Handbook of Chronic Fatigue Syndrome

Leonard A. Jason
Patricia A. Fennell
Renée R. Taylor

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CHAPTER 2

Differential Diagnosis in Medical Assessment

AUDRIUS V. PLIOPLYS

Audrius V. Plioplys, MD, FRCPC, FAAP, CMD
Chronic Fatigue Syndrome Research Center
Mercy Hospital and Medical Center
Chicago, Illinois

CHRONIC FATIGUE SYNDROME (CFS) is often misunderstood. Indeed, many physicians doubt its existence. It does exist, however; and it can have a devastating impact, as patients who were formerly active and fully employed may become virtually bedridden and unable to work.

The syndrome has a long medical history. Over the years, it has had numerous other names including chronic Epstein-Barr virus syndrome, chronic mononucleosis syndrome, postviral fatigue syndrome, and epidemic myalgic encephalomyelitis. Sir Richard Manningham, in 1750, reported patients who had symptoms of "listlessness with great lassitude and weariness all over the body." In 1869, Dr. George Miller Beard proposed the term *neurasthenia*. Every century has contributed new symptoms, names, and diagnostic criteria for this debilitating illness, but its etiology and pathogenesis are still unknown. In 1988, the case definition of CFS was first introduced by the Centers for Disease Control ([CDC]; Holmes et al., 1988). Since then, investigators all over the world, but especially in Australia and Great Britain, have made numerous attempts to better define CFS (Lloyd, Hickie, Boughton, Spencer, & Wakefield, 1990; Sharpe et al., 1991). More recently, the CDC, the National Institutes of Health (NIH), and the International Chronic Fatigue Syndrome Study Group proposed new diagnostic criteria (Fukuda et al., 1994). The 1994 revised criteria for the diagnosis of CFS are presented in Table 2.1.

CFS is characterized by the sudden onset of debilitating fatigue together with symptoms such as fever, sore throat, painful lymph nodes, weakness, muscle aches, headaches, depression, sleep disturbance, memory difficulties, and confusion. These symptoms can persist from 6 months to many years and can dramatically reduce the patient's quality of life. Since the primary symptoms are muscular fatigue and pain, along with symptoms of encephalopathy (lethargy and cognitive difficulties), it has been proposed that CFS be renamed myalgic encephalopathy (S. Plioplys & Plioplys, 1995).

The issue of why Chronic Fatigue Syndrome should **not** be diagnosed in children appears on pages 35-36.

Table 2.1
Revised Criteria for the Diagnosis of Chronic Fatigue Syndrome by the Centers for Disease Control, the National Institutes of Health, and the International Chronic Fatigue Syndrome Study Group

Major Criteria

1. Unexplained, persistent, or relapsing chronic fatigue that is of new or definite onset (not lifelong).
2. Fatigue is not due to ongoing exertion.
3. Fatigue is not substantially alleviated by rest.
4. Fatigue results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

Additional Symptoms

1. Self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities.
2. Sore throat.
3. Tender cervical or axillary lymph nodes.
4. Muscle pain.
5. Multijoint pain without joint swelling or redness.
6. Headaches of a new type, pattern, or severity.
7. Unrefreshing sleep.
8. Postexertional malaise lasting more than 24 hours.

Source: "The Chronic Fatigue Syndrome: A Comprehensive Approach to Its Definition and Study," by K. Fukuda et al., 1994, *Annals of Internal Medicine, 121*, pp. 953–959.

Note: A case of CFS must fulfill all the major criteria, plus 4 or more of the additional symptoms. Each additional symptom must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue. A patient who does not fully meet the CFS criteria may be diagnosed as having Idiopathic Chronic Fatigue.

CFS affects mainly young and middle-aged adults. The most common age for onset is between 20 and 40 years. The female-to-male ratio is 2 or 3:1. The mean time to recovery, when it occurs, is about 2 years, but a review of follow-up studies showed full recovery for less than 10% of CFS patients (Joyce, Hotopf, & Wessely, 1997). All socioeconomic groups are represented, and the majority of patients are women, minority groups, and persons with lower levels of education and occupational status (Jason et al., 1999). Based on our epidemiological study results, the prevalence of CFS in the United States is 422 per 100,000 (Jason et al., 1999).

CLINICAL MANIFESTATIONS

Doubt and misunderstanding about CFS are fueled in part by the range of its clinical manifestations. One must remember that CFS is not a disease but a syndrome. A disease is a discrete pathogenic process, usually with clearly defined diagnostic procedures and treatments. In contrast, a syndrome may have multiple etiologies producing a similar, but variable, symptom complex.

