
AN APPROACH TO CHRONIC FATIGUE SYNDROME IN ADULTS

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BACKGROUND– The neurologist is often asked to evaluate patients with a chief complaint of fatigue. Many neurologists do not believe in the pathologically based disease known as chronic fatigue syndrome (CFS), yet as a group, neurologists are well suited to guide the diagnostic work up of such patients to pinpoint treatable disorders in the realm of neurology, general medicine, and psychiatry.

REVIEW SUMMARY– Every patient should be carefully evaluated for certain medical, psychiatric, and neurologic disease that can cause fatigue as the most prominent symptom. This is most pressing because new work in virology, immunology, and imaging holds promise but still does not provide any diagnostic test or a mechanism for the production of these symptoms. Only a few treatments meet with even modest success in CFS. The goal of this paper is to provide the clinical neurologist with a framework for the investigation and management of this challenging group of patients.

CONCLUSIONS– Neurologists are typically also trained in psychiatry and general medicine, and this is a strong position to evaluate the patient with fatigue. Because no presently available test can make the diagnosis of CFS, the assessment is vital to seek out more treatable illnesses.

KEY WORDS *fatigue, postviral fatigue, diagnosis of fatigue, treatment of fatigue, nervous system disorders producing fatigue*
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“Susanna approaches the Count, asking him for a bottle of smelling salts for her mistress who has the vapors. She thanks him and promises to return it. ‘Oh no’ says the count, keep it for yourself.’ Susanna replies that a girl of her class can’t enjoy the luxury of the vapors.”

Do you feel about chronic fatigue syndrome (CFS) a bit like the maid, Susanna, does about the countess’ vapors in Mozart’s *Marriage of Figaro*? Most neurologists, in my experience, do not believe that such an entity exists. Many neurologists have a sinking feeling when they hear that fatigue is the chief complaint of their next patient. One neurologist has instructed his secretary to ask such patients when they first make an appointment, “Would you rather see a doctor who believes in CFS?” The real issue is whether you

wish to treat complex patients of this sort. There are difficulties; this is the only article in this journal in which the existence of the syndrome under discussion is widely doubted. There are no pathogenic agents, no target organs, no definitive physical findings, no pathologic tissue changes, and no diagnostic testing. All of this is made even more troubling by the deep investment many patients have in their personal view of their illness. These views may be complicated by financial issues and spurred on by a culture awash in victimization, an attitude which in turn has been provided with the solidarity of a cause, especially by the internet. These factors can result in a patient encounter that is nontherapeutic and may become even bellicose. Nevertheless, neurologists’ strong traditional bedside skills make them eminently suitable to diagnose and treat such patients and at the same time prevent them from being forced into the hands of quacks or squandering their resources on the expensive, useless remedies of internet hucksters.

The purpose of this study is to review the problem of chronic fatigue and develop a plan for appropriate diagnosis

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and management of these patients. Although there are crucial gaps in our knowledge, physicians disposed by suitable temperament may enjoy the challenge of caring for a group of patients in whom the problem is not resolved by an algorithm, neuroimage, or laboratory test.

CFS has numerous aliases (Table 1), and Shorter (1), in his book *Paralysis and Fatigue*, makes the case that every generation has had an illness of this sort, which presumably gave a "respectable" organic disease label for a psychogenic or "character flaw" problem. The earliest full description of this disorder can be credited to Beard in his 1869 work on neurasthenia (2).

THE OUTBREAKS

The modern version of CFS traces back to a series of outbreaks from 1934 (Los Angeles) to the Tahoe cases in 1985 (3). Although these epidemics are generally used to support the organicity of this entity, careful review of the original reports and follow-ups reveals that the evidence is alloyed. The nurses caring for patients in Los Angeles during an epidemic of polio were severely affected by this "new" disease, but their patients, husbands, boyfriends, and other close contacts were entirely spared. The report states that "certain observers were of the privately expressed opinion that hysteria played a large role in this outbreak" (4, p. 69). In the outbreak that affected the tiny community of Punta Gorda, Florida, where a house-to-house survey was done, there were no African Americans affected (5). This racial distinction was also noted in a South African outbreak (6). I

