



A practical approach to chronic fatigue syndrome

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■ Chronic fatigue may have several physical causes, but a psychiatric condition is often involved. A substantial minority of patients are not diagnosed by conventional tests and do not respond to antidepressant therapy. These patients should be referred for psychiatric opinion or observed for new developments. Extensive virologic testing and unorthodox treatment approaches have no scientific basis at present. Claims of dramatic new diagnostic tests or therapy should be treated with caution because of the long history of unsuccessful attempts to categorize chronic fatigue into one diagnosis and the strong placebo effect shown in controlled trials.

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FATIGUE is one of the most common and least understood complaints presented to clinicians. Typically, patients say that they lack get-up-and-go, have no energy, are tired all the time, or are generally unable to function comfortably, if at all. Often, they will have other poorly defined complaints as well.

Because chronic fatigue is poorly understood by physicians and scientists, and because the popular press has promoted several "diagnoses," patients may have been told (or may have decided) that they suffer from hypoglycemia, chronic Epstein-Barr virus infection, "systemic candidiasis," brucellosis, or Lyme disease.

Not surprisingly, many patients are frustrated by the inability of physicians to provide a definitive diagnosis and treatment for their condition. As a result, they may seek alternative therapies, such as clinical ecology, hair analysis, or other unproven techniques. Often such patients are unwilling to consider, let alone accept, psychological factors as a cause of their condition.

There is no doubt that patients with fatigue suffer prolonged disability and may consume large amounts of health care resources, especially if the fatigue is one of many complaints or part of a somatization disorder. They are a source of frustration to themselves and to their families and physicians. It is therefore surprising that no clearly recognizable physical or psychological entity has been identified to explain the problem and permit effective therapy.

CLINICAL SPECTRUM

Many acute illnesses are followed by *short-term fatigue* that may last for a few weeks. For most people, this type of fatigue is common and is usually easily accepted. The major symptom is lack of energy that results, in part, from muscular weakness. The physical and psychological effects of deconditioning are undoubtedly involved with this weakness, although in more prolonged cases, muscle breakdown may occur.¹

Chronic fatigue, however, is characterized by lassitude or general lack of energy, not by simple muscular fatigue. When does fatigue become abnormal? The working definition for chronic fatigue syndrome (CFS) proposed by Holmes and others² (Table 1) in 1988,

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requires that the fatigue "be sufficient to reduce or impair average daily activity below 50% of a patient's premorbid activity level for a period of at least 6 months." In practice, the fatigue becomes abnormal whenever the patient perceives it to be a problem. However, others have found that few fatigued patients fit the Holmes definition of CFS, and that the diagnosis may be obscured by the concomitant presence of psychiatric disorders.³ It is difficult to know whether fatigue is primarily a psychiatric problem or a symptom of a larger psychiatric problem. Physicians in private practice will likely have a different perspective on this question than will physicians who work in referral centers.

It was observed at the Cleveland Clinic (F. Schecter, 1988, unpublished data) that fatigued patients were generally younger and less well-educated than nonfatigued controls, more likely to be female, and more likely to have histories of interrupted sleep and lower alcohol consumption.

Few studies have been done on the natural history of fatigue, and most of these were poorly controlled and retrospective. A prospective study by Manu and associates,³ describes 135 consecutive patients with 6 months or more of debilitating fatigue. Few patients met the criteria for CFS as defined above, and 91 (67%) had psychiatric disorders, as judged by the Diagnostic Interview Schedule of the National Institute of Mental Health. In 34 (25%), no physical cause was identified, nor did these patients meet the criteria for CFS. Only 7 (5%) patients had a physical condition (sleep apnea, asthma, panhypopituitarism, seizure disorder, and polymyalgia rheumatica) that accounted for their fatigue. Of 6 (4%) patients who met the diagnostic criteria for CFS, probable multiple sclerosis developed in one, two were felt to have somatization disorder, and one improved after taking antidepressants.