Variability in CFS begins with its onset. In our clinical experience, CFS develops acutely in about 75% of cases. In the other 25%, the onset is gradual, or the

patient may have intermittent episodes that eventually become chronic (A. V. Plioplys & Plioplys, 1997). Typically, a previously healthy patient experiences an acute flu-like illness; the fever subsides, but the fatigue and muscle and joint symptoms continue. Cases typically occur in isolation, but there are reports of clusters in which several patients have developed chronic fatigue after the same viral illness (Holmes et al., 1987). However, CFS is not virus-specific and may follow infection with any number of viruses that cause a flu-like illness.

Abnormal immune system activation appears to be the central event in CFS. Although we do not have specific markers for CFS, subtle abnormalities in cell-mediated and humoral immunity have been detected in affected patients (S. Plioplys & Plioplys, 1995). The abnormalities often vary from study to study, but taken together, they support the notion of immune dysregulation. If the mechanism of CFS involves a continuing immune response to an initial viral infection, the production of cytokines, including interferons and interleukins, may cause some of the symptoms. These immune mediators can cause muscle and central nervous system (CNS) symptoms, including fatigue.

Fatigue is, of course, a daily occurrence in almost everyone's life. It has normal variations; some people experience more fatigue than others or react to fatigue more negatively. In addition, fatigue is a prominent feature in many medical conditions. The major diagnostic criteria shown in Table 2.1 are intended to differentiate the fatigue of CFS from that of other conditions.

The first major criterion is that the fatigue cannot have been a lifelong condition. The second is that it is not caused by overwork. We have seen patients who had two or three jobs, got very little sleep at night, and were chronically tired. That is not CFS; it is sleep deprivation.

The third major criterion is that rest does not significantly alleviate the fatigue. Patients with chronic fatigue can sleep undisturbed through the night, yet wake up feeling just as tired as when they went to bed. During the day, they can nap for two to three hours at a stretch, but feel no better on awakening.

The fourth major criterion is that the fatigue must have resulted in a substantial reduction in previous levels of occupational, educational, social, or personal activities.

The additional symptom criteria (Fukuda et al., 1994) focus on characteristic clinical features of CFS that the physician should specifically ask about when taking the history. For example, the fatigue may affect mental as well as physical functioning. In our clinical experience, over 90% of CFS patients have cognitive deficits, most often affecting memory and concentration. Another characteristic feature is postexertional fatigue. When patients with CFS overexert themselves, they often experience two to three days of such extreme fatigue that they are bedridden.

ADDITIONAL SYMPTOM CRITERIA

Besides having to meet all of the four major criteria, the patient must meet four of the eight additional symptom criteria listed in Table 2.1 for the diagnosis of CFS (Fukuda et al., 1994). In our clinical CFS practice, the most common additional symptoms have been memory and concentration difficulties, unrefreshing sleep, and postexertional malaise.

DIFFERENTIAL DIAGNOSIS

Table 2.2 lists medical illnesses for the differential diagnosis of CFS (Komaroff, 1994). These illnesses must be considered by the physician during the initial and subsequent medical evaluations of the CFS patient. Although each of these diseases may produce chronic fatigue, this is not a list of exclusionary criteria. Also, this list is not exhaustive. Many other, albeit rare, medical conditions may also produce chronic fatigue.

CLINICAL HISTORY

In evaluating someone with fatigue symptoms, besides reviewing the diagnostic criteria for CFS (Table 2.1), the physician must obtain a thorough medical history. It is essential to try to identify a medical, psychological, or environmental cause for the fatigue, which then can be appropriately addressed. Alcohol or other substance

Table 2.2
Differential Diagnosis of Chronic Fatigue Syndrome

Endocrine
- Hypothyroidism
- Diabetes
- Addison's disease
- Cushing's disease

Rheumatological
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Fibromyalgia
- Sjogren's syndrome
- Polymyalgia rheumatica
- Polymyositis

Neurological
- Sleep disorders
- Multiple sclerosis
- Myasthenia gravis

Infectious
- Lyme disease
- Human immunodeficiency virus infection
- Chronic hepatitis B and C infection
- Fungal disease
- Tuberculosis
- Subacute bacterial endocarditis

Hematologic
- Anemia
- Lymphoma

Metabolic
- Hypokalemia
- Hypomagnesemia
- Hyponatremia
- Hypercalcemia

Psychiatric
- Depression
- Psychosis

Other
- Chronic illness (cardiac, hepatic, pulmonary, renal)
- Chronic pain
- Medication side effects (e.g., beta-blockers)
- Alcohol or other substance abuse
- Heavy-metal toxicity
- Occult malignancy
- Sarcoidosis

Modified from "Clinical Presentation of Chronic Fatigue Syndrome," by A. L. Komaroff, 1994, in S. E. Straus (Ed.), *Chronic Fatigue Syndrome*, pp. 61–84, New York: Marcel Dekker.