can add that I have never seen a chronic fatigue case in the patient population of an inner-city hospital in 30 years. Is this because inner city patients will not seek medical help for these nonspecific problems, or is this the effect that Mozart's Susanna was alluding to? Nonanatomical "give-way" weakness is frequent, and sensory loss is nonanatomical. Samples of maps of the sensory loss encountered in the outbreak at the Royal Free Infirmary also seem to be nonanatomical (7, Fig. 1). Several outbreaks were associated with epidemics of much-dreaded poliomyelitis in the same community and may have been akin to the dancing manias on the approach of the Black Death in earlier times.

Most victims are young females and often health care workers. A recent well-documented report of an outbreak of mass psychogenic illness shares many features with some of the CFS outbreaks (8). The initial event was a teacher reporting the smell of gasoline developing nausea, headache, shortness of breath, and dizziness. Within minutes of the teacher being carted off in an ambulance, the malady spread, and eventually 101 students and faculty were taken to the emergency room. Thirty-eight were kept overnight. The symptoms were associated with detecting an odor, knowing a classmate was ill, and being female.

THE CLINICAL PICTURE

The diagnostic criteria shown in Table 2 reveal the inevitable vagueness that is the source of confusion and difficulty in achieving both an accurate diagnosis as well as a satisfactory degree of homogeneity in research cohorts (9). There seems little reason for excluding fibromyalgia patients from these same considerations. If one palpates the 18 key spots in CFS patients, they are usually tender and allow the diagnosis of fibromyalgia to be added to CFS.

The core feature in this group of patients is overwhelming fatigue, which is trimodal, ie, precipitated by vigorous physical activity, prolonged intense mental concentration, or inadequate sleep. These are the same factors that cause fatigue in all of us, but the patient with CFS complains of a pernicious persistent debilitating exaggeration of all of these 3 forms of normal fatigue. There are also flu-like myalgias and migratory arthralgias. Although the muscles ache and the patient complains of weakness, these symptoms largely relate to an enhanced sense of muscular effort. Actual clinically detectable weakness is not part of CFS (although sometimes listed in case definitions), and laboratory studies have failed to show any consistent problem in peripheral nerves, neuromuscular junctions, or muscles that could not be attributed to deconditioning. Quadriceps weakness in patients with CFS, compared with depressed and sedentary normal individuals, was found in one study where a mechanical isometric apparatus plus twitch interpolation was used for testing (10). The patients with CFS also had greater sense of effort, greater body mass index, and less exercise capacity than controls. Graded exercises showed reversal of these deficits as measured by less increase in pulse with physical activity.

Table 1.

Other Names for Chronic Fatigue Syndrome and Its Close Relatives

Aliases for chronic fatigue syndrome

- Postviral fatigue syndrome
- Benign myalgic encephalomyelitis
- Myalgic encephalopathy or encephalomyelitis
- Chronic fatigue immune dysfunction syndrome (CFIDS)
- Royal free disease
- Icelandic disease
- Akureyri disease
- Yuppie Flu
- Chronic fee syndrome

Historical entities

- Epidemic neurasthenia
- Phlegmasia
- Vapors
- Chronic hypoglycemia
- Vagotonia
- Chronic brucellosis
- Battle fatigue/shell shock
- Neurasthenia
- Imaginary invalidism

Table 2.
Diagnostic Criteria

Chronic Fatigue Syndrome is defined by the presence of the following:

Fatigue that is

- Clinically evaluated, unexplained, or persistent or relapsing chronic fatigue that is of new or definite onset (has not been life-long)
- Is not the result of ongoing exertion
- Is not substantially alleviated by rest
- Results in substantial reduction in previous levels of occupational, social, or personal activities

The concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue:

- 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
- Sore throat
- Tender cervical or axillary lymph nodes
- Muscle pain
- Multijoint pain without joint swelling or redness
- Headaches of a new type, pattern, or severity
- Unrefreshing sleep
- Postexertional malaise lasting longer than 24 hours

Adapted from Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med.* 1994;121:953–959.

