Chronic fatigue syndrome/myalgic encephalo-myelitis – pathophysiology, diagnosis and treatment

The underlying pathophysiology in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is unclear, and there is disagreement in the field over diagnostic criteria and treatments. Here, we review the literature and comment on the debate around this condition.

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a common – and serious – condition characterised by pervasive fatigue (particularly after minimal exertion) and chronic pain as well as impairments in concentration and memory (1).

Pathophysiology
Hereditry can predispose to chronic fatigue syndrome/myalgic encephalomyelitis (2), as can certain personality traits such as high levels of perfectionism (3). Long-lasting infections, such as mononucleosis, are established triggers (4), but critical life events can also play a part (5).

Maintaining factors include altered cognitive function, especially executive dysfunction (6), increased sympathetic and decreased parasympathetic nerve activity, which affects cardiovascular regulation (7, 8), and reduced responsivity of the hypothalamic-pituitary-adrenal axis (HPA axis) (9).

A number of studies have also reported immunological changes characterised by mild systemic inflammation (increase in proinflammatory cytokines) and impaired NK cell function (10), but here there are contradictory findings. One problem is publication bias, whereby sporadic positive findings are reported because they are original and exciting, but in time turn out to be false positives.

This problem was illustrated in a recently published review article (11). The authors examined 38 articles featuring a total of 77 immunological markers, many of which were reported as positive in single studies. The only replicated positive marker was TGF-β, the others were negative in the vast majority of studies. Whether TGF-β is a biomarker for chronic fatigue syndrome/myalgic encephalomyelitis remains to be shown. Several of the studies upon which the review was based used biological material that was collected in a suboptimal manner, and techniques that are now out of date.

We assayed 27 cytokines (excluding TGF-β) in the plasma of a group of patients to test the hypothesis that the patients had mild systemic inflammation (12). There were no differences from a comparable control group, either in the main analysis or in subgroup analyses. Our negative findings were published in a high impact journal, thereby helping to counter publication bias.

Integrated models have been developed in which empirical findings from research on chronic fatigue syndrome/myalgic encephalomyelitis are not viewed as contradictory, but rather as distinct facets of a complex phenomenon (13–15). A good place to start may be the patients’ overwhelming fatigue.

Neurobiological studies indicate that fatigue may have commonalities with pain, both in terms of neurological substrate (partially overlapping neural networks) and evolutionary function. Where pain perception is an «alarm» about tissue damage, fatigue may be an «alarm» about excessive energy expenditure (16, 17). Activating the «fatigue alarm» ensures that the individual rests, but at the same time – in common with pain – activates a stress response characterised by cognitive, neuroendocrine and immune changes. Evolution dictates that both «alarms» must be plastic – they must be modified by learning to ensure that maladaptive behaviours are not repeated. The «alarms» must also have high sensitivity – they must be activated by all potentially threatening situations. However, the price of this evolutionary adaptation will be a high risk of «false alarms».

It is plausible that chronic infection may trigger a «false fatigue alarm». Initially, the immune response will be directly responsible for the fatigue because proinflammatory cytokines (such as interleukin-1β) affect the brain (18). But the longer the immune response lasts, the greater the risk of an association with neutral stimuli through classical conditioning (19). The «fatigue alarm» and accompanying stress response may then continue even if the infection spontaneously resolves and the immune response is normalised (20).

A sustained stress response may in turn account for many of the maintaining factors in chronic fatigue syndrome/myalgic encephalomyelitis (13). Stress responses affect cognitive functions (21), are marked by increased sympathetic and decreased parasympathetic nerve activity (22) and can reduce HPA axis responsivity over time (23), analogous to what is seen in chronic fatigue syndrome/myalgic encephalomyelitis. This will in turn have immunological consequences: Increased catecholamine levels, reduced parasympathetic nerve activity and reduced HPA responsivity promote the inflammatory response (24–26).

Empirical findings in chronic fatigue syndrome/myalgic encephalomyelitis may thus be related as shown in Figure 1. This model is in keeping with established knowledge on treatments: Cognitive behavioural therapy can be thought of as a method for «unlearning» a «false fatigue alarm». The sympathetic inhibitor clonidine normalises parts of the stress response in chronic fatigue syndrome/myalgic encephalomyelitis, but does not improve symptoms or functioning – a likely explanation is that clonidine does not affect the «fatigue alarm» itself (27).

