

## Chronic fatigue syndrome

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### Introduction

Chronic fatigue syndrome (CFS) is a major cause of illness and disability. Although increasingly recognised, it is not a new diseases process, but rather a clearer appreciation of a pattern of symptoms previous characterised in many different ways. The clinical features enabling it to be distinguished from other causes of fatigue are: new onset of unexplained fatigue, lasting for over six months, **not related to ongoing exertion**, and not substantially alleviated by rest, associated with a range of other symptoms<sup>1,2</sup>. The prevalence of patients fulfilling the criteria for CFS is about 0.5%, with different studies giving valued between 0.1 and 2.6%<sup>3,4,5</sup>. CFS can affect people of either sex, and any age or social group. Severity and duration, and the resulting disability vary considerably, but many patients suffer profound ill-health, and greatly reduced physical and cognitive function, interfering with actives of daily living, employment and education.

Aetiology and pathogenesis are unknown. A substantial proportion of patients relates the onset of CFS to an infection. A community-based study<sup>6</sup> showed that, after Epstein-Barr virus infection, up to 10% of patients may fulfil definitions of it. CFS has also been seen after other herpes viruses, enterovirus and hepatitis virus infections and nonviral infections such as Q fever, toxoplasmosis, salmonellosis, brucellosis and Lyme disease.<sup>4</sup> Whether infections act simply as a trigger in predisposed individuals or have a specific role in the continuing illness is unclear. There is no consistent evidence of abnormal viral persistence, but non-specific immunological changes, resembling those in acute infections, may persist and be relevant.<sup>7</sup> CFS may be a variant of more shortlived post-infectious fatigue.

Other triggers are reported, including some immunisations and chemotherapy. A familial component is possible. Events and **stressors around the onset may influence the occurrence** or maintenance of the altered state.<sup>5</sup> In a recent community-based study<sup>5</sup>, about 60% of subjects had no prior psychiatric diagnosis, though the illness itself appeared to increase evidence of psychosocial stress.

Patients suffering from CFS may show features of other syndromes notably irritable bowel syndrome and fibromyalgia; and patients with these conditions may also have some of the characteristic features of CFS. This suggests that they may share similar pathogenetic predisposing

or triggering factors, perhaps representing a family of related disorders.

The relationship between CFS and depression and the interacting stigma of both have caused much misunderstanding. Patients with primary depression may have fatigue and other symptoms that can resemble CFS, and patients with CFS may show some symptoms usually associated with depression. Patients with the syndrome may develop secondary depression or anxiety due to their illness, especially if it is unrecognised. Patients with a history of depression can subsequently develop CFS. However, studies on the clinical features and laboratory findings suggest that they are distinct. Similarly, CFS can usually be distinguished on symptom pattern from somatisation disorder<sup>8</sup>.

### **Symptoms**

The two widely used sets of criteria for CFS, Centers for Disease Control (CDC)<sup>1</sup> and Oxford<sup>2</sup> are primarily designed for surveillance and research, and are probably **too narrow** for clinical use by virtue of exclusions. The central feature is unexplained persistent or relapsing fatigue of over six months duration, unrelieved by rest. This is typically both physical and mental fatigue, and is clearly distinguished by patients from everyday fatigue. While fatigue may not always be the dominant feature, it is always present, and its characteristics are valuable at diagnosis.

Characteristically, exacerbations of fatigue are delayed, usually starting in the day or two after increased physical or mental activity, and lasting several days or weeks. They are often associated with profound (post-exertional) malaise with other physical and cognitive symptoms. Intercurrent infections, immunisations and psychological stresses may also precipitate setbacks. There is often a striking exacerbation of symptoms the day after drinking alcohol.

Physical and cognitive symptoms may be many and various. They must be present continuously or intermittently, and the pattern may evolve. The most common include: muscle pain, joint pain without signs of inflammation, sore throat, tender lymphadenopathy, headache, postural or rotational dizziness, altered temperature sensation, paraesthesiae, and sensitivity to light and sound. Symptoms of irritable bowel syndrome and food intolerance are common. Palpitations, an altered awareness of respiration without classical dyspnoea, or fibromyalgic tender points may also be described.

