmental antigens in almost 50% of CFS patients.
- Kennedy et al¹⁹ demonstrated increased neutrophil apoptosis in CFS sufferers, an immunological reaction which also occurs in patients with infection.
- A Japanese study²⁰ found autoantibodies against type 1 muscarinic cholinergic receptors in subgroups of CFS patients, and another by Masuda et al²¹ reported suppressed NK-cell activity in both postinfectious and non-infectious CFS subjects.
- A Dutch study by Nijs et al²² found evidence of immune activation in patients with CFS, whereas disturbed glucocorticoid regulation of interleukin-10 was found in CFS subjects by Visser et al.²³

Far from giving any conclusive answers about the possible role of immune dysfunction in the aetiology of CFS, these more recent studies further highlight the fact that no single, consistently present immunological abnormality has yet been identified in CFS patients.

Given the multitude of positive findings in immunological studies of CFS sufferers, it does, however, seem likely that some type of immune dysfunction may play a role in the pathogenesis and/or perpetuation of this disease.

Neuroendocrine factors

HPA-axis dysfunction—One of the neuroendocrine systems that has been the subject of many CFS related studies is the hypothalamic-pituitary-adrenal (HPA) axis. Cleare²⁴ has reviewed the relevant literature published up to 2002 and reports that about half of the studies reviewed in this way found evidence for lowered cortisol levels—at least at some point during the day.

Moreover, trials of replacement therapy have been able to tentatively link this hypocortisolemia to the production or perpetuation of some of the symptoms experienced by CFS sufferers.^{25–27}

As many factors (such as sleep disturbance, psychiatric comorbidity, medication, and chronic stress) may influence the HPA axis in CFS, Cleare suggests that the aetiology of this HPA axis disturbance is probably multifactorial. Nevertheless, evidence suggesting that the hypocortisolism frequently seen in CFS may at least partially be caused by enhanced negative feedback of corticosteroid receptors in the hypothalamus or pituitary gland was found to be fairly consistent.

Two studies^{28,29} also reported a reduced maximal secretory capacity of the adrenal cortex for cortisol in response to a challenge with adrenocorticotrophic hormone (ACTH). This may be linked to an overall reduction in adrenal gland size which was observed in CFS patients with such a blunted cortisol response in another study.³⁰ However, Cleare reports that studies using subjects that had been suffering from CFS for a long time appeared to be more likely to find reduced basal cortisol levels than those using patients that had been ill for a shorter period.

This finding suggests that hypercortisolism might be a result rather than a cause of CFS. At least two studies published after Cleare's review also support the hypothesis of reduced HPA axis activity in CFS indicated by lowered levels of salivary³¹ or blood³² cortisol.

Autonomic nervous system dysfunction—Orthostatic intolerance leading to neurally mediated hypotension has been found in some CFS sufferers, which suggests a disturbance of the baroreceptor reflex that controls blood pressure via the sympathetic nervous system and the parasympathetic fibres of the vagus nerve.^{33,34} Abnormalities in vagal regulation of heart rate have also been observed in CFS patients.^{35,36} This may offer an explanation for the reduced cardiovascular response to exercise seen in some cases of CFS. Overall, there thus seems to be an autonomic imbalance with slight sympathetic predominance in CFS.³⁷

Central sensitisation—Several studies have found increased perception of pain (hyperalgesia) in CFS sufferers, which may be due to central sensitisation—i.e. an exaggerated response of central nervous system (CNS) neurons to peripheral noxious stimuli.³³ Another theory for this hyperalgesia in CFS, however, is offered by Scott et al³⁸ who suggest that a reduction in opioid levels that was found in CFS sufferers may cause this exaggerated sensitivity to pain.

This latter hypothesis is also supported by the decreased beta-endorphin levels that were found in CFS patients by Conti et al.³⁹

In conclusion, it thus appears likely that down-regulation of the HPA-axis, a disturbance of the autonomic nervous system, and certain neuroendocrine dysfunctions causing hyperalgesia may be either involved in the pathogenesis of CFS or contribute to its perpetuation.

