Review Article

Chronic fatigue syndrome: A review

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ABSTRACT

Chronic fatigue syndrome is a disorder that is characterized by severe and debilitating fatigue of at least 6 months duration not explained on the basis of medical and psychiatric illnesses and has other associated characteristics. The disorder has a resemblance to many other disorders described in the past including myalgic encephalitis and post-infective fatigue; however, the term itself and the criteria for diagnosing this disorder were first laid out in 1988. The disorder has received attention from a wide range of clinicians and researchers. The mechanism of causation of this disorder has been poorly understood, though biological, psychological and social factors seem to play a role. The disorder causes significant impairment and is highly comorbid with other disorders. Non-pharmacological measures like graded exercise therapy and cognitive behavior therapy seem to work better for treatment than pharmacological measures. This narrative review takes an overview of chronic fatigue syndrome from a generalist standpoint and looks into the clinical features, etiopathogenesis and management of this disorder.

Keywords: Chronic fatigue syndrome, etiopathogenesis, myalgic encephalitis, management, review

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Introduction

Chronic fatigue syndrome (CFS) is a debilitating illness characterized by persistent and unexplained fatigue resulting in severe impairment in daily functioning. Although the term 'chronic fatigue syndrome' and the criteria for diagnosing the disease were introduced in 1988, illnesses with symptom profiles resembling this disease like neurasthenia, post infective fatigue, myalgic encephalitis, 'Raggedy Ann syndrome', Royal Free disease, etc have been reported for the past two centuries.[1]

CFS is encountered by general physicians, specialists like rheumatologists and other researchers like immunologists. Hence, knowledge of this disorder is useful for clinicians on the bedside and researchers on the bench. This paper attempts to provide a broad overview of CFS and issues pertaining to this disorder. Though excellent reviews are available relating to various nuances of CFS,[2-5] this review attempts to give a general perspective of CFS and incorporate the latest findings from research.

Before discussing CFS per se, it is relevant to understand the term fatigue. Fatigue has been described as weariness or exhaustion from labor, exertion, or stress. It has also been defined as a subjective feeling of tiredness or exhaustion or a need to rest because of lack of energy or strength.[6] Fatigue is distinct from weakness, which is a lack of physical or muscle strength and the feeling that extra effort is required to move arms, legs, or other muscles and thus weakness can be objectively measured.[6] Fatigue is a subjective feeling which cannot be measured, and hence is a symptom rather than a sign. Fatigue can be physical or mental or both. It may be temporary, prolonged (more than a month but less than 6 months) or chronic (lasting for 6 months or more).

Fatigue is a commonly experienced symptom, but not all patients with fatigue can be diagnosed as having CFS [Figure 1]. A proportion of patients with fatigue have chronic fatigue. A sub-proportion of these patients have idiopathic chronic fatigue, i.e. when there are no psychiatric or medical disorders to explain the chronic fatigue.[7] CFS comprises an even smaller part of these patients in whom fatigue is associated with other symptoms characteristic of the disorder. It should be remarked that chronic fatigue itself can be associated with other disorders like autoimmune, hematological, cardiovascular, renal, hepatic, infectious and neoplastic diseases.

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Evolution of the Concept of Chronic Fatigue Syndrome

As mentioned previously, illnesses resembling CFS have been reported since the 19th century. One such illness has been neurasthenia, which was described separately by George Beard, a neurologist, and Van Deusen, a psychiatrist.[8] Neurasthenia was defined as a condition of nervous exhaustion, characterized by undue fatigue on slightest exertion, both physical and mental, with which abnormal functioning of the nervous system were present. Several etiologies were studied, including neurological, social, and later psychogenic. Neurasthenia was accepted to a larger extent in the United States but found few takers among the medical fraternity in United Kingdom. Diagnosis of neurasthenia reduced with the use of psychoanalytic explanation of symptoms and the symptoms were considered a variant form of hysteria. Various infectious agents were named as causes of chronic fatigue. In the 1930s, chronic brucellosis was proposed to be a cause for chronic fatigue, but the concept aborted when no evidence of the organism was found in laboratory tests. Over time, many other infections had been implicated as causes of chronic fatigue like typhoid, encephalitis lethargica, yellow fever vaccine, schistosomiasis, St Louis encephalitis, Epstein Barr virus, varicella, Coxsackie B virus, human herpes virus-6, rubella immunisation, Lyme disease, hepatitis B vaccine, HTLV-2, Spumavirus, Rubella vaccine and Rickettsiae. Later, the concept of myalgic encephalitis emerged in the 1950s. Several outbreaks resulting in chronic fatigue with a plethora of other symptoms had occurred including the 'Royal Free disease'.[9] Terms like 'myalgic encephalomyelitis' were used to reinforce the organic etiology of the illness despite the lack of clear evidence of infection, and prominence of symptoms of emotional disturbance.

