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The chronic fatigue syndrome – an update

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Background – In this article, current scientific knowledge on the chronic fatigue syndrome (CFS) is reviewed. The US case definition of CFS (the CDC-definition) is most widespread in research and clinical practice. Estimates of prevalence vary from 0.2% to above 2%. The female–male ratio is approximately 3:1. *Clinical Features* – Severe fatigue is the dominating complaint; it is worsened from exertions and not substantially relieved by rest. In addition, the patients might have a varying combination of accompanying symptoms. Clinical evaluation should be based upon standardized guidelines, including an assessment of functional impairments. *Pathophysiology* – The pathophysiology should be interpreted within a biopsychosocial framework. Present knowledge suggests that certain genetic polymorphisms and personality traits might be regarded as predisposing factors, some infections and severe psychosocial stress constitute precipitating factors, whereas disturbances of immunity, skeletal muscle, cognitive abilities, endocrine control and cardiovascular homeostasis are possible perpetuating factors. *Treatment* – Cognitive behavioural therapy and graded exercise therapy are of proven value in randomized controlled trials. Several pharmaceutical measures have been explored and found to have no beneficial effect. Most patients might expect long-term improvement, but full recovery is rare; however, the prognosis is better among adolescents.

Vegard Bruun Wyller[1,2]

[1]Department of Pediatrics, Rikshospitalet-Radiumhospitalet Medical Centre, Oslo, Norway; [2]Department of Physiology, University of Oslo, Oslo, Norway

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Vegard Bruun Wyller, Department of Pediatrics, Rikshospitalet-Radiumhospitalet, N-0027 Oslo, Norway
Tel.: +47 23 07 00 00
Fax: +47 23 07 45 10
e-mail: brwylle@online.no

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Introduction

The *chronic fatigue syndrome* (CFS) is a common and – in many instances – severely disabling disease (1, 2). Different case-definitions exist; most widespread – in research as well as in clinical practice – is the one developed by the US Centers for Disease Control and Prevention, commonly referred to as the CDC-definition (3) (Table 1). Here, the main criterion is persistent or relapsing fatigue of 6 months duration or more, severely affecting daily activities. In addition, patients should report at least four of eight specific accompanying symptoms.

Other case-definitions in current use are the so-called Oxford-definition (4), the Australian definition (5) and the Canadian definition (6). Neither of these deviate strongly from the CDC-definition, but there are important nuances. More specifically, the Oxford-definition requires the presence of 'mental fatigue' and accepts symptoms that might indicate psychiatric disorder; the Australian definition does not require a new or definite onset of fatigue; whereas the Canadian definition excludes patients with any symptoms of mental illness.

The different case-definitions – and their interrelations – have been substantially debated. Two questions are of particular importance: First, are the different definitions more or less interchangeable, or do they define distinctly different subgroups of patients? Second, how is the validity of these definitions? So far, these questions await their solution.

The complexity is even higher when it comes to terminology. CFS is the preferred term among most scientists and clinicians. *Myalgic encephalomyelitis* (ME) is commonly used among patients' organizations (2). Whether CFS and ME designate identical or different (though related) disorders, is widely disputed. Some maintain that *neurasthenia* – primarily used within the field of psychiatry – is a synonymous term (7). Other less common terms are *post-infectious fatigue syndrome* and *chronic*

Table 1 The CDC-definition of chronic fatigue syndrome (3)

Main criterions (patients must adhere to all)
Persistent or relapsing fatigue of 6 months duration or more
Fatigue is not explained by any concurrent somatic or psychiatric condition
Fatigue is new or definite in onset
Fatigue is not the results of ongoing exertion
Fatigue is not alleviated by rest
Additional criterions (patients must adhere to at least 4)
Impaired memory and/or concentration
Sore throat
Tender cervical and/or axillary lymph nodes
Muscle pain
Multi-joint pain
New headaches
Unrefreshing sleep
Post-exertional malaise

fatigue and immune dysfunction syndrome. Some argue that even entities such as *gulf war-syndrome* and *multiple chemical sensitivity* should be added to this list (8).