Odd sensations of numbness also abound. This numbness typically proves to be different from that in the usual neurologic diseases. On close questioning, the numbness is in the muscles in the bones, over the chest, around the mouth, and over the nose. A plethora of bizarre adjectives will often follow if the patient is given enough time. No consistent pattern of anatomic sensory loss can be found on repeated sensory examinations. Patients with CFS also complain about their neuropsychologic functioning. These complaints focus on memory difficulties, poor concentration, periodic confusion, and emotional lability. Formal testing has not given uniform results. Some studies have shown deficits most often in verbal memory, concentration, and tasks, whereas other studies have found above-average neuropsychological functioning in patients with CFS. In general, the abnormalities point to psychological factors interfering with results rather than localizable brain injury (11,12).

There is an associated change in sleep patterns, and although there may be either excessive sleep or insomnia, the common thread is that the patients fail to feel refreshed no matter how much sleep they get (nonrestorative sleep) (13). Several reports note that CFS and fibromyalgia are comorbid with other conditions, but these turn out to be equally

controversial and indistinct entities, such as temporomandibular joint syndrome, chronic headache, irritable bowel syndrome, interstitial cystitis, and postconcussive syndrome (14). Although this clustering, on first thought, would seem to confirm suspicions of the psychological nature of these entities, another unifying theme might relate a postulated abnormality in central nervous system pain control systems, which results in lowered pain threshold to a variety of otherwise banal human conditions (15).

THE DIFFERENTIAL DIAGNOSIS

Postinfectious Fatigue

The most convincing cases of chronic fatigue as a truly distinctive entity are those that are associated with a viral illness. These patients can name the day and often the hour that the fatigue came on and demonstrate a definite tendency to improve in 3 to 5 years (16). The outlook for these patients is much better than the prognosis for CFS patients overall.

The core feature in this group of patients is overwhelming fatigue.

The patients with postviral fatigue suffer a reactive depression, but they still take pleasure in whatever favorite activities they can continue (no anhedonia); there is no self-blame or guilt, and self-esteem is not destroyed. The name postinfectious myalgic encephalomyelitis has been largely abandoned because it implies that actual inflammation in the nervous system has been documented, but it is worthwhile to retain a separate category for these cases. Postviral fatigue is a suitable term. The formal diagnostic criteria do have vestiges of this syndrome contained within them. Certain features, such as painful nodes, and physical findings, such as low-grade fever, recurrent pharyngitis, and palpable posterior cervical nodes, are often seen in the postviral syndrome but are not frequently seen in the patient with ordinary CFS. Many of these patients also often develop alcohol intolerance.

Psychiatric Diagnoses

Some patients have picked up the chronic fatigue label during a lifetime of low energy. These folks never had the energy to play sports, study vigorously, or keep up their side of healthy long-term social relationships. They had practically no extracurricular activities listed beneath their high school yearbook picture, if they even managed to get their picture there at all. They would have declined work-associated promotions because the stress would be intolerable.

Another portion of patients presenting with chronic fatigue are depressed and have an accompanying somatization

disorder. Depression was exclusionary in the 1987 Center for Disease Control criteria, but the 1991 panel relented on this controversial point. The diagnostic problem is much easier to solve if the patient has never been clinically depressed before the diagnosis of CFS. A reactive depression may often be attributed to the impact that disabling fatigue has made on their lives. This can complicate the differential diagnosis, because, besides fatigue, there are other overlap symptoms, such as nonrestorative sleep, poor appetite, and gastrointestinal dysfunction. In addition, both disorders share the debilitating effect of muscular deconditioning and cause the complaints of difficulty with prolonged mental concentration and memory. In various studies of groups of CFS patients with various control groups, 25% to 35% are not depressed. Several studies have indicated there is a substantially higher incidence of prior depression in patients who come to be diagnosed with CFS than in matched controls.

Patients fail to feel refreshed no matter how much sleep they get.