The appearance of 'Chronic Epstein Barr Virus syndrome' in the 1980s in the US paved the way for the description of CFS. An epidemic of fatigue at Lake Tahoe Nevada which was called as the 'Raggedy Ann syndrome' was initially thought to be caused by the Epstein Barr virus (EBV).[10] However, when no evidence for infection was found on laboratory tests done on the victims, an expert consensus coined the term 'Chronic Fatigue Syndrome' and gave the first set of diagnostic criteria for the same (Centers for disease control and prevention (CDC) criteria or the Holmes criteria).[11] This gave way to further research and defining of other criteria including the Fukuda criteria in 1994,[12] which is the most commonly used.

Clinical Aspects of Chronic Fatigue Syndrome

The Fukuda criteria of CFS are shown in Table 1. This is the most commonly used criteria used for research and diagnostic purposes. The other definition and criteria for diagnosis of CFS include Oxford Definition,[13] the Australian Definition,[14] the Canadian Definition[15] and NICE Guidelines Definition.[16] Of the definitions of CFS, the Fukuda criteria are the more restrictive one. The diagnosis seems to be empirically valid across a range of countries.[17]

The rates of fatigue as a symptom in the community ranges from 5% to about 20%[18-20] while that in the primary care setting in the range of 10% to 25%.[21-23] However, the prevalence rates of CFS in the community have been significantly lower in the range of 0.07% to 0.56% because of the restrictive criteria, and the requirement of presence of other symptoms.[22-26]

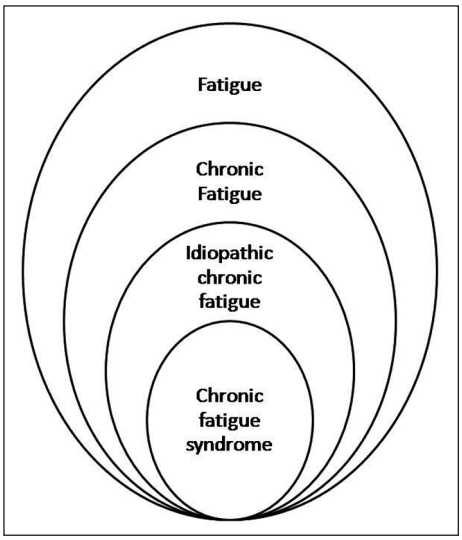

Figure 1: Patients with chronic fatigue syndrome

Table 1: Diagnostic criteria for chronic fatigue syndrome[5]

Chronic fatigue syndrome
CFS is clinically evaluated as unexplained, persistent, or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong). The fatigue is:
not the result of ongoing exertion
is not substantially alleviated by rest
and results in substantial reductions in previous levels of occupational, educational, social, or personal activities.
Four or more of the following symptoms should be concurrently present, and all must be persistent or recurrent during 6 or more months of the illness and not predate the fatigue:
Self-reported persistent or recurrent impairment in short-term memory or concentration severe enough to cause reductions in previous levels of occupational, educational, social, or personal activities
Sore throat
Tender cervical or axillary lymph nodes
Muscle pain
Multiple joint pain without joint swelling or redness
Headaches of a new type, pattern, or severity
Unrefreshing sleep
Postexertional malaise lasting more than 24 hours

The average age of onset of CFS has been found to be 30-40 years.[14,25] Women are affected more commonly than men and the disorder is more common among the lower classes.[25,27] Based upon the severity of symptoms of chronic fatigue symptoms, it can be categorized into mild, moderate and severe.[28] Patients with mild CFS are mobile, can care for themselves and can do light domestic tasks with some difficulty. Patients with moderate CFS have reduced mobility and are restricted in their activities of daily living. They may have peaks and troughs in their activity throughout the day. Patients with severe CFS are incapacitated and are able to do minimal tasks only.

