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## *Chronic Fatigue Syndrome— A Challenge to Internists*

*PK Bhattacharya*

**Abstract:** Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue, with cognitive and musculoskeletal symptoms, with sleep disturbances. No specific diagnostic tests or biological markers exist for CFS and the diagnosis is clinical, based on the CDC criteria and after excluding other causes of fatigue.

The pathophysiology of the syndrome is still unclear. Current knowledge suggests that genetic, physiological, and psychological factors work together to predispose an individual to the condition and also to precipitate and perpetuate the illness. Additional evidence is emerging that CFS may be familial.

The dilemma for both patient and physician is that CFS has no pathognomonic features; its diagnosis is by exclusion, and treatment is symptomatic. Often, patients with CFS share features of other subjective disorders like fibromyalgia and irritable bowel syndrome.

Treatment of CFS should be multidisciplinary, symptom-based, and include pharmacological and behavioral strategies. Treatment should be individualized. Cognitive behavior therapy and graded exercise programs are the most effective tools in treating fatigue and in alleviating associated symptoms in some patients. Controlled therapeutic trials have established that anti-virals and immunomodulators are of little or no value. The disease is usually non progressive; many patients improve significantly and a few even fully recover. In children with CFS early therapeutic interventions should be made and the prognosis is usually better than in adults.

### **INTRODUCTION**

Fatigue is a common symptom in the community and up to one half of the general population reports fatigue in large surveys. Other studies have noted that fatigue is reported by 20-25% of patients seeking medical care.<sup>1-3</sup> This fatigue is usually transient, self limiting and can be explained by the prevailing circumstances or co-morbid conditions. But in a minority of persons this fatigue may be persistent and debilitating. When such fatigue cannot be explained by an underlying medical condition it may represent Chronic Fatigue Syndrome (CFS). This syndrome is not new, and in the past patients diagnosed to have various conditions like Myalgic Encephalomyelitis, Epidemic Neuromyasthenia, Post Viral fatigue Syndrome etc. might have been in fact suffering from what is currently called CFS.

### **DEFINITION**

Although there are several definitions of CFS, the most widely used definition is the 1994 revised definition by the US Centers for Disease Control and Prevention (CDC) (Table 49.1), that require 6 months of persistent fatigue substantially reducing the person's level of activity along with at least 4 out of 8 symptoms occurring with fatigue in the 6 months period.<sup>4</sup>

Medical conditions that may explain the prolonged fatigue and certain psychiatric disorders (e.g. eating disorders, psychotic disorders, bipolar disorders, melancholic depression and substance abuse within 2 years of onset of fatigue) exclude the diagnosis of CFS. Those not meeting the fatigue severity or symptom criteria can be diagnosed as Idiopathic Chronic Fatigue. Many non-psychotic psychiatric and overlapping disorders need not be excluded to make a diagnosis of CFS. Like psychiatric diagnosis, CFS is defined on basis of expert consensus, and its diagnosis is made on the basis of symptom criteria.

## **EPIDEMIOLOGY**

CFS is twice as common in females as compared to males and is found mainly in the age group 25-45 years. Using the current definition of CFS, the prevalence of the syndrome ranges from 0.007 to 2.8% in the general adult population, and from 0.006 to 3.0% in primary care or general practice;<sup>5</sup> CFS also occurs in children and in adolescents but the prevalence rate is less.<sup>6</sup>

## **PATHOGENESIS**

In spite of extensive research over the years the etiology of CFS is not clear. There have been many theories for the pathophysiology of the syndrome. Earlier theories suggested an acute viral illness or a psychiatric disorder. However, recent investigations have documented abnormalities in various other areas, including subtle abnormalities of the CNS, neuro-endocrine regulation, sleep architecture and chronic activation of the immune system, together with changes in exercise capacity or diverse psychological profiles.<sup>7</sup>

Recent investigations have focused on understanding the heritability of Chronic Fatigue and CFS. Evidence is emerging that CFS may be familial. Many investigators have postulated that CFS is a condition of complex and multifactorial etiology and that genetic, physiological, and psychological factors work together. Some of these elements may predispose an individual to develop CFS; others may precipitate the illness or still others may perpetuate the disorder.<sup>7,8</sup>

Recent data<sup>9</sup> suggests that disabling childhood illness and very little or no outdoor sports activity at about the age of 10 may act as predictors for the development of CFS in adults. Further it has also been observed that premorbid psychological distress in either mother or child did not predict the illness.

## **CLINICAL FEATURES**

CFS usually starts with unbearable exhaustion in a previously active person after a brief flu like illness or other acute stress. Other symptoms like headache, sore throat, tender lymph nodes, muscle and joint pain develop and persist for weeks, while other symptoms like sleep disturbance, depression, etc. gradually become evident. Most patients remain functionally active enough to carry out basic activities; however, a few may require help for daily living activities. Fortunately, CFS does not progress; many show gradual improvement and a few recover fully.

