



REVIEW

Neuroaetiology of chronic fatigue syndrome: An overview

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Abstract

Chronic fatigue syndrome (CFS) is now recognized as a medial disorder. In contrast to recent related reports, the present review focuses primarily on aetiological aspects of CFS. Four major hypotheses are reviewed. (1) Although CFS is often associated with viral infection, the presence of viruses has as yet not consistently been detected. (2) It is not clear whether anomalies of the HPA axis often observed in CFS, are cause or the consequences of the disorder. (3) Immune dysfunction as the cause of CFS is thus far the weakest hypothesis. (4) The psychiatric and psychosocial hypothesis denies the existence of CFS as a disease entity. Accordingly, the fatigue symptoms are assumed to be the consequence of other (somatic) diseases. Other possible causes of CFS are oxidative stress and genetic predisposition. In CFS cognitive behavioural therapy is most commonly used. This therapy, however, appears to be ineffective in many patients. The suggested causes of CFS and the divergent reactions to therapy may be explained by the lack of recognition of subgroups. Identification of subtypes may lead to more effective therapeutic interventions.

Key words: *Chronic fatigue syndrome, HPA axis, virus infection, depression, inflammation*

Introduction

Chronic fatigue associated with constitutional symptoms has been described under different names, since the 18th century (Marshall 1999). Terms used to describe this disorder include neurasthenia, post-viral fatigue syndrome, chronic fatigue and immune dysfunction syndrome and myalgic encephalomyelitis. Most experts favour the term chronic fatigue syndrome (CFS), because the aetiology is unclear. This unclear aetiology resulted in the frequent assumption that CFS is a psychiatric illness. However, often physical anomalies in patients with CFS have been reported, suggesting some kind of physical vulnerability for the development of CFS. Although several studies have been performed to unravel the aetiology of CFS, there is as yet little consensus about this issue. In contrast to the recently published reviews by Jason et al. (2005) and Prins et al. (2006) focusing on the definition and diagnosis, the present review is primarily concerned with the neuroaetiology of CFS.

CFS is characterized by disabling physical and mental fatigue, lasting at least 6 months, without an apparent physical cause with the presence of four of the following symptoms: sore throat, tender cervical

and axillary lymph nodes, difficulties in concentrating, muscle or joint pain, un-refreshing sleep, sleep disorders, headache, and post-exertion malaise. (Fukuda et al. 1994) The fatigue results in an impairment of daily functioning. Over the years several case definitions of CFS have been proposed; the last set of criteria were published in 1994 by an international collaborative group (Fischler 1999) (Table I). The minor criteria must have persisted or recurred during six or more consecutive months, and must not have predated the fatigue. The diagnosis of idiopathic chronic fatigue is used in cases where the major criteria are fulfilled, but less than four of the minor criteria were scored. This case definition has been criticized as being dependent on subjective clinical diagnosis and patient self-report (Jason et al. 2000).

Because subjects meeting the criteria are a heterogeneous group, the 1994 case definition paper encourages the division of the patients into subgroups. However, this concept is not being utilized in subsequent literature, with subjects simply being described as “meeting the CFS case definition.” Dividing the patients into subgroups might be useful to help understand the aetiology of CFS, because the

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Table I. Case definition of chronic fatigue syndrome (CFS).

Inclusion criteria

Clinically evaluated, medically unexplained fatigue of at least 6 months duration that is:

- of new onset (not lifelong)
- not the result of ongoing exertion
- not substantially alleviated by rest
- a substantial reduction in previous level of activities

The occurrence of four or more of the following symptoms (minor criteria):

- subjective memory impairment
- sore throat
- tender cervical or axillary lymph nodes
- muscle pain
- multiple joint pain without joint swelling or redness
- headache of a new type, pattern or severity
- un-refreshing sleep
- post-exertion malaise lasting more than 24 h