Attempts had been made to differentiate the different phases of the disease. The four 'Fennell' phases[29-31] consist of crisis, stabilization, resolution and integration. In the phase of crisis, an individual enters into a state of emotional disturbance crisis after initial onset of illness. Stabilization involves continuation of emotional turmoil as the symptoms begin to stabilize. Resolution involves acceptance of the ambiguous and chronic nature of their illness, and construction of meaning out of the experience of the illness. Integration involves achievement of integration between the pre and the post illness states. The different coping strategies that have been observed in patients with CFS include maintenance of activity, reducing activity to accommodate to the illness, focusing on symptoms and information seeking.[32]

The studies on outcome of the patients with CFS suggest that the diagnosis remains stable in most cases.[33] It has been suggested that about half of the patients of CFS show some improvement, and about 30% continue to remain disabled.[34,35] Recovery rates of adult CFS have been shown in the range of 5%[33] but are better for children and adolescents.[36] Return to work ranges from 8% to 30% among the patients with CFS.[33] Mortality with CFS was rare. Some of the cases of CFS undergo transition to other medical illnesses like hypothyroidism, cancer, anemia, systemic lupus erythematosus and diabetes mellitus.[36]

Etiopathogenesis of Chronic Fatigue Syndrome

The question of causation of CFS has not been answered fully yet. Various themes of research have been carried out to understand the causation of CFS, both from biological and psycho-social standpoints. Table 2 mentions the purported risk and etiological factors of CFS.

Modest evidence from family and twin studies suggest that genetic factors may play a part in predisposing individuals to CFS. In a study, concordance for CFS was found to be 55% in monozygotic when compared to 20% in dizygotic twins.[37]

Table 2: Etiological and risk factors for chronic fatigue syndrome

Biological	Psychosocial
Genetic	Personality factors
Infections	Perceived stress
Neuroendocrine changes	Depression
Immunological changes	Catastrophizing
Neurophysiological changes	Life events
	Low self-efficacy
	Poor social supports
	Support groups for advocacy of the illness

Chronic infections with infectious agents like Epstein Barr virus, cytomegalovirus, Herpes virus, mycoplasma, etc have been proposed to be precipitating and perpetuating factors, but findings have been inconsistent. Links with xenotropic murine leukemia virus-related virus had been suggested[38] but the association failed to be replicated.

Immunological factors have been extensively studied in the genesis of CFS and enhanced Th2 (humoral) response with reduced Th1 (cellular) response has been a relatively consistent finding. Decreased natural killer cell function and correlation of the same with EBV reactivation has been found in some of the studies.[5,39] Abnormal activation of the T-lymphocyte subsets and a decrease in antibody-dependent cell-mediated cytotoxicity, increase in number of CD8+ cytotoxic T lymphocytes, reduced IFN-γ (inhibitory pathway) production by CD4+ cells and decreased CD11b expression and enhanced expression of CD28+ T subsets have also been found.[40] Reduced levels of serum immunoglobulin G (IgG) and higher frequencies of various autoantibodies have been proposed to be perpetuating factors. However, a systematic review of immunologically related studies concluded that there is no consistent pattern of immunological abnormalities in CFS patients, and a trend toward changes in T-cell activity was found.[5,39] There is a suggestion that instead of particular cytokine or cell type affected, the research should focus upon inter-relation and interaction of the immune parameters.[41]

Neuroimaging studies have revealed various findings like glucose hypometabolism in the frontal cortex and brain stem, with decreased number and or affinity for the receptor protein for serotonin in the hippocampus and decreased number and affinity for serotonin transporter proteins in the cingulate gyrus.[42,43] Neuroendocrine changes like low basal levels of cortisol in urine, plasma and saliva as well as blunted hypothalamic pituitary adrenal (HPA) axis response and disturbance of normal circadian rhythm of HPA activity have been reported.[44] Abnormalities of circulatory homeostasis like orthostatic intolerance with head-tilt test

and greater increases in heart rate, diastolic BP, mean BP, and total peripheral resistance index were found in patients with CFS.[45]

