REVIEW ARTICLE

Review of clinical and psychobiological dimensions of the chronic fatigue syndrome: differentiation from depression and contribution of sleep dysfunctions

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Chronic fatigue syndrome (CFS) is a disabling condition characterized by subjective fatigue, mental and physical fatigability, a whole range of somatic symptoms and a poor quality of sleep. Its physiopathology is largely unknown. Several clinical and biological differences were observed between CFS and major depression. A classical conceptualization of masked (or somatized expression of) depression is therefore no longer tenable. Sleep anomalies were reported in all studies published to date. However, these sleep anomalies do not seem to explain a major part of the symptomatology of CFS. The contribution of sleep abnormalities to the development and chronicity of CFS should be further studied. CFS can be considered as a somatoform condition. CFS is like most functional disorders a clinically and biologically heterogeneous condition. The best available treatment to date is cognitive-behavioural therapy.

Key words: fatigue, sleepiness, chronic fatigue syndrome, fibromyalgia, depression, anxiety, sleep

Definitions of fatigue

Fatigue in general is defined as the decline in performance that occurs in any prolonged or repeated task. Fatigue can be subdivided into physical and mental fatigue; physical fatigue is the failure to sustain force or power output [1] whereas mental fatigue refers to time related decrement in the ability to perform mental tasks. Both physical and mental fatigue can be evaluated by neurophysiological and neuropsychological assessments respectively (see below). Physical fatigue can be distinguished from weakness, which is the failure to generate force [1].

However, fatigue is also a subjective sensation experienced by the patients, overlapping with other negative sensations such as general malaise or pain, especially...
sensations of heaviness or myalgia. Because of its largely subjective nature, several authors pointed to the difficulty of objectively assessing subjective fatigue. All existing scales intended to measure fatigue are multidimensional; the underlying dimensions are very similar among different scales and represent subjective, mental and physical fatigue. In chronic fatigue syndrome (CFS) high levels of all of these fatigue dimensions were observed. The use of such scales could be worthwhile in sleep clinics, for patients complaining of fatigue, in order to assess the different dimensions of fatigue [2,3].

Sleepiness is yet another type of complaint, related to the tendency to fall asleep during daytime and the effort needed to resist it. Clinically, some patients with CFS do rest or sleep a lot during daytime, but attribute this to exhaustion after minor activity rather than to sleepiness (see also section of sleep). Our findings do not show a high level of sleepiness in CFS subjects (as measured with the multiple sleep latency). Interestingly, sleepiness (as measured with the multiple sleep latency test) was not found to be predictive of the high level of fatigue demonstrated in subjects with psychophysiological insomnia [4]. Sleepiness and fatigue in CFS and other patient populations thus appear as two separate dimensions (see also the section on sleep).

Definitions and research diagnostic criteria of chronic fatigue syndrome

There is no empirically derived definition of CFS, but several consensus-derived, criterion-based definitions, all sharing the cardinal symptoms of fatigue and fatigability.

In 1988, the United States Centers for Disease Control (CDC) led a group of investigators in developing a working case definition of CFS [5]. The definition relied entirely on a combination of symptoms and signs (not laboratory data), and on the exclusion of chronic active organic or psychiatric illness that can produce chronic fatigue. The two major criteria consisted of a new onset of disabling fatigue lasting for more than 6 months, severe enough to reduce average daily activity by >50% and the exclusion of other potential causes. Minor criteria included mild fever, sore throat, tender lymph nodes, generalized muscle weakness, myalgia, arthralgia, headache of new onset, sleep disturbances, physical fatigability, complaints of neuropsychological dysfunction and acute onset. In order to make the diagnosis, the two major criteria as well as eight of the 11 minor criteria had to be fulfilled. In 1991, a workshop was held at the US National Institute of Health to address critical issues in the research concerning CFS. Specific recommendations were made regarding the inclusion of other major confounding diagnoses, and a standard panel of laboratory tests was specified for the initial patient evaluation. Instead of excluding all psychiatric conditions, representing a high proportion of patients, it was recommended to exclude only psychotic disorders, bipolar disorder, psychotic depression and substance abuse, and to include other affective and anxiety disorders as well as somatization disorder. The major and minor inclusion criteria remained essentially unchanged [6].