Psychiatric factors

Many of the symptoms of CFS (such as fatigue, cognitive dysfunction, and sleep disorders) are also present in some nonpsychotic psychiatric disorders. For this reason, some physicians consider CFS to be a psychiatric condition.⁶ CFS patients, however, usually disagree with such a categorisation and complain that they are mistakenly given a psychiatric label. This impression was confirmed by a study, which found that a large proportion of CFS sufferers had, indeed, been wrongfully diagnosed with a psychiatric condition in the past.⁴⁰

Nevertheless, personality disorders are quite prevalent among CFS sufferers⁴¹ and cannot always be explained as a result of the experience of this chronic illness alone.^{42,43} Comorbid depression, for example, is commonly associated with CFS.^{44,45} Nevertheless, the depression seen in CFS appears to differ significantly from that usually associated with psychiatric disorders.

CFS patients, for example, have been found to rate their current health status lower, show a stronger illness identity and greater impairment in physical functioning, complain more of bodily pain, attribute their condition more to external factors, and show a greater reduction in vitality and social functioning than subjects suffering from major depression.^{46,47}

The lack of self esteem and the tendency towards self-blame often observed in patients with major depression also appears to be rare in CFS sufferers.⁴⁸ Moreover, there seems to be a significant difference in the neuroendocrine aspects of CFS and major depression: While an up-regulation of the HPA axis has often been observed in major depression, CFS sufferers more often show reduced HPA axis activity.²⁸ Given this distinct nature of the depression seen in CFS, it thus seems unlikely that this disease is simply a result of a pre-existent state of major depression.

Nevertheless, there is also a substantial amount of evidence pointing towards a possible involvement of psychiatric factors in the pathogenesis and perpetuation of CFS. A study by Hatcher and House,⁴⁹ for example, found that stressful events, especially such as were characterised as dilemmas, often seem to precede the onset of CFS.

Conclusion

In spite of the presence of abundant research, the aetiology and pathogenesis of CFS still remains unknown. Given the fact that disturbances to a number of body systems as well as to the mental status of CFS sufferers have been found, it seems likely that the causes of this illness are multifactorial and may vary from patient to patient.⁵⁰

From the evidence reviewed above, it appears possible that an infectious agent may trigger the onset of the CFS, especially in patients that are experiencing a dilemma or

that are already suffering from a psychiatric condition which might impact on their immune status. Changes to the immune, and possibly the neuroendocrine system, might then be caused or perpetuated either by the infection becoming chronic or because of exaggerated illness worry and identification with the disease.

For the treatment of CFS, a multi-directional approach may be most likely to prove beneficial. This, however, is dependent upon improved and more thorough diagnostic procedures. Instead of simply dismissing CFS sufferers as psychiatric cases, as has often been the case in the past, the patient should be assessed to look for known medical conditions that may explain at least some of their symptoms.

An important step in this direction would be a more uniform application of the battery of clinical tests suggested by the 1994 CDC study group.³ The diagnostic protocol proposed by this group includes history taking; physical and mental examination; complete blood count (CBG) and urine analysis (UA); as well as tests to determine erythrocyte sedimentation rate (ESR) and levels of alanine aminotransferase (ALT), total protein, albumin, globulin, alkaline phosphatase, Ca, phosphorus (PO₄), glucose, blood urea nitrogen (BUN), electrolytes, creatinine, and thyroid stimulating hormone (TSH).

A systematic review of various approaches to the treatment of CFS suggests that cognitive behavioural therapy as well as graded exercise programmes seem to be most beneficial in the treatment of CFS.⁵¹ Both of these approaches do, however, appear to primarily help improve patients' coping skills rather than eliminating or reducing the symptoms of CFS. The identification and specific treatment of possible aetiological, contributory, or predisposing factors should therefore remain an important concern of primary health care providers.

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