Note: This is a list of illnesses that must be considered by the physician during the initial and subsequent medical evaluations of the CFS patient. This is not a list of exclusionary criteria. Please note that this list is not exhaustive.

abuse, prescription and over-the-counter medication intake, and food supplements used must be carefully reviewed. Questioning about past medical and psychiatric history is necessary, as is a review of the medical and psychiatric histories of relatives. This section includes a discussion of several clinical topics that have frequently come up in clinical practice at the CFS Research Center.

DEPRESSION

Many physicians think that CFS is a psychiatric disorder—in particular, a depression. It is true that most depressed patients are tired, some significantly so, and fatigue is one of the diagnostic criteria for major depression. Depression is also common in CFS, but it is a consequence of the disorder rather than intrinsic to it. Patients with CFS become depressed because of the limitations the illness imposes on their lives. On the other hand, 25% to 40% of patients with CFS do not have depression or another psychiatric disorder (Kruesi, Dale, & Straus, 1989).

Often direct questioning can enable distinguishing between the two conditions. We simply ask the patient, "What is the primary problem? Is the fatigue making you depressed or is the depression making you tired?" Most patients—perhaps 85%—will easily choose one or the other. For patients who are unsure, other aspects of the history can provide the answer.

In the history, the chronology of events can often provide the distinction. A typical history of CFS shows this pattern: "This illness came on, I became unable to work and I lost my job, and now I'm depressed about my situation in life." In a depressed patient, the events often follow a different order: A stressful event occurred—often a major loss, such as a divorce, death of a relative, or loss of a job—followed by the onset of fatigue and other depressive symptoms.

Further, the CFS patient and the depressed patient describe their conditions in different terms. Depressed patients explain their lack of physical activity in terms of motivation: "I'm not interested" or "I don't care." Patients with CFS speak in terms of physical impediment: "I want to, but I can't."

Tolerance of physical activity is another diagnostic clue. In CFS, too much physical activity exacerbates the condition. In depression, physical activity improves the sense of well-being.

Sleep patterns in the two disorders also are different. In our CFS clinical experience, once asleep, patients with CFS generally sleep through the night. Depressed patients typically wake up early in the morning and cannot fall asleep again.

The final distinction is the response to antidepressant medication. In patients with endogenous depression, the agents can produce significant improvement, whereas patients with CFS show minimal improvement. We would stress, however, that antidepressants should not be used to differentiate the two conditions. Antidepressant therapy may be appropriate in CFS, but only to provide symptomatic relief of secondary depression.

SLEEP DISORDERS

Specific questions should be directed toward uncovering sleep disorders—especially obstructive sleep apnea and narcolepsy, which may be confused with CFS. The physician should consider disorders that can disrupt sleep and lead to sleep

deprivation, such as restless legs syndrome. Environmental factors may also be involved: A crying infant, traffic, or other noises can interfere with sleep, or the patient may be working nights and find it difficult to sleep during the day. Patients with urinary or gastrointestinal tract illnesses may wake up repeatedly during the night to use the bathroom. Their sleep would be fragmented and ineffective, thus producing daytime fatigue.

Inquiries should be made about snoring, which is a characteristic of obstructive sleep apnea syndrome. Narcolepsy is classically accompanied by sleep paralysis, hypnagogic or hypnopompic hallucinations, and cataplexy. When patients have restless legs syndrome, the bed partner often can attest to how much kicking occurs during sleep (and may in turn suffer fragmented sleep and fatigue). Each of these fully treatable, specific sleep disorders can lead to chronic fatigue and would thus exclude the diagnosis of CFS.

A sleep inventory, which should be taken in every patient with possible CFS, can include these questions. Other items in the inventory are the hours of sleep patients get each night, the naps taken during the day, and sleep quality (do they sleep deeply; is the sleep restorative). If aspects of the history suggest a sleep disorder, the patient should be referred to a polysomnography laboratory for a formal sleep study.

Medications

The history should include a review of all medications the patient is taking, since fatigue is a recognized side effect of various agents. Patients who are taken off beta-blockers, for example, may suddenly become much more energetic.

