Peer reviewed article

Chronic fatigue syndrome (cfs)

A review and a proposition of a bio-psycho-social model of the chronic fatigue syndrome

Rolf H. Adler

Summary

The Chronic Fatigue Syndrome (CFS) is described based on the revision of Fukuda et al. The question "whether CFS can be discussed as a homogenous disorder?" has been reviewed and the answer is "no". Other overlapping syndromes are mentioned. Disorders with fatigue as a symptom are depression, somatisation, irritable bowel syndrome, effort-syndrome, hyperventilation, conservation-withdrawal. Among the pathogenetic factors of CFS immune systems disorders, neuroendocrine abnormalities, autonomic activity, neuroimaging, neuropsychological abnormalities, exercise capacity and muscle function and psychological processes (attribution, perception, symptom avoidance and neutralisation of conflicts) are discussed. Since CFS cannot be comprehended without knowledge of the ontogenetic development of the affect "fatigue", it is extensively described. Based on this knowledge, fatigue as an affect and the CFS are embedded in a context, which has as its basis the fight-flight reaction and the conservation-withdrawal reaction. Weighing the evidence, it is concluded that CFS in its varieties can best be understood as a manifestation of the activation of the two biological emergency reactions: fight-flight and conservation-withdrawal. The physician should interview and examine each individual patient according to the Harvey Cushing dictum: The physician should not only study the diseased organ, but the man with his diseased organ, and not only these. He should comprehend the man with his diseased organ in his environment. This leads to study of the biological, psychological and social factors contributing to each patient's illness. Work-up and therapy have to be based on this integrated approach. The latter encompasses conflict centred psychotherapy, stepwise increasing physical activation and antidepressive drugs.

Description of the syndrome

Outbreaks of a disorder characterized by severe, debilitating and longstanding fatigue, designated as CFS, neuromyasthenia or myalgic encephalomyelitis [1] led the United States Centers for Disease Control and Prevention to designate this disturbance as CFS [2]. In 1994 the definition of CFS was revised [3]: at least six months of persistent fatigue that substantially reduces the person's level of activity. In addition four or more of the following symptoms must occur with fatigue in a six month period: impaired memory or concentration, sore throat, tender glands, aching or stiff muscles, multijoint pain, new headaches, unrefreshing sleep, and postexertional fatigue. Medical conditions that may explain the prolonged fatigue as well as a number of psychiatric diagnoses (i.e. eating disorders, psychotic disorders, bipolar disorder, melancholic depression and substance abuse within two years of the fatigue) exclude a patient from the diagnosis of CFS. Those who do not meet the fatigue severity or symptom criteria can be given a diagnosis of idiopathic CF [4]. Note that no laboratory test is required for the diagnosis of CFS.

Is CFS a homogenous disorder?

The synonymous use of the terms CFS, epidemic neuromyasthenia and myalgic encephalomyelitis and the clinical impression that CFS shares numerous features with fibromyalgia (FM), multiple chemical sensitivity (MCS), irritable bowel syndrome (IBS), effort syndrome, and temporomandibular syndrome raises the suspicion that it is not a homogenous disorder. As many as 70% of CFS-patients showed features of FM, and 35% of MCS. Forty-two percent of female FM-patients

No financial support declared.

share the criteria for CFS [5–9]. Ciccone and Natelson [10] have observed in women with CFS that 37% met the criteria for FM, and 33% those for MCS. With the exception of FM-related pain and disability, there were few differences between CFS only and CFS with comorbid illness groups. Patients with additional illness were more likely to have major depression and a higher risk of psychiatric morbidity compared with patients in the CFS-only group ($p < 0.01$). Rates of life-time depression increased from 27.4% in the CFS-only group to 52.3% in the CFS/FM-group, 45.2% in the CFS/MCS-group and 69.2% in the CFS/FM/MCS-group. Reviewing the subject of similarities among these syndromes led to the conclusion that patients with CFS, FM and MCS suffer from the shared proneness to somatise or misconstrue the significance of normal physiological sensations. Definitions, symptomatology and comorbidity in the patients with CFS, FM, MCS and IBS led Wessely et al. [11] to suggest that these disorders are different manifestations of the same somatic and psychological disturbances. Other illnesses with fatigue, pain and other symptoms in the absence of physical signs, which overlap with the above mentioned syndromes are temporomandibular disorder, interstitial cystitis, chronic tension-type headaches, post-concussive syndrome, chronic pelvic pain and chronic low-back pain; e.g. 18% of patients with temporo-mandibular disorder meet FM-criteria and 75% of FM-patients show temporo-mandibular disorder criteria [12].

Disorders with fatigue as a symptom

Depression: Among the sensory symptoms of depression, e.g. feeling numb, empty, fatigue may be one of the complaints. If fatigue predominates and is of long duration, CFS may become the diagnosis. CFS-patients rarely express worthlessness, guilt, self-depreciation and suicidal ideation. Concentration difficulties, memory impairment, sleep disturbance, and moodswings occur in CFS-patients as well as in depressed individuals. CFS-patients usually show intensification of symptoms to activity and exercise, whereas depressed patients may react with elevation of mood [13]. Depressed patients show a loss of interest while CFS-subjects state to feel motivated. Consequently studies of CFS-patients present a high correlation with depression. About 30 to 70% of CFS-patients show the features of major depression [14–16], but it is not easy to decide in an individual patient if he suffers from CFS and shows features of depression, or vice versa. The premorbid rate of psychiatric disorder including depression in CFS-patients is increased [17].