Substance abuse is an exclusionary factor in the CDC diagnostic criteria, so that occult alcoholism and other substance abuse must be ferreted out. Schizophrenia is also excluded, but that leaves hypochondriasis, somatization disorder, generalized anxiety, and malingering in the differential.

Medical Diseases

Medical illness must also be assessed, and the patient must be questioned closely for symptoms of hypothyroidism, hypopituitarism, and hypoadrenalism as well collagen-vascular and rheumatological disease. In the elderly, the apathetic form of hyperthyroidism can present with fatigue. Occult malignancy, liver or kidney failure, nutritional disorders, and chronic anemia, especially vitamin B-12 deficiency, are also diagnostic considerations. Cardiac failure, bradyarrhythmias, and silent myocardial infarctions are easier to rule out. A detailed look at the drugs the patient is taking is also vital. Brust (17) lists 154 drugs, many only by category, that cause fatigue. Interferons reproduce the syndrome completely. β -blockers give a good imitation of the disease as well. Infectious diseases to consider are mononucleosis, acquired immune deficiency syndrome, and Lyme disease. In other places or other times, chronic tuberculosis and brucellosis would be the primary considerations.

Lyme disease – Lyme disease and CFS may share many clinical features, but the overly popular notion of seronegative Lyme disease as a sole basis for fatigue flies in the face of

several excellent studies (18,19). A fatigued patient is unlikely to test positive for Lyme disease unless there has been clinical evidence of *Borrelia* infection, such as erythema migrans, facial palsy, or large joint arthritis (20). Some patients with Lyme disease who have been adequately treated do have persistent symptoms of chronic fatigue or fibromyalgia, but these cases are more reasonably considered as a postinfectious phenomenon. These patients do not respond to repeated courses of antibiotics (21,22).

Every patient with fatigue requires that both blood pressure and pulse be determined while supine and while standing during a 5-minute period. The syndrome of orthostatic intolerance or neuropathic postural tachycardia resembles CFS in several important ways, but most patients will indicate that their symptoms are worse when they are standing upright. Typical patients are 20- to 40-year-old women. A recent study of twins with this syndrome documented a failure of rapid clearance of norepinephrine from the synaptic clefts attributable to a genetic impairment in the norepinephrine transporter. This mechanism accounts for the clearance of 80% to 90% of norepinephrine released from the synapse by uptake into the neuron, so that only 10% to 20% appears in the systemic circulation (23). In other studies, the syndrome seemed to follow a viral illness and was associated with an autonomic neuropathy thought to cause sympathetic denervation of the leg veins (24). These patients not only have postural wooziness, palpitations, leg weakness, shakiness, and rarely syncope but also complain of fatigue, pain, abdominal bloating with early satiety, diarrhea, and vascular headaches, not all of which were dependent on posture. The legs may become bluish-red on standing. These patients are also mostly women and often completely disabled early in the illness, but 90% were able to return to work in one case series with prolonged follow-up. This syndrome could easily be confused with a postviral fatigue syndrome. The sine qua non for this diagnosis is a 30 bpm heart rate increase upon assumption of the upright posture sustained for 5 minutes, without a significant fall in blood pressure. Measurements of venous norepinephrine in the extremities after various types of adrenergic stimulation (cold pressor, tyramine, and nitroprusside) show less of an increase in levels from the lower extremities in the patients versus the control group (25). Short-term relief of symptoms may be seen with an oral α_1 adrenergic receptor agonist midodrine (26). Treatment with β -blockers, fludrocortisone, or salt supplementation has also been advocated.

Neurally mediated hypotension – In the mid-1990s there was considerable interest in patients with postexertional fatigue and lightheadedness on standing who also met criteria for CFS. Tilt table studies, sometimes with isoproterenol infusions, showed significant (≥ 30 mm Hg) falls in blood pressure. Treatment with β -blockers or disopyramide along with increasing salt intake may provide relief for these patients. Although they constitute only a small proportion of

CFS cases, they are an important treatable subgroup to identify (27,28).