Meanwhile, in the United Kingdom [7] as well as in Australia [8] other consensus case definitions were published. In the Oxford (UK) criteria, less emphasis was on somatic symptoms whereas more emphasis was placed upon the definite onset and not life-long duration. Post-infectious fatigue syndrome was proposed as a subtype with definite evidence of infection at onset. A study by Katon and Russo [9] showed that a higher number of somatic symptoms was associated with a higher level of psychopathology and, thus, that the inclusion of many somatic criteria in the case definition selected CFS patients with psychiatric co-morbidity. The Australian criteria
Chronic fatigue syndrome

Table 1 Case definition of CFS

Inclusion criteria
Clinically evaluated, medically unexplained fatigue of at least 6 months’ duration that is:
- of new onset (not lifelong)
- not 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:
- subjective memory impairment
- sore throat
- tender lymph nodes
- muscle pain
- joint pain
- headache
- unrefreshing sleep
- post-exertional 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 or bulimia nervosa
- Alcohol or other substance misuse
- Severe obesity


included specific immunological dysfunctions and thereby selected a subgroup of CFS patients. To date there is no evidence to suggest that immunological criteria discriminate between more homogenous subgroups of CFS subjects.

In 1994, a new set of CDC criteria was published [10] (Table 1). The 50% criterion of disability disappeared as well as some somatic symptoms and physical examination criteria because of methodological problems in defining or measuring them with precision. CFS was defined as: (1) clinically evaluated, unexplained, persistent or relapsing fatigue (for >6 months) that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social or personal activities; and (2) the concurrent occurrence of four or more of the following somatic symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness, and must not have predated the fatigue (see Table 1). The diagnosis of idiopathic chronic fatigue is used in cases where criterion (1) but not (2) is fulfilled.

It must be emphasized that the afore-mentioned case definitions have no scientific validity and have to be considered as tools for ongoing research.

Fibromyalgia (FM) is possibly related to CFS and is characterized by diffuse bodily pain and tenderness. Fatigue is very prevalent in FM.

The diagnostic criteria of CFS should be assessed in all patients consulting a sleep clinic for chronic fatigue.
Epidemiological findings: prevalence of fatigue and chronic fatigue syndromes

Wessely has written a recent review article on the epidemiology of CFS [11]. Community surveys have repeatedly shown that complaints of fatigue are extremely common in developed countries. Fatigue is a common symptom in primary practice. Recent studies with systematic case ascertainment in primary care reported a different picture, with a point prevalence of 0.3 up to 2.6%. Nearly all published studies reported that women were over-represented in specialist samples of CFS, and one recent study demonstrated that women are also over-represented in primary care. When depression was controlled for, the sex ratio difference disappeared in one study but not in two other studies. The female: male ratio was found to increase as a function of the intensity of the fatigue syndrome.

In most published articles, the mean duration of CFS is of several years. The naturalistic course over the long run (>10 years) is not known.

Biological hypotheses

CFS has been considered by several authors as an organic and not a functional condition; until now, few data seem to support this hypothesis.

Viral and infectious hypothesis

There are three recent review articles on this subject [12–14]. Globally, it can be stated that most authors cannot prove that CFS is caused by one or several viruses; however, in particular cases it is thought that a viral illness can trigger the development of CFS. White et al. [15] have demonstrated the existence of a post-Epstein Barr virus (EBV) fatigue syndrome (of shorter duration than CFS) [15]. Hotopf et al. [16] reported recently that after a viral meningitis, 12.6% of patients developed CFS, a rate which is higher than reported estimates of prevalence from primary care attenders, suggesting that moderate to severe viral infections may play a role in the aetiology of some fatigue states. However, in that study, the best predictor for the development of post-viral meningitis CFS appeared to be past psychiatric illness.

Immunological hypotheses

Over 30 studies of various immunological parameters in CFS have been published to date and reviewed by Strober [17]. Some authors considered CFS to be an immunological disorder possibly somehow related to AIDS. However, the reported immunological abnormalities have been generally modest and inconsistent.

