

CHRONIC FATIGUE SYNDROMEManabendra Nayak¹, P.C. Bhattacharyya²¹Postgraduate Teacher/Senior Consultant, Department of General Medicine, National Board of Examination, Down Town Hospital, Guwahati.²Formerly Professor and HOD/Senior Consultant, Academic Incharge, Department of General Medicine, Gauhati Medical College, Down Town Hospital, Guwahati.**ABSTRACT****BACKGROUND**

Chronic Fatigue Syndrome (CFS) is a complicated disorder characterized by extreme fatigue which worsens the physical or mental activity. Of all chronic illnesses, CFS is one of the most mysterious, unlike infections, it has no clear cause. The large majority of cases are said to occur between the age of 18 and 60 years, the mean age being 35 years. Cases are recognised all over the world. Most are sporadically found, but many clusters have also been reported. Chronic fatigue syndrome is a disorder of unknown etiology, which probably has an infectious basis with immunological manifestation. One or more viruses have been implicated as the cause of CFS excluding Epstein-Barr virus (EBV), but no causal relationship between any virus and CFS has been proven. It is now believed that CFS is not specific to one pathogenic agent but could be a state of chronic immune activation, possibly of polyclonal activity of B-lymphocytes, initiated by virus. Diagnostic imaging studies have also provided preliminary data to suggest that patients with CFS may have neurologic abnormalities. Magnetic resonance imaging has shown the presence of cerebral lesion in white matter, predominantly in frontal lobe. Patients with CFS presents with signs and symptoms similar to those of most common viral infections. The signs and symptoms of CFS can last for months or years. Since there is no known cure for CFS, treatment is supportive. Numerous clinical trials of pharmacologic agents have been conducted but no definitive therapeutic benefit has been identified. To date, no type of therapy has been shown to attenuate the cause of the disease. Instead, treatment protocol tends to focus on ameliorating the symptoms of the condition rather than seeking to cure the condition.

KEYWORDS

Chronic Fatigue Syndrome, CFS, Viruses.

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BACKGROUND

Chronic fatigue syndrome or CFS is a debilitating and complex illness that can be challenging to diagnose and treat. These challenges often leave both patients and health care professional locked in a cycle of frustration. Chronic fatigue syndrome (CFS) is a complicated disorder characterized by extreme fatigue that doesn't improve with bed rest and may worsen with physical or mental activity. According to the Center for Disease Control and Prevention (CDCP), Atlanta, USA, which has recently carried out research on this disorder, women are four times more likely to be CFS victims as also people in high stress jobs. Children and adolescents, according to the CDCP'S findings are also susceptible to the effects of CFS- with girls being more vulnerable than boys. Due to insufficient research, exact data about CFS in India is not available till date.

DEFINITION

The definition of CFS accepted by most research group is fatigue of new onset lasting more than six months with a 50% reduction in activity. There are a number of other characteristics which are frequently found in those diagnosed with condition but, unlike chronic fatigue, none of these characteristics are considered to be essential for the diagnosis to be made. In an effort to resolve this issue, an international panel of CFS research experts convened in 1994 to draft a definition of CFS that would be useful both to researchers studying the illness and to clinicians diagnosing it; a patient must satisfy following two criteria.^{1,2}

- Have severe chronic fatigue of six months or longer duration with no other known medical conditions excluded by clinical diagnosis, and
- Concurrently have four or more of the following symptoms: sore throat, substantial impairment in short term memory, concentration, muscle pain, tender lymph nodes, polyarthralgia without swelling or redness, headache of a new type, pattern or severity, unrefreshing sleep, and post exertional malaise lasting more than 24 hours.

EPIDEMIOLOGY- The large majority of cases are said to occur between the age of 18 and 60 years, the mean age being 35 years. Dowsett et al³ report that 75% of patients

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shown to have CFS were female. The female to male ratio reported in recent Australian study was 1.3:1.⁴ Cases are recognized all over the world.⁵ The popular perception that the condition is more prevalent in the middle and upper social classes is not substantiated by objective analysis. Lloyd et al found equal distribution across all social classes.⁴ Wallace likewise has found the prevalence of CFS to be about equally distributed across the social classes, with a slight over-representation in lower socio-economic groups.⁶ Community based studies revealed that 100 to 300 individuals per 1,00,000 population in the United States meet the current CDC case definition.⁶ There is a wide variation in the incidence of the disease with near universal acceptance that the prevalence of the condition is probably higher than reported. This is particularly so for epidemiological studies conducted using the original CDC criteria which exclude inclusion of suspected cases with psychiatric disease. To date, there have been no major studies reported to suggest an increased or decreased prevalence according to region or climate.