PHYSICAL EXAMINATION

Because CFS is largely a diagnosis of exclusion, the physician must consider the possibility of other medical conditions. Therefore, the physical examination must be very thorough. In general terms, almost all CFS patients that we have seen have had normal physical examination findings. Thus, any abnormalities detected during this step of the evaluation must be carefully and thoroughly evaluated. An exclusionary criterion that is readily detected at the start of the physical examination is that the body mass index must be less than 45 (Fukuda et al., 1994). The reason is that severe obesity itself can be a cause of chronic fatigue, and we agree with this exclusionary criterion. In actual clinical practice, we have never seen a case for evaluation of CFS who fit into this exclusionary category.

Particular attention must be placed on the physical examination when an aspect of the patient's history is not typical for CFS. For example, we have seen patients who are older than usual for CFS—in their late 50s or early 60s—who complained of progressive fatigue, both with mental and physical activity becoming increasingly difficult. On physical examination, they had increased muscle tone and a blank facial expression. Their diagnosis was Parkinson's disease. We have also seen a patient in her early 20s, which is somewhat young for CFS. Physical examination disclosed ataxia and lower extremity hyperreflexia. An MRI (magnetic resonance image) of the brain showed plaques compatible with multiple sclerosis. Fatigue can be the presenting complaint in multiple sclerosis and may become more debilitating than the neurological impairment.

NEURALLY MEDIATED HYPOTENSION

There have been reports that patients with CFS may have neurally mediated hypotension, a condition in which blood pressure may drop with standing. Treatments include mineralocorticoids, beta-blockers, and increased dietary sodium. Using identical tilt-table protocols (Bou-Holaigah, Rowe, Kan, & Calkins, 1995), we have not been able to reproduce these results in 10 investigated CFS patients.

Some autonomic nervous system disorders, such as idiopathic orthostatic hypotension and the Shy-Drager syndrome, involve abnormal blood pressure regulation and often produce severe fatigue. These disorders respond to the pharmacological treatments used for neurally mediated hypotension. Although patients with autonomic nervous system disorders might present first at a CFS center, that would be an extremely rare phenomenon. In our clinical experience with over 300 referred CFS cases, we have not identified a single patient who had an autonomic nervous system disorder. Thus, this disease process most likely will account for less than 1% of CFS cases.

It is likely that most of the patients described as having neurally mediated hypotension actually have chronic intravascular volume depletion. It is most probable that the individuals studied have been involved in long-standing food faddism (e.g., sodium restriction because "salt is bad for you"), and the resulting volume contraction is exacerbated by a warm climate. Evidence to support this hypothesis is an epidemiological study of CFS in England, in which in adjoining areas, there was a 10-fold greater incidence of CFS in an affluent community, as opposed to a lower income community. It is likely that in the lower income community, food high in salt content was not restricted (A. V. Plioplys, 1999).

In many cases, there is the compounding difficulty of antidepressant use, which can directly affect autonomic nervous system functioning. The treatments proposed, mineralocorticoids, have long-term complications including osteoporosis, diabetes, increased susceptibility to infections, and cataracts. The other commonly used category of medicine, beta-blockers, likewise can have significant side effects including depression and fatigue. One of our young CFS patients who started taking beta-blockers for neurally mediated hypotension, against our medical advice, lapsed into severe depression and tried to commit suicide. These proposed pharmacological treatments can be dangerous.

A recent report by the authors who first reported neurally mediated hypotension is of considerable concern (Rowe et al., 2001). In this study of 100 CFS patients with neurally mediated hypotension, fludrocortisone acetate improved function in only 14% of cases, whereas placebo improved function in 10% of cases—a result that was not statistically significant. This result of a treatment failure in the hands of the primary authors who described this condition strongly argues against the role of neurally mediated hypotension as causing CFS symptoms.

LABORATORY STUDIES

The standard laboratory workup that we have used in all cases seen for CFS includes a complete blood count, a comprehensive serum metabolic panel (including glucose, electrolytes, calcium, liver function tests, renal function tests), magnesium, thyroid function tests, erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody titer, urinalysis, and an intermediate-strength purified

protein derivative. We have also performed serum carnitine levels (total, free, and acyl) because carnitine deficiency conditions may produce chronic fatigue (A. V. Plioplys & Plioplys, 1995; A. V. Plioplys & Plioplys, 1997). Although this screening panel is slightly broader than that currently recommended (Fukuda et al., 1994; Schluederberg et al., 1992), these tests are all essential. If any of the screening tests are abnormal, then additional investigations should be done as necessary.