An increased proportion of CD8+ cells (suppressors, cytotoxic cells) expressing the HLADR activation marker have been reported in several studies, especially in subjects with a high illness burden. Elevated levels of cytokines in serum and cerebrospinal fluid were found in some, but not all, studies. Interestingly, plasma cytokines were found to be elevated in disorders of excessive daytime sleepiness; this was hypothesized to play a physiopathological role in the fatigue and sleepiness associated with these
disorders [18]. It is unknown whether immunological abnormalities in CFS are related to the presence of primary sleep disorders (see the section on sleep). Since inhibition of cellular immunity (natural killer cell activity, mitogen induced proliferation of lymphocytes) and immune activation (higher number of activated lymphocytes) were also reported in major depression, acute and chronic stress, it remains unclear whether these anomalies are secondary to depression. Personal unpublished data showed that immune activation and other immune abnormalities in CFS are unrelated to the comorbidity of major depression (MD) and to the intensity of depression. A recent prospective study, did not find the reported immune anomalies in CFS [19]. Moreover, despite the fact that a clinical improvement was obtained with cognitive-behavioural therapy, no immunological changes were observed.

The contradictory immunological findings in CFS possibly reflect the heterogeneity of CFS populations, the involvement of stress, primary sleep disorders or the absence of any pathophysiological significance of immune anomalies in CFS.

Endocrine hypothesis

A recent review by Demitrack et al. [20] demonstrated anomalies of the hypothalamo-pituitary-adrenal (HPA) axis including lower urinary excretion rates of free cortisol and reduced evening plasma cortisol concentrations in conjunction with an elevated plasma adrenocorticotropic hormone (ACTH). These findings were interpreted as reflecting a hypothalamic problem of secretion or synthesis of corticotropin release hormone (CRH). Demitrack et al. [20] hypothesized that CRH deficiency could be of physiopathological significance in asthenia and lethargic states beyond diagnostic borders and suggested that the hypocortisolemic state could explain the hyperimmune state reported in some CFS patients. In any case, these anomalies in CFS are markedly different from the HPA activation found in MD.

Several studies pointed to the possibility of an increased sensitivity of 5HT hypothalamic receptors [21,22] which is in marked contrast with a decreased sensitivity in MD. Cerebrospinal fluid concentrations of 5HIAA were demonstrated to be in the normal range in contrast to reduced levels in depression.

Psychiatric and psychosocial hypotheses

Psychiatric hypotheses

High prevalence rates of current MD were reported in the early controlled psychiatric studies on CFS—a finding that could not be replicated in more recent (generally uncontrolled) studies. Almost all studies report high prevalence rates of lifetime MD. Findings on the appearance of MD before or after CFS onset are quite conflicting. High prevalence rates of panic disorder (PD) and somatization disorder (SD) were reported in CFS. Fischler et al. [23] have recently demonstrated that the prevalence of anxiety disorders, especially the generalized anxiety disorder (GAD) was very high in CFS (56%), whereas the prevalence of current affective disorders was not significantly different from controls. It was hypothesized that GAD was a risk factor for the development of CFS.

The psychiatric hypothesis denies the mere existence of CFS as a separate condition
Table 2  Pathophysiologic processes in CFS and depression

<table>
<thead>
<tr>
<th></th>
<th>CFS</th>
<th>Major depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td>Patient history</td>
<td>Unusual</td>
</tr>
<tr>
<td>Initiating virus</td>
<td>Investigated but no convincing evidence</td>
<td>Unknown</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
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<tr>
<td>Chronic virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td>Reduced lymphocyte function, immune</td>
<td>Reduced lymphocyte function, immune</td>
</tr>
<tr>
<td>Immune disturbance</td>
<td>activation of CD8 cells</td>
<td>activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuroendocrine</strong></td>
<td>May be decreased</td>
<td>Typically increased</td>
</tr>
<tr>
<td>Cortisol</td>
<td>May be increased activity</td>
<td>Decreased activity</td>
</tr>
<tr>
<td>Serotonergic system</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical function</strong></td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Exercise performance</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Muscle function</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiorespiratory</strong></td>
<td>Some evidence</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Only minority of CFS patients</td>
<td>Only with anxiety</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Brain imaging</strong></td>
<td>Reduced but also augmented blood</td>
<td>Reduced blood flow to certain areas,</td>
</tr>
<tr>
<td></td>
<td>flow to certain areas,</td>
<td>especially L frontal</td>
</tr>
<tr>
<td>Functional</td>
<td>R&gt;L. temporo-parietal asymmetry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormalities of uncertain significance</td>
<td>Abnormalities of uncertain</td>
</tr>
<tr>
<td>Structural</td>
<td></td>
<td>significance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td>Impairment</td>
<td>Impairment</td>
</tr>
<tr>
<td>Information processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td><strong>Sleep abnormalities</strong></td>
<td>Reduced slow wave</td>
<td>Loss of SWS early in the night</td>
</tr>
<tr>
<td>Reduced REM latency</td>
<td>Some conflicting evidence</td>
<td>Typical</td>
</tr>
<tr>
<td></td>
<td>Not found</td>
<td></td>
</tr>
</tbody>
</table>