ETIOLOGY- Chronic fatigue syndrome is a disorder of unknown etiology, which probably has an infectious basis. The role of viruses as possible causative agents for CFS has been intensively studied, but no causal relationship between any virus and CFS has been proven. In particular, an early study⁷ reported that patients with CFS presented with symptoms similar to acute infectious mononucleosis and were found to have high titers of IgG antibodies to EBV. However subsequent research refuted a correlation between titer of EBV antibodies and severity of symptoms in CFS, and showed that patients with CFS did not have significantly higher titer to EBV compared with healthy control subjects.⁸ Elevated titers of various types are reported to be more frequent in CFS patients than in the general population and these agents play a role in the causation of CFS or its variant. Some studies show elevated titer of human T lymphocyte virus (HTLV), HTLV type II and human herpes virus type 6 in CFS patients.⁹ Although a number of virus-like Coxsackie virus, human herpes virus 6, Cytomegalovirus, measles, and HTLV II have also been implicated as etiologic agents of CFS, there is no consistent or conclusive data to suggest any causal relationship.¹⁰ It is now believed that CFS is not specific to one pathogenic agent but could be a state of chronic immune activation, possibly of polyclonal activity of B-lymphocytes, initiated by virus.¹¹ The implication of immune disorder in patients with CFS is supported by reports that lymphocyte markers including CD4 + cell counts and adhesion molecules may be increased in patients with CFS, these findings, however, have been inconsistent among studies.¹² In a recent study patients with CFS showed normal natural killer cell numbers but low natural killer activity. It suggested that this is a result of an inability to replenish activated natural killer cells.¹³ Evidence supports that CFS may be an illness mediated by the central nervous system. Magnetic resonance imaging has shown the presence of cerebral lesion in white matter, predominantly

in frontal lobe in some studies. Regional cerebral flow studies using single photon emission computed tomography analysis have shown impaired regional cerebral blood flow in patient with CFS compared with healthy control subjects.¹⁴

The relationship between psychiatric disease and chronic fatigue syndrome remain one of the most controversial etiological issues. A number of studies from the United Kingdom and United States suggested that patients were likely to have psychological disorder before the onset of CFS raising the possibility that CFS may occur in psychologically vulnerable individuals. A more recent study by Hick et al found that the premorbid incidence of major depression was 12.5% in those with CFS; a rate similar to estimates of major depression in the general community.¹⁵ Another recent study suggested that patients with CFS have a higher occurrence of allergies compared with normal population. Given the association between CFS and allergies, there is a strong possibility that allergies are essential to the pathology of CFS. Not only do the patients with CFS present with positive skin test to allergens, but they also have elevated levels of circulating eosinophilic cationic proteins compared with healthy subjects.¹⁶

Signs and Symptoms- Patients with CFS presents with signs and symptoms similar to those of most common viral infections. The signs and symptoms of CFS can last for months or years. Chronic fatigue syndrome has eight possible primary sign and symptoms.¹ These are-

- Unexplained muscle soreness.
- Sleep disturbance.
- Loss of memory or concentration.
- Painful and mildly enlarged lymph nodes on cervical regions or axilla
- Sore throat
- Extreme exhaustion after normal exercise or exertion.
- Headache of a new type, pattern or severity.
- Pain that move from one joint to another without swelling or redness.

Patients with CFS have presented with various other signs and symptoms that are not part of the official definition of CFS determined by the International Chronic Fatigue Syndrome Study Group. These symptoms may peak and become stable early. Some patients go on to recover completely, while others grow progressively worse. Most patients remain capable of meeting family, work or community obligation despite their symptoms, discretionary activities are abandoned first.

DIAGNOSIS

Diagnosing chronic fatigue syndrome can be challenging for physicians. A number of factors add to the complexity of making a CFS diagnosis:

- There is no diagnostic laboratory test for CFS,
- Fatigue and other symptoms of CFS are common to many illnesses,
- Many people with CFS do not look sick in spite of their profound disability,

- Symptoms vary from person to person in type, number and severity and
- Symptom may vary in an individual patient over time.

According to the International Chronic Fatigue Syndrome Study Group – a person meets the diagnostic criteria of CFS when unexplained persistent fatigue occurs for six months or more with at least four of the eight primary signs and symptoms being present. Holmes et al of CDC formulated the Diagnostic criteria for CFS, according to them for diagnosis, both major criteria must be present, plus the following minor criteria: (i) at least 6 of 11 symptoms and at least 2 of 3 physical signs or (ii) at least 8 of 11 symptoms.¹⁷

Major Criteria

1. New onset fatigue lasting longer than 6 months with a 50% reduction in activity.
2. No. other medical or psychiatric condition that could cause symptoms.