Somatoform disorders, i.e. psychogenic illnesses presenting with somatic symptoms can be confounded with CFS. Around 30% of CFS-patients seen in tertiary medical centres suffer from somatisation [18]. Somatisation usually starts in adolescence and reaches its full expression at age 25, whereas CFS is characterized by sudden onset usually around age 30 [19]. Somatisation is a purely descriptive concept. It has no explanatory power and does neither offer a theoretical frame of reference nor a developmental perspective.

Irritable bowel syndrome (IBS) complaints overlap with those of CFS: nausea in 50–60%, diarrhoea in 30–40% [20]. Live time rate of IBS in CFS-patients is 92% [11, 12]. The prevalence of emotional distress and disorder in patients who attend hospital with functional syndromes such as IBS is higher than in patients with comparable medical conditions, such as inflammatory bowel disease [21]. The overlap of CFS and IBS and the observation [22] that IBS-patients often have suffered from physical and sexual abuse in childhood indicates that it would be valuable to look for such events in CFS-subjects. Egle U et al. (unpublished data) recently have observed an elevated rate of sick parents in the childhood of later CFS-patients and more childhood abuse than expected in later FM-patients.

The effort-syndrome shows surprising similarities with complaints observed in CFS [23]. Of 100 consecutive patients with CFS 93 showed chronic hyperventilation in pulmonary function tests. The history of the patients suggested that the presented illness was not the beginning of the disorder, but a “deeper vegetative phase” after an initial period of anxiety, panic states and phobic disorders, neurological complaints, cardiovascular deconditioning and cardiovascular instability with chest pain, palpitations and breathlessness [24], i.e. the second phase in the form of a conservation-withdrawal reaction [25].

Pathogenetic models of CFS

Infections

The first descriptions of CFS (and its earlier synonyms) were linked with infective disorders, e.g. Epstein-Barr virus [26], brucellosis [27], influenza [28]. Iloyd et al. [29] enumerate 12 viral, 6 bacterial and 3 parasitic disorders that were thought to play a role in CFS, among them enteroviruses, human herpes virus-6, and retroviruses. No study has shown that an infection is causative in CFS. In some cases an infection seems to have contributed to long lasting fatigue [30]. Many studies are retrospective and selection biases confound the results. Several ways of interaction between infection and CFS can be imagined: a) the infection triggers physiological pathways which cause fatigue (e.g. a virus stimulates T-cells to produce cytokines which lead to fatigue), b) an infection weakens an individual's capability to tolerate psychosocial stress, which brings about physiological decompensation, and c) an individual already fatigued succumbs to an infective agent, e.g. vitally exhausted subjects [31] show higher chlamydia- and cytomegalus-antibody titers in atherosclerotic plaques than non-exhausted subjects.

Immune systems disorders

A prolonged activated state of immune responses has been thought to cause CFS [32]. Low levels of natural killer cells have been observed in CFS, but the levels were not related to disease severity and outcome [33]. An elevated level of the enzyme R Nase L, which is thought to degrade viral RNA, has been observed in CFS-patients compared to healthy controls [34]. Higher levels of R Nase activity correlated with diminished health in CFS-subjects, and improvement with normalization of the level [35]. Cytokines (interleukins IL-1, IL-2, IL-6), tumour necrosis factor and interferons are released by cells activated by infective agents. Cytokines might cause fatigue. Altered delayed type hypersensitivity skin responses have been observed in CFS-subjects, but not uniformly [29]. Alteration of cytokine levels in serum and spinal fluid in CFS [36, 37] was observed.

The magnitude of these alterations in immunity appears to be minor, does not correlate with disease severity and is not associated with clinically significant consequences such as infection or malignancy [29].

Neuroendocrine abnormalities

In about one third of CFS-patients the hypothalamic-pituitary adrenal (HPA) axis is down-regulated centrally [38]. The neuro-hormone cortisol shows low levels. CFS-subjects have shown an increased adrenocortical sensitivity to ACTH and a blunted reaction to CRH. According to Cleare [39] an increased negative feedback and glucocorticoid receptor function is observed. ACTH and cortisol responses to various stimuli are lower. No specific dysfunctional pattern has been observed. The dysfunctions are probably of multifactorial origin. CFS-patients have a low prolactin-response to insulin-induced hypoglycemia [40]. Cortisol replacement has yielded equivocal symptomatic improvements [41, 42]. Administration of serotonin agonists has induced an elevated prolactin-response in CFS-subjects [43].

Autonomic activity

Hypotension with bradycardia or tachycardia upon vertical tilting has been observed in CFS-patients [44, 45]. Naschitz et al. [46] have observed in the head up tilting test a higher haemodynamic instability score in CFS (>–0.98) than in non-CFS groups (non-CFS fatigue, fibromyalgia, neurally mediated syncope, general anxiety disorder, familial Mediterranean fever, arterial hypertension, healthy controls).