and considers these patients to be suffering from MD, PD or SD along with fatigue symptoms and an external, physical attributions pattern [3,24]. Table 2 summarizes the biological differences between CFS and MD, as reported in the various parts of this review (see later).

Another psychiatric view of CFS is the somatoform conceptualization which is similar to the way that some consider the irritable bowel syndrome, FM, etc. This means that CFS cannot be reduced to another axis-I condition and that the somatic symptoms are medically unexplained. Interestingly, fatigue is a common symptom to all these “somatoform” conditions.

**Depression as a result of CFS**

Personality factors that possibly play a role in the aetiopathogeny of CFS, such as over-achievement in order to stabilize self-esteem (see later), could be risk factors for the development of depression as incapacitation could potentiate low self-esteem and thereby induce depression. The hypothesis that depression merely represents a normal
reaction to the illness burden has been criticized on the ground that three controlled studies of CFS using chronic medical illnesses with similar illness burden (multiple sclerosis, neuromuscular disorders, rheumatoid arthritis) as control groups, found a higher level of depression in CFS [3,25,26]. However, the fact that CFS is not recognized and accepted by many, including physicians, is possibly another illness burden for which the aforementioned studies did not control.

**Psychological views on CFS**

Ware [27] presented an anthropological view of CFS based on clinical observations. Themes concerning the existential meaning of illness were found to be negative life events and chronic life difficulties, abuse in the past, low self-esteem, fear of displeasing others, feelings of being overwhelmed by multiple commitments and a hectic pace. Incapacity to refuse things, high standards for personal performance and a tendency “to do for others” converge as the driving force behind this whirlwind of activity.

Results on life events and CFS are conflicting. Life events during the illness process do appear to worsen CFS.

**The cognitive-behavioural model**

Besides the more behavioural approach developed by Wessely and Powell [3], Surawy et al. [28] emphasized a number of cognitive components such as the role of pre-morbid personality characterized by a marked achievement orientation, perfectionism and high standards for work performance, responsibility and personal conduct. The most common theme was high standards with the implication that failure to meet them would indicate failure as a person or unacceptability to others. The second most common theme concerned the importance of psychological strength and not admitting to weakness or negative feelings. The onset of illness is suggested to be preceded by life changes and/or chronic relationship and work difficulties that place a heavier burden on the person’s high standards of achievement. This apparently leads the patients to try even harder despite the increasing exhaustion, and to enter a state of chronic exhaustion, frustration and demoralization. It is suggested that the symptoms of fatigue, poor concentration and myalgia result from the physiological changes accompanying chronic emotional distress and inactivity. The central role of avoidance is also emphasized. Oscillations in activity from avoidance as a consequence of the physical attributions and illness worry to bursts of activity because of underlying standards of achievement are supposed to fuel the vicious circle, leading to chronic frustration, preoccupation with symptoms, and disability.

**Physical fatigue: muscle dysfunction hypothesis**

This topic was reviewed by Edwards et al. [29]. The popular hypothesis of a muscle disease in CFS is by no means established. Several studies demonstrated that there is no weakness nor diminution of physical force in CFS. There is also no objective evidence of a delayed appearance of abnormal post-exertional muscle fatigability.