Psychological attributes like obsessional type of personality, action-proneness, childhood and adult neglect, abuse and maltreatment have been suggested to predispose to development of CFS.[46] Among the psycho-social factors, increased stress especially associated with dilemma has been related to CFS.[47] Illness beliefs have been found to play a significant role in progression of CFS. These can be related to attribution to the disease, significance given to the symptoms by the patient in the form of catastrophic thinking, and self efficacy to do things despite the problems.

Avoidance of activity, over-vigorous activity alternating with resting for long periods, symptom focusing, and disturbed sleep pattern have also been commonly seen in patients with CFS. Comorbid psychiatric disorders like generalized anxiety disorder, panic disorder, depression, cognitive impairments, personality traits like perfectionism and conscientiousness have also been found to worsen the prognosis of CFS. Social factors also play a crucial role in progression of CFS. Illness beliefs and coping behavior when influenced by a peer support group are related to a poorer outcome.[48]

It is unlikely that CFS is produced by any one etiological factor. A bio-psycho-social model may explain the genesis of CFS to a better extent than singling out specific etiologies [Figure 2].

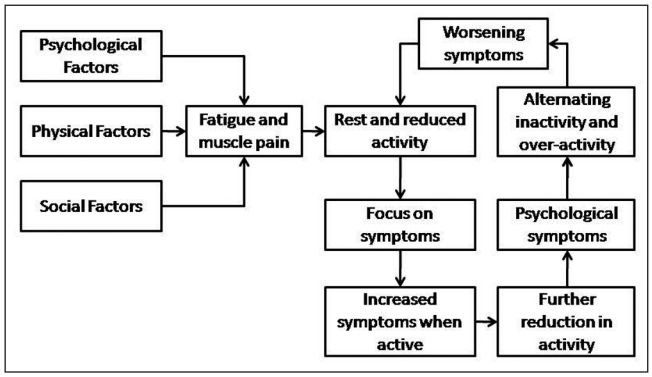

Figure 2: Chronic fatigue syndrome: etiopathogenesis

Table 3: Differential diagnosis of CFS

Physical disorders
Common: anemia, thyroid disorders, statins, sleep apnea
Occasional: chronic infections like HIV, hepatitis C, tuberculosis, endocarditis, osteomyelitis, Lyme disease, occult abscess, neoplastic disorders like lung cancer, leukemia, pulmonary conditions like asthma, obstructive lung disease, interstitial lung disease, symptomatic hyperparathyroidism, congestive cardiac failure, fibromyalgia
Infrequent: systemic lupus erythematosus, polymyositis, dermatomyositis, myopathy, myasthenia gravis, multiple sclerosis, narcolepsy, inflammatory bowel diseases
Psychiatric disorders
Depression, dysthymia, generalized anxiety disorder, somatoform disorder, dementia, protracted withdrawal from opiates

Differential Diagnosis and Work-up of Chronic Fatigue Syndrome

A wide array of differential diagnosis has been suggested for CFS, some of which have been listed in Table 3. As fatigue is a common symptom of various medical and psychiatric conditions, proper evaluation of the symptoms is necessary.

Fibromyalgia seems to share a lot of characteristics with CFS. Most patients who have received the diagnosis of fibromyalgia are also likely to meet the diagnostic criteria for CFS.[49,50] A latent class analysis of the symptoms of more than 600 patients of either diagnosis of fibromyalgia or CFS failed to identify separate syndromes.[51] Simplistically speaking, CFS can be considered as fatigue with pain while fibromyalgia is pain with fatigue.

Many functional somatic syndromes have been described by medical and surgical specialties which share some commonalities with CFS.[52] These have included irritable bowel syndrome and non-ulcerative dyspepsia encountered by gastroenterologists, non-cardiac chest pain and DaCosta's Syndrome seen by cardiologists, and fibromyalgia dealt with by rheumatologists, multiple chemical sensitivity encountered by allergy specialists and others.