In a study by Kroenke and colleagues,⁴ patients were classified as fatigued if their symptoms had lasted more than 30 days. (In fact, 41% of their patients had been fatigued for more than 5 years.) Patients under psychiatric care or with identified chronic disorders were excluded. The fatigue had had a major impact on the functioning of each patient, as judged by the Sickness Impact Profile (SIP), which measures functional impairment in 12 categories. The SIP scores were similar to those of patients suffering from major medical illnesses. Laboratory investigations were not helpful.

After 1 year of follow-up without specific intervention, only 28% of the patients had improved. Three patients were treated with thyroxine for borderline

TABLE 1
DIAGNOSTIC CRITERIA FOR THE CHRONIC
FATIGUE SYNDROME*

Major criteria

1. New onset of persistent or relapsing, debilitating fatigue (no previous history of similar symptoms; average daily activity reduced or impaired below 50% for 6 mo)
2. Exclusion of other clinical conditions that may produce similar symptoms

Minor criteria

Symptom criteria (persistent or recurrent for 6 mo)

1. Mild fever (37.5° to 38.6°) or chills
2. Sore throat
3. Painful cervical or axillary lymph nodes
4. Unexplained generalized muscle weakness
5. Muscle discomfort or myalgia
6. 24 h fatigue after usually tolerated exercise
7. Generalized headaches, unlike previous headaches
8. Migratory arthralgia
9. Neuropsychologic complaints
10. Sleep disturbance
11. Symptoms developing over a few hours to a few days

Physical criteria documented at least twice at least 1 mo apart

1. Low grade fever (oral 37.6°C to 38.6°C; rectal 37.8°C to 38.8°C)
2. Nonexudative pharyngitis
3. Palpable cervical or axillary lymph nodes, 2 cm or less

*From Holmes.²

Cases of chronic fatigue syndrome must fulfill major criteria 1 and 2 and the following minor criteria: eight minor symptom criteria or six symptom and two physical criteria.

elevation of thyroid-stimulating hormone (TSH), but did not improve. The authors did not indicate whether the duration of fatigue prior to inclusion in the study was a factor in recovery or nonrecovery. This information is important since it seems likely that fatigue of long duration would be associated with an unfavorable prognosis. Of interest is the fact that patients in this study did not use disproportionate amounts of clinic or hospital resources.

POSSIBLE CAUSES

Because fatigue is such a frequent and nonspecific feature of disease, there are many possible causes.⁵ In most cases, the chief complaints will, of course, indicate whether some major medical disorder is present. According to Solberg,⁵ fatigue has a physical cause in 26% to 39% of patients. An additional 12% have what is termed "physiological fatigue" that results from work- or lifestyle-related problems, recent illness, or environmental stress (such as disturbing sounds or temperatures).⁶

Chronic viral illness

The search for a physical cause of CFS in the past 10 years has focused on chronic viral illness, chiefly that

TABLE 2
EPSTEIN-BARR VIRUS ANTIBODY TESTS

	Acute infection	Past infection
Viral capsid antigen IgM	+	—
Viral capsid antigen IgG	—	+
Early antigen	+	—
Nuclear antigen	—	+

caused by the Epstein-Barr virus. This virus is associated with Burkitt's lymphoma in Africa and with nasopharyngeal carcinoma in Africa and the Orient (but not in the United States) and it may be a cocarcinogen.

Epstein-Barr virus replicates in B lymphocytes and may be present in the throat for up to 18 months after recovery from acute illness. Various Epstein-Barr antibodies have been found, generally those to viral capsid antigen (VCA IgG and IgM), early antigen, and nuclear antigen. Several authors have suggested associations between chronic fatigue and antibodies to early antigen and to VCA IgM.^{2,7-10} These associations were not replicated, however,^{11,12} and close examination of the early reports reveals no clear relationship between chronic fatigue and Epstein-Barr virus antibodies. Table 2 shows how antibodies can help in diagnosing the stage of infection.

