Chapter 160
Chronic Fatigue Syndrome: A Review

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INTRODUCTION
Chronic fatigue syndrome (CFS) is essentially a very debilitating disease that can cause persistent fatigue leading to deterioration of productive activity of the sufferer along with loss of quality of life, mental peace and happiness. It can pose a very serious threat to health.

Fatigue, even persistent fatigue, can be a common symptom of many medical conditions, but CFS is remarkably different from these conditions in many aspects. The most important being the severity of persistent fatigue with a sudden onset that is precipitated but not relieved by rest and the absence of any other fatigue producing medical condition. This CFS has been recognized as an independent clinical entity.

There had been different attempts to define this medical condition. Notable among these are the Oxford criteria (1991), the Canadian Clinical working definition (2003) and the most commonly used the United States Centers for Disease Control and Prevention (CDC) definition (1994). This is also called Fukuda definition and it is based on a scoring system originally propounded by Holmes in 1988 where besides fatigue four more symptoms out of a list of eight needs to be present. As this is the most widely used criteria both for clinical diagnosis and medical research we shall be using it in the present discussion.

There is still no unanimity regarding nomenclature of this condition and within the broad ambit of CFS several different subsets are sought to be described depending on prevalence of this or that characteristics. We can at best say that our knowledge and understanding of this condition is still in the process of evolution and it will require some time to reach unanimity.

HISTORY
The disease has a fascinating history. In 1934, there was an outbreak of fatigue disease affecting large numbers of doctors and nurses of Los Angeles County Hospital which was very similar to CFS. It was then called atypical poliomyelitis. A similar outbreak in Royal Free Hospital, United Kingdom in 1955 was named Royal Free disease or benign myalgic encephalomyelitis. Symptomatically, these were considered as prototypes of CFS. The name CFS was first used in 1987 to describe a condition similar to chronic active Epstein-Barr virus (EBV) infection but without any evidence of EBV infection and in 1988 CFS was recognized as a disease entity.

INCIDENCE
Though fatigue as a result of various medical conditions may be quite widespread—almost daily encountered by a busy physician, CFS, however, is not that common. It is quite rare. One million Americans and a quarter million of British are said to be suffering from CFS. Some have estimated the prevalence to be 7 cases per 100,000 whereas some think it is much more prevalent—up to 3% which obviously is an unrealistic figure. The various figures of prevalence suffer from a selection bias. Women are said to be more affected then man. There are no real population-based studies available from India that can give a picture of actual prevalence of this condition in the population. What early studies we get from India (Goa particularly) tries to grapple with the problem of trying to find a prototype an Indian female patient suffering from CFS (with some success) (Source: Chronic fatigue in developing countries: population based survey of women in India. BMJ. 2005;330:1190.). Beyond saying that it is a condition being increasingly recognized by Indian doctors any estimation about its prevalence in our country would be pure guesswork at the present.

It will not possibly be incorrect to say that serious clinical search and research on CFS has started in India in the last decade only.

NO CONSENSUS ON NOMENCLATURE
Internationally, there is yet no consensus regarding nomenclature of this disease condition. The commonly used name is CFS (Source: J Intern Med. 245.). Other names that are proposed by different groups at different times are:

- Myalgic encephalomyelitis (ME)
- Post-viral fatigue syndrome (PVFS)
- Akureyri disease
- Benign myalgic encephalomyelitis
- Chronic fatigue immune dysfunction syndrome
- Chronic infectious mononucleosis.

In the United Kingdom to effect a compromise between the two major groups a compromise was reached to call this condition as CFS/ME whether this compromise effort has a sound scientific basis and whether it will hold; only time can tell. It will possibly be simple to use the name CFS only because a name need not always reflect the pathogenesis hypothesis.

CLINICAL SPECTRUM

Risk Factors
Statistically, many factors have been associated with increased risk of development of CFS. Though all ethnic and racial groups are susceptible to CFS, in the United States of America, it was seen that African and Native Americans have a significantly higher risk than whites. Though females outnumber males by 3:2 in CFS it has been...
General

said that the incidence in males may be underreported. The most common age group when CFS manifest is from 40 years to 59 years and it is much less prevalent amongst children and adolescents compared to adults. Blood relatives of CFS patients have been found to be more prone to develop it. Though a familial and genetic predisposition is suspected, it will require further definitive data for confirmation. Risk factors of CFS till now are statistical association, their predictive value is yet uncertain.

Onset

The onset of the condition is usually sudden. This means that the main symptom of fatigue (along with other symptoms) may appear only from a particular point of time before which they did not exist. The onset is usually preceded or accompanied by a "flu-like" disease, quite similar to a common cold or viral infection. This has promoted the association of virus and viral infection with the etiopathogenesis of the disease with the postulation that such viral infections somehow cause meningoencephalitis resulting in CFS. Both pathogenic as well as nonpathogenic viruses are sought to be associated with the etiopathogenesis of the disease.

In some cases, the onset of the disease follows a prolonged period of adverse stress. The period of stress may be of several months duration and this stress can be either physical or mental, or both. Some authorities consider these as precipitating factors whereas some consider them as actiological factors.

Fatigue

The main symptom is fatigue or exhaustion. The fatigue is always of new onset which means that it was not present to any significant degree in the past. The duration of the fatigue is prolonged and to qualify as CFS it must be of more than 6 months duration.

The fatigue is usually unexplained. It cannot be attributed to any known or immediate cause. It is not directly related to exertion. It is not as a result of physical exertion, but physical exertion always exacerbates it.

It is not significantly relieved by rest unlike the usual fatigue that follows exertion.

The level of fatigue is such that it causes significant reduction of previous activity levels of the person.

Chronic unexplained fatigue unrelieved by rest that incapacitates the patient is the hallmark of CFS.

Additional Symptoms

Various additional symptoms can also accompany CFS in various combinations. The commonest symptoms being impaired memory or concentration, postexertional malaise (PEM), unrefreshing sleep, myalgia, arthralgia, headache of new kind or of greater severity, frequent sore throat and tender cervical or axillary lymph nodes.

The above mentioned symptoms are included in CDC diagnostic criteria.

Other Symptoms

Certain other symptoms which are rare can also occur in CFS. Some of these are quite varied in nature:

- Difficulty maintaining upright position (orthostatic instability), irregular heartbeat, dizziness, balance problems or fainting
- Psychological problems (depression, irritability, mood swings, anxiety, panic attacks)

Diagnostic Criteria

To make a clinical diagnosis of CFS, various diagnostic criteria have been put forward. Out of these, the most commonly used diagnostic criteria is the United States CDC criteria. This criteria is also extensively used for research purpose. This is also called Fukuda definition and is based on Holman 1988 scoring system.

The recommendation of CDC is that to qualify as CFS the following three criteria has to be fulfilled.

1. The first criteria is fatigue, second is reduction of physical activity. The third criteria consists of a list of eight symptoms out of which four or more symptoms have to be present for more than 6 months or more.

The CDC Diagnostic Criteria

1. Fatigue: A new onset (not lifelong) of severe fatigue for 6 consecutive months or greater duration which is unrelated to exertion, is not substantially relieved by rest, and is not a result of other medical conditions.
2. The reduction of physical activity: The fatigue causes a significant reduction of previous activity levels.
3. Four or more of the following symptoms that last 6 months or longer:
   - Impaired memory or concentration
   - Postexertional malaise, where physical or mental exertions bring on “extreme, prolonged exhaustion and sickness”
   - Unrefreshing sleep
   - Muscle pain (myalgia)
   - Pain in multiple joints (arthralgia)
   - Headaches of a new kind or greater severity
   - Sore throat, frequent or recurring
   - Tender lymph nodes (cervical or axillary)

There is a tussle between physician and psychiatrist as to whose domain this particular clinical entity CFS should belong. As there is large psychological element to CFS manifested by significant depression, anxiety, mood swings, etc. Psychiatrists claim that this basically is a psychological disease.

In addition to above, two other aspects also need our attention:

1. Decrease of cognitive functions: There is marked impairment and decrease of cognitive functions in a significant number of cases of CFS. Decreased attention, memory and reaction time are impaired and the level of impairment may affect day-to-day activities. Both simple and complex information processing faculty and its speed may be significantly affected over long periods of time. On the other hand, patient’s perceptual abilities, motor component of speech, language, reasoning and intelligence are not significantly altered.

2. Functional ability impairment: Patients suffering from CFS exhibit impairment of functional ability. In a significant number of them, there is critical reduction of physical activity. This reduction of physical activity in CFS is much more marked in CSF compared to other fatigue producing conditions such as rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), lupus, chronic renal failure (CRF) and late stage acquired immunodeficiency syndrome (AIDS). Along with reduction of physical activity and functional status in CFS the well-being is also much more affected, sometimes even more so than multiple sclerosis (MS), chronic cardiac failure (CCF) and type II diabetes mellitus (DM). The impairment of functional status of patients spread over a wide spectrum with some patients able to lead
normal life while some patients become entirely bed ridden and incapable of self care. Both genders show nearly equal impairment. Work capacity for the employed patients also greatly varies. About 66% are limited in their work. Sick leaves, prolonged disability leave and benefits are much more in this group. Only about 20% of the patients can work in their job full time. This depends on the nature of jobs they do.

**PATHOPHYSIOLOGY**

Pathophysiology of CFS is largely unknown at the present moment. There are no diagnostic laboratory tests for CFS. In fact, no abnormal lab findings characteristic of CFS has been identified so far. There are number of hypotheses which try to explain the pathogenesis of the disease. Broadly these fall into two categories (Table 1).

Evidence of viral infection with cause and effect relationship has not been found in CFS so far. Similar is the case of bacterial infection. But that an inflammatory (may not be infective or postinfective) condition exists along with CFS has been surmised from such findings as arthralgia, myalgia, flu-like prodrome and tender lymphadenopathy.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Diagnosis of CFS is always by a process of exclusion. All conditions that can account for such severe fatigue must be excluded first and only when these conditions are excluded can a diagnosis of CFS be made. The common conditions that need exclusion included in the Table 2.

From the above list it is clear that diagnosis of CFS without any specific laboratory and pathological finding and diagnostic test is essentially one of exclusion. As CFS as an independent disease entity has been recognized quite late there is also a lack of awareness among the doctors about this condition. Consequently, many patients have been not reported. The laborious process of exclusion and the need to follow a rigid criteria has also contributed to this situation. Awareness among doctors is still low about his disease.

### TABLE 1 | Hypotheses to explain the pathogenesis of chronic fatigue syndrome

<table>
<thead>
<tr>
<th>Category I</th>
<th>Category II</th>
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</thead>
<tbody>
<tr>
<td>• Biomedical abnormality</td>
<td>• Hypothalamic pituitary adrenal axis abnormality</td>
</tr>
<tr>
<td>• Oxidative stress</td>
<td>• Psychological factors</td>
</tr>
<tr>
<td>• Genetic predisposition</td>
<td>• Psychosocial factors</td>
</tr>
<tr>
<td>• Infection by viruses both pathogenic and nonpathogenic</td>
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<tr>
<td>• Infection by bacteria</td>
<td></td>
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<tr>
<td>• Immune dysfunction</td>
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</tbody>
</table>

### Table 2 | Common conditions that need exclusion: Diagnosis of chronic fatigue syndrome

<table>
<thead>
<tr>
<th>Medical conditions</th>
<th>Psychiatric conditions</th>
<th>Other conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic obstructive pulmonary disease</td>
<td>• Major depression</td>
<td>• Alcohol abuse</td>
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<tr>
<td>• End-stage renal disease (CRF)</td>
<td>• Schizophrenia</td>
<td>• Substance abuse</td>
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<tr>
<td>• Systemic lupus erythematosus</td>
<td>• Bipolar disorders</td>
<td>• Morbid obesity</td>
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<tr>
<td>• Rheumatoid arthritis</td>
<td>• Anorexia nervosa</td>
<td></td>
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<tr>
<td>• Multiple sclerosis</td>
<td>• Bulimia</td>
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<tr>
<td>• Chronic renal failure</td>
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<tr>
<td>• Type II diabetes mellitus</td>
<td></td>
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<tr>
<td>• Hypothyroidism</td>
<td></td>
<td></td>
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<tr>
<td>• Anemia</td>
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**MANAGEMENT**

The management of this condition is quite laborious and takes a long time. While some of the patients respond quite well with improvement of fatigue and functional ability, in many cases the results of treatment are not satisfying. In some the progressive downhill course of the disease can be arrested to certain extent. Medication plays almost negligible role in the overall management scheme except for sedatives and tranquilizers.

Various modalities of treatments have evolved to treat this condition, some of which are quite unconventional and involve use of herbs and other remedies. Over the time three main forms of treatment have emerged. A brief discussion is given below:

1. **Cognitive behavioral therapy (CBT):** This is basically a psychological therapy. It has been used to treat chronically ill patients. The mainstay of treatment is to help patients to understand their symptoms and the disease and to help evolve strategies to improve day-to-day functioning. It also aims to dispel wrong impressions and beliefs that may perpetuate the disease.