Neurologic Diseases

Fatigue may be the chief complaint of up to 40% of patients with multiple sclerosis (MS) and is independent of neurologic deficits (29). MS patients indicate that their fatigue is different from normal fatigue in that it actually stops them from performing normal daily activities. This fatigue often responds to amantadine or modafinil (30). Fatigue may be the very first symptom of multiple sclerosis. PET scanning has shown decreased glucose metabolism in the basal ganglia and frontal cortex of fatigued patients with MS compared with a control group of nonfatigued patients with MS (31).

Every patient with fatigue requires that both blood pressure and pulse be determined while supine and while standing during a 5-minute period.

Some internet-savvy patients will ask about the possibility of having neurosurgery for treatment of their fatigue. Several neurosurgeons have noted dramatic alleviation of fatigue and symptoms of fibromyalgia after suboccipital decompression for Chiari malformations. They insist that patients must have definite clinical features of Chiari malformations before neurosurgery would be considered. Of course, fatigue would not be a reimbursable diagnosis in neurosurgery. No results have yet been published, although hundreds of patients have undergone surgery. There are some studies in the rheumatologic literature associating fibromyalgia with the Chiari malformation and suggesting that a disturbance in brainstem levels of substance P is the unifying factor (32).

LABORATORY EVALUATION

Routine Laboratory

Most patients should have a laboratory evaluation, including a complete blood count with an erythrocyte sedimentation rate (ESR), electrolytes, calcium phosphorus, creatine phosphokinase, liver function studies, and serum protein electrophoresis and thyroid function studies. A rheumatological workup may be indicated in patients with prominent musculoskeletal pain and tenderness.

Imaging Studies

Unless a neurologic problem such as multiple sclerosis is suspected, no sufficiently diagnostic features on imaging are present in CFS to justify routine imaging. Many patients show small, scattered, punctate, predominantly frontal white matter T2 hyperintense areas (33,34). These could be dilated Virchow-Robin spaces. Similar nonspecific findings are seen in patients with migraines.

RECENT RESEARCH IN PATHOPHYSIOLOGY

Investigators have reported a myriad of immunologic findings, but only a few seem to have stood the test of time (35). Natural killer-cell function is depressed, T-cell responses to certain antigens and mitogens are decreased, and some delayed hypersensitivity responses are decreased. A case for a state of heightened immune system activation has been suggested because of the frequent finding of increased autoantibodies and immunoglobulin G. The precision with which interleukin therapy can reproduce the features of CFS has led to a search for abnormal levels of cytokines in these patients. Various reports have shown abnormalities in interleukin (IL)-6, IL-1 α , IL-1 β , T-cell growth factor (TGF)- β , and tumor necrosis factor (TNF)- α , but none of these immunologic abnormalities in the serum or spinal fluid have proven specific or repeatable enough to be diagnostically helpful.

Endocrine evaluations of patients with CFS show frequent lowering of corticotrophin releasing factor with consequent lowering of the corticotrophin releasing factor→adrenocorticotrophic hormone→cortisol system. The alterations in the regulation of the hypothalamic pituitary axis are different from those seen in depression, posttraumatic stress disorder, and perhaps fibromyalgia, but these changes are not sufficiently diagnostic to be useful in daily practice (36,37).

A recent magnetic resonance imaging spectroscopy study has reported decreased concentrations of N-acetylaspartate in the right hippocampus (38). Regional cerebral perfusion studies show a pattern of increased flow in the right thalamus, pallidum, and putamen similar to the patients with depression in the same study (39). The patients with depression did have less flow in the prefrontal region than the CFS group.