Immunodeficiency

An Australian study reported significant reductions in total peripheral lymphocyte count in CD2, CD4, and CD8 subsets. In addition, T cell function was reduced and immunoglobulins, particularly IgG3 and IgG1 subclasses were lower.¹³

Endogenous opioids

An intriguing finding by Prieto and colleagues is that monocyte function was reduced in 85% of patients with chronic fatigue syndrome and that this was improved by incubation of the monocytes with naloxone, an opiate antagonist, suggesting that endogenous opioids are involved in the chronic fatigue syndrome.¹⁴ The clinical significance of these findings is unknown but suggests a need for further work in this area.

Chronic brucellosis

Chronic brucellosis was alleged to be the cause of a chronic fatigue condition in the 1940s and 1950s.

However, when patients who recovered quickly from acute brucellosis were compared with those who had chronic symptoms, no differences in the findings during their initial illness were found. Their psychological assessment revealed evidence of emotional disturbance, especially depression, in the patients who were chronically ill.¹⁵ Indeed, their descriptions are strikingly similar to those of patients seen today with symptoms of chronic fatigue. There is therefore little likelihood that chronic fatigue syndrome is caused by brucellosis.

Chronic candidiasis

Chronic candidiasis also has been popularized as a cause of fatigue and chronic systemic symptoms. Investigators at a major medical center studied 100 patients with chronic fatigue and found no historical, physical, or laboratory differences between the eight patients who believed they had chronic candidiasis and the other fatigued patients who did not have this belief.¹⁶ In keeping with known microbiological facts, this study shows a lack of support for candidiasis in the etiology of chronic fatigue.

Benign encephalomyelitis

Outbreaks of benign myalgic encephalomyelitis have occurred during the past 30 years, one of the most famous being at the Royal Free Hospital in London.¹⁷ In this condition the familiar symptoms of fatigue, weakness, memory loss, and depression were associated with normal laboratory values and cerebrospinal fluid examinations, with some patients having prolonged sickness.¹ It remains unknown whether this condition has a specific cause, but it can probably be grouped with chronic fatigue syndrome.

Vitamin deficiency

Another proposed cause of CFS is vitamin B₁₂ deficiency, most recently described as a cause of neuropsychiatric disorders in an elderly population,¹⁸ although the patients all had normal red blood cells. Such a deficiency is less likely in the young. In a recent controlled, crossover trial, a liver extract containing both vitamin B₁₂ and folic acid was no better at relieving symptoms than was a placebo.¹⁹ In practice, patients can be assessed for B₁₂ deficiency, but the yield is likely to be low.

Sleep apnea

Sleep apnea, which may be difficult to diagnose without specific studies, can be a cause of fatigue.

Depression

The finding of some researchers that depression is the diagnosis in half of fatigued patients should come as no surprise.³ Almost all depressed patients experience fatigue. In the end, the diagnosis of depression may be most strongly supported by a response to antidepressant therapy.

Drug therapy

One frequent potential cause of fatigue not to be overlooked is drug therapy, particularly with sedatives and beta blockers, and especially with lipophilic drugs such as propranolol and nadolol. These drugs are sometimes given to treat mitral valve prolapse, a condition which also may have received too much attention as a cause of systemic symptoms.

ASSESSING CHRONIC FATIGUE

When a patient presents with fatigue, the primary objectives are to identify any potential physical cause, to explore the psychological and social aspects of the patient's condition, and to establish a good relationship with the patient, who has often been to numerous other practitioners without success and who may feel alienated from the medical profession.

The patient's history is often most informative. It should include not only the usual questions about physical symptoms, but also an assessment of previous episodes of fatigue or depression, personal and family history of alcohol or other substance abuse, and a detailed occupational history. Many patients have more than one job among other responsibilities, few resources, and little support. A frequently encountered subgroup seems to be university students who are away from home, having difficulty recovering from minor illnesses, and who have to drop out of school for a semester or two.