There are no specific laboratory investigations to diagnose CFS. The diagnosis is thus based upon exclusion. In that respect, the diagnosis is more similar to a psychiatric disorder than a medical one, which is usually based upon a demonstrable and measurable abnormality. The extent and the battery of investigations suggested to exclude the other possible medical disorders remains a matter of prudent judgment. The CDC Guidelines[53] suggest a minimum of the following tests which should be in the normal range before a diagnosis of CFS is made: complete blood counts, electrolytes, fasting glucose, creatinine, calcium, phosphorus, thyroid function tests, urinalysis, anti-nuclear antibodies and rheumatoid factor, c-reactive protein, erythrocyte sedimentation rate, total protein, albumin, globulin, alanine aminotransferase and aspartate transaminase serum level, and alkaline phosphatase. However, undue hasty and excessive investigations are likely to yield more false positives than true positives as shown by the VAgue Medical Problems In REsearch (VAMPIRE) trial.[54] Unnecessary repeated investigations may result in additional diagnostic procedures, redundant medication, or

even referral to secondary care, hospitalization, and surgery leading to unfavorable additional effects like patient anxiety, somatization, high costs, iatrogenic somatic fixation, and the development of chronic illness behavior.

Comorbidity with Other Psychiatric Disorders

Studies suggest that many psychiatric disorders are commonly associated with CFS. Whether psychiatric conditions are a cause, consequence or coincidental overlap of symptoms has been rather debated. Overlap of symptoms between CFS and other psychiatric disorders throw an additional challenge in using diagnostic instruments and making reliable diagnoses.

Most patients with CFS meet criteria for a depression or an anxiety syndrome.[2,55] Those who do not fulfill diagnosis of anxiety or depressive disorder are likely to meet DSM criteria for a somatoform disorder or an ICD-10 diagnosis of neurasthenia. There are inherent difficulties in the diagnosing CFS with instruments used for psychiatric disorder, but Structured Clinical Interview for DSM-IV (SCID) has been considered more appropriate because of its open-ended nature.

Depression has been found to be commonly associated with CFS. There are certain similarities between CFS and depression, with fatigue being a core symptom of both. Other overlapping symptoms include cognitive dysfunction (impairment in attention/ concentration) and sleep disturbance. An international study of more than 5000 primary care patients found that 67% of the patients with chronic fatigue also had an ICD-10 diagnosis of depressive syndrome.[56,57] Studies of clinic attendees with CFS reported that more than 25% have a current DSM major depression diagnosis, and 50%-75% have a lifetime diagnosis of depression.[18]

High rates of depression in CFS has been postulated to be a result of many factors including overlapping symptoms between CFS and depression, a depressive emotional response to disabling fatigue, common viral or immune changes in both the conditions, as well as alterations in brain physiology. However, certain distinguishing factors have been suggested to differ between depression and CFS.[58] Symptoms such as sore throat, adenopathy, and arthralgias are not typically seen in depression, but are seen in CFS. Also, classic depressive symptoms of anhedonia, guilt, and lack of motivation are seen in depression but not seen in CFS. HPA axis down-regulation is seen is CFS while up-regulation is seen in depression.[59] Reduced REM latency and increased REM density which are typically seen in depression are not usually present in CFS.[60] Also, therapeutic doses of anti-depressants which help a large number of patients with depression are not quite helpful in patients with CFS.[61]

Elevated rates of other psychiatric disorders have been found in patients suffering from CFS. Higher rates of panic disorder and generalized anxiety disorder are found in patients with CFS than the general population.[55,62] The literature points to a significant overlap between CFS and anxiety disorders in symptomatology. Neurobiological similarities between CFS and generalized anxiety disorder have been observed including decreased cerebral blood flow, sympathetic overactivity, and sleep abnormalities.[2]

Due to similarity of symptoms it may be difficult to differentiate somatoform disorder from CFS.[63] The fatigue in somatoform disorder is suggested to be only physical, while it can be both physical and mental in CFS. Neurasthenia has been described as a disorder with either persistent and distressing complaints of increased fatigue after mental effort, or persistent and distressing complaints of bodily weakness and exhaustion after minimal effort; with the presence of other symptoms like muscular aches and pains, dizziness, tension headaches, sleep disturbance, inability to relax, irritability and dyspepsia.[64] Due to similarity of the symptoms, neurasthenia and CFS have been regarded as culture-bound counterparts of the same symptomatic experience.[65]

Management

Various guidelines are available for management of CFS.[15,53,66] All focus upon a thorough history, a meticulous physical examination, and a mental status examination. A minimum array of laboratory tests as necessary should be conducted to exclude other disorders. Attribution of symptoms to physical etiology may cause patients to expect many diagnostic tests, hence laboratory and imaging investigations should be ordered with restraint.