Cognitive problems typically include poor concentration and short-term memory, word-finding difficulty, and inability to cope with multiple stimuli. Psychological distress, whether as a feature of CFS or a reaction to it is not uncommon, and can induce mood swings, panic attacks, and depression. Sleep is typically unrefreshing, and its disturbance may comprise hypersomnia, early morning waking and disruption of the sleep-wake cycle.

### **Diagnosis**

Diagnosis of CFS rests on the characteristic clinical history. There are no validated laboratory or other tests to confirm it. Diagnosis therefore requires a careful narrative history, characterising the symptoms carefully and using patient recognition. Listening and making a firm (even if provisional) diagnosis can be therapeutic for a person who is puzzled, frightened, angry or depressed about this often overwhelming, undermining, and debilitating condition. It then remains to exclude other conditions that may resemble it.

The clinical features may suggest a wide range of differential diagnoses. Common and important ones are thyroid disease, chronic infective or inflammatory conditions, metabolic disease, depression, and somatisation disorder. These can generally be excluded on clinical grounds and simple screening tests. However, **over investigation can also be harmful and counterproductive to the managements of these patients, raising inappropriate concerns and causing them to seek abnormal test results to validate their illness.**

Tests to exclude common and important differential diagnoses include a full blood count, C-reactive protein (or erythrocyte sedimentation rate), urea, creatinine, electrolytes, urinalysis, liver and thyroid function tests, creatine kinase, and, where indicated rheumatoid factor and antinuclear antibodies. Some symptoms may necessitate further tests such as neuroendocrine or muscle function, electromyography, electrocardiography or electroencephalography: or exclusion of coeliac disease or inflammatory bowel disease. All symptoms at the outset and subsequently should be evaluated carefully so as not to miss concurrent disease.

### **Management**

Management is essentially supportive, with reassurance that there is no other serious underlying disease. Patients should be reassessed if new symptoms or signs appear. **It is helpful to establish with the patient a way of thinking about the illness** providing reasonable explanations for distressing symptoms and disability, **while not undermining the patient's ability to recover.** This is easier if patients feel they have been listened to and believed, and realise that clinicians will be alert to development of new symptoms or signs, rather than dismissing them as part of CFS.

There is no established drug treatment for CFS, though many have been tried and continue to be studied<sup>3,4</sup>. **Patients may need guidance about claims** in the popular press and **from other practitioners.** Preliminary results and unsubstantiated assertions are often overpromoted, raising expectations and leading to considerable expense and distress. Clinicians can help patients make informed decisions and strike the right balance between standard approaches and novel interventions.

### **Activity Management**

**Activity should be managed to assist natural recovery and limit secondary problems, which are intrusive or may interfere with recovery** such as sleep disturbance. Many patients attempt too high a level of activity until they relapse, leading to cycles of over and underactivity. **Others overcompensate and avoid activity, fearing relapse, but then develop symptoms of deconditioning (cardiovascular and muscular unfitness) or excessive awareness of physiological changes.** It is essential therefore, to establish a baseline that does not provoke relapse and then build up by small tolerable increments slowly ('pacing'). **The benefits of graded exercise have been shown by randomised controlled trials**<sup>3,4,9,10</sup>. Graded rehabilitation programmes must be individualised for the patient's symptoms, level of disability and personal circumstances.

Adjustment to the illness, and **a behavioural response limiting its impact** while maximising the extent and rate of recovery **is crucial.** As with other illnesses, **cognitive behavioural therapy,**

**tailored to the patient's needs, can substantially reduce secondary distress and optimise rehabilitation**<sup>3,4,10,11</sup>. Sadly, many perceive cognitive behavioural therapy as treatment for psychiatric disease, rather than a means to assist adjustment and recover.