## **CLINICAL EVALUATION OF CFS AND OVERLAPPING CONDITIONS**

The symptoms of chronic fatigue and CFS itself, are often associated with other 'functional' illnesses such as fibromyalgia, multiple chemical sensitivities, irritable bowel syndrome, and temporomandibular joint disorder<sup>10</sup> (Fig. 49.1). CFS has been best studied in relation to fibromyalgia, a syndrome characterized by tender points and chronic diffuse body pain. Although the definitions of these two disorders are different, 20-70% of patients with fibromyalgia also meet the criteria for CFS and conversely, 35-70% of those with CFS-like illnesses have concurrent fibromyalgia.

The overlap in case definition, symptomatology, patient characteristics, and treatment strategies for these functional somatic syndromes, has led some workers to suggest that these

conditions are arbitrarily classified and should be considered as different manifestations of the same biomedical and psychosocial processes.<sup>11</sup> It is possible that variable expressions of a common pathophysiology may explain the extensive overlap among these conditions.<sup>12</sup> It is possible that research on the etiology of one of these conditions may help in the better understanding of other conditions. In the clinical setting, an appreciation of the coexistence of these disorders will help physicians as well as the patients to consider additional treatment options and achieve more satisfactory overall care (Fig. 49.2).

## **TREATMENT**

CFS does not have a clear etiology, there are many overlapping conditions associated with this syndrome and the diagnosis is mainly based on symptoms. Therefore, there are no definite and established treatment recommendations for CFS. Treatment must be individualized and should be built on a foundation of patient-physician respect and advocacy.

The patients should be informed about the illness, its potential impact upon different aspects of their lives, and its prognosis. Most of the symptoms of CFS respond to symptomatic treatment (Table 49.2). Periodic assessment is important to identify symptoms developing later in the course of the illness. In practice, therapy whether pharmacological or non-pharmacological has been generally directed toward relieving symptoms and improving function. Two recent works<sup>13,14</sup> summarize the findings of 44 controlled trials and case-control treatment studies with CFS diagnosed according to an established definition. These treatment studies have evaluated immunological substances, pharmacological products, nutritional supplements, physical therapies, and multidimensional treatments. With the exception of findings for physical and multidimensional treatments [i.e., behavioral interventions like cognitive behavior therapy (CBT) and graded aerobic exercise therapy], the results of these controlled treatment studies have been negative or inconclusive. It is, therefore, important to guide patients away from those therapeutic modalities that are too expensive, harmful and yet ineffective and unreasonable and to stick to treatment of symptoms as and when they arise, and behavioral interventions like CBT and graded aerobic exercise.

## **CHRONIC FATIGUE IN INDIA**

Chronic fatigue is common in developed countries and is strongly associated with psychological factors. In developing countries, fatigue in women is often attributed to anemia and nutritional deficiencies. A very recent study,<sup>15</sup> conducted in western India, found a prevalence of chronic fatigue in 12.1% of the 2494 women studied. They observed that psychological factors, notably symptoms of common mental disorders and somatoform disorders, and marital sexual violence were strongly associated with chronic fatigue. Low body mass index was associated with chronic fatigue, but anemia was not found to be associated with chronic fatigue as was reported earlier.

## **CHRONIC FATIGUE SYNDROME IN CHILDREN**

The management of CFS in children is somewhat different from the adult plan of management<sup>16</sup> (Table 49.3). The duration of disabling fatigue has been restricted to 3 months in children on the ground that prolonged fatigue in children needs identifying earlier because of greater sensitivity of children to the consequences from a developmental perspective.<sup>17</sup>

## **PROGNOSIS IN CHRONIC FATIGUE SYNDROME**

In tertiary care referral settings, 17 to 64% of patients with chronic fatigue syndrome show improvement, less than 10% fully recover, and another 10 to 20% worsen during follow-up. Outcomes in primary care settings have a substantially better prognosis. Prognosis is poorer with

older age, longer duration illness, severe fatigue, co-morbid psychiatric illness, and in those with a physical attribution for CFS. Conversely, children and adolescents appear to recover faster.<sup>13</sup>

## CONCLUSION

Diagnosis of chronic fatigue syndrome is mainly clinical, after excluding other causes of fatigue. The pathophysiology of the syndrome is still unclear, with abnormalities in different domains, suggesting that CFS is a heterogeneous condition of complex and multifactorial etiology. Additional evidence is emerging that CFS may be familial. Future studies will examine the extent to which genetic and environmental factors play a role in the development of CFS. Treatment is symptomatic and includes pharmacological and behavioral strategies with a multidisciplinary approach, when necessary. Cognitive behavior therapy and graded exercise programs are the most effective tools in treating fatigue in the majority of patients. In addition, one has to deal with co-morbid conditions such as major depression and sleep disturbances, reduce painful symptoms, and advise increasing activity, improve coping skills, and reduce catastrophic thinking, with the goal of improving the patient's level of functioning. CFS in children requires special care with early intervention as compared to adults. The greatest problem faced by both patient and physician alike is that CFS has no pathognomonic clinical features or laboratory test, no definite etiology and hence no specific treatment. Added to this, many patients with CFS share features of other subjective disorders like fibromyalgia and irritable bowel syndrome.

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