The history often suggests specific psychiatric disorders, but it may be necessary to speak to family members to get a complete and accurate account. Although many fatigued patients are suffering from depression, several other psychiatric diagnoses were made in the study by Manu,³ including, in 31% of the patients in the series, somatization disorder, panic disorder, dysthymia, social phobia, and bipolar disorder.

It is helpful to find out why the patient is seeking medical attention, and whether he has done so of his own volition or at the urging of his spouse, employer, or friend. Patients who come on their own are more likely to be insightful and willing to comply with a physician's

suggestions for treatment. In addition, since many of these patients are unable to work, the question of disability often arises and should be addressed early. The patient must understand the need to comply with the recommendations of the evaluation, such as referral for psychiatric assessment or for physical therapy, if the physician is to certify an inability to work.

Likely medical problems, such as endocrine, hematologic, or metabolic diseases, should be ruled out early with tests that are indicated by the history and physical examination. Tests such as erythrocyte sedimentation rate⁴ or antinuclear factor are not helpful in the absence of a clear indication of connective tissue disease. Likewise, although it is sometimes difficult to resist the patient's request to order Epstein-Barr virological studies, the results are usually not helpful, regardless of whether they appear to show past infection; no treatment is available and the results are often misinterpreted and may lead patients into further false beliefs about the nature of their illness. In a patient with a protracted course of infectious mononucleosis, however, the EBV IgM may be elevated—a diagnostic finding.

Many patients resort to unorthodox medical assessments, which range from such items as food allergy and chronic fungal disease to hypoglycemia. Explanation of the lack of a scientific basis for such diagnoses may be appropriate; unfortunately, many patients persist in a usually fruitless search for an answer in these areas of "alternative medicine."

MANAGEMENT

Clearly, as with all medical therapy, treatment should be directed at the underlying cause of the symptom, if possible. However, even after careful evaluation and screening, there remains a core of patients who have chronic and, to some extent, disabling symptoms and in whom no definite cause can be found for their fatigue. Many of these patients are suffering from an atypical depression and most, if followed, will eventually be willing to try antidepressant therapy, even if they initially refused. In time, they recognize that trying something is preferable to doing nothing and to continue to feel as they do.

Titration of the antidepressant dosage against symptomatic response can be supplemented in some cases with tests of blood drug levels, which show not only whether serum levels are in the therapeutic range, but also whether the patient is taking the medication at all.

Some patients do not respond to the smaller doses of antidepressants commonly used by non-psychiatrists. When this is the case, psychiatric consultation is advisable and probably preferable to the use of tests such as the Minnesota Multiphasic Personality Inventory. Testing can be helpful, but more for the edification of the physician than the patient, who is no more likely to accept these results than the physician's opinion.

Patients frequently resist psychiatric referral for various reasons, including lack of understanding about psychotherapy, the stigma of being a "mental patient," damage to self-esteem for being "weak," or a sense of rejection by insensitive family and friends. Careful explanations may help to overcome such barriers.²⁰

Other therapies for chronic fatigue have been tested and found to be no more effective than placebo. For example, acyclovir was tested in a placebo-controlled trial by Straus and associates.²¹ Both acyclovir- and placebo-treated patients improved to the same extent. There was some nephrotoxicity from the high dose of

acyclovir (initially 7 days of intravenous therapy followed by 30 days of oral treatment). Epstein-Barr virus antibody titers were the same for both groups.

The trial of liver extract containing vitamin B₁₂ and folic acid noted above failed to show any difference between placebo and extract, although the placebo effect was strong.¹⁹

These illustrations of the strength of the placebo effect should warn us to beware of claims made for therapy that are not based on a placebo-controlled clinical trial.

ADDENDUM

An article in *Science* (Palca J. Does a retrovirus explain the chronic fatigue puzzle? *Science* 1990; 249:1240-1241) discussed reports that a retrovirus, HTLV-2, is a possible cause of the chronic fatigue syndrome. The results appear to be very preliminary and should be viewed with caution until further work is performed.

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