Exclusion criteria

- Active, unresolved, or suspected disease
- Psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)
- Psychotic disorders
- Dementia
- Anorexia of bulimia nervosa
- Alcohol or other substance misuse within 2 years before the onset of CFS or at anytime afterward
- Severe obesity (Body Mass Index ≥ 45)

different subgroups might point to different aetiologies and different therapeutic approaches (Jason et al. 2005). Patients have been subtyped on socio-demographic variables like gender, age and socio-economic status. Selection by these criteria shows that woman, old people and people with a low socioeconomic status are at relatively high risk for developing CFS. However, factors like mode of illness onset, the presence or absence of premorbid psychiatric conditions and presence of a stressful life and symptom severity are other factors enabling subtyping (Jason et al. 2005). Subtyping could also be accomplished by identification of anomalies in physiological parameters such as cortisol levels or T-cell levels. Because of lack of consensus, more research is needed to define subgroups. Some psychiatric disorders that are not used as exclusion criteria, like major depression (MD) – without *Diagnostic and Statistical Manual* (DSM)-IV-defined melancholic features – and anxiety disorders, are frequently co-morbid with CFS (Cleare 2003). Depressive illness is present in up to 50% of CFS patients (Wessely et al. 1998). So, when defining subgroups of CFS one should also consider MD as either a core or as auxiliary symptom.

Epidemiological findings

Estimates of the prevalence of CFS in the community vary from 0.5 to 1.5% (Wessely et al. 1998). Studies have repeatedly shown that complaints of fatigue are very common in developed countries and

white people (Wessely 1995). This could mean that non-white patients are less vulnerable to CFS, but these differences have most probably to be attributed to differences in health-seeking behaviour and the accessibility to care. More recent epidemiological surveys have indeed confirmed evidence for such biases (Steele et al. 1998; Jason et al. 1999).

More women than men suffer from chronic fatigue, although the estimated ratios differ among the various studies. When depression was controlled for, the sex ratio difference disappears in some studies, but not in all. The female:male ratio was found to increase as a function of the intensity of the fatigue syndrome (Wessely 1995). It has been discussed that the gender difference is an artifact, caused by differences in illness behaviour and referral pattern (Ranjith 2005).

Although most of the studies concerning CFS are focused on the adult population, the illness does strike younger individuals, most commonly after puberty (Bell 1995). A prevalence of 2333/100,000 indicates that fatiguing illnesses are a major health problem among adolescents (Jones et al. 2004).

MRI abnormalities

A number of symptoms associated with CFS has also been associated with abnormalities in central nervous system (CNS) functioning. Studies that focused on white matter abnormalities produce conflicting results. Some studies found an increased number of white matter abnormalities in CFS

(Lange et al. 1999; Schwartz et al. 1994), whereas others did not reveal such abnormalities (Cope et al. 1995; Cope and David 1996).

A recent study (de Lange et al. 2005) showed that patients suffering from CFS showed a marked decline in gray matter volume. Also a relation between the level of gray matter reduction and physical activity was found, whereas there was no relation with the duration of the disease. These findings suggest that the CNS plays an important role in CFS, although it is not clear whether the gray matter reductions found in this study are a cause or consequence of CFS.

The activity of various brain areas during a fatigue was tested with fMRI (Tanaka et al. 2006). Patients with CFS had particular trouble responding to stimuli that were not a part of the original task. They found also that the sensation of fatigue was correlated with the attenuation rate for the responsiveness of task-independent brain regions. These investigators could distinguish CFS patients from healthy subjects using fMRI during this fatigue test and suggested that their approach has diagnostic potential.

Hypotheses of aetiology

The importance of viral, endocrine, immune, psychological and other factors in the aetiology of CFS will be discussed in the following section. Besides their aetiological relevance these factors may contribute to the symptomatology of CFS as well.

Viral hypothesis

Because symptoms of CFS are often associated with an active virus infection, several studies have focused on the hypothesis that CFS is induced by a virus. High antibody titres to enzymes encoded by Epstein-Barr virus (Straus et al. 1985), enterovirus (Chia 2005), human herpes virus 6 (HHV-6) and other herpes viruses have been found in many, but not all CFS patients (Sairenji et al. 1995).