Several mechanisms appear to be involved in the physical fatigability in CFS and
FM: submaximal exertion related to an enhanced perceived exertion (perception of effort) due to central mechanisms, deconditioning with a premature increase of the heart rate and lactate during effort and a hyporeactivity of the sympathetic drive at cardiac level during exercise. The inability to reach 85% of maximal heart rate during effort was found to be associated with a higher degree of disability [30]. This finding supports the cognitive-behavioural theory emphasizing the role of avoidance of effort in disability (see below). Interestingly, in the aforementioned study, no association was found between physical fatigability, avoidance of submaximal effort and depression, providing another reason to think that depression is not involved in physical fatigue in CFS.

**Mental fatigue: CNS dysfunction hypothesis**

Cope and David [31] have written a recent review article on brain imaging in CFS.

**Magnetic resonance imaging (MRI) studies**

A higher number of punctuate areas of high signal intensity in the white matter of the brain of CFS patients was reported in some, but not all, MR studies. However, several confounding variables have not been controlled for.

**SPECT studies**

Previous single photon emission computed tomography (SPECT) studies in CFS reported a generalized lower cerebral blood flow, in particular at frontal and temporal regions but also at subcortical areas such as the brain stem, thalamus and nucleus caudatus. However, Fischler et al. [32] did not find reduced global or regional cortical blood flow in CFS but, on the contrary, regions of hyperperfusion when compared with MD and healthy controls (HC). Several studies demonstrated a statistically significant higher R>L asymmetry at temporal and infero-parietal level in CFS when compared with HC and MD. However, the intensity of the asymmetry did not appear to be associated with clinical features of CFS and, thus, its physiopathological meaning remains unknown.

**Neuropsychological studies**

A comprehensive recent review of this literature can be found in [33]. One of the most frequent complaints in CFS is poor attention and memory. Many studies tried to objectify and dissect the different neuropsychological functions in CFS. The subjective experience of cognitive impairment appeared to outweigh objective findings on formal testing in several studies. Global mental deterioration has been ruled out in CFS. Reaction times were found to be significantly prolonged in some but not all studies in CFS. Several studies reported poor performance on tests requiring divided attention and inhibition of competing information and on tests requiring the simultaneous processing of multiple
elements of complex verbal or visuospatial information. These anomalies could not be explained by MD co-morbidity nor by the intensity of depression (except for one study). They cannot merely be explained by the motor component of the task nor by stimulus identification or perceptual difficulties. Most anomalies can be conceptualized as a consequence of response selection, programming and/or execution (including motor speed) processes. One can conclude that there are no primary memory deficits in CFS, but that there is a reduced attentional capacity that results in an impaired performance on tasks requiring a sustained effort and divided attention. Acquisition of verbal memory appears to be more a problem than storage or retrieval of verbal information. When speed of processing is part of the memory task, then impairment is found in CFS. Cognitive dysfunction in FM were found to be characterized by slower speed on performance of complex tasks. These anomalies were found to be possibly related to a longer stage 1 sleep [34].

Sleep studies

A substantial proportion of CFS patients have complaints of sleep dysfunction starting after the onset of illness [35]. Poor, unrefreshing sleep is one of the eight minor criteria of the recent diagnostic criteria for the diagnosis of CFS (Table 1). Sleep abnormalities can potentially explain part of the symptomatology of CFS since post-exertional fatigue, myalgia and neuropsychological impairment were shown to be consequences of sleep deprivation [36].

Three controlled polysomnographic studies in CFS have been published. Whelton et al. [37] and Morriss et al. [38] reported a reduced sleep efficiency and a longer sleep onset in CFS patients. In addition, a reduction of rapid eye movement (REM) sleep and a longer time awake when compared with controls were demonstrated in the former and latter study, respectively. In addition, the study by Fischler et al. [39] reported a lower percentage and time at stage 4.

Longer sleep onset, an increased frequency of microarousals, a higher percentage of time awake and a reduction of stage 2, stage 4 and REM sleep were reported in several, but not all, controlled studies in FM. Moldofsky et al. [40] demonstrated a longer sleep onset time and a longer REM latency in FM with post-febrile onset when compared with controls and FM without a viral infection-like onset.