The performance of more than just the basic laboratory studies depends on the history and physical examination. We have routinely tested for HIV and hepatitis B infections (with an assay for hepatitis B surface antigen). However, in over 300 evaluations, we have yet to have a positive result. One can reasonably argue that these two tests should only be ordered for those patients who have risk factors for these infections. We measure antibody titers for Lyme disease in patients who have a history of possible exposure to ticks, since chronic fatigue can be a symptom of this disease. Sleep studies are appropriate if a primary sleep disorder is suspected; an MRI head scan may be necessary in selected cases. We performed a tilt-table test looking for neurally mediated hypotension in 10 CFS cases and obtained normal results in all. We had used an identical protocol to that previously described (Bou-Holaigah et al., 1995). Instead of doing an expensive tilt-table test, an excellent, and totally free, screening procedure is to check orthostatic blood pressures during the initial physical examination. The blood pressure and pulse are checked with the patient lying down, then while sitting up, and finally while standing. If there is a significant drop in blood pressure, further cardiovascular investigations may be warranted.

REVIEW OF EXCLUSIONARY CRITERIA

In the revised criteria for the diagnosis of CFS (Fukuda et al., 1994), in the section dealing with conditions that would exclude the diagnosis of CFS, the first exclusionary condition is "any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea, and narcolepsy, and iatrogenic conditions such as side effects of medication." We fully agree with this statement.

In clinical practice, it is important to use good clinical judgment, based on clinical experience, in deciding whether an illness is the cause of the fatigue, or whether it is simply an incidental illness that is not contributing to fatigue. In the revised criteria for the diagnosis of CFS (Fukuda et al., 1994), the second exclusionary condition is "any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness. Such conditions may include previously treated malignancies and unresolved cases of hepatitis B or C virus infection." Furthermore, Fukuda et al. clarified the issue of previous medical illnesses; once adequately treated and documented as such with laboratory tests (such as hypothyroidism and asthma), they should not exclude the diagnosis of CFS. Furthermore, illnesses such as Lyme disease or syphilis that have been fully treated should not exclude the subsequent development and diagnosis of CFS. We fully agree with all of these statements.

The difficulty with the exclusionary criteria as presented by Fukuda et al. (1994) occurs in the sections dealing with psychiatric diagnosis and substance abuse.

PSYCHIATRIC DIAGNOSES

Active serious psychiatric illnesses, including major depressive disorder with psychotic or melancholic features, bipolar disorder, schizophrenia, delusional disorders, anorexia nervosa, or bulimia nervosa can be associated with significant fatigue and should exclude the diagnosis of CFS. However, the exclusionary requirement that "any past" significant psychiatric condition should exclude the diagnosis of CFS is extreme. We have seen many patients who had an episode of significant depression, years or decades previously, who then came down with a classic history and picture of CFS. In these cases, the psychiatric historical illness should be considered in the same way as a medical illness. Once a medical illness is fully resolved, it then cannot account for fatigue and should not exclude the diagnosis of CFS. Similarly, once psychiatric illnesses are fully resolved, according to the clinician's best clinical judgment, they should not exclude the diagnosis of CFS.

For research purposes, psychiatric past histories and current comorbid psychiatric conditions should be closely documented and tracked to enable analyzing subsets of CFS patients separately in doing data analysis. For example, in CFS patients without comorbid psychiatric histories, there is a significant association with abnormal brain MRI scan findings, but not in CFS patients with psychiatric histories (Lange et al., 1999).

SUBSTANCE ABUSE

Active alcohol or substance abuse can produce fatigue and should exclude the diagnosis of CFS.

Obtaining accurate information from the patient can be a major problem for the clinician. Chronic alcoholics will uniformly significantly underestimate and underreport the amount of alcohol they consume. Individuals who abuse illegal substances may not report this activity for fear that the medical record may be used for criminal prosecution against them. If the clinician has not received information about the substance abuse taking place, then naturally the diagnosis of CFS is not going to be excluded on this basis.

However, the way this exclusionary criterion is worded is of concern (Fukuda et al., 1994). The stated substance abuse issue would exclude the diagnosis of CFS if it occurred 2 years before the onset of CFS symptoms, or at any time after the onset. We have seen patients who reported various degrees of substance abuse that had occurred and had been fully resolved well before the onset of CFS symptoms, but not outside the 2-year window. In these cases, we used the diagnosis of CFS since the issue of substance abuse appeared to have been medically fully resolved. Furthermore, we have seen cases of classic CFS where the patients, during their CFS illness, would occasionally abuse substances. In these cases, our own best clinical judgment was that they indeed had CFS, and the substance abuse was not causing fatigue.

Incidentally, the exclusionary criteria (Fukuda et al., 1994) do not include a definition of what constitutes substance abuse. Although criteria for alcohol and other substance abuse have been defined within the psychiatry community (American Psychiatric Association [APA], 1994), in actual medical practice, these criteria are seldom, if ever, used. I have frequently seen patients diagnosed with alcoholism

who would drink only one or two glasses of wine a day. If alcohol or other substance use (not abuse) takes place in low dosages or infrequently, then this should not exclude the diagnosis of CFS.

