Chronic Fatigue SYNDROME

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Abstract

Chronic fatigue syndrome is one of the most common medical problems in the Western World, but at the same time diagnosis and treatment is not well understood. Fatigue is a common complaint in the primary care setting, with studies showing that over 20% of patients find fatigue a major problem. Chronic fatigue syndrome (CFS) is characterised by subjective complaints of chronic, debilitating fatigue lasting longer than six months that is exacerbated by minimal physical activity. It can disrupt normal daily activities over several months or years. The aetiology is unsure and the diagnosis is currently one of exclusion reached only after organic and psychiatric illnesses known to produce fatigue have been investigated. Because fatigue affects cognitive function including memory and attention, as well as sensory control, visual perception, various visual functions and emotional control (panic attacks and depression), the behaviourally orientated optometrist can play an important role in providing both functional and rehabilitation assistance for CFS patients.

Key Words

chronic fatigue syndrome, fibromyalgia, pathological fatigue, panic attacks, post-sedative fatigue, stress-induced relapses,

Chronic fatigue syndrome has been defined according to a working case definition developed by the Centre for Disease Control (CDC) in the United States. By definition, the patients have been ill for at least six months, have significant functional impairment and have no evidence of physical or psychiatric illness which could account for the fatigue.

Fibromyalgia is a syndrome with many similarities to CFS, with fatigue often being the main complaint, as well as tenderness of the joints. The diagnostic criteria are listed in Table 1.

Whiting believes there are at least two crucial weaknesses of the CDC definition with respect to diagnosis:[1]

- Most of the diagnostic criteria for CFS are subjective in nature and degree.
- It is possible that a person may have several non-CFS conditions, which when seen together, provide the list of symptoms required for the diagnosis of CFS.

The fallibility of human subjectivity is the deficiency in the CDC definition. Whiting also stresses the weakness of the definition in its failure to emphasise the critical and unique characteristics of pathological fatigue itself, i.e., features that differentiate CFS from normal fatigue.

The CDC has selected 50% disability as being the cutoff point for normal fatigue, but some fatigue sufferers who have a lesser degree of disability still have had to forfeit their jobs because their judgement, concentration or vision is impaired (e.g., bus drivers, airline pilots), or they may have cognitive disabilities that affect their ability to study (e.g., students), and their future career hopes are impeded. Any degree of lowered performance causing physical disability (e.g., athletes, manual workers) can be very stressful for these people to accept.

Whiting has called the fatigued state where "core" fatigue symptoms exist "pathological fatigue" as opposed to normal fatigue. Pathological fatigue (as with normal fatigue) can be divided into three separate areas:[1]

(1) motor fatigue
(2) cognitive fatigue
(3) diminished arousal

Patients experience different mixes of these three types of fatigue, or all three. Whiting suggests that pathological fatigue has specific characteristics that fall into four distinct areas:

(1) Types of Relapse

Patients have some good days but have bad days more frequently, as well as variations of their symptoms during the day. They have improved cognition on better days.

Patients may suffer post-activity attacks which generally occur 24-48 hours after increased activity, or the symptoms may occur during activity in very severe cases. Following activity they may be very

TABLE 1.
DIAGNOSTIC CRITERIA

Chronic Fatigue Syndrome *

Major Criteria

1. Exclusion of any systemic condition that may cause similar symptoms
2. New onset of persistent or relapsing severe fatigue

Minor Criteria

1. Debilitating fatigue for at least six months
2. Chronic headache
3. Sleep disturbance
4. Neuropsychiatric symptoms
5. Migratory joint pains
6. Unexplained muscle weakness
7. Myalgias
8. Sore throat
9. Painful lymph nodes
10. Fatigue prevents usual activity
11. Symptoms began abruptly
12. Fever

Physical Findings

1. Low-grade fever
2. Non-exudative inflamed pharynx
3. Palpable or tender cervical or axillary lymph nodes

*Must fulfill major criteria and either six or more of the 12 minor criteria and two or more of the three physical criteria or eight or more of the 12 symptom criteria.

