"I'm so Tired"

When does a patient really have chronic fatigue syndrome?

By Denis Phaneuf, MD, MSc, FRCPC

Case Study: Does Aaron Have a Virus?

Aaron, 35, has been noticing a rapid decline in his energy levels. He finds it difficult to get up in the morning, and simple tasks feel like exercise. Aaron is unable to go to his job as a car salesman on some days, and his boss is beginning to lose patience. Last Sunday, Aaron took his two young sons to the park and played with them on the playground. The next day he was unable to get out of bed. Aaron wonders if he's got "some kind of virus," because, along with the fatigue, he has been getting sore throats and headaches, and his muscles feel stiff.

Question: What treatment do you suggest for Aaron?

Discussion on page 38.

Dr. Phaneuf is a microbiologist at Centre Hospitalier de l'Université de Montréal (Campus Hôtel Dieu), Montreal, Quebec.

Since the beginning of humanity, man has probably suffered from periods of great fatigue. Since Manningham's treatise on febricula in 1750, many attempts have been made to develop psychologic or biologic explanations for fatigue. More than a thousand names have been used to describe lengthy periods of fatigue that include symptoms of muscle pain and cognitive/neurologic impairment. The term "neurasthnia," popularized by George Beard in 1869, was widely used until recent research redefined the condition as "chronic fatigue syndrome" (CFS). In the United States, etiologic studies on CFS resumed in 1982 using the names Lake Tahoe Syndrome and Yuppie Syndrome.[1]

The diagnosis of CFS excludes other causes of fatigue. Studies show that, in general practice, 20% to 27% of patients present with fatigue lasting more than two weeks. American studies indicate that only 0.3% to 1% of this population will actually have CFS for more than six months, whereas an Australian study presents the figure as low as 0.04%. The ratio of women to men ranges from 3:1 to 1.3:1 and the average age is 28. A number of cases are known in children, but there are very few in the elderly.

Synonyms still used in Europe for CFS are "myalgic encehalomyelitis" and "post-viral syndrome." Some conditions may present with similar symptoms to CFS. Fibromyalgia is similar to CFS, but does not have as large a degree of neuropsychologic impairment. "Burnout" is *not* related to CFS.

Practice Pointer

Study indications for patients presenting with cfs

Fatigue lasts for more than six months.

Ratio of men to women ranges from 3:1 to 1.3:1.

Average age is 28.

A number of cases are known in children, but there are very few cases in the elderly.

Definition

In North America, the US Centers for Disease Control (CDC) have made slight variations to the definition of CFS since 1988. The last definition from December 1994 comprises the following:

1. The presence of unexplained, persistent fatigue that is not relieved by rest and that results in a substantial reduction in occupational, social and personal activities.

2. The concurrent presence of at least four of the following symptoms for a minimum of six months, with no antedating fatigue:

- Impairment of short-term memory or concentration, severe enough to cause a substantial reduction in the patient's normal activities;
- Sore throat;
- Tender cervical or axillary lymph nodes;
- Muscle pain, multi-joint pain with no joint swelling or redness;
- New headache;
- Unrefreshing sleep; and
- Post-exertion malaise lasting more than 24 hours.

In 1988, this definition included fatigue with a Karnofsky scale score of 50% (patients who are bedridden and able to care for themselves) for daily activities. In 1992, depression and panic attacks were added to this definition. In 1994, the CDC also added idiopathic chronic fatigue as a criterion.

What is the Assessment?

In view of the large number of patients presenting with fatigue and the fact that most diseases cause fatigue, an extensive health questionnaire and medical examination are necessary for diagnosis. Since there are no specific tests for CFS, first line laboratory tests should be done to eliminate other diseases. Recommended first line tests are a complete blood count with sedimentation rate, blood sugar, serum creatinine, alanine aminotransferase (ALT), electrolytes, sodium (Na), potassium (K), calcium, phosphorus, urinalysis and thyroid-stimulating hormone (TSH). If malnutrition is obvious, proteins and albumin should also be included. More specifically, for persons at risk, purified protein derivative (PPD) and chest x-ray or serologic testing for hepatitis B and C and human immunodeficiency virus (HIV) should be carried out. A neurogenic hypotension investigation might be beneficial in some patients. A secondary line of investigation, generally restricted to research, can include viral serology, brain single photon emission computed tomography (SPECT), or more specific serology (*e.g.,* for Lyme disease). CFS has been classified among the hyperimmune syndromes, but current investigation is only at the research level. Likewise, the possible pathogenesis of the disease as discussed by Fukuda will not be covered in this article.[2]