Most authors cannot prove that CFS is caused by one or several viruses. A viral illness may trigger the development of CFS by induction of immunopathology. It has been hypothesized that synthesis of viral proteins can cause a modulation in the response of a subpopulation of leukocytes, with subsequent effects on cytokine and chemokine synthesis or on T-cell or NK-cell function (Glaser and Kiecolt-Glaser 1998). A related hypothesis assumes that an infection causes the induction of auto-antibodies against adrenocorticotrophic hormone (ACTH), which interferes with cortisol secretion (Wheatland 2005).

Stress may also play an important role in CFS, possibly by the reactivation of a latent virus. Therefore, the combination of stress and the subsequent reactivation of a virus may cause CFS (Glaser et al. 2005). However, this idea has as yet to be further investigated.

Incomplete reactivation of the latent virus may explain why no high antibody titres were found in some patients (Glaser and Kiecolt-Glaser 1998). Studies using polymerase chain reaction did not show a relationship between antibody titres and any of the viruses tested (Buchwald et al. 1996; Koelle et al. 2000). Thus, whereas several clinical studies support the virus hypothesis, biochemical confirmation is as yet lacking.

Endocrine hypothesis

The observation that low circulating cortisol is associated with a condition of fatigue resulted in a wealth of studies that investigated this relation. Several papers report anomalies of the hypothalamus-pituitary-adrenal (HPA) axis in CFS. Unfortunately, many of these studies ignored the influence of psychiatric disorders and medication on the HPA axis.

An overview of the best designed studies on the role of the HPA axis in CFS has recently appeared (Cleare 2003). In total 17 studies were reviewed. About half of the studies found evidence for lowered cortisol levels. The most supportive studies were those measuring 24-h urinary (free) cortisol. It has, however, been argued that this parameter is an unreliable indicator of HPA axis activity (Thompson et al. 1992). Salivary or blood cortisol provides less convincing evidence for low cortisol levels in CFS.

Two recent studies (Jerjes et al. 2005, 2006) found reduced salivary cortisol levels in CFS. These patients were controlled for depression and medication. In the 2005 study, Jerjes and co-workers found that the cortisol:cortisone ratio was normal in CFS patients, but increased in depression. However, these results have not yet been replicated. Another study (Di Giorgio et al. 2005) found reduced blood levels of ACTH during the circadian cycle, also indicating hypoactivity of the HPA axis. This hypoactivity is opposite to the hyperactivity of the HPA axis found in MS patients (Gottschalk et al. 2005), pointing to different underlying mechanisms of fatigue for both diseases.

Other papers have suggested additional hypotheses about the role of the HPA axis in CFS, like hypersensitivity of the adrenal cortex to ACTH (Demitrack et al. 1991) and enhanced negative feedback of glucocorticoid receptors on

the hypothalamus or pituitary (Gaab et al. 2002). None of these papers was completely convincing, because other studies found contradictory results or because the number of subjects was too small. To understand the implication of these varying findings, it was argued that it is unlikely that there is a single, uniform change to the HPA axis in CFS (Cleare 2003). Instead, it is more likely that there are several factors influencing the HPA axis such as medication, depression, sleep disturbance and ongoing stress, some of which may be consequences of the illness (Cleare 2004).

Allostatic load is another factor associated with functioning of the HPA axis in CFS. Allostasis is the concept that maintenance of homeostasis takes place by adaptation to change. CFS can be considered as a state characterized by a high allostatic load (Maloney et al. 2006), implicating difficulties with managing stress. The allostatic load is found to be related to symptoms (Goertzel et al. 2006) and the severity of symptoms has been explained by compromise of the integrity of the blood–brain barrier by stress. The subsequent increased permeability of the blood–brain barrier may contribute to the development of symptoms (Bested et al. 2001).

Immunological hypothesis

Immune dysfunction in patients with CFS has been widely, but inconsistently reported. This inconsistency could be due to several factors: using groups of patients with different primary symptoms and/or different duration of illness, failing to control for potential confounding factors and using different laboratory procedures (Strober 1994; Lyall et al. 2003). Abnormalities of immune function, like a reduced number of T-cells, reduced levels of cytokines, altered function of NK-cells and altered levels of the immunoglobulin IgG have been reported. These observations have not led to convergent and consistent ideas to explain the symptomatology of CFS (Lloyd and Klimas 1994; Patarca-Montero et al. 2000).

A few systematic reviews have rated the studies on immunology of CFS. It appeared that the best studies found no change in the levels of B-cells, NK-cells, cytokines or immunoglobulins (Lyall et al. 2003). In particular, the studies investigating NK-cell number showed a trend for an inverse association between methodological quality and the probability of finding low NK-cell number. Also the presumed relationship between quality and findings and the trend towards increases in T-cell activation in CFS could not be maintained (Lyall et al. 2003).

Psychiatric and psychosocial hypothesis

The psychiatric hypothesis denies the mere existence of CFS as a separate condition and considers these patients to suffer from MD, panic disorder or somatization disorder along with fatigue symptoms and an external, physical attributes pattern (Wessely and Powell 1989; Manu et al. 1988).

Although MD is often co-morbid in CFS, findings on the appearance of MD before onset of CFS are conflicting. Factors that possibly play a role in the aetiology of CFS, like high personal standards of performance and perfectionism, could also be risk factors for the development of depression. The level of disability that comes with CFS, causes people to be unable to fulfil those high standards. However, the hypothesis that depression represents a normal reaction to the illness burden has been criticized. Studies of MD in CFS using chronic medical illnesses with similar illness burden as control groups, found a higher level of depression in CFS (Katon et al. 1991; Wood et al. 1991), suggesting a difference in coping with the stress of disability.

A recent study suggested that negative life events and chronic life difficulties contribute to the onset of illness (Hatcher and House 2003), though these findings need to be replicated. This study also found that the onset of CFS does not seem to be mediated by depression. Results on life events and CFS are conflicting. Negative life events during the illness process appear to worsen CFS.

Other possible aetiologies

Another factor that has been implicated in CFS is oxidative stress. Oxidative stress is defined as a disturbance to the equilibrium status of pro-oxidant and anti-oxidant systems in favour of pro-oxidation. Oxidative stress may lead to the production of free radicals, thereby inducing cellular injury. Studies by Maes et al. (2006a,b) found that CFS is accompanied by a low serum zinc status and increased oxidative stress. A study by Kennedy et al. (2005) revealed that CFS patients showed an elevated level of oxidative stress.

Genetic studies on CFS are scarce. CFS is possibly moderately heritable (Hickie et al. 1999; Buchwald et al. 2001). The genes which are possibly involved appear to have a role in the functioning of the HPA axis and the sympathetic nervous system (Hampton 2006). Nevertheless, environmental influence seems to be the main factor predicting the onset of CFS (Sullivan et al. 2005). Pilot genetic studies on CFS have recently appeared, searching for genes or gene-expression in blood cells. So far the criticism is that the investigated cohorts are

too small and inconsistent to reach firm conclusions (for comments, see Kaiser, 2006). There are claims that some polymorphisms of HPA-related genes and immune-related genes are associated with CFS. Most of these claims apply to subclasses of CFS only, as no markers for an entire cohort could be identified (e.g., Carmel et al. 2006; Fang et al. 2006; Fostel et al. 2006; Goertzel et al. 2006; Smith et al. 2006). These studies, taking advantage of the potential of lymphocytic gene-expression (e.g. Gladkevich et al. 2004), signify a trend to provide a biological basis for CFS.