Neuroimaging

Buchwald et al. [47] and Lange et al. [48] have observed areas of high signal in the white matter of the central nervous system with MRI in CFS-patients. Others [49] have found no differences compared to healthy subjects. Using SPECT-scans Schwartz et al. [50] have observed lower regional blood flow throughout the brain compared to healthy subjects. In a study of a twin with CFS and his healthy sibling no difference in perfusion has been observed [51]. According to Rosen et al. [23] the symptoms in hyperventilation are similar to those in CFS. In 100 consecutive CFS-patients the time course and the respiratory findings were characteristic of chronic habitual hyperventilation in 93 of them. Hypocapnia is a powerful cerebral vasoconstrictor. When the arterial pCO_2 has fallen by 2 mm Hg below normal, reduction in cerebral blood flow sets in. Hypoperfusion of the brain stem might therefore be attributable to hyperventilation [52]. Costa et al. [53] have argued that in hyperventilation blood flow reduction concerns the total brain and not specifically the brainstem.

Neuropsychological abnormalities

No objective failure of cognition has been found [54, 55]. De Luca et al. [56] and Grafman et al. [57] have observed minimal deficits in complex information processing. Afari and Buchwald summarized that a modest but significant deficit in information processing, impaired working memory and poor learning of information is found in CFS-subjects.

Exercise capacity and muscle function

Muscle function is normal [58]. Many CFS-patients are deconditioned due to passivity [59], and perform poorly in exercise [60]. They claim that exercise leads to a worsening of symptoms and

consequently they rest and avoid physical activity [61]. Increased lactic acid after exercise, reduced oxygen transport capacity and decreased number of muscle mitochondria are the result. In some studies they were comparable to sedentary control subjects [4]. Mc Cully et al. [62] found no deficit in blood flow or oxidative metabolism in 19 CFS-subjects compared to 11 normal controls. Blood flow was measured by Doppler ultrasound after ischemia and exercise. Muscle oxygen delivery rate was assessed by post-exercise and post-ischemia oxygen haem saturation.

Psychological processes able to contribute to CFS

Attribution

Patients with CFS seen in specialist clinics attribute their illness to organic factors. They refute the physician's notion that the illness might have a psychological background. They insist on more laboratory tests when the laboratory work-up has not shown an explanation of the illness [63, 64]. Patients who have joined a self-help group for CFS insist to a higher degree on an organic cause of CFS and are more resistant to therapy than other CFS-patients.

Perception

The idea has been put forward that CFS-patients register body processes more intensely than healthy people [65] and interpret them in a hypochondriacal manner [66].

Symptom Avoidance

CFS-patients convinced of an organic cause of their illness may start to avoid exercise, withdraw from activity and prefer to rest [60]. They show a poor prognosis [18].

Neutralisation of conflicts

According to Abbey and Garfinkel [67] patients with CFS solve a psychosocial conflict by neutralising it with an illness (i.e. CFS). The need to achieve in their job, in social activities, in their family and home, and to set high self-set goals leads to the threat of exhaustion. Compelled to achieve and threatened to give-up they "solve" this conflict by developing CFS, which relieves them and punishes them simultaneously. La belle indifférence shown by some CFS-patients while describing their suffering caused by their illness corresponds with this model, i.e. conversion. Moreover, conversion should be diagnosed based on positive criteria [68]. Taerk and Gnam [69] describe the therapy of two CFS-patients by means of a psychoanalytical approach. They stress the intimate relationship over time of fatigue symptoms to disturbance in object relationship, particularly within the transference, the improvement in symptoms when this relationship is seen and understood, and the importance of the patient-therapist bond as a facilitating medium for clinical improvement.

Weighing of the evidence

It has become obvious that no singular factor can explain the CFS.

Infection: Some cases develop after a viral infection, but in many no infection foreruns CFS. An individual suffers on the average from four to six viral infections per year, which augments the chance of co-occurrence of infection and CFS. Nevertheless correlations between infection and CFS are probable. Several studies [70] have shown that subjects under psychological stress are more prone to viral infections [31].

Immune reactions: In some CFS-patients immune parameters are deranged, but the aberrations do not correlate with intensity or duration of CFS [33]. In a number of cases no deviations of immune reactions were found. Note that these deviations are also found in humans after the loss of the spouse, divorce, depression, etc. [36].

Neuroendocrine abnormalities: In some but not more than a third of the CFS-subjects the HPA-axis is down-regulated [38]. Again it is remarkable that similar observations have been made in withdrawn patients during or before medical procedures.

Autonomous activity: Hypotensive reactions with compensatory tachycardia during tilt manoeuvres have been observed in CFS-patients [46]. In humans disappointed by important others bradycardia, tachycardia and sudden cardiac death (foremost in persons with coronary artery disease) have been noted. Hypotension has been observed in frightened persons unable to escape from the threatening situation. Again similar cardiovascular reactions are seen in CFS-patients and in subjects forced to withdraw [71].

Neuroimaging: Hypoperfusion of the brainstem has been noticed in CFS-subjects. According to Rosen et al. [23] most CFS-subjects hyperventilate. This might indicate that those subjects are caught in a struggle between fight-flight (overbreathing) and conservation-withdrawal (fatigue).

Neuropsychological abnormalities: Minimal deficits in complex information processing, impaired working memory and poor learning of information is found in some CFS-patients [4]. Similar observations can be made in depressed subjects. Clinically similar observations are common in individuals during conservation withdrawal episodes.

Exercise capacity and muscle function: No specific pattern typical for CFS has emerged [62]. The changes seen are subjective. In humans (infants, prisoner of war) in severe states of withdrawal a diminished muscle tone and a slumping of the body have been found. Again what is seen in CFS is similar to observations during conservation-withdrawal [73].