Treatment of CFS

There is no specific treatment for CFS. Treatment is, therefore, symptomatic, and responses vary widely from patient to patient. It is, therefore, useless to continue treatment for more than four to six weeks, unless some slight improvement in symptoms occurs. In most cases, medication (particularly antidepressants) can be started at one-third to one-half of the normal adult dose. Treatment is generally both pharmacologic and nonpharmacologic. When the diagnosis is definite, the patient must be told the following:

- No particular mortality is associated with CFS;
- Symptoms generally improve over time; and
- Although no specific treatment is available, a number of products can prove helpful.

Nonpharmacologic Treatment

Making some lifestyle changes can benefit CFS patients. While bedrest does not necessarily guarantee a faster recovery, the patient must exercise self-discipline in their daily routine, such as rising early in the morning (*i.e.,* before 10 a.m.) and eating at regular hours. It should be noted that patients with CFS usually function best between 10 a.m. and 2 p.m.

Intense exercise (*i.e.,* aerobics) is not well-tolerated by these patients, but a gradual program of light exercise, as simple as a routine 10-minute walk, is recommended. Some specialists recommend swimming or post-infarction-type exercises. Even patients with severely disabling fatigue must carry out a certain amount of exercise at home.

Massage, particularly stretching, may be beneficial or harmful, and experimentation will determine the benefits.

If there is acute muscle pain, particularly in the scapular region, visiting a pain clinic can help for some weeks, but this does not seem to be a long-term solution.

Depression is often associated with patients who have CFS. Some patients benefit from support groups. Others may become depressed when they meet people whose conditions are worse than their own. Psychotherapy generally helps such patients. When a psychiatric approach is needed (*i.e.,* to clarify the diagnosis), it is recommended you tell patients you will continue treating them.

Finally, when fibromyalgia and concentration problems improve, you should discuss a gradual return to work or mild social activities for the patient, as this may be excellent therapy.[3]

Over-the-Counter Drug Treatments

A number of non-prescription drug treatments have been used by patients; some have been the subject of studies, while others are anecdotal. For example, there have been many studies on essential fatty acids (*i.e.,* fish oil and vegetable oil, such as evening primrose) with respect to CFS, but results vary widely. Likewise, vitamin and mineral supplements (particularly magnesium) have been used successfully in England, but not in the U.S. A number of products, however, have been proven ineffective. Such products include the sole use of multivitamins, zinc supplements, acyclovir and cortisone. Immune modifiers, such as isoprinosine or interferon, have also provided no significant results.

Prescription Drugs

Prescription drugs used to improve CFS symptoms are found in Table 1.[4] In most cases, the recommended dosage of prescription drugs for CFS patients is lower than that generally used in adults. However, gradual escalation up to normal dosage levels is possible, particularly in the case of

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Table 1

Drugs Used To Improve Chronic Fatigue Syndrome

Clinical Symptom	Drugs	Remark
Muscle spasms	**1st line:**	
	Clonazepam 0.5 mg at bedtime	Benzodiazepine; tolerance possible Mainly used at night
	2nd line:	
	Cyclobezaprine 10 mg 3x daily	Antispasmodic; to be used for less than three weeks
	Carisoprodol 350 mg 3x daily	Musculoskeletal relaxant Not checked for use in CFS
Chronic muscle pain	**1st line:**	
	Amitriptyline 10-25 mg at bedtime	Tricyclic antidepressant; acts in four days; maximum effect in four weeks
	Imipramine 10-25 mg at suppertime	Same
	Desipramine 10-25 mg at suppertime	Same
	2nd line:	
	Lithium; 300 mg/day	Proven effective in fibromyalgia only; toxicity determination after three weeks
	Anti-inflammatory agent	Never alone; only for a short period

antidepressants. The simultaneous use of several classes of drugs is possible, but not all crossover effects are provided in the literature, and caution is required.