Fibromyalgia**

Major Criteria (mandatory)

1. Same
2. Generalised aches or stiffness involving three or more anatomic sites for at least three months
3. At least six typical and reproducible tender points

Minor Criteria

1. Generalised fatigue
2. Same
3. Same
4. Same
5. Subjective joint swelling but none objectively
6. Numbness, tingling sensation
7. Irritable bowel syndrome
8. Modulation of symptoms by activity, weather, stress

**Must fulfill major criteria and at least four minor criteria.

disabled for several days, which can make their lives very unpredictable and in many cases affect their ability to work. Patients may suffer an "acute crash" which often occurs following significant physical, mental or emotional activity or exposure to aromatic substances. Prolonged extreme fatigue may follow. Acute somnolence, where they experience transient lapses of concentration or go "blank," can occur even in the middle of a conversation. Acute cognitive "blankouts" can occur, revealing a complete breakdown in concentration ability and inability to focus attention.

Panic attacks may also occur, where the patient experiences hyperventilation and becomes apprehensive. In pathological fatigue, certain visual phenomena can trigger an attack (e.g., movement in peripheral vision when driving or as a passenger, or crowding of peripheral field when in supermarkets). This can lead to phobic behaviours.

Post-sedative fatigue is characteristic of CFS, and is an intolerance that most patients experience to the sedative effects of certain medications, especially some tricyclic anti-depressants.

Stress-induced relapses can occur if these patients are exposed to additional stress (viruses, illness, work pressures, etc.). They tend to work at their full capacity but are unable to handle extra loads. Gradual relapses are often seen by others as the person being "run down." They experience a gradual decline in their ability to cope and finally decompensate.

(2) Sleep Disturbances

Sleep disturbances in some people continue after supposedly adequate rest and in the absence of factors that affect sleep. Sleep quality, duration and timing are all sensitive in CFS, especially if there has been increased activity. Initially they sleep frequently and for long periods for the first few months, followed by insomnia. Other factors can affect sleep in CFS, such as night sweats, myalgias, or increased auditory sensitivity, etc.

Whiting believes that any stress which causes a person to suffer chronic sleep deprivation predisposes him/her to CFS, as additional trigger events (such as menopause, puberty, persistent stressor work load, viral/bacterial infections, general anaesthetics, insecticides or solvent exposure, acute psychological shock) may trigger the pathological fatigue.[1] It appears that some individuals who suffer chronic sleep loss do not necessarily return to normal sleep patterns once the cause has been removed and thus progress to develop CFS. In all cases of pathological fatigue they suffer from unrefreshing sleep, feeling still very tired on waking and/or they have difficulty staying awake (maintaining normal arousal) throughout the day or at certain times during the day.

Several studies indicate that immunological changes similar to those seen in CFS can occur in stress, anxiety, and depression, but they specifically appear to reflect the degree of sleep disturbances resulting from these conditions. Whiting supports these findings and has also found that the T-cell changes that occur in pathological fatigue can be reversed with medication or measures to improve sleep quality and duration. This supports the hypothesis that immunological changes in CFS may be secondary to sleep disturbances that are caused by the fatigued states. Hence the immunological disturbances represent an epiphenomena rather than a cause of CFS. Another recent study which assessed treatment of CFS patients with Bupropion (which is active at dopaminergic sites) produced a reversal in the T-cell count, lending further support to a neurological basis for the immunological changes in CFS.

(3) Cognitive Dysfunction

This appears to the observer to be particularly severe and variable. Patients report difficulty remembering things. Short- and long-term memory is affected and patients are often concerned they have Alzheimer's disease. They experience difficulty sequencing letters or numbers visually, verbally and in writing. They also have difficulty with opposites and confuse left and right directions; this frequently happens driving and they may become hopelessly lost.

They will often report they are unable to watch TV as they lose concentration and cannot follow the story. They may not remember they have seen a film from one day to the next and watch it again. They need to constantly write things down. Frequently these patients have previously held jobs which required good memory.

During their visual examination it is not uncommon to have to continually repeat what is required of them in a test.

They have difficulty remembering a simple sequence of instructions.

Other fatigue symptoms (neurological phenomenon) that cause distraction and attention difficulties result from their heightened sensory awareness (see below).

Cognitive deficits (which are variable but prominent) occur without exception in pathological fatigue. Patients' cognitive abilities improve to some extent with rest, and appear to be dependent on rest and arousal status (i.e., alertness). Arousal is influenced by:[1]

1. The efficiency of sleep, both qualitatively and quantitatively, in maintaining one's sleep quota.
   An adequate sleep quota also prevents adverse long-term, and possibly more fixed cognitive effects, which are not specifically related to arousal levels, but which occur as a consequence of chronic sleep deprivation.
2. The functional responsiveness of the neocortex and deep subcortical structures to activation by the reticular activating system.
3. The functional integrity and ability of the reticular activating system to activate the neocortex and deep subcortical structures.