Epidemiology and history

Epidemiological data on CFS are confusingly non-consistent. This is partly explainable from the varying case-definitions. For instance, two US community-based surveys, using the CDC-definition, found prevalences of 0.23% and 0.42% (9, 10), whereas a British primary care study, using the same case-definition, found a prevalence of 2.6% (11).

Less is known about the impact of different sociodemografic variables. Most studies have reported the prevalence in women to be about three times higher than in men (2). CFS is relatively rare in children younger than 10 years, whereas the vulnerability seems to be much higher in adolescents 10–17 years. An Australian survey found a prevalence of 5.5/1,00,000 and 48/1,00,000 in these two age groups, respectively (5), whereas a British study indicates much higher numbers (12). Further, the prevalence of fatigue syndromes seems to be higher in well-developed countries than in underdeveloped (13), at least partially justifying the notion of CFS as a disease of 'modern civilization'.

Historically, descriptions of *febricula* – a CFS-like condition – can be traced back to the 1750s (14). The term *neurasthenia* was first introduced by the neurologist George Beard and the psychiatrist E Van Deusen in 1869 (15). The first recorded epidemic outbreak of a CFS-like condition occurred in 1934 in LA, USA, among health care professionals of several hospitals (16). Similar outbreaks have been described later on; the most prominent in Akureyri, Iceland (1948); Adelaide, Australia (1949); the Royal Free Hospital, London, UK (1954) and Great Ormond Street Hospital, London, UK (1970). The term *myalgic encephalomyelitis* originated from these events, but an infectious agent was never detected. Retrospectively, it is impossible to determine whether all or some of these medical conditions correspond precisely to the modern definition of CFS.

Clinical features

As indicated in the name, *fatigue* is the dominating complaint in patients with CFS (1, 2). It is important to recognize this symptom as different from common tiredness or sleepiness, experienced by everyone from time to time (Fig. 1). The patients use notions like 'overwhelmingly exhausted', 'totally empty of energy', etc. and they describe the fatigue as qualitatively different from earlier experiences (17). Limited exertions, whether mental or physical, disproportionately worsen the sensation of fatigue. Likewise, rest or sleep does not substantially relieve it. The onset can be gradual or acute (2).

In addition, the patients are to a varying extent bothered by accompanying symptoms, some of which are required according to the CDC-definition (Table 2) (2, 17). However, no one of them is specific for CFS. In a majority of patients, the symptom intensity is fairly stable, but some report distinct fluctuations (18).

A diagnose of CFS requires a thorough clinical evaluation (19). No single diagnostic test exists. Therefore, several guidelines have been developed for adults (6, 20), as well as children/adolescents (21). Although not identical, the main messages from these guidelines are common, prompting the practitioner to:

– Identify and recognize the patients' characteristic symptoms, especially their experience of fatigue.

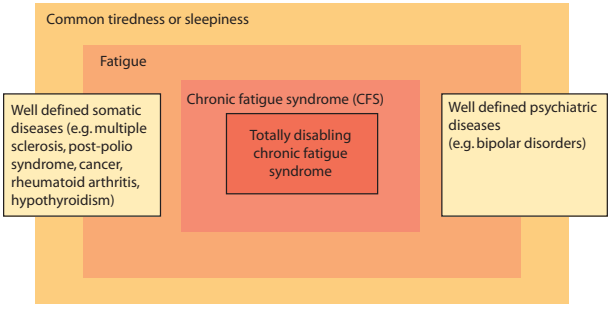

Figure 1. Schematic outline of how CFS should be differentiated from well-defined somatic and mental diseases as well as other subjective complaints (like common tiredness and sleepiness). (Adopted from (19) and slightly modified, with permission.).

Table 2 List of common accompanying symptoms in CFS, putatively organized according to organ systems

Organ system	Symptom
Nervous system	Headache
	Dizziness
	Problems of balance
	Increased sensitivity towards light, sounds and smells
	Subjective temperature sensitivity (feeling too hot or cold)
	Impairments of memory and concentration
	Sleep disturbances
Musculoskeletal system	Muscle pain
	Multi-joint pain
Circulatory system	Orthostatic intolerance
	Palpitations
	Paleness
Digestive system	Abdominal pain
	Diarrhoea
	Nausea
Immune system	Tender lymph nodes
	Sore throat
	Night sweats

– Rule out differential diagnoses by a standardized and comprehensive (but not exhaustive) set of investigations.