Thus, substance abuse should be equivalent to a medical illness—once the problem has been resolved, it cannot further produce fatigue and should not exclude the diagnosis of CFS. However, the clinician should be ever vigilant for significant underreporting and active denying of this problem.

CFS IN CHILDREN

The issue of diagnosing CFS in children has been raised (Bell, 1995). If CFS were a distinct disease process, there is no a priori reason why it should not occur in younger individuals. Diagnosing CFS in adolescents may not be difficult. The same criteria used in adults may be applied, or simply modified. Defining CFS in children less than 13 years of age is an entirely different problem (A. V. Plioplys, 1997).

The clinical manifestations of fatigue in younger individuals are extremely different from those seen in adults. In young children, fatigue-producing diseases most commonly manifest paradoxical symptoms. Sleep deprivation and the sedative effect of phenobarbital, when used for epilepsy, do not produce the fatigue that is seen in adults. Instead, they produce inattention, hyperactivity, and behavioral disorders.

Fatigue is a nonspecific symptom that can arise from varied medical conditions. There are many more diseases with the potential to produce fatigue in young children than in adults. Categories of additional illnesses that need to be considered include central nervous system (CNS) infections (acute or chronic), degenerative CNS disorders, genetic-metabolic disorders, CNS space-occupying lesions, convulsive disorders, myopathies, neuropathies, and mitochondrial disorders. It would be impossible to arrive at an exclusionary list of possibilities. It would also be impossible to define a recommended minimal list of diagnostic procedures that should be performed to rule out fatigue-causing diseases, as has been done in adults (Fukuda et al., 1994). In addition, psychiatric processes may produce chronic fatigue. Besides depression, anxiety disorders, and somatization disorder—which occur in adults—school phobia, parental pressure, and dysfunctional family dynamics are among the possibilities in children.

It is paramount not to miss diagnoses of childhood neurological diseases because there are many treatable conditions. Also, among those that are incurable, many inherited diseases may recur in subsequent pregnancies or in other family members. In these cases, knowledge of the disease is important for family genetic counseling.

For the past 10 years, the author has provided all of the child neurology consultation services to a managed care program serving approximately 200,000 members in the Chicago area. Although many children and adolescents were referred with fatigue symptomatology, in all cases a medical or psychological explanation for the fatigue was found.

In the CFS Research Center, we have seen and evaluated over 300 referred patients. There were no referred children and only six adolescents. In each of the adolescent cases, the patient showed tremendous belligerence to the medical history and physical examination and did not comply with recommended diagnostic tests or with suggested treatment programs. The impression of these adolescents

was that their basic problem lay in a psychological disturbance, probably in relation to familial dynamics.

There is no urgency to label a younger individual with CFS, since there is no specific treatment for this condition. However, diagnosing CFS in children may lead to (1) a delay in the diagnosis of a treatable medical disease; (2) termination of investigations for rare or novel conditions that may respond to novel therapies (such as the treatment of lethargy in children with chronic neurological handicaps and Rett's syndrome [A. V. Plioplys, Bagherpour, & Kasnicka, 1994; A. V. Plioplys & Kasnicka, 1993]); (3) failure to detect psychological or familial difficulties that may lead to fatigue; (4) the development of a lifelong disability lifestyle in the patient and family.

Financial pressures should be a serious consideration in making medical choices. Managed care organizations are trying to decrease the amount spent on medical evaluations and medicines. Once a label of CFS is applied, these organizations may refuse to pay for even the most basic laboratory investigations. This problem is particularly acute in childhood where more extensive, and expensive, initial evaluation procedures may be clinically necessary.

Caution is necessary when diagnosing CFS in adolescents. A condition that has received much publicity is neurally mediated hypotension (discussed earlier). Claims have been made that up to 95% of CFS patients suffer from it. The treatment of neurally mediated hypotension includes the use of fludrocortisone and beta-blockers (Bou-Holaigah et al., 1995). The most likely explanation for postural hypotension in adolescents is that they are simply fluid and electrolyte depleted and develop fatigue as a secondary symptom. This is not an inconsequential problem since these adolescents are being subjected to all of the potential complications of long-term mineralocorticoid use. Furthermore, a recent study (Rowe et al., 2001) reported no significant benefit from using fludrocortisone in the treatment of this condition.