(4) Adaptive Behavioural Strategies

CFS patients tend to use one of three strategies to cope:

- Pushers tend to push themselves to their tolerance level. They are more likely to continue working in some capacity.
- Pacers tend to accept their illness and seem to be happy with enjoying the few good days they have. They were possibly pushers in the past.
- Opportunists have the most severe form of the illness and make the most of the occasional good day. CFS patients will often forget to be cautious when they achieve some real progress in their recovery, and they crash to a sometimes worse level than experienced previously.

The question arises: "What causes the transformation from normal fatigue to pathological fatigue"? Whether patients are psychiatric or non-psychiatric, their fatigue can either be reversible normal fatigue or abnormal pathological fatigue that is difficult to reverse and is associated with neurological or cognitive dysfunction. Pathological fatigue can occur in various physical diseases (e.g., multiple sclerosis, lupus), after viruses, and in the absence of psychiatric disturbances. It can also occur secondary to a known psychiatric condition.

Generally, medical acceptance of CFS holds two opposing views:

(1) physical

(2) psychiatric

Where pathological fatigue occurs in either of these settings, the fatigue is responsive to the same forms of pharmacological intervention, suggesting an abnormal neurological basis for the fatigue based on the fact that rest, counselling, and behavioural therapy are less effective in reversing the fatigue symptoms. As fatigue occurs at the mind-brain-body interfaces, it becomes a challenge to conceptualise its source. Many of these patients are hard-driving achievement-orientated personalities and the influence of these and other stressors (either emotional, physical or environmental) on the physiological well-being of the patient cannot be ignored. Eliminating as many of the known stressors as possible (including visual stress) helps in the overall recovery of these patients. Whiting firmly believes that the appropriate vision care (removal of visual stress) from these patients is critical to their recovery.

INFECTION IN CFS

CFS patients commonly describe the onset of their fatigue symptoms as occurring following a respiratory (acute) or gastrointestinal infection. Acute infections are commonly considered as precipitants of CFS and this has led to such terms as the post-viral fatigue syndrome. In most cases the diagnosis of the respiratory or gastrointestinal illness is not definite.

The relationship of herpes viruses to CFS has received much attention over the last 10 years, especially Epstein-Barr virus (EBV) and cytomegalovirus, and the more recently discovered (1986) human herpes virus type 6 (HHV-6). Enterovirus infection has also been found to be active in CFS.

EBV infects over 95% of humans, most often without producing illness. When the primary infection strikes an adolescent or early adult, infectious mononucliosis may develop. The virus remains latent in salivary glands and B lymphocytes, but reactivation, although frequent, is not known to be symptomatic except in the setting of profound immune deficiency. Researchers now suggest the actual presence of EBV seems to have nothing to do with CFS, but among patients who experience the onset of CFS symptoms following acute mononucleosis or who have extremely abnormal results of EBV serology (as measured by laboratory tests), chronic mononucleosis is usually suspected.

Cytomegalovirus in its acute state is also capable of triggering chronic fatigue, but in general there appears to be no evidence of active CMV infections in individuals with chronic fatigue. EBV and acute CMV infection may precede CFS, and non-specifically elevated levels of antibodies are common.

HHV-6 is the cause of exanthem subitum (roseola infantum), a common childhood illness which is characterised by a high fever followed by a rash. Antibodies have been found in sera of 60%-90% of the general population and 80%-100% of CFS patients. The role of HHV-6 in CFS is unknown; possibly HHV-6 causes the viral symptoms of CFS, or alternatively CFS reactivates HHV-6 and produces the antibody response. It is also not known whether high titers of antibodies to HHV-6 in CFS are due to nonspecific polyclonal stimulation.

Postviral CFS has also been reported with other infections, including hepatitis A, influenza, rubella, varicella, Toxoplasma gondii, Giardia lamblia, Brucella abortus, Mycoplasma pneumoniae, Borrelia burgdorferi, Campylobacter, jejuni, Escherichia coli, group A streptococcus.

CHRONIC FATIGUE AND PSYCHIATRIC ILLNESS

Psychiatric diagnoses including depression, anxiety, and somatoform disorders have been made in 42%-82% of patients with CFS. It has not been established whether depression is the cause or the result of CFS, or even whether the two conditions can separately co-exist. So far no study has found patients with CFS to be uniformly affected by psychiatric disorders; these findings indicate psychiatric disease cannot fully explain CFS.

Evidence suggests that psychiatric disorders, and especially depression, predispose patients to CFS. Firstly, depression

has been diagnosed in CFS patients two to three-and-three-tenths times more frequently than in those with other chronic illnesses. Secondly, a lifetime prevalence (24%-50%) of prior psychiatric disorders has been reported in patients with CFS. Thirdly, depression and stress are considered to play a role in promoting infection. Unfortunately, a prime source of frustration for most patients with pathological fatigue is that in the eyes of many, any amount of emotional trauma to the patient is enough evidence to cast doubt on, or provoke alternative explanations for, their chronically fatigued state. The usual implication is that there is a psychiatric problem rather than a physical problem, unless the fatigue has been demonstrated to be immunologically or virologically driven.

The cognitive complaints led Komaroff and Goldenberg and others to perform neuropsychological tests of cognition.[2] The preliminary results have shown that the cognitive impairment particularly involves concentration and attention. They indicate that the pattern of test performance suggests an "organic" deficit rather than cognitive dysfunction secondary to a mood disorder.

Whiting believes the immunological changes in the presence of psychiatric disease should make the psychiatrist aware of the likelihood that a secondary pathological fatigue state may exist.[1] Chronic fatigue symptoms overlap those of various psychiatric disorders: e.g., general depression (non-psychotic), and somatoform disorders.

ALLERGIES IN CFS

Many CFS patients have associated allergies. Approximately 65% of patients with CFS have a premorbid history of allergies to food, drugs, or inhalants. Cutaneous reactivity to inhalants or foods occurs in 50% of patients with CFS, compared to 20%-30% of the general population.

Immunological studies have shown a positive correlation between allergy severity and the magnitude of the Epstein-Barr Virus serology response. Allergen-induced responsiveness is greater when both CFS and positive EBV serology are present.

Candidiasis hypersensitivity syndrome (yeast allergy) has symptoms that overlap with CFS but so far there is no evidence of an epidemiological link.

ORGAN SYSTEM INVOLVEMENT

CFS has a multi-system involvement:

(1) Immune System

Increased levels of certain immune cytokines (interferon and interleukin) from a hyper-responsive immune system may have a direct influence on neurotransmission of the central nervous system.

The significance of the immunogical dysfunction in CFS is relatively unknown, although recent research indicates that the reduction in the T-cell subset may make an individual more vulnerable to developing pathological fatigue if exposed to further trigger stressors.

(2) Central Nervous System

The cognitive and psychiatric symptoms are consistent with organic central nervous system dysfunction. Recent research studies using SPECT (Single Photon Emission Computer Tomography) scans of the brain have shown diminished uptake of Ceretec in various areas of the cerebral cortex, and more especially in the brain stem of CFS subjects, supporting the possibility that the brain stem is one of the key areas of neurological disturbance in CFS.

(3) Endocrine System

Adrenal insufficiency secondary to a deficiency of either corticotropin-releasing hormone (CRH) or another stimulus of the pituitary-adrenal gland axis has been shown. Hypothalmic hypo-androgenaemia is often present in men with CFS. Low normal, or deficient levels of total and free testosterone are present. Women show low free testosterone levels. Men also can demonstrate osteopoeina and osteoporosis especially after prolonged fatigue. It has been observed that after several months of desipramine therapy (Pertofran, a tricyclic antidepressant), the testosterone abnormalities may recover.[1]

The immune, central nervous and endocrine systems are closely linked. An effect on one system can produce dysfunction in the others, whether the influence is organic (infection or allergies) or psychological in nature. Evidence suggests that both processes are involved, producing the somatic and psychiatric symptoms. The debility of CFS is out of proportion to the pathology findings. Whiting suggests that pathological fatigue is likely to represent neuro-transmitter dysfunction resulting from either habituation of chronically abnormal sleep patterns or the outcome of various immunological, hormonal, and neurotoxic insults that probably target on the reticular activating system (RAS) of the brain stem. He suggests dysfunction at the level of the RAS would logically explain the differences between normal fatigue and pathological fatigue (e.g., pathological fatigue does not respond to adequate rest, where normal fatigue does).

(4) Muscle Histology and Physiology

Accumulated evidence of physiological studies in muscle reveals normal muscle function, which supports the view that the fatigue reported in CFS is central in origin, reflecting abnormal drive rather than peripheral failure of force generation. CFS patients' symptoms fluctuate from day to day and week to week. At times CFS patients can exercise with little fatigue; at other times they are bed bound. This also suggests a central process produces the subjective fatigue. Studies in Australia matched deconditioned (vicious spiral of progressively reduced physical fitness) healthy controls with each CFS patient and found no difference in their muscle strength, endurance or recovery.[3,4] No matter what structural abnormality is found in the muscle, it appears that this cannot be the cause of the profound fatigue in these patients with CFS because there is now ample evidence of normal muscle function in these patients. CFS patients complain of pain, but this is not because there is something wrong with their muscle; it may be that their sensory threshold for pain is reduced since pain is a symptom that is experienced in the brain.