Minor Criteria

- A) Symptoms (must begin at or after the onset of fatigue)
 1. Low grade fever.
 2. Generalized muscle weakness.
 3. Sore throat.
 4. Myalgias.
 5. Painful cervical or axillary lymphadenopathy.
 6. Headache.
 7. Fatigue lasting 24 hours or more after moderate exercise.
 8. Migratory arthralgia.
 9. Sleep disturbance.
 10. Neuropsychological complaints (one or more of the following– photophobia, visual scotomas, forgetfulness, irritability, confusion, difficulty in concentrating, depression.)
- B) Physical signs-
 1. Low- grade fever.
 2. Pharyngitis (non-exudative.)
 3. Cervical or axillary lymphadenopathy.

Investigation

Medical investigation of patients suspected of having CFS has two main objectives. (1) Tests are used to exclude other fatigue causing diseases and (2) They may be helpful in making the diagnosis of CFS. Investigations should be limited and need not be extensive unless an individual patients history justifies it. Kroenke.¹⁸ recommends the following investigations to be done routinely: complete blood count, ESR, serum electrolytes, LFT and thyroid function tests. In CFS laboratory abnormalities are not specific except low ESR, which approaches zero. Typically patients with CFS have an ESR of 0 - 3 mm/h.¹⁹ If the ESR is elevated or even in the high normal range, another diagnosis is suggested. The WBC count in patients with CFS is normal. Leucopenia, leukocytosis, abnormal cell differential count indicates a diagnosis other than CFS. Thyroid, adrenal and liver function tests are useful in

excluding disorders that may have a fatigue component. Most patients with CFS usually have 2 or 3 of the following abnormalities.¹⁹

- Elevated IgM / IgG coxsackie virus B titer.
- Elevated IgM / IgG HHV – 6 titer.
- Elevated IgM / IgG titer.
- Decreased NK cells, either the present or their activity.

Sleep studies, radiological imaging and endoscopy should be limited to only those with the appropriate clinical symptoms. There would appear to be little justifications for performing test like CAT scanning, MRI, positron emission tomography, single photon emission computed tomography. Results of CT scans and MRI are normal in patients with CFS.¹⁹ Extensive immunological testing is not indicated on patients with CFS because it is neither diagnostic nor specific for CFS.

Treatment

Since there is no known cure for CFS, treatment is symptomatic. Numerous clinical trials of pharmacologic agents have been conducted but no definitive therapeutic benefit has been identified. To date, no type of therapy has been shown to attenuate the cause of the disease. Instead, treatment protocols tend to focus on ameliorating the symptoms of the condition rather than seeking to cure the condition. In general, treatment protocol should be directed at treating the major and disability symptoms. Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIS) are common therapy for patients with CFS. Tricyclic antidepressants have proven to be effective in reducing clinical depression and improving sleep patterns and are reportedly beneficial for patients with chronic fatigue. A recent investigation of nicotinamide adenine dinucleotide (NADH) therapy reported promising results, decreased adenosine triphosphate level, when alleviated by NADH therapy improves muscle atrophy and neuroendocrine abnormalities.²⁰

Several other treatment modalities are currently under investigation. These included antibiotics of any type, transfer factor (a low molecular weight protein extracted from donor leucocytes) interferons, interleukin-2 acyclovir, cyclophosphamide, azathioprine, corticosteroids, vitamins, special diets, treatments aimed to eliminate candida and other fungal infections, herbal remedies, acupuncture, homeopathy, aromatherapy, reflexology, colonic irrigations and a number of other alternative medical therapies.²¹

Cognitive behavioural therapy is helpful for the patients suffering from CFS. It helps patients to cope with their illness and change perceptions and behaviours that can contribute to symptom expression, it can also improve fatigue and activity levels along with their quality of life. Other psychological treatments such as support group and a positive doctor–patient relationship have proven to be beneficial in the long term management of CFS.²² The role of exercise in treating patients with CFS has recently been emphasized. Carefully supervised physical therapy may also

be part of treatment for CFS. However, symptoms can be exacerbated by ambitious physical activity. A very moderate approach to exercise and activity management is recommended to avoid over activity and to prevent deconditioning. Alternative therapy like deep breathing, muscle relaxation techniques, massage and healing touch and movement therapies like stretching, yoga can be beneficial for some CFS patients in reducing anxiety and feeling of good. Studies have reported the use of supplements including oral NADH, high doses of vitamin B₁₂, essential fatty acid, vitamin- C and coenzyme Q 10 in patient with CFS. These studies show inconsistent results but symptom improvement was reported in some subjects. Multidisciplinary intervention, consisting of medical, psychiatric, behavioural, and psychological evaluations and therapy has been demonstrated to be effective at restoring gainful employment and improvement of patients overall condition.²²