In addition, the practitioner should assess the patients' functional impairments, which might be severe, causing school and work absenteeism, social isolation and eventually breakdown of normal family life (2). A four-stage functional classification system has been proposed (20): *Mild* designates mobile patients, who are able to carry out e.g. ordinary housework. *Moderate* means reduced mobility and limited ability to perform daily activities. *Severe* labels patients who use wheelchair and whose performance is restricted to some very simple activities, like teeth-brushing. *Very severe* is the category for completely disabled patients, who are bedridden and not able to take care of personal hygiene.

Qualitative research indicates that CFS patients might have problematic relations towards doctors and other health care professionals, feeling unaccepted, marginalized and not prioritized (22). Doctors, on the other hand, report helplessness and scepticism confronted with a condition of undetermined nature (23). These findings underscore how CFS raises fundamental social and ethical challenges within the doctor–patients relationship. Without neglecting the several complicated aspects of these issues, it seems pertinent to emphasize the doctor's obligation to pay attention to and acknowledge the patients' subjective experience of symptoms, despite the lack of objective signs.

Pathophysiology

Research on the pathophysiology of CFS has been conducted along several tracks, reflecting the great uncertainty about the condition as well as the different scientific traditions among the researchers. The result is a vast amount of papers; a recent PubMed search using 'chronic fatigue syndrome and pathogenesis' as criterion generated more than 1,600 hits. Still, there is, at present, no coherent theory, and CFS is often labeled 'mysterious' or 'controversial' (24). Several experts in the field argue that the condition should be interpreted within a *biopsychosocial framework* instead of a traditional, Cartesian-inspired scheme classifying medical phenomena as either 'physical' or 'mental' (2, 25).

Genetics – Twin studies indicate a moderate heritability of CFS (26). In a recent comprehensive attempt to integrate clinical and epidemiological data with genomic and proteomic profiles, findings suggest that chronic fatigue is related to polymorphisms of genes involved in CNS control of autonomic and endocrine effector systems, including the genes for monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) (27, 28).

Infections – Chronic fatigue syndrome often has an acute onset with symptoms strongly resembling an infection. Therefore, a substantial amount of research has aimed at detecting a possible infectious agent. In the 1980s, much attention was given to Epstein-Barr virus (EBV), as infectious mononucleosis may have a prolonged course or – in the worst case – develop into CFS (29). However, a specific role of EBV has not been established; rather, EBV-infection should be regarded as one of many possible precipitating and eventually perpetuating factors (1). The same view applies to several other microorganisms that may similarly elicit severe fatigue and prolonged recovery in a subset of patients; examples include cytomegalovirus, parvovirus B19, *Brucella* species, *Toxoplasma gondii*, *Coxiella burnetii*, *Mycoplasma* species and *Chlamydia pneumoniae* (30). However, it should also be noted that common, non-specific infections (like upper respiratory tract infections) are not likely to trigger CFS (31).

A possible pathogenetic role of enteroviruses has been thoroughly debated. Using PCR technique, Gow and co-workers reported enteroviral RNA in muscle biopsies in a majority of adult CFS patients; however, enteroviral RNA was also detected among some controls (32). In a recent review, Chia argued that enteroviruses might have

a pathogenetic role in CFS patients, possibly causing chronic inflammatory changes in skeletal muscle (30).

Immunity – The significance of immune system disturbances in CFS has been a matter of controversy. Based on a systematic review of studies addressing T-cell function, B-cell function, NK-cell function, immunoglobulins and cytokines, Lyall and co-workers concluded that there is no consistent pattern of immunological abnormalities in CFS patients, although they found a trend towards changes in T-cell activity (33). Recent studies have reported reduced level of the cytokine TGF-β1 (34), which normally inhibits antibody production, increased levels of IL-6 (35), which stimulates the acute phase response and alterations in the 2-5A synthetase/ribonuclease L pathway (36), which participate in intracellular defense against viruses. More generally, there seems to be evidence of a trend towards Th2 immune responses (humoral) at the cost of Th1 immune responses (cellular) (26). This is consistent with frequent reports of reduced NK cell activity (1), as these cells are important effectors in the Th1 immune reaction.