The reduction of the pain threshold could be explained on the basis of a sleep disorder, or an alteration in neurotransmitters in the hypothalmus or thalmus. On physiological and pathological grounds it is now clear that CFS is not a myopathy. Psychological/psychiatric factors appear to be of greater importance in this condition. Weakness in these patients is apparently due to submaximal effort rather than intrinsic muscle weakness. Fatigue could be due to abnormal perception of muscle force.

TREATMENT OF CFS

Treatment for many CFS sufferers is still a matter of treating symptoms as the condition to this date is still poorly under-

stood. CFS sufferers need emotional support, as many of them feel isolated or have been rejected by their families, inferring laziness or unwillingness to help oneself. The patients need to be told that CFS is a real illness and is not life-threatening. They should reduce or stop strenuous exercise and minimize stress to avoid immuno-suppression. Behavioural therapy (cognitive strategies) can help to treat the avoidance behaviour to help get them gradually into physical activity.

Pharmacological treatment, using medications, may effectively relieve the CFS symptoms, such as depression, anxiety, sleep disorders, or myalgias. Tricyclic antidepressants (TCAs) benefit severely depressed patients, as well as mildly depressed patients, in general practice, especially if there is a sleep disorder. TCAs have been found to be of benefit in fibromyalgia patients to help sleep disorders. Recently, Whiting has shown that the initial treatment of CFS needs to involve the restoration of sleep quality and normal sleep patterns to help with the recovery of the fatigue symptoms. Low doses of trimipramine (Surmontil, an antidepressant) are used for one-two months. This appears necessary (to increase the natural killer T-cells) prior to the introduction of desipramine. Desipramine is used to improve the arousal status which has its activity predominantly at the noradrenergic synapses in the central nervous system. These doses are also started at a very low level, sometimes as low as once a week, or sleep disturbances recur, causing a relapse. (In some patients, I have found a noticeable improvement in oculomotor control once desipramine is used and has reached a certain level for that particular patient.)

The latest (unpublished) research being carried out in Newcastle, NSW, provides further hope for CFS sufferers. Researchers have identified a urine marker which may explain the specific metabolic disturbances in CFS. Glutamate, which is a principle excitatory neutrotransmitter of the brain, and is also present in the retina, has been found to be synthesised at lower levels than normal. Glutamate is a precursor of Gamma-aminobutyric acid (GABA), a natural equivalent of Valium. If there is a decrease in the levels of GABA, patients are more likely to become anxious. The MNDA (glutamate) recaptors are responsible for our short term memory, and CFS patients commonly suffer short term memory loss.

The researchers have thus been able to provide further support to a somatic rather than purely psychiatric basis for CFS symptoms. Interestingly, in people coming down with the flu, the plasma glutamate levels fall. Similar findings are present in people who over-exercise and develop fatigue symptoms. Treatment using Aminocarbe and glutamine is showing good results in some patients.

Other recent work being done in New Zealand has found that the shape of the red blood cells is different in CFS patients compared to normals. The RBCs would not pass through the small capillaries, causing impaired tissue oxygenation and relative ischaemia. As patients improve, the RBC appearance improves. Changes in metabolism correlate with a change in the RBCs as there is insufficient energy to fuel certain cellular functions. The treatment being recommended is evening primrose oil or vitamin B12, depending on the shape of the RBCs.

PROGNOSIS OF CFS

The mean duration of the illness in various surveys has varied from 37.1 months to 52.6 months. The response to placebo of CFS patients was 42% in six months in one survey. Without treatment the CFS symptom score decreased by 50% in 10 months, and 40% of patients had no symptoms after one year.

CONCLUSION

Chronic fatigue syndrome is a relatively prevalent but poorly recognised condition which has severely debilitating physical and mental effects on sufferers. Current medical understanding of the condition is still relatively controversial, but does provide some understanding of the aetiology and symptomatology of the syndrome. It is important that patients who may have the condition are assessed, counselled and managed by professionals experienced in and sympathetic to a syndrome of signs and symptoms which is still denied by many in the community and medical professions as real rather than imagined.

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