The ontogenetic development of the affect "fatigue"

Before developing a biopsychosocial model of CFS, the ontogenesis of the affect "fatigue" has to be elucidated. Without outlining the ontogenesis of the affect "fatigue", this affect cannot be conceptualised in the context of CFS with respect to the biological emergency reactions.

A baby, in the first days of his life, has been fed several hours ago. It begins to stir, to awake, to move and finally to cry. His physical homoeostasis is disturbed, he is hungry and thirsty. His mother reacts, changes his diapers and feeds him. We assume that the baby feels something like unpleasure, bodily sensations, impressions from his environment, including his mother, but only parts like dots of light, smells, touch, without any coherence. These feeding episodes are experienced repeatedly and the connections between partial impressions become more and more tied. Finally he carries within himself representations of his body, his affects and his environment.

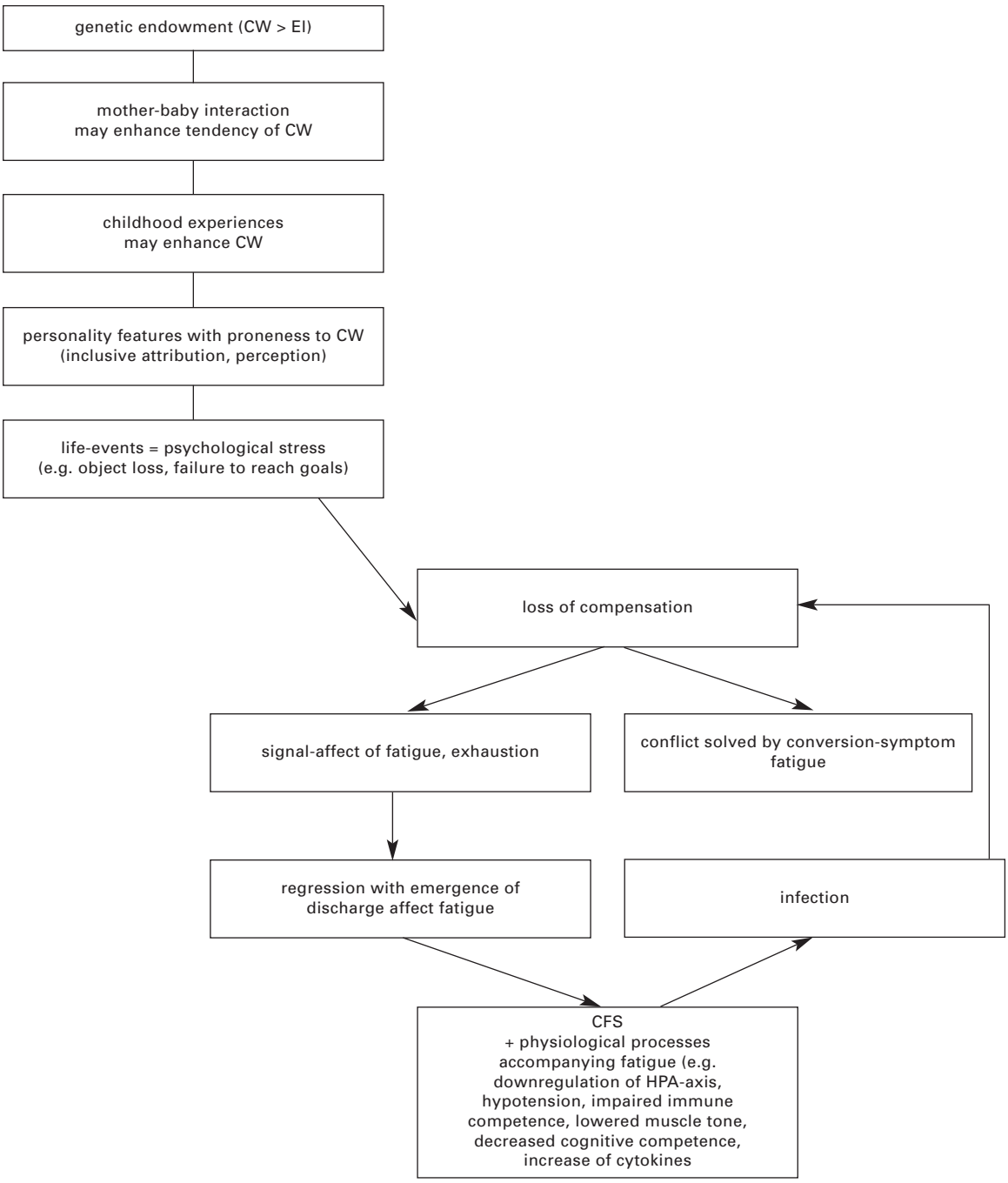


Figure 1

Genetic endowment determines proneness to engage or withdraw. Mother-baby interaction co-determine these tendencies. Childhood experiences may foster this proneness to fatigue and withdrawal. It may become ingrained in the personality make-up. In times of stress fatigue and exhaustion may be felt as "signed affects". If no solutions for dealing with the situation emerge, the affects, inclusive fatigue intensify, finally accompanied by physiological processes. Infection may directly disturb the psychological capacity to remain compensated under stress; infection may indirectly follow upon changes in physiological processes, e.g. immune function. CW = conservation withdrawal EI = Engagement-Involvement Psychological decompensation may become neutralised by the symptom-formation of fatigue as conversion-symptom.