Despite all of the arguments cautioning against the use of the diagnostic term CFS in childhood, the number of reported cases seems to escalate and the number of published articles on the subject expands. In certain pediatric circles, the diagnosis of CFS has become epidemic (not the illness—but the overuse of the term). The entire subject has become surrounded by a degree of fanaticism. This emotional commitment to the diagnosis of childhood CFS has led to the publication of poor clinical and research reports in prestigious medical journals. One example will suffice (Krilov, Fisher, Friedman, Reitman, & Mandel, 1998). In this report of 58 children and adolescents, 50% had symptoms for less than 6 months. Many acute medical and psychological illnesses may take up to 6 months to fully resolve. Thus it is not surprising that at the time of follow-up, 43% were cured and 52% had significantly improved. Furthermore, 24% of the cases had laboratory test abnormalities that would have explained their fatigue. Finally, 60% of the studied group had "significant allergies, often including asthma" (allergic symptoms are frequently accompanied by fatigue). Thus, the majority of the cases in this report had other readily identifiable medical conditions—all of which were confused with the diagnosis of CFS.

Given all of the uncertainties and difficulties associated with trying to diagnose CFS in children and adolescents, it is preferable to simply not use this diagnosis at all.

MEDICAL THERAPY

For the most part, treatment of CFS is symptomatic. Before prescribing medications, however, the physician should offer the patient advice on common issues that face patients with CFS.

Numerous dietary therapies have been proposed, including megadoses of vitamins and very restricted and specialized diets. These can be expensive, and there is no evidence that they have any beneficial effect. Certainly it is sensible for patients to adhere to sound nutritional practices, and taking a multivitamin supplement is a reasonable recommendation, as it would be for anyone.

Scheduled physical activity is also important. CFS patients must balance two opposing needs. On the one hand, they must engage in some physical activity or they will suffer worsening fatigue from muscle atrophy and cardiovascular deconditioning. On the other hand, a sudden burst of physical activity can precipitate a relapse. Hence, patients must learn to pace themselves. Each patient will have a different capacity for physical activity. Each must determine what that is, then continue to test his or her limits, planning to do just a little bit more every day.

We recommend that patients record their exercise in a daily diary to document progress and provide psychological support. Patients may see, for example, that six months ago all they could do was walk around the house, and now they can go out and walk around the block; while they are not yet completely well, they are at least on the road toward recovery. Each person's recovery will be different: One will improve quickly; another will make slow progress, and a few may not improve at all.

Whereas patients need to have a positive long-term mind-set, for the short term they must respect that they have a physical disability. They cannot force themselves out of their condition by sheer willpower alone. Patients who try to do so end up triggering relapses and in some cases progressive deterioration.

PHARMACOLOGICAL THERAPY

Medical therapy for CFS is symptomatic. Antidepressants can be of benefit for the secondary depression often seen in these patients. As in primary depression, the usual first-line agents are the selective serotonin reuptake inhibitors—fluoxetine, paroxetine, bupropion, and sertraline.

Because patients with CFS often are sensitive to medicines, treatment should be started at a very low dose. A standard dose—for example, 20 mg a day of fluoxetine—is usually too strong. We tend to be extremely cautious and start fluoxetine at 5 or 10 mg a day, using pediatric formulations. After several weeks, the dose can be increased slowly. While these agents may help with mood and depression-related sleep problems, they will not relieve the fatigue.

Ironically, CFS patients frequently have difficulty falling asleep because they are so tired. Clonazepam works very well for that. Often 0.5 mg is sufficient, but one can titrate upward if necessary. Clonazepam or alprazolam can be useful for relief of anxiety, another major concomitant of CFS.

A nonsteroidal anti-inflammatory agent may be of benefit for the myalgias and arthralgias of CFS. Patients must take care not to overuse such an agent to avoid gastric problems.

We enrolled 30 CFS patients into a crossover medication trial comparing the effectiveness of amantadine and L-carnitine. Our previous investigations have shown L-carnitine to be a very effective medicine in treating the lethargy seen in different neurological conditions (A. V. Plioplys et al., 1994; A. V. Plioplys & Kasnicka, 1993). Our results showed that L-carnitine is of significant benefit in CFS patients and is tolerated without side effects (A. V. Plioplys & Plioplys, 1997).

Many other medications have been used to treat CFS. We have tried other medicines in our patients, but have been unable to duplicate the success reported by other groups. For example, isolated reports have suggested that amantadine—which is one of the most effective agents for relieving fatigue in patients with multiple sclerosis—might also work in patients with CFS. We found this medicine to be ineffective and actually poorly tolerated by our patients (A. V. Plioplys & Plioplys, 1997).