Fischler et al. [39] have shown that sleep abnormalities in CFS such as longer sleep onset, higher number of stage shifts/h and a lower percentage of time at stage 4 were similar in CFS patients with and without psychiatric co-morbidity and with and without FM. Moreover, no association could be found between these sleep variables and the intensity of depression. This means that sleep anomalies in CFS are not a mere consequence of psychiatric or FM co-morbidity. Similar conclusions can be drawn from a recent study by Morriss et al. [35] demonstrating few differences in the prevalence or nature of sleep complaints between CFS patients with or without psychiatric co-morbidity. The nature of frequent awakening in CFS could be different from depression since feeling cold or hot and pain were more frequently reported as causes of awakening in CFS than in depression. It can be speculated that disrupted sleep continuity in CFS is linked to physiological and/or psychological mechanisms of pain sensitivity and temperature regulation.

Morriss et al. [38] demonstrated an association between sleep disorders and functional disability in CFS and suggested that sleep disorders may be aetiologically important
Table 3 Primary sleep disorders in CFS: comparison of different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>PLMs (%)</th>
<th>Apnoeas (%)</th>
<th>Narcolepsy (%)</th>
<th>Idiopathic hypersomn.(%)</th>
<th>Sleepiness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whelton et al. (1993)</td>
<td>14</td>
<td>7</td>
<td>14</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Krupp et al. (1993)</td>
<td>16</td>
<td>25</td>
<td>12.5</td>
<td>6**</td>
<td>n.a.</td>
<td>25†</td>
</tr>
<tr>
<td>Manu et al. (1994)</td>
<td>30</td>
<td>20</td>
<td>13</td>
<td>3.3</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Buchwald et al. (1994)</td>
<td>38</td>
<td>11</td>
<td>47</td>
<td>5**</td>
<td>8**</td>
<td>41‡</td>
</tr>
<tr>
<td>Lebon et al. (submitted)</td>
<td>53</td>
<td>4.3</td>
<td>6.3-45.8*</td>
<td>0***</td>
<td>0***</td>
<td>30‡</td>
</tr>
</tbody>
</table>

* Depending on criteria used for sleep apnoea.
** Sleep criteria only.
*** Global criteria (clinical sleep).
† Mean MSLT less than 8.5 min.
‡ Mean MSLT less than 10 min (moderate and severe).
PLM: periodic leg movements.
MSLT: multiple sleep latency time.

in CFS. Fischler et al. [39] could not reproduce these findings. In another study, Morriss et al. [35] showed a relationship between certain types of sleep complaints (waking during the night for more than 1 h and restless legs syndrome) and the number of sleep complaints on the one hand and disability on the other.

All studies on CFS show that the mean REM latency (and the percentage of subjects with a shortened REM latency) is similar in CFS and healthy controls. Preliminary data indicate that REM latency is also normal in CFS patients with major depression [39]. No published data are available on tonic REM activity in CFS.

A decreased slow wave sleep (SWS) was also reported in exhausted men. Fatigue and myalgia could possibly be related to the combination of physical deconditioning (see above) and stage 4 impairment since noise-disruption of stage 4 induced fatigue and myalgia in sedentary but not physically well-trained subjects [40]. However, the latter findings could not be reproduced in a recent study.

Alpha intrusion in non-rapid eye movement (NREM) sleep rather than SWS duration per se could perhaps have physiopathological relevance in FM and CFS. Studies about alpha sleep in CFS showed conflicting results [37,38,41]. The role of alpha sleep in the physiopathology of FM has been questioned recently [42]. In FM, differences in alpha sleep and alpha/delta ratio as compared with controls were reported across successive sleep cycles [43].

It can be speculated that the association found between disability and sleep complaints is essentially the consequence of the degree of day napping, avoidance of physical activities and inactivity. It is unknown whether inactivity can cause sleep disorders and, thus, whether a link between chronic fatigue and sleep disorders is essentially the consequence of inactivity.

It has been shown that the prevalence of sleep apnoea (of moderate intensity generally well beyond the limit where treatment is warranted) in CFS range between 12.5% and 47% (Table 3) [44–46]. Fischler et al. [39] demonstrated that sleep apnoea
did not contribute to the degree of disability in CFS. Personal unpublished data demonstrate a lack of association between attentional, memory and psychomotor dysfunctions and sleep apnoea in CFS patients. The prevalences of other primary sleep disorders in CFS are also shown in Table 3.