The experience of the affect fatigue is imbued with experiences like being thirsty, crying, moving, having to wait, falling asleep, etc. At first the affect of being fatigued is experienced intensively with only a few associations (discharge affect), later the affect leads to the emergence of many associated experiences. Certain of these experiences evoke the feeling of fatigue, without triggering the whole gamut of sensations, images and physical actions related to it. The "discharge affect" of fatigue has developed into a "signal-affect" which indicates to the infant that if prolonged, the fatigue will become intensive and unpleasurable. The infant has also learned how to deal with the threatening affect-signal and to find realistic solutions, i.e. toddle to the kitchen and indicate to the mother his wish to get a drink.

The extent to which an individual finds suitable solutions to his problems depends on his genetic endowment – i.e. the tenacity to fight for something or to resign and withdraw –, on early experiences, on later experiences and the present social circumstances. The active engagement, involvement, has been designated by Cannon as the fight-flight reaction [72]. The resignation, disengagement, withdrawal and saving of energy in a hopeless situation, has been designated by Schmale and Engel [73] as the conservation-withdrawal reaction (CW). It is closely tied with the signal-affect of fatigue, and if no solution has been found, it is also tied with the discharge affect of fatigue and its mental and physical associations. The signal-affect may emerge long before the physical exhaustion. It is opposed to the signal-affect of fear. It indicates – contrary to fear, which stimulates action to be taken – that some actions have been performed too long, and that something has to be done to save energy. Fight-flight and conservation-withdrawal reactions are biological emergency systems. Early in life they are unpleasure-sensations, accompanied by physiological and biochemical processes; later they represent signals which make the subject aware that something has to be done or has been done excessively. The clinical presentation of fatigue depends on the level of development to which the affects refer, and which kind of experiences were related with fatigue during childhood.

Fatigue is characterized by lack of motivation, failing interest for relationships, lack of pleasure for activities, the desire to rest, to abstain from thinking, and heaviness and weakness. Fatigue may set in upon intellectual or physical exertions. Fatigue is felt as a disease, if it is present on intellectual or physical exertions, which were handled with ease formerly, if it sets in at uncommon times or if it does not lessen upon resting. According to former experiences and momentaneous evaluation of the situation it may set in earlier or later than the naive observer would expect. Life experiences which have induced trust, optimism and realistic expectations of oneself augment the threshold for reactions of fatigue, as do motivation and interest, while experiences of help- and hopelessness, too high expectations of achievement and failure to reach self-set goals lower it.

Physiological processes related to the conservation-withdrawal reaction.

The vasovagal syncope in its second phase, occurring in threatening situations without the possibility to escape, encompasses elements of conservation-withdrawal (CW): slowing of cardiac frequency, leading even to ventricular standstill. In the upper gastrointestinal tract, reduction of acid-production – including histamine-refractory achylia [75] and reduction of gastric mucosal blood-perfusion – and muscular activity have been observed. In the colon, hypotonia of the muscles and reduction of mucosal blood-perfusion have been noticed in periods of hopelessness and when feeling rejected. Reduced reactions of T-cells to mitogens have been observed after the loss of a spouse, and the loss of a job. A decrease in the number and activity of natural killer cells, and a change in the ratio of helper/suppressor T-cells have been seen after a divorce. In hopeless patients before cardiac surgery and during cardiac catheterism lowered levels of 17-0HCS in plasma have been observed [75].

Toward a biopsychosocial model of CFS

The genetic endowment determines if a baby is more prone to get involved with its environment and tenaciously attempts to reach its goal (e.g. try to get at the nipple) or if it is prone to give up relatively early. The mother-baby interaction co-determines if the baby remains involved or withdraws. At this stage of development we assume that the withdrawing, disengaging baby feels unpleasure imbued with the "discharge" affect fatigue. Childhood experiences then further co-decide an infant's proneness to remain involved tenaciously or to tend to give up and withdraw by disengaging.

These experiences contribute to the development of characteristic patterns of feeling, thinking and overt behaviour, which we may determine as character traits.

Certain character traits predispose to disengagement, withdrawal, fatigue and exhaustion in times of psychosocial stress, i.e. loss of a key-person, loss of a job, threat of physical disintegrity, loss of ideals, threat of not reaching high self-set goals, failure to remain independent, disappointment by important others. In general, the form of the response to stress is less a function of the particular stress than it is of the individual's basic personality structure; that is the more or less characteristic

modes of defence and coping with stress that have evolved out of the interaction between biological givens and environmental influences during development (Engel, unpublished manuscript).

Thus each personality type includes persons functioning relatively effectively and comfortably in everyday life (compensated), persons functioning with limitations but still getting along (marginally compensated), and persons who are disabled (decompensated). Many of the later CFS-victims have shown antedating psychological difficulties and belong to the marginally compensated group (s.2. CFS – a homogenous disease). Persons depending on key-figures, those who stress independence (high self-set goals) to ward off dependency needs, those living in symbiotic relationships, and those with depressive traits, are prone to feel fatigued under stress and withdraw.

At first fatigue and exhaustion are felt as signal-affects on and off. If the stressful situation prevails, the subject regresses (on his developmental axis), the affects grow more intensive and finally the physiological processes which accompany those affects emerge. Infection may contribute to decompensation and fatigue directly and indirectly: by liberating cytokines, by weakening psychological coping mechanisms, by being enhanced through psycho-physiological processes, i.e. impaired immune function. Fatigue may then be accompanied by down-regulation of the HPA-axis, hypotension, impaired immune function, decreased muscle tone, and weakness and exercise intolerance.