Initial management delves around forming a therapeutic relationship by acknowledging patient's symptoms, giving the diagnosis and explaining what it means, and what is currently known about the syndrome. General advice about fitness for work and education, and the adjustments needed for the same can be discussed with the patient.

Associated anxiety and depression in CFS can be treated using SSRIs (escitalopram, paroxetine, sertraline, fluoxetine) and SNRIs (venlafaxine, milnacipran). Pain symptoms can be treated using tricyclic antidepressants (imipramine, amitriptyline, nortriptyline), duloxetine or milnacipram. Associated sleep disturbances can be treated with benzodiazepines and non-benzodiazepine hypnotics like

trazodone. It should be emphasized that psychotropics like SSRIs by themselves do not improve chronic fatigue, nor does wakefulness promoting agents like modafinil.[67] A variety of pharmacological agents have been tried for the treatment of CFS[61,68] including fluoxetine, moclobemide, phenelzine, milnacipran, fludrocortisone, hydrocortisone, interferons, acyclovir, immunoglobulin G, amantadine, nutritional supplements, growth hormone, etc. One of the agents rintatolimod (a TLR-3 agonist) has shown promising results in relieving the fatigue of CFS.[69]

Psychotherapeutic measures seem to work better than pharmacotherapy for CFS. Among the various measures, cognitive behavior therapy (CBT), graded exercise therapy and adaptive pacing therapy have been more extensively studied.[70,71] CBT aims to address unhelpful cognitions, including fears about symptoms or activity by testing them with behavioral experiments. Collaboratively planned gradual increases in physical and mental activity are attempted, while anxious, unhelpful thoughts are replaced with new, more realistic, more helpful alternatives. Graded exercise therapy attempts to reverse physiological changes of de-conditioning and avoidance of activity associated with CFS and thereby reduces fatigue and disability. Establishment of a baseline of achievable exercise or physical activity, followed by negotiated increments in the duration of time spent physically active is attempted. Adaptive pacing therapy aims to achieve optimum adaptation to the illness, by helping the patient to plan and pace activity to reduce or avoid fatigue, achieve prioritized activities, and provide the best conditions for natural recovery. One of the largest non-pharmacological randomized trials of CFS (PACE trial) suggests the superiority of CBT and graded exercise over specialist medical care as well as adaptive pacing.[72]

Some variables and attributes of patients with CFS have been associated with poorer outcomes. These include socio-demographic factors like older age, poor social support, unemployed status, and claiming sickness/disability benefits.[33] Illness-related characteristics like higher fatigue severity at onset of illness, greater number of minor criteria fulfilled, and longer illness duration are related to poorer prognosis.[73] Psychological factors like attribution of symptoms to 'viral illness' or physical causation, subjective cognitive difficulty, low internal locus of control and comorbid dysthymia have been found to be associated with poorer outcome.[33]

Conclusions

Over time, attempt has been made to operationalize chronic fatigue syndrome (CFS). Different lines of etiopathogenesis has been suggested, however there is difficulty in replicating the studies and proving causality. Comorbidity of CFS with psychiatric illnesses is high and requires attention. Non-pharmacological interventions particularly CBT and graded exercise therapy seem to work better in the treatment of CFS.

In the future, a holistic and multidisciplinary approach to research and treatment of CFS is required. The etiopathogenesis needs to be studied with regard to the interplay of biological and psycho-social factors. Empirical research to differentiate from other psychiatric disorders, especially somatoform disorders based upon large community samples would be beneficial to establish discriminant validity. Lastly, awareness about the disorder needs to be increased in practicing clinicians.

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