Sleepiness as assessed with multiple sleep latency could not be demonstrated in CFS. Sleepiness as assessed with the Stanford Sleepiness Scale shows mean values between 3 and 4 in CFS, which are moderately elevated values. However, this scale appears to be essentially correlated to anxiety and depression scales and not to other sleep anomalies (including the intensity of sleep apnoea) or cognitive dysfunctions (unpublished personal observations). This means that this scale is not suited to assess sleepiness in CFS. Sleepiness should be assessed with the question related to the tendency to fall asleep during daytime and the effort needed to resist it. Personal clinical experience demonstrates that few CFS patients report it spontaneously or after inquiry but that primary sleep disorders are often demonstrated in these CFS patients (unpublished observations). Classical behavioural approaches for sleep problems have not yet been tried out systematically in CFS. These techniques should probably be used to determine the type of "sleep behaviour" and not for background diagnosis such as an anxiety disorder or CFS. Behavioural techniques improving activity levels during daytime and diminishing long rest phases during daytime are of paramount importance in the treatment of CFS (see below).

In conclusion, sleep complaints and definite sleep abnormalities are prevalent in CFS. However, it is still unclear whether these abnormalities contribute significantly to the physiopathology of some symptoms of CFS. As with axis-1 psychiatric disturbances such as MD, CFS cannot be reduced to a somatic expression of a primary sleep disorder.

Prospective studies are clearly needed in order to better understand the relationship between sleep anomalies and the development and progression of fatigue.

**Functional impairment**

CFS is associated with a high degree of functional impairment, comparable with chronic medical conditions and even more severe than in the case of MD. Interestingly, the pattern of functional impairment and its association with other clinical variables is quite dissimilar from the one seen in medical conditions and depression. The intensity and the number of somatic symptoms appear to be the best predictor for functional impairment. Psychic distress is only significantly related to the emotional dimensions of the quality of life rating scales [47].

Functional status is heavily impaired in CFS and MD. However, the main attribution behind it is very different between both groups. In depression, low mood and loss of interest are used as main reasons behind dysfunctioning, while in CFS these are the lack of energy and the presence of disabling somatic symptoms such as heaviness in the legs.

It is also important to stress that some patients suffer a major functional impairment; these patients lie down for more than 22 h a day, can no longer watch television or read, cannot walk for more than a few minutes, cannot sustain any long conversation and become totally dependent. In general, these patients have the most radical physical
attributions to their illness and refuse to consider any link with stress or other psychosocial problems. Attitudes of family members, general practitioners and even psychologists and psychiatrists are frequently critical and even hostile to these patients who are difficult to treat.

Treatment

Pharmacological

A detailed review of the medical treatment for CFS is beyond the scope of this review—Hirata-Dulas et al. [48] provide a recent review. Double-blind trials will be briefly summarized: acyclovir, an antiviral agent, was found to be ineffective. There are contradictory findings regarding the efficacy of immunoglobulin treatment. One double-blind study with ampligen showed a diminution of the disability in heavily impaired patients. Improvement was also observed with essential fatty acids. A recent double-blind study of fluoxetine suggested that it was ineffective in CFS [49]. However, it is possible that the dose of fluoxetine used (20 mg) was too high for CFS patients, since during the early phase of the study patients treated with fluoxetine had worse results than patients on placebo. Many clinicians use low doses of trazodone or amitryptiline to improve sleep quality. Personal unpublished prospective polysomnographic data demonstrated an improvement in sleep efficiency with 50 mg of trazodone in CFS. Many CFS patients use hypnotism.