Fatigue might also take the form of a conversion-symptom, neutralising conflicts (e.g. about too high self-set goals and the wish to rest) (s. section 4). Cognitive processes may contribute to the heightened perception of the signal affect of fatigue, i.e. through attribution, perception and symptom avoidance.

The concept expressed here is similar with the conclusions of Afari and Buchwald [4], who stated that CFS is unlikely to be caused or maintained by a single agent. Findings to date suggest that physiological and psychological factors work together to predispose an individual to the illness and to precipitate and perpetuate the illness. The concept presented here encompasses the developmental steps involved and understands the illness as an expression of the biological emergency reaction "withdrawal-conservation", intermingled in some patients with features of the fight-flight pattern, e.g. hyperventilation.

A fatigued patient deserves to be thoroughly understood in his biopsychosocial development, his experiences contributing to his fatigue-proneness, his personality make-up with his vulnerability in times of psychological stress, in the dynamics of symptom-formation of fatigue, and finally in his illness-behaviour. Accordingly, the therapy can be tailored to the individual patient. We should keep in mind that the use of clichés like CFS, FM, IBS etc. serves mainly research and statistical purposes, but not the individual patient. Various treatments of CFS have been tried with little or no success. To date therapy encompasses conflict oriented psychotherapy, graded stepwise physical activation, and antidepressive drugs.

Correspondence:
Rolf Adler, MD
Professor of Medicine emeritus
University of Berne Medical School
Leiserenweg 4
CH-3122 Kehrsatz
Switzerland
E-Mai:l rolf.adler@tele2.ch

References

1 Briggs NC, Levine PH. A comparative review of systemic and neurological symptomatology in 12 outbreaks collectively described as chronic fatigue syndrome, epidemic neuromyasthenia and myalgic encephalomyelitis. Clin Infect Dis 1994;18 (suppl. 1):S32–S42.
2 Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LE, Straus SE, et al. Chronic Fatigue Syndrome: A working case definition. Ann Intern Med 1988;108:387–9.
3 Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121: 953–9.
4 Afari N, Buchwald D. Chronic fatigue syndrome: A review. Am J Psychiat 2003;160:221–36.
5 Goldenberg DL, Simms RW, Geiger A, Komaroff AL. High frequency of fibromyalgia in patients with chronic fatigue seen in a primary care practice. Arthritis Rheum 1990;33:381–7.
6 Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 1994;154:2049–53.
7 Pollet C, Natelson BH, Lange G, Tiersky L, Deluca J, Policastro T, et al. Medical evaluation of Persian Gulf veterans with fatigue and / or chemical sensitivity. J Med 1998;29:101–13.
8 Jason LA, Taylor RR, Kennedy CL. Chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivities in a community based sample of persons with chronic fatigue syndrome-like symptoms. Psychosom Med 2000;62:655–63.
9 Hudson JL, Goldenberg DL, Pope HG, Keck PE, Schlesinger L. Comorbidity of fibromyalgia wiht medical and psychiatric disorders. Am J Med 1992;92:363–7.
10 Ciccone DS, Natelson BH. Comorbid illness in women with chronic fatigue syndrome: A test of the single syndrome hypothesis. Psychosom Med 2003;65:268–75.
11 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936–9.
12 Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia and temporo-mandibular disorder. Arch Intern Med 2000; 160:221–7.
13 Moore KA, Blumenthal JA. Exercise training as an alternative treatment for depressions among older adults. Alternative Therapies in Health and Medicine 1988;4:48–56.
14 Kruesi MJP, Dale J, Straus SE. Psychiatric diganoses in patients who have chronic fatigue syndrome. J Clin Psychiatriy 1989; 50:53–6.