While we believe this to be the most plausible model of the condition’s pathophysiology, further research is needed to confirm or disprove it. One strategy might be functional imaging of the central nervous system: preliminary results from our research group suggest functional changes in the brain regions that control the stress response.
There are no biomarkers for chronic fatigue syndrome/myalgic encephalomyelitis; the diagnosis must therefore be based on the patient’s description of their symptoms. The most widely used set of criteria (from 1994) requires prolonged (6 months), unexplained and incapacitating fatigue, while at least four of eight accompanying criteria must also be fulfilled (28). This definition was based on a pragmatic consensus and has subsequently been criticised. The requirement for four of eight accompanying criteria, for example, has no rational basis and is not supported by empirical validation studies (29, 30).

Subsequent developments have tended towards definitions that are, in some cases, less detailed; in others, more so. For example, the British NICE criteria (31) require chronic fatigue and one additional symptom, whereas the Canadian criteria (32) and the closely related «international consensus criteria» (33) have extensive symptom requirements. All in all, 20 different definitions have been proposed, but none has been thoroughly validated (34).

Based on existing evidence, we recommend a broad diagnostic definition, both scientifically and clinically. The reasons are several:

• A broad definition allows subgroup analyses based on a more detailed set of criteria, which helps with validation. Using such an approach, we have shown that the Canadian criteria seem to lack discriminant and predictive validity (35)

• The detailed definitions presuppose a clear association between symptoms and underlying pathophysiology. Empirical data indicate, however, that this assumption is incorrect: In adolescents with chronic fatigue syndrome/myalgic encephalomyelitis, for example, there was no association between symptoms that might suggest an inflammatory process (such as feverishness, tender lymph nodes) and plasma markers of inflammation (12)

• Persons with chronic fatigue require medical assistance – a broad definition would ensure that patients in need of help do not slip through the net

**Figure 1 Model of the pathophysiology of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)**

**Diagnostics**

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**Treatment**

A systematic review from 2006 concluded that cognitive behavioural therapy is the treatment with the most evidence to support it (36). This conclusion has subsequently been strengthened through several large-scale studies of adults and adolescents (37–40), and the evidence base now includes several thousand patients. The effect size is, however, modest, and there is limited evidence of efficacy in the sickest patients.

Cognitive behavioural therapy can be given both individually and in groups (37). In adolescents, internet-based consultations may be effective (39). Individually adjusted
increases in activity are an integral part of cognitive behavioural therapy but may also have a beneficial effect alone (38, 40, 41). There is no sign of any increase in serious adverse events following these types of treatments (38, 41, 42).

With the possible exception of the immunomodulatory drug rintatolimod, a recent systematic review failed to show efficacy of any pharmaceutical therapies for chronic fatigue syndrome/myalgic encephalomyelitis, be it immunoglobulins, hydrocortisone, selective serotonin reuptake inhibitors or antiviral agents (38). In Norway, treatment with rituximab attracted attention after a small, placebo-controlled study (30 patients) suggested beneficial effects (43).

There was, however, no effect on the primary endpoint, the results have so far not been reproduced, and the risk of adverse effects is unclear. Reported adverse effects of rituximab in other contexts (such as neutropenia and infections) give reason for caution (44).

We believe the evidence base for cognitive behavioural therapy is so solid that all patients with chronic fatigue syndrome/myalgic encephalomyelitis should be offered this treatment. The sickest patients are often bedridden in darkened rooms. This can have serious physical and mental consequences over time (45, 46). We therefore believe that cognitive behavioural therapy must also be attempted in this subgroup, even though the evidence base is weaker. The minimal risk of adverse effects suggests that failing to treat the most severely ill patients is more risky than providing such treatment.

Debate – dualism and scientific abdication

Chronic fatigue syndrome/myalgic encephalomyelitis is a favourite topic of debate (47, 48). One frequent assertion is that the condition must be understood as a «biomedical» disease and that «psychosomatic accounts» – including studies that show efficacy of cognitive behavioural therapy – are not credible. Contributions are often emotionally charged and employ specific rhetorical devices in an attempt to weaken others’ professional credibility and right to express an opinion. The debate in many other countries follows a similar pattern and can acquire militant characteristics – promoted with rhetorical devices – we will have given up on finding scientific truths.

An engaged and critical exchange of views is part of the scientific process and should of course be welcomed, but it must follow the established rules. This includes an intention to actually seek out the truth – not simply to triumph over your opponent. It is only the truth that can benefit patients.

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