Cognitive-behavioral techniques have also been used with success in CFS patients. Counseling and support groups may help patients cope with their symptoms and socioeconomic problems that often occur as a result of this illness. A major problem facing many CFS patients is not medical but financial. Most of them have been very productive, holding full-time jobs and perhaps following a profession. When their illness strikes, suddenly they cannot work—and loss of job often leads to loss of medical insurance. Eventually, most of these patients apply for disability benefits.

CLINICAL EXPERIENCE

During the first year of the operation of the CFS Research Center, the number of patients referred for evaluation of CFS was 75. The final diagnoses in this group of patients are presented in Table 2.3. All of the patients had undergone extensive medical evaluations before seeing us, and all carried the diagnosis of CFS as

Table 2.3
List of Final Diagnoses

CFS:	**50**	Idiopathic hypersomnia	1
		Obstructive sleep apnea	1
Neurological Disorders	**6**		
Multiple sclerosis	2	**Other Diseases**	**5**
Tension headaches	2	Medication side effects	2
Brain stem stroke	1	Chronic allergic rhinitis	2
Early Parkinson's disease	1	Carnitine deficiency	1
Psychiatric Disorders	**6**	**Incomplete Evaluation**	**4**
Depression	5		
Anorexia nervosa	1	**Other Diagnoses Total**	**21**
Sleep Disorders	**4**		
Narcolepsy	1		
Restless legs syndrome	1		

Note: In the first year of operation of the CFS Center, a total of 75 patients were seen and evaluated for this condition. The final diagnoses are listed. Of all the patients, 21 (28%) had diseases other than CFS.

made by the referring physicians. Yet, 28% of these presumed CFS patients had entirely different diseases that required different management. For comparison, the misdiagnosis rate in referred CFS patients to the CDC was 18% (Fukuda et al., 1994).

During follow-up of our CFS patients, five of them developed a significant medical disease that required a change in medical management. Two developed diabetes mellitus, one hypothyroidism, one hyperthyroidism, and one Cushing's disease from an adrenal tumor. These clinical developments underscore the need for reevaluations of patients with CFS on a regular basis. These patients are not immune to medical illnesses and may become ill from another chronic condition. Furthermore, in these cases, it is possible that the original medical cause of their fatigue only become apparent years after the onset of fatigue, and years after the diagnosis of CFS.

Comparison with Previous Clinical Reports

Our results differ from a previous report in which 405 fatigued patients were evaluated in a chronic fatigue medical clinic (Manu, Lane, & Matthews, 1993). There was no prescreening of patients—anyone who had fatigue for more than one month in duration could make an appointment and be seen. Of these 405 patients, 74% had a psychiatric diagnosis explaining their fatigue (depression being the primary one) and only 7% had other medical diseases. Our patient population, in contrast, was a highly referred population that had undergone extensive previous medical testing. Only 6 out of 75 patients seen (8%) had a psychiatric explanation for their fatigue. None of our patients were seen for the first time for fatigue-related symptoms. Thus, our results cannot be compared with this report (Manu et al., 1993).

It is interesting to compare our results with reports from yet other outpatient medical clinics. Kroenke, Wood, Mangelsdorff, Meier, and Powell (1988) reported that of 102 fatigued patients seen in a medical clinic, 80% had a psychiatric diagnosis. In another study of 1,000 patients seen in a general medical clinic, 271 had significant fatigue of more than 6 months' duration (Bates et al., 1993). Of these 271 patients, 171 (63%) had an identifiable medical cause for their fatigue, 9 (3%) had a psychiatric diagnostic explanation, and 6 (2%) had substance abuse. Thus, in different medical clinics, a psychiatric explanation of chronic fatigue can range from 3% to 80%. This again emphasizes that our clinical results cannot be directly compared with previously published ones.

CONCLUSION

CFS is a frustrating condition both for the patients and for the physicians attempting to elucidate the cause of this process and to provide their patients with effective treatments. The important first step in the medical evaluation process is a thorough history and physical examination. Once this first step has been accomplished, the clinician can sort the majority of fatigued patients into potential diagnostic categories. Even though the initial screening laboratory tests are most commonly entirely normal, on occasion they indicate other treatable conditions and, therefore, should be done in all cases seen. Careful and thorough medical follow-up is necessary because the underlying cause of CFS may eventually

manifest itself, and patients with CFS are not immune to the development of other medical diseases.

The diagnostic criteria in use today (Fukuda et al., 1994) are an excellent starting point. We agree with the great majority of differential diagnostic recommendations that have been made, but not with all of them. For research purposes in particular, stratification of subsets of CFS patients on the basis of medical and psychiatric historical details, comorbid conditions, and laboratory test findings may be of value in elucidating the cause of CFS in well-defined subsets of patients.

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