If muscle spasms occur, particularly when they prevent the patient from sleeping, 0.5 mg of clonazepam at bedtime can be used. If spasms occur during the day, cyclobenzaprine or carisoprodol can be used for short periods.

Chronic Muscle Pain

Tricyclic antidepressants are by far the most effective with respect to muscle pain in CFS. Serotonin-reuptake inhibitors, which are useful in depression, have little effect in this respect. Tricyclic antidepressants are slow-acting, and at least four to six weeks must elapse before stopping or changing them. Low-dose lithium (sub-therapeutic from a psychiatric point of view) can be considered as a second-line treatment of chronic muscle pain, as it has an effect on fibromyalgia. However, given the renal and blood toxicities of lithium, the dosage should be checked approximately three weeks after treatment is initiated. It should be noted that one does not necessarily want a dosage level that would be normal in psychi-

Table 1

Drugs Used To Improve Chronic Fatigue Syndrome (cont'd)

Clinical Symptom	Drugs	Remark
Depression	Tricyclic antidepressants, but at higher doses than for muscle pain Serotonin-reuptake inhibitor	
	Fluoxetine, 10-20 mg/day	Slow acting (4-6 weeks) possible headache
	Sertraline, 25-50 mg/day	Same
	Paroxetine, 20 mg/day	Same
	Nefazodone, 50-100 mg bid	Same
Neurogenic hypotension	**1st line:**	
	Midodrine, 2.5 mg 3x daily	Decubitus hypertension
	Fludrocortisone, 0.1 mg 1/2 to 1 pill/day	Headache, edema
	2nd line:	
	Propranolol, 10 mg 4x daily	Use if severe tachycardia with hypotension

atry, but one that simply avoids toxicity. Anti-inflammatory agents act on muscle pain to some extent, however, when used alone, they are not known to be very active, and are generally used only for short periods because of related gastric problems.

Depression

After one year, CFS patients regularly develop classic depression. At this point, tricyclic antidepressants can be used at standard doses, or slowly and gradually, as can serotonin-reuptake inhibitors.

If insomnia occurs and patients do not want to depend on benzodiazepams, trazodone is suggested as a second choice. Trazodone, however, can cause hypotension and syncope, particularly in this fragile population.

Neurogenic Hypotension

Drugs must be used to treat neurogenic hypotension when this condition has been proven by repeated syncope or a tilt-table test. Medodrine and fludrocortisone both increase blood pressure and reduce syncope, but they can also cause decubitus hypertension and headache. Although these drugs represent first-line medication, they are not used regularly in treating CFS. Low doses of propranolol taken sever-

Discussion of Case Study: Aaron's Treatment

There are three types of treatments recommended for Aaron to help him get through this period of increasing fatigue, which you diagnose as CFS.

Pharmacologic treatment.

a) Amitriptyline: begin dose at 10 mg, slowly increasing every three weeks, if necessary.

b) Clonazepam: begin dose at 0.5 mg to be taken at night, if nightly muscle cramps are experienced.

Non-pharmacologic treatment. Two tablespoons of primrose oil per day.

Other.

a) Exercise: begin with slow and progressive exercises. Concentrate heavily on exercises that involve the legs, such as walking.

b) If there is no presence of hypertension, add salt to the diet.

al times a day are used as second-line medication if patients present with severe tachycardia following hypotension. Propranolol can also be used as an adjunct in the management of headache in such patients, but the dosage must remain low because these patients are easily subject to bradycardia. Other beta blockers are difficult to use in patients with CFS.

Interesting anecdotal reports have been received with respect to anti-parkinson drugs (*i.e.,* selegiline and amantadine).

The Prognosis

CFS is never fatal. The disease lasts for an average of 37 to 52 months.[5] Studies indicate that 10% to 15% of patients are completely cured after two years, whereas 63% to 70% improve sufficiently to become functional after this period. It should be remembered that in 2% to 7% of cases, the main diagnosis will change during treatment, and that 19% to 24% will present with major depression at the end of the four-year followup period.[6] Other short-term studies over an 18-month period, report cures at 3% and improvements at 17.7%.[7] There are no studies showing that treatment affects a patient's prognosis.

CFS is a challenge for physicians. CFS requires the skills to eliminate other similar conditions and empathy for followup. CME

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