15 Hickie I, Hooker AW, Hadzi-Pavlovic D, Bennett RK, Wilson AJ, Iloyd AR. Fatigue in selected primary care settings: Sociodemographic and psychiatric correlates. Med J Aust 1996; 164:585–8.
16 Pawlikowska T, Chalder T, Heisch SR, Wallace P, Wright DJM, Wessely SC. Population based study of fatigue and psychological distress. BMJ 1994;308:763–6.
17 Hickie I, Iloyd A, Wakefield D, Parker G. The psychiatric status of patients with chronic fatigue syndrome. Brit J Psychiatry 1990;156:534–40.
18 Clark MR, Katon WJ. The relevance of psychiatric research on somatization to the concept of chronic fatigue syndrome. In: Strauss S et al., ed. Chronic fatigue syndrome, New York: Marcel Dekkker, 1994; 329–49.
19 Friedberg F, Jason LA. Chronic fatigue syndrome and fibromyalgia: clinical assessment and treatment. J Clin Psychology 2001;57:433–55.
20 Komaroff AL. Clinical presentation of chronic fatigue syndrome. Wiley, Chickester (Ciba Foundation Symposium) 1993; 43–61.
21 Walker EA, Roy Byrne PP, Katon WJ, Li L, Amos D, Iranek G. Psychiatric illness and irritable bowel syndrome: a comparison with inflammatory bowel disease. Am J Psychiat 1990;147: 1656–61.
22 Leserman J, Drossman DA, Toomy TC, Nackman G, Glogan L. Sexual and physical abuse history in gastroenterology practice: how type of abuse impact health status. Psychosom Med 1996;58:4–15.
23 Rosen SD, King JC, Wilkinson JB, Nixon PGF. Is chronic fatigue syndrome synonymous with effort-syndrome? J Royal Soc Med 1990:83:761–4.
24 Sargent W. Battle for the mind. London, Heinemann, 1957, 22–36.
25 Engel GL. Anxiety and depression-withdrawal: The primary affects of unpleasure. Internat J Psychoanalysis 1962;43:89–97.
26 Isaacs R. Chronic infective mononucleosis. Blood 1948;3: 858–61.
27 Evans AC. Chronic brucellosis. JAMA 1934;103:665–7.
28 Wessely S. The history of chronic fatigue syndrome. In: Straus SE, ed. Chronic fatigue syndrome, New York, Marcel Dekker, 1994; 3–44.
29 Iloyd AR, Hickie I, Peterson PK. Chronic fatigue syndrome: current concepts of pathogenesis and treatment. Curr Clin Top Infect Dis 1999;19:135–59.
30 White PD, Thomas JM, Amess J, Grover S, Kangro H, Clark A. The existence of a fatigue syndrome after glandular fever. Psychol Med 1995;25:907–16.
31 Appels A, Bar F, Bar J, Bruggeman C, de Baerts M. Inflammation, depression and coronary artery disease. Psychosom 2000; 62:601–5.
32 Straus SE, Dale JK, Wright R, Melcalfe DD. Allergy and the chronic fatigue syndrome. J Allerg Clin Immunol 1988;81: 791–5.
33 Whiteside TL, Friberg DL. Natural killer cells and natural killer cell activity in chronic fatigue syndrome. Am J Med 1998; 105:27–34.
34 Suhadolnik RJ, Reichenbach NL, Hitzges P, Sobal RW, Peterson DL, Henry B, et al. Upregulation of the 2–5A synthetase / R Nase L antiviral pathway associated with chronic fatigue syndrome. Clin Infective Dis 1994b;18(Suppl 1):96–104.
35 Suhadolnik RJ, Peterson DL, Cheng PR, Horvath SE, Reichenbach NL, O'Brien K, et al. Biochemical dysregulation of the 2–5A synthelase / R Nase L antiviral defense pathway in chronic fatigue syndrome. J Chron Fatigue Syndrome 1999;5: 223–42.
36 Straus SE, Dale JK, Peter JB, Dinarello CA. Circulating lymphokine levels in the chronic fatigue syndrome. J Infect Dis 1989;160:1085–86.
37 Cannon JG, Angel JB, Abod LW, Vannier E, Mileno MD, Fagioli L, et al. Interleukin-1, interleukin receptor antagonist and soluble interleukin-1 receptor type II secretion in chronic fatigue syndrome. J Clin Immunol 1997;17:253–61.
38 Demitrack MA, Crofford LJ Evidence for and pathophysiological implications of hypothalamic-pituitary-adrenal axis dys Regulation in fibromyalgia and chronic fatigue. Annals of the New York Academy of sciences 1998;840:684–97.
39 Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. Endocr Rev 2003;24:236–52.
40 Bearns J, Allain A, Coskeran P, Munro N, Butler J, Mc Gregor A, et al. Neuroendocrine responses to d-fenfluramine and insulin hypoglycemia in chronic fatigue syndrome. Biol Psychiat 1995;37:235–52.
41 Mc Kenzie R, 0'Fallon A, Dale J, Demitrack M, Sharma G, Deloria M, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome. JAMA 1998;280:1061–6.
42 Parker AJR, Wessely S, Cleare AJ. The neuroendocrinology of chronic fatigue syndrome and fibromyalgia. Psychol Med 2001;31:1331–45.
43 Cleare AJ, Bearn J, Allain T, Mc Gregor A, Wessely S, Murray RM, et al. Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. J Affect Disord 1995;35:283–9.
44 Soetekouw PM, Lenders JWM, Bleijenberg G, Thien T, van der Meer JWM. Autonomic function in patients with chronic fatigue syndrome. Clin Auton Res 1999;9:334–40.
45 Poole J, Herell R, Ashton S, Goldberg J, Buchwald D. Results of inoproterenol tilt table testing in monozygotic twins discordant for chronic fatigue syndrome. Arch Intern Med 2000;160: 3461–8.
46 Naschitz JE, Rosner I, Rosenbaum M, Naschitz S, Musafia-Priselac R, Shaviv N, et al. The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome. QJM 2003;96:133–42.
47 Buchwald D, Goldenberg DL, Sullivan JL, Komaroff AL. The "chronic" active Epstein-Barr virus infection syndrome and primary fibromyalgia. Arthritis Rheum 1987;30:1132–6.
48 Lange G, De Luca J, Maldjian JA, Lec HJ, Tiersky LA, Natelson BH. Brain MRI-abnormalities exist in a subset of patients with chronic fatigue syndrome. J Neuro Sci 1999;171:3–7.
49 Cope H, David AS. Neuroimaging in chronic fatigue syndrome. J Neurol Neurosurg Psychiatry 1996;60:471–3.
50 Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolcig FA, et al. Detection of intracranial abnormalities in patients with chronic fatigue syndrome. Nucl Med Commun 1992;13:767–72.
51 Lewis D, Mayberg F, Fischer M, Goldberg J, Ashlon S, Graham MM, et al. Monocygotic twins discordant for chronic fatigue syndrome; regional cerebral bood flow. SPECT Radiology 2001;219:766–73.
52 Nixon PGF. Brainsem perfusion in CFS. Q J Med 1995;89: 163–4.
53 Costa DC, Tannock C, BrostoffJ. Brain stem perfusion is impaired in patients with chronic fatigue syndrome. Quarteerly J Medicine, 1995;88:767–73.
54 Sheffers MK, Johnson R, Grafman J, et al. Attention and short-term memory in chronic fatigue syndrome patients: an event-related potential analysis. Neurology 1992;42:1667–75.
55 Schmaling KB, Di Clementi JB, Cullum CM, Jones JF. Cognitive functioning in chronic fatigue syndrome and depression: A preliminary comparison. Psychosom Med 1994;56:383–8.
56 De Luca J, Johnson SK, Natelson BH. Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. Arch Neurol 1993;50:301–4.
57 Grafman J, Schwartz V, Dale JK, Scheffers M, Houser C, Straus SE. Analysis of neuropsychological functioning in patients with chronic fatigue syndrome. J Neurol Neurosurg Psychiatry 1993;56:684–9.
58 Edwards RH, Gibson H, Clague JE, Helliwell T. Muscle histopathology and physiology in chronic fatigue syndrome. Ciba Found Symp 1993;173:102–17.
59 Salit B, Blomquist G, Mitchel JH. Response to exercise after bedrest and after training. Circulation 1968;38: – (5. Suppl) VII 1–78.
60 Sharpe M. Chronic fatigue syndrome. Consultation-Liaison Psychiatry. The psychiatric Clinics of North America 1996;19: 549–73.
61 Vercoulen JH, Swanink CM, Galama JM, Fennis JF, Jongen PJ. Hommes OR, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. J Psychosom Res 1998;45:507–17.
62 Mc Cully, Smith S, Rajaei S, Leigh JS, Natelson BH. Blood flow and muscle metabolism in chronic fatigue syndrome. Clin Sci (Lond) 2003;104:641–7.
63 Surawy C, Hackmann A, Hawton K, Sharpe M. Chronic fatigue syndrome: a cognitive approach. Behav Res Ther 1995;33: 535–44.
64 Wessely S, Powell R. Fatigue syndromes: a comparison of chronic "postviral" fatigue with neuromuscular and affective disorders. J Neurol Neurosurg Psychiatry 1989;52:940–8.
65 Barsky AJ, Goodson JD, Lane RS. The amplification of somatic symptoms. Psychosom Med 1988;50:510–9.
66 Mann P, Affleck G, Tennen H, Horse PA, Escobar JI. Hypochondriasis influences quality – of- life outcomes in patients with chronic fatigue. Psychother Psychosom 1996;65: 76–81.