Treatment

Cognitive behavioural therapy

The most used treatment for CFS is cognitive behavioural therapy (CBT). This therapy focuses mainly on the factors that may maintain fatigue rather than those that triggered it. CBT involves planned activity and rest, graded increases in activity, a sleep routine and cognitive restructuring of unhelpful beliefs and assumptions.

Most randomized controlled trials investigating the outcome of CBT, found a positive effect of CBT on most patients with CFS (Sharpe et al. 1996; Deale et al. 1997; Prins et al. 2001). A recent study (O'Dowd et al. 2006) found also that CBT group therapy has a positive effect on function and sense of well-being of patients with CFS (i.e. mental health scores), gave better walking performances and the patients reported feeling less fatigue. Post-intervention, there were no significant, if any, remaining improvements observed.

CBT is not effective in all patients with CFS. Some predictors of poor outcome were poor social and occupational functioning prior to becoming ill, passive activity pattern and a high level of focusing on bodily symptoms. Research into predictors of response to treatment is still in an early stage.

Graded exercise therapy

Graded exercise therapy (GET) involves a structured activity management programme that aims for a gradual increase in aerobic exercise, usually walking. Randomized controlled trials investigating the effect of GET on CFS found a beneficial effect on fatigue. (Powell et al. 2004; Fulcher and White 1997) GET is associated with a higher drop-out rate than CBT (Ridsdale et al. 2004).

Other treatments

Randomized controlled trials investigating antidepressants, corticosteroids and other pharmaceutical agents did not find conclusive positive effects in CFS. Studies investigating immunological and dietary interventions also produced inconclusive evidence (Rimes and Chalder 2005). There is no evidence that prolonged rest is beneficial; on the contrary, there is indirect evidence that it may prolong or worsen the fatigue (Hotopf et al. 1996).

Discussion and conclusion

Here we provide an overview of the physical and psychosocial factors that could cause CFS (for a summary, see Table II), and its treatment. It has become clear that CFS is a disabling condition with subjective fatigue, mental and physical fatigability and a whole range of somatic symptoms. As long as the aetiology remains unclear, it can be debated whether CFS has primarily physical or psychosocial causes. The importance of dividing patients with CFS into subgroups seems to be underestimated. The lack of subgroup distinction may explain the conflicting results found on viral, endocrine, immunological and psychosocial grounds. Defining subgroups might help to bring consensus in the results. Future studies should also control for the influence of medication and psychiatric disorders.

Table II. Overview of possible causes CFS.

Hypothesis of aetiology	Cause of CFS	Observations
Viral hypothesis	Viral infection	High antibody titres in some studies Reactivation latent virus by stress
Endocrine hypothesis	HPA axis anomalies	Hypo-activity of HPA axis High allostatic load
Immunological hypothesis	Immune dysfunction	Anomalies in B-cell, NK-cell, T-cell number Changes in levels of cytokines and immunoglobulins
Psychosocial hypothesis	Not a separate condition Caused by stress, perfectionism	Finding MD before onset CFS
Other causes	Oxidative stress Genetic predisposition	Elevated level of oxidative stress/free radicals Changes in genes involved in HPA axis and sympathetic nervous system

MD, major depression; HPA axis, hypothalamus–pituitary–adrenal axis.

There is now ample evidence in favour of a physical cause of CFS. Whether the biological basis is a general physical vulnerability caused by a viral infection, an immunological dysfunction, genetic, metabolic or a combination of physical anomalies, remains elusive. There could well be distinctive physical causes in the various subgroups. Different causes may explain the various and in-predictable reactions of patients to medication. Psychosocial factors could possibly effect the time of onset or determine the severity of the condition, but they do not seem to be able to cause CFS by themselves. However, psychosocial factors can cause the vicious cycle in which the patients end up. Breaking through this vicious cycle through CBT or GET appears to help patients recovering. The present review is based on cross-sectional studies only. As yet, there are no long-term studies that have focused on normalization of the various claimed abnormalities. Such studies may give clues on the importance of such anomalies for the persistence and recovery of CFS irrespective of the therapeutic intervention.

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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