Skeletal muscle function – Several early studies concluded that CFS patients have perfectly normal skeletal muscle strength, endurance and recovery. However, recent reports indicate that patients are weaker than sedentary controls as judged from maximum voluntary contraction and that their performances are further attenuated 24 h later, indicating delayed recovery (37). Neurophysiological experiments suggest that one probable explanation is altered activation of cortical motor areas in the central nervous system of CFS patients; this phenomenon being even more pronounced when the isometric exercise induced a subjective experience of fatigue (38, 39). Related findings of altered cortical excitability are reported during non-fatiguing movements (40).

Neuroimaging – Studies using functional MRI and SPECT techniques indicate alteration in information processing (41), planning of motor activities (42), cortical perfusion in general (43) and brain stem perfusion (44). However, a twin study concluded that resting regional blood flow pattern in the brain is similar in patients and their healthy co-twins (45). A few PET scan studies have been undertaken in CFS patients. Tirelli and co-workers documented glucose hypometabolism in the frontal cortex and brain stem (46), whereas Siessmeier and co-workers found alterations of brain glucose metabolism among half of the included patients, though no clear pattern could be defined (47). Recently, two independent groups have reported decreased number and/or affinity for the receptor protein 5-HT_{1A} in the hippocampus (48) and the serotonin transporter proteins in the cingulate gyrus (49).

Mental processes – Cognitive tests of CFS patients have revealed disturbances of memory, attention and information processing, also in those patients devoid of any psychiatric comorbidity (50). Albeit the evidence is not uniform, a recent review concluded that CFS patients do have modest, but significant, cognitive impairments (51). Some reports indicate that cognitive performance deteriorates further during exercise (52).

The possible relations between CFS and psychiatric disorders have been – and still are – matters of great controversy. The prevalence of panic disorders and generalized anxiety disorders seems to be higher among CFS patients than in the general population, both in adults (53) and adolescents (54). Further, depression is common among CFS patients, but recent evidence confirms that depression and CFS are two distinct entities (1, 2, 26).

Although CFS often has an infection-like onset, investigations suggest that critical life events (e.g. loss of spouse), severe physical stressors (trauma, surgery) and perceived chronic difficulties – in particular those described as dilemmas – may precipitate the disorder (55). Besides, some studies report that certain personality traits, like perfectionism and conscientiousness, predispose for CFS (56).

Psychological and social issues are often regarded important perpetuating factors in CFS (2). Certain illness perceptions, like poor sense of control over symptoms and strong focus on bodily sensations, correlate to increased impairments in several studies (57). Likewise, CFS patients express a fear of physical exercise that does not correspond to their physical disability (58), they perceive their cognitive performance as poorer than reality (59) and they sleep better than what they subjectively report (60). Patients' attributions also seem to come into play, as a one-sided focus on somatic processes is related to poorer outcome (57).

These inappropriate cognitions might be strengthened from social interactions with family, friends and health care professionals (2). Reduced self-esteem is a common complaint (54), and lack of social support, which is often experienced by CFS patients, may worsen the situation further (61). Finally, the social role as ill might – despite obvious undesirable consequences – also be poten-

tially rewarding, causing an unconscious circle of reinforcement (2).

Endocrinology – The hypothalamus–pituitary–adrenal axis (HPA axis) has been extensively explored in CFS, and there seems to be general agreement on subtle alterations, although the results are far from uniform (2, 26, 62). Most researchers in this field report low basal levels of cortisol in urine, plasma and saliva as well as enhanced negative feedback, possibly due to increased sensitivity or number of glucocorticoid receptors in the brain (62). The normal circadian rhythm of HPA activity is also disturbed, particularly attenuating cortisol secretion in the morning (26). As for challenge tests, most studies indicate blunted HPA axis response to exercise, hypoglycemia and administration of stimulating pharmaceuticals (62). The underlying mechanisms for these disturbances as well as their functional consequences remain unresolved; however, a relation to the documented immune abnormalities is an obvious possibility (26).

Reports on catecholamines are sparse; existing evidence indicate increased basal levels of epinephrine, but normal plasma levels of norepinephrine (63, 64).