The search for a viral cause for CFS has had several moments of high hope, but no single agent has yet been indicted. One of the most exciting early findings was the identification of enterovirus RNA fragments by polymerase chain reaction from muscle biopsies of patients with CFS, but these data have never been confirmed (40). EBV became the most widely known suspect in the 1980s, because several groups of investigators found altered patterns of immunoglobulin G that were interpreted as serological evidence of ongoing/reactivated infection (41). There were several difficulties, because similar immunoglobulin patterns occur for up to a decade in 22% of patients with documented EBV infections. Prolonged fatigue is seen in approximately 20% of

patients after EBV infection. The pattern of immunoglobulins may reflect a disordered immune regulation. Intensive study has not supported a primary role for EBV. The same is true for HHV6, HHV7, cytomegalovirus, and Borna virus, all of which have been suspects at various times. At this time, ordering special virological studies is not helpful in the usual patient presenting with chronic fatigue.

MANAGEMENT

The first problem is what to tell the patient about the diagnosis. Wessely (42) urges that it is the duty of the neurologist "first to question his or her underlying assumptions about these illnesses, second to provide a diagnosis acceptable to both scientific rigour and the patients' own view of their illness, and third to use this diagnosis in a constructive fashion" (p. 43). If you indicate that this is simply a psychiatric disorder, the patient is likely to react with anger and frustration. Your consultation will have a negative therapeutic impact. If, on the other hand, you label the patients as suffering from the incurable immune attack on the brain known as CFS, you run the risk of endorsing unhealthy behaviors. You must instead explain that although the patient meets a set of operational criteria for CFS, the understanding of this entity is very limited. In addition, the following points should be made.

First, because no actual damage to the brain, nerves, or muscles has ever been demonstrated, it is not necessary to remain inactive. A supervised gradually increasing conditioning exercise program may relieve symptoms.

Second, indeed, the neuromuscular negative effects of deconditioning are severe and well-documented. The patient may recall the withered appearance of a limb when a cast was removed. Studies of this phenomenon have shown that disuse results in atrophy of both type I and type II muscle fibers. Twitch force may be preserved, but tetanic force is reduced; voluntary force and fatigability are even more reduced (43). A cerebral activation abnormality has been postulated. Several studies have shown very promising results with supervised, gradually increasing conditioning exercise programs (44). This is a vital part of any management program to reverse the pernicious effects of disuse.

Several studies have shown very promising results with supervised, gradually increasing conditioning exercise programs.

Third, making a new career out of seeking justice for fellow sufferers, rumination about one's symptoms, and dog-

gedly pursuing disability claims are always associated with worsening functional status.

The patient must be persuaded to buy into a sense of responsibility for his or her own recovery. A contract with the patient might be appropriate regarding length of visits and expectations for disability, pain medications, and other support. The physician, in turn, will offer a thorough diagnostic assessment and sage advice to help the patient avoid the numerous threats to health and pocketbook that patients with this problem are prey to and to consider seriously the patient's complaints and give the best possible treatment advice.

Cognitive behavioral therapy has shown positive results in several controlled studies and nicely compliments a program of graded physical exercises. However, not all CFS patients are willing to enter this type of therapy. The dropout rate is significant, and the therapy team should have experience dealing with these patients. One recent study showed that cognitive behavioral therapy was more effective than guided support groups (45).

Cognitive behavioral therapy has shown positive results in several controlled studies.

Small doses of amitriptyline (10 mg every night) have proven useful in fibromyalgia, and it is worth considering antidepressants in CFS (46). A variety of other remedies have been assessed in crossover studies (47). Transient improvement with steroids seem nonspecific and not worth the long-term consequences of steroid therapy. A small study showed positive results with intramuscular injections of magnesium, but a larger study needs to be done to ascertain this. No magnesium deficiency has been found in patients with CFS. Immunotherapy using IgG or interferon- α has not been effective. Acyclovir has also been shown to be ineffective in a careful study (48). Most treatment is supportive and uses symptomatic drug therapy.

Despite best efforts, the prognosis is poor in CFS, with only a small percent of patients returning to normal after 5 years. This underscores the importance of separating the cases of postviral fatigue, which have a much better outlook, and using careful diagnostic assessment to find treatable causes. In one recent longitudinal study, only 3% of the patients felt normal and 17% reported improvement after 18 months. Predictive factors for improvement were milder fatigue, less attribution of the symptoms to physical factors, and a sense of control over the symptoms (49).

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