**Patients** with a less severe illness can generally be managed by GPs and physicians, but those with a more severe and protracted illness or with **adjustment difficulties may benefit from more structured input** from a team including, for example, physiotherapists, occupational therapists, clinical psychologists, dieticians, and social workers. **Complementary therapists** may also provide a supportive role for many patients, but they **sometimes introduce or reinforce unhelpful illness beliefs**. **Patients may need much help** in obtaining appropriate sickness and invalidity benefits and in **managing appropriate (return to) work or study arrangements**.

### **Symptom control**

Measures to suppress or alleviate distressing symptoms are important adjuncts to management, and are sometimes forgotten or underutilised. **Approaches can be behavioural or pharmacological**, using measures established in other settings, but **adapted to this patient group**. Patients with chronic fatigue seem to suffer adverse drug reactions more readily than others and may require care with dose and type of agent used<sup>4</sup>.

Low dose tricyclic antidepressants may improve sleep rhythm in patients with early morning waking or light, dreamy sleep. The rationale must be explained. Amitriptyline, doxepin or nortriptyline, starting at 10 mg or trazodone 50 mg at night are useful; if excessive sedation or antimuscarinic adverse effects occur, alternatives should be tried. Short term, occasional, use of non-benzodiazepine hypnotics can help patients with major difficulties in getting off to sleep to re-establish a normal sleep pattern.

Tricyclic agents can also alleviate pain, especially if it has a neuropathic quality as can sodium valproate and carbamazepine. Regular analgesics are often of limited longterm efficacy. Muscle pain associated with spasms or twitching can be reduced by baclofen or other muscle relaxants. **Cognitive behavioural therapy** and simple advice (eg. avoiding caffeine and alcohol) **can help both sleep and pain management**.

**Postural dizziness can improve as cardiovascular fitness improves, and does not require drug treatment**. Cinnarizine or betahistine may alleviate rotational vertigo. Frequent or persistent headaches, especially those of a migrainous quality, may be helped by prophylaxis with lowdose tricyclics, pizotifen or sodium valproate.

Selective serotonin reuptake inhibitors do not help CFS patients without depression<sup>10</sup>. If depression needs treatment, tricyclics can be useful, though slow dose titration is important.

Selective serotonin reuptake inhibitors are less well tolerated<sup>10</sup>, but of this group, citalopram and setraline seem most useful in my experience. **Panic attacks and mood swings respond to behavioural management**.

Modifying fibre intake, usually by reducing it, may help irritable bowel syndrome. Mebeverine or low-dose tricyclics may reduce bloating, cramps and diarrhoea. Some **patients** find that certain

foods increase gut and other symptoms, but they **may need guidance about some more radical dietary interventions suggested by other practitioners**. A dietician can help manage these aspects and weight change, which may result from altered activity and eating patterns. There is no clear evidence that dietary supplements with vitamins and minerals, although widely promoted, are necessary or beneficial for most patients.

Recent studies of low-dose corticosteroid treatment have given conflicting results<sup>10</sup> and more data are needed before considering their use in clinical practice.

### **Prognosis**

The outlook for CFS is extremely variable. Because some patients recover relative early, experience in specialist units and self-help groups are inevitably skewed towards those who do less well. Certainly some patients remain disabled and symptomatic for many years. Nevertheless, patients can be helped to make the best of their situation while they are ill. Strategies should be geared towards long-term recovery and avoid short-term tactics that inhibit it, such as over or underactivity. Early appropriate management appears to improve prognosis. However, even patients with longstanding disease can improve with careful management and support.

### **Conclusion**

- CFS is a cause of significant ill-health and disability.
- It can be diagnosed on the basis of its characteristic symptoms.
- **The essence of treatment is activity management and graded rehabilitation.**
- Sleep disturbance and other intrusive symptoms can be alleviated.
- Supportive management can reduce its impact and enhance the prospects for recovery.

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