Circulatory homeostasis – The first papers on cardiovascular disturbances in CFS emerged in the 1990s, reporting neurally mediated hypotension during head-up tilt test (65, 66). Subsequently, variants of haemodynamic instability during orthostatic challenge – most commonly neurally mediated hypotension or orthostatic tachycardia – has been described by many investigators in adult as well as pediatric patients (67–69). Similar baseline abnormalities have also been reported (68, 69). More sophisticated analyses of cardiovascular variability indicate a sympathetic predominance in the modulation of heart rate and total peripheral resistance during rest and orthostatic challenge (70).

Hemodynamic disturbances have been documented in other organ systems as well. Brain stem hypoperfusion was an early finding (44). A general reduction in cerebral blood flow upon standing has also been reported (71). McCully and co-workers found normal oxidative metabolism in working skeletal muscle, but subtle alterations in blood flow after dynamic exercise, possibly due to sympathetically induced vasoconstriction (72). Finally, there is evidence of altered skin circulation, as CFS patients are more sensitive to the vasodilative effect of locally applied acetylcholine (73).

Towards a unifying model of chronic fatigue syndrome pathophysiology – The need of a unifying model of CFS pathophysiology is generally recognized. As a starting point, one fruitful approach might be to differentiate between predisposing, precipitating and perpetuating factors, as proposed by Prins and co-workers (2), and indicated in Fig. 2. However, further research is needed to establish its validity.

Treatment and prognosis

Various treatment of CFS has been subjected to randomized controlled trials. However, recent reviews conclude that only cognitive behavioural therapy (CBT) and graded exercise therapy (GET) have a scientifically proven beneficial effect (19, 74). Important components of CBT are explanation of pathophysiologic theories on CFS, challenging of fatigue-related cognitions and gradual increase of physical activity (2). In this way, simply speaking, the patients learn to acquire control over their symptoms. CBT is also of proven value among adolescents with CFS (75). Its success, however, does not necessarily imply a 'psychological' or 'mental' etiology. GET exposes the patient to an individually adjusted and structured exercise program (2). The aim is a gradual increase of activity level; thus GET might be regarded a component of CBT. If the patients experience the exercise to be too strenuous, compliance falls. Thus, a very careful and gradual approach seems to be most beneficial (19). How these principles of treatment relate to subgroups of CFS patients remain a question of debate. It is important to note that the severely disabled patients are scarcely represented in the trials.

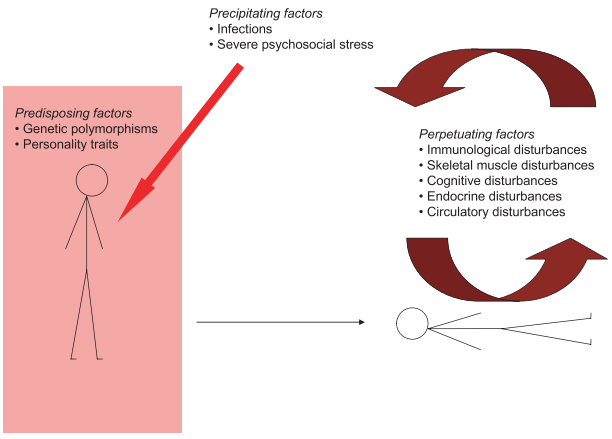

Figure 2. Possible unifying model of the chronic fatigue syndrome based upon differentiation between predisposing, precipitating and perpetuating factors.

Other therapeutic approaches that have been subjected to research include glucocorticoids, mineralcorticoids, antidepressants, anticholinergic agents, antiviral drugs, growth hormone, immunoglobulins, dietary prescriptions and alternative/complementary therapy. For all, the present evidence is inconclusive or indicates no beneficial effect (19, 74).

Management of CFS patients should also include attention to possible complications, like secondary depression and dietary deficiencies in the severely disabled. Further, patients need appropriate assistance on social and economical issues. In children and adolescents with CFS, particular effort should be devoted to their situation at school, establishing courses adjusted to patients' individual capacity (21).

The long-term prognosis of CFS is uncertain, but a recent review reported 5% median full recovery and 40% median improvement across different primary studies (76). The prognosis of children and adolescents with CFS seems to be considerably better, with full or partly recovery in 60–80% (77).

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