Psychotherapeutical

During the last few years, cognitive-behavioural therapy (CBT) seems to be the treatment of choice for several somatoform conditions. An early uncontrolled evaluation of this type of treatment produced promising results in many patients; however, this treatment was unacceptable to others. Two subsequent controlled trials found CBT to offer no benefit over non-specific management. However, it was suggested that the form and the number of sessions used may have been inadequate. Sharpe et al. [50] showed that 73% of the recipients of CBT and 27% of patients who were only given medical care achieved a satisfactory outcome. A recent study with relaxation as a control condition essentially showed similar data with improvement being sustained over 6 months of follow-up and, thus, much less of an effect with relaxation [51]. There is discussion among cognitive-behavioural therapists about the fact whether the improvement in activity level is necessary or sufficient to obtain a global therapeutic effect. It would be interesting to evaluate prospectively with CBT the evolution of sleep anomalies in parallel with the clinical evolution of CFS.

CBT is also used in MD. Behavioural and cognitive techniques used for MD are dissimilar from these used in CFS. The differences in behavioural techniques are related to the fact that in CFS patients the activities are structured and homogeneously distributed in time meaning that “hyperactivity, or activity in a tense way” are also tackled. In MD, patients are stimulated to become active. Cognitive techniques are
aimed at the depressive cognitions in MD and aimed in CFS towards the cognitions developed in the section on the cognitive-behavioural model.

**Prognostic factors**

There is a recent comprehensive review of the prognostic factors in CFS [52]. Consistently reported risk factors for poor prognosis are older age, an increase in chronic illness, having a co-morbid psychiatric disorder and holding a belief that the illness is due to physical causes. It is unknown whether sleep anomalies contribute to the prognosis of CFS.

**Practice Points**

1. In all patients complaining of chronic fatigue, an assessment of axis-I disorders and diagnostic criteria for CFS and FM should be performed. In cases of diffuse muscle pain, a rheumatologist should assess the tender points. Medical causes for fatigue should be excluded systematically.
2. Assess the presence of sleepiness clinically and if necessary with multiple sleep latency.
3. Assess sleep hygiene and treat consequently. Treat sleep disorders as usual.
4. For medico-legal procedures or for quantification of mental and physical fatigue, neuropsychological testing and cycle ergometry can be performed.
5. Treat the co-morbid axis-I psychiatric disorders properly. Avoid debating with the patient with regard to the organic/psychiatric dichotomy and use the biopsychosocial model applicable to all medical disorders. Give medical information to the family regarding the disability and the philosophy of treatment. Most importantly, the patient must feel recognition of the real character of his symptoms. Functional hypotheses may not give the patient the impression that his complaints are not taken seriously. If necessary use a neurobiological model of stress.
6. Redirect the interviews towards the lifestyle of the patient and propose a disease model including the former and the cognitive-behavioural model.
7. Do not prescribe rest but a progressive and gentle enhancement of physical activities and a structured cognitive-behavioural treatment by an experienced therapist (with patients with somatoform disorders).

**Research Agenda**

Since the contribution of sleep anomalies to the physiopathology of CFS remains largely unknown, several studies could be undertaken on the following topics:

1. prospective studies assessing the interactions between anxiety, fatigue, rest and sleep dysfunctions;
2. relationship between mental and physical fatigue and sleep anomalies.

Besides these topics, the neurobiology of fatigue, especially of the sense of physical and mental effort, should be studied further with brain imaging techniques (using activation studies). Recent studies demonstrate anomalies of pain processing at the level of the anterior cingulate and at the prefrontal cortex in somatoform pain conditions. Recent studies also point to specific REM sleep anomalies in the irritable bowel disorder. The predictive factors for response to CBT should be further studied.
General conclusion

CFS is a disabling condition with subjective fatigue, mental and physical fatigability, a whole range of somatic symptoms and a poor quality of sleep. Its physiopathology is largely unknown. Several biological differences were observed between CFS and major depression. A classical conceptualization of masked or somatized expression of depression is no longer tenable. CFS is a biologically and clinically heterogeneous population which in the future should be divided into more homogeneous sub-populations according to psychobiological mechanisms. Future studies should systematically assess several clinical dimensions besides the use of a categorical approach. The place of sleep anomalies in this psychobiological dissection of chronic fatigue states remains unclear to date. Studies in CFS can possibly contribute to a better understanding of the psychobiology of fatigue in general.

Acknowledgements

The author thanks Véronique De Gucht for reading the manuscript and Olivier LeBon for the authorization to present Table 3, which is not yet published.

References


* The most important references are denoted by an asterisk.
Chronic fatigue syndrome