   This form of therapy may be quite useful in some patients when used alone. But sometimes this therapy is used in combination with other forms of treatment modalities. This may prove beneficial in some care. A meta-analysis of trials “carried out in 2010 showed that though CBT can decrease fatigue significantly the activity level remains unaltered by CBT. There is no direct correlation between changes in fatigue level and changes in physical activity. The conclusion was that the effect of CBT is not mediated by change of physical activity”.

   In some cases, CBT may worsen a patient’s condition. This has to be recognized early.

2. **Graded exercise therapy (GET):** This is a physical therapy unlike CBT and pacing. It has been reported that GET has a beneficial effect in the first 6 months after initiation and the levels of fatigue is decreased compared to the control group after 12 weeks of GET. However, after 6 months the difference between the group receiving GET and the control group becomes insignificant. GET does not seem to improve the functional capacity. In some cases, however, GET may cause deterioration of patient’s condition, therefore care must be taken so that it does not occur.

3. **Pacing:** This starts with the premise that the energy available to a particular patient is fixed and it may be so used that the daily necessary activities can be carried out without exacerbation of the fatigue or development of PEM. Therefore, after each scheduled activity a period of rest is to be built in the therapeutic schedule. Two forms of pacing are recognized. First form is symptom-contingent pacing, where the decision to stop a particular activity is dictated by awareness of worsening of symptoms. Then the patient either takes a rest or changes the activity (usually to passive one say, watching TV or listening to music or reading). The second form is time-contingent pacing, where a activity schedule is prepared beforehand in consultation with the patient.
which the patient can carry out over the day without exacerbation of fatigue or PEM. Pacing, therefore, aims at a programmed existence as regards activity and rest. Sometimes both the forms are combined.

The results of pacing can be varied. In Norway, the trial reports are quite encouraging with 96% patients reporting benefit.

Other Treatment Interventions

Many other treatment interventions may be required for patients of CFS which may be helpful from case to case. In a recent review carried out by Teitel AD, Langone Medical Center, New York University (NYU) on February 2, 2012 the following modalities have been recorded:

- Healthy diet
- Sleep management techniques
- Medications to reduce pain, discomfort, fever (when present)
- Medications to treat anxiety (antianxiety drugs) and depression (antidepressant drugs)
- Maintaining active social life through various mediums of contacts
- Relaxation and stress-reduction techniques such as:
  - Biofeedback
  - Deep breathing techniques
  - Hypnosis
  - Massage therapy
  - Meditation
  - Muscle relaxation techniques
  - Yoga

The review has also provided certain activity management tips such as:

- Avoiding doing too much on days when you feel tired.
- Balancing your time between activity, rest and sleep.
- Breaking big tasks into smaller, more manageable ones.
- Spreading out more challenging tasks throughout the week.

Certain Problems of Management

Chronic fatigue syndrome patients may suddenly show inexplicable deterioration. Sometimes some therapeutic interventions (as outlined) may trigger or cause this. The use of antidepressants may be quite useful in some, but not always. These patients may be quite sensitive to sedative drugs and they also show chemical and food sensitivities. Psychological-psychiatric interventions also have low responses.

PROGNOSIS

The recovery rate of CFS is quite low. In 1997 review of CFS carried out by Joyce et al. it was shown that:

- Median full recovery rate was 5% (0–31%)
- Improvement during follow-up (median proportion of patients) was 39.5%
- Return to work at follow-up ranged from 8–30%.

Cases where the initial fatigue level was low showed a better prognosis and children showed a better recovery than adults.

The mortality rates of CSF are significantly not different from standardized mortality rates; however, the age of death is significantly younger and common causes of death are heart failure, suicide and cancer.

THE FUTURE

The economic cost and loss of productivity due to CFS coupled with the treatment cost is said to be quite heavy. In the USA, the cost burden is estimated to be around 18.7–24 billion dollars per annum. This is likely to increase. In India, in absence of database it is not possible to come into an estimate of cost burden, but both the problem and its personal, social and economic impact are likely to increase. Social support groups, though not very effective in CFS, do provide an important way of social intervention in this debilitating illness.

BIBLIOGRAPHY