Indian Scenario-

Disorders of fatigue are important in clinical practice but inadequately studied in developing countries including India. Questions about their consistency and variation across cultures also require attention. The standard professional diagnostic formulation of disorders for chronic fatigue syndrome is not used widely in India, perhaps due to lack of research and poor appreciation of their clinical significance. There has been dramatic upward spiral in the number of CFS cases in India over the last decade, and CSF is a life style – linked disorder. However, sociologists²¹ fill that women are also more prone to CFS because of the changing dynamics of the Indian family, and may be one of the reasons for them succumbing to CFS– says one researcher of Delhi University.²¹

Prognosis-

The course of CFS is highly variable, depending on the severity of the condition and the premorbid state of the patients. CFS affects each individual differently. Some patients with CFS remain homebound and others improve to the point that they can resume work and other activities. Recovery rates for CFS are unclear. Improvement rates varied from 8% to 6% in a 2005 review of published studies, with a median of 40% of patients improving during follow-up.

CONCLUSION

Future technologic advances in neuroimaging, genotype profiling, immune assays and pharmaco therapy may bring greater consistency to scientific research and possibility of improved therapy for people suffering from chronic fatigue syndrome.

REFERENCES

[1] Dowsett EG, Ramsay AM, McCartney RA, et al. Myalgic encephalomyelitis – a persistent enteroviral infection? *Postgraduate Med J* 1990;66(777):526-530.

- [2] Lloyd AR, Hickie I, Boughton CR, et al. Prevalence of chronic fatigue syndrome in an Australian population. *Medical Journal of Australia* 1990;153(9):522-528.
- [3] Wallace PG. Epidemiology: a critical review. *British Medical Bulletin* 1991;47(4):942-951.
- [4] Grant P. Chronic fatigue syndrome. *Clinical Med Au* 2003;1:62.
- [5] Jones JF, Ray CG, Minnich LL, et al. Evidence for active Epstein-Barr virus infection in patients with persistent, unexplained illnesses: elevated anti-early antigen antibodies. *Ann Intern Med* 1985;102(1):1-7.
- [6] Linde A, Andersson B, Svenson B, et al. Serum levels of lymphokines and soluble cellular receptors in primary Epstein-Barr virus infection and in patients with chronic fatigue Syndrome. *J Infect Dis* 1992;165(6):994-1000.
- [7] Gow JW, Behan WMH, Simpson K, et al. Studies on enterovirus in patients with chronic fatigue syndrome. *Clin Infect Dis* 1994;18(Suppl5):126-129.
- [8] Craig TDU, Kakumanu S. Chronic fatigue syndrome: evaluation and treatment. *American Family Physician* 2002;1:13.
- [9] Gupta S, Vayuregula B. A comprehensive immunological analysis in chronic fatigue syndrome. *Scand J Immunol* 1991;33(3):319-27.
- [10] Whiteside TL, Friberg D. Natural killer cells and natural killer cell activity in chronic fatigue syndrome. *Am J Med* 1998;105(3A):S27-S34.
- [11] Lange G, Wang S, Deluca J, et al. Neuroimaging in chronic fatigue syndrome. *Am J Med* 1998;105(3A):S50 -S53.
- [12] Hickie L, Lloyd A, Wakefield D, et al. The psychiatric status of patients with chronic fatigue syndrome. *British Journal of Psychiatry* 1990;156:534-540.
- [13] Conti F, Magrini L, Priori R, et al. Eosinophil cationic protein serum levels and allergy in chronic fatigue syndrome. *Allergy* 1996;51(2):124-127.
- [14] Holes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Annals of Internal Med* 1988;108(3):387-389.
- [15] Kroenke K, Mangendorff AD. Common symptoms in ambulatory care: incidence, evaluation, therapy and outcome. *Am J Med* 1989;86(3):262-266.
- [16] Culb BA. Chronic fatigue syndrome. *Medicine from wed MD*. 2006:1-18.
- [17] Forsyth LM, Preuss HG, MacDowell AL, et al. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 1999;82(2):185-191.
- [18] McBride SJ, McCluskey DR. Treatment of Chronic fatigue syndrome. *British Medical Bulletin* 1991;47(4):895-907.
- [19] Sharpe M. Cognitive behavior therapy for chronic fatigue syndrome: efficacy and implications. *Am J Med* 1998;105(3A):S104-S109.
- [20] Goshorn RK. Chronic fatigue syndrome: a review for clinicians. *Semin Neurol* 1998;18(2):237-242.

[21] Pralika V, Agashe M. Prevalence of clinically significant functional fatigue or weakness in specialty outpatient clinics of Pune, India. J Clin Med 2009;4:24-32.

[22] Lal N. The Chronic Fatigue Syndrome. J Soci Med 2007;14-27.