67 Abbey SE, Garfinkel PE. Neurasthenia and chronic fatigue syndrome: the role of culture in the making of a diagnosis. Amer J Psychiat 1991;148:1638–46.
68 Engel GL. Conversion symptoms, in Signs and Symptoms, applied pathological physiology and clinical interpretation, 5th ed. Edited by CM MacBryde and RS Blacklow. Philadelphia, Lippincott, 1970, 650–68.
69 Taerk G, GNAM W. A psychodynamic view of the chronic fatigue syndrome. The role object relations in etiology and treatment. General Hosp Psychiatry 1994;16:319–25.
70 Totman R, Riff J, Reed SE, Craig JW. Predicting experimental colds in volunteers from different measures of recent life stress. J Psychosom Res 1980;24:155–63.
71 Engel GL. Fainting: Physiologic and psychological considerations. 2end ed. Springfield, Jll., Charles Thomas, 1962.
72 Cannon WB. Bodily changes in pain, hunger, fear and rage. Appleton. New York, 1929.
73 Schmale AH, Engel GL. The role of conservation- withdrawal in depressive reactions. In: Depression and human existence; ed. EJ Anthony and T Benedek. Boston, Little brown, pp 199–223, 1975.
74 Engel GL, Reichsman F, Segal HL. A study of an infant with a gastric fistula. I. Behavior and the rate of total hydrochloric acid secretion. Psychosom Med 1956;18:374–98.
75 Greene WA, Conron G, Schalch DS, Schreiner BF. Psychological correlates of growth hormone and adrenal secretory responses of patients undergoing cardiac catheterization. Psychosom Med 1970;32:599–614.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

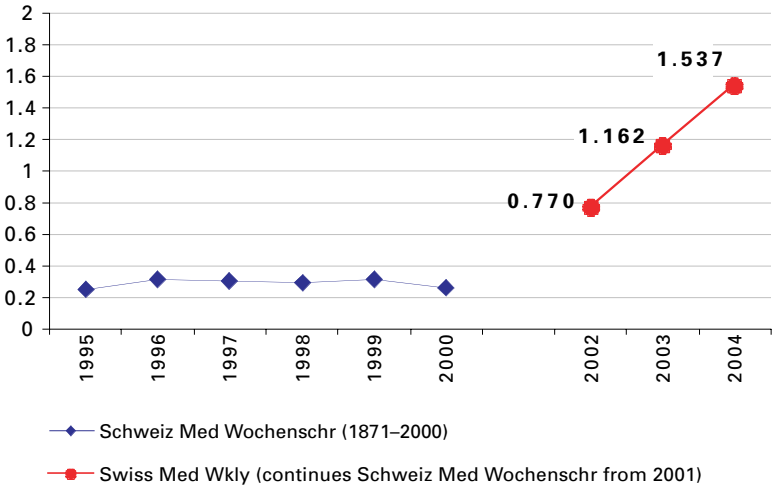
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch