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CHRONIC FATIGUE SYNDROME Chronic fatigue syndrome (CFS) (referred to as myalgic encephalomyelitis in the United Kingdom and Canada) is characterized by 6 months or more of severe, debilitating fatigue, often accompanied by myalgia, headaches, pharyngitis, low-grade fever, cognitive complaints, gastrointestinal symptoms, and tender lymph nodes. The search continues for an infectious cause of chronic fatigue because of the high percentage of patients who report abrupt onset after severe flu-like illness. The syndrome of chronic, debilitating fatigue has been an important clinical syndrome for psychiatry and neurology since the post-Civil War era in the 19th century. At the time the condition was known as neurasthenia or neurocirculatory asthenia. The disorder decreased in frequency during the mid-20th century but reappeared in the United States in the mid-1980s. In 1988, the US Centers for Disease Control and Prevention (CDC) defined specific diagnostic criteria for CFS. The disorder is classified in the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) as an ill-defined condition of unknown etiology under the heading "Malaise and Fatigue" and is subdivided into asthenia and unspecified disability.

Epidemiology The exact incidence and prevalence of CFS are unknown, but the incidence ranges from 0.007 percent to 2.8 percent in the general adult population. The illness is observed primarily in young adults (ages 20 to 40). CFS also occurs in children and adolescents but at a lower rate. Women are at least twice as likely as men to be affected. In the United States, studies show that about 25 percent of the general adult population experience fatigue lasting 2 weeks or longer. When the fatigue persists beyond 6 months, it is defined as chronic fatigue. The symptoms of chronic fatigue often coexist with other illnesses, such as fibromyalgia, irritable bowel syndrome, and temporomandibular joint disorder.

Etiology The cause of the disorder is unknown. The diagnosis can be made only after all other medical and psychiatric causes of chronic fatiguing illness have been excluded. Scientific studies have validated no pathognomonic signs or diagnostic tests for this condition. Investigators have tried to implicate the Epstein-Barr virus (EBV) as the etiological

agent in CFS. EBV infection, however, is associated with specific antibodies and atypical lymphocytosis, which are absent in CFS. Results of tests for other viral agents, such as enteroviruses, herpesvirus, and retroviruses, have been negative. Some investigators have found nonspecific markers of immune abnormalities in patients with CFS; for example, reduced proliferation responses of peripheral blood lymphocytes, but these responses are similar to those detected in some patients with major depression. Several reports have shown a disruption in the hypothalamic-pituitary-axis (HPA) in patients with CFS, with mild hypocortisolism. Because of this, exogenous cortisol has been used to reduce fatigue but with equivocal results. Cytokines such as interferon (IFN)- α and interleukin (IL)-6 are under investigation as possible etiologic factors. Elevated levels have been found in the brains of some patients with CFS. Some magnetic resonance imaging (MRI) studies have found a decrease in volumetric regional gray and white matter in patients with CFS. CFS may be familial. In one study, the correlation within twin pairs for monozygotic twins was more than 2.5 times greater than the correlation for dizygotic twins. Further studies are needed, however.

Diagnosis and Clinical Features Because CFS has no pathognomonic features, diagnosis is difficult. Physicians should attempt to delineate as many signs and symptoms as possible to facilitate the process. Although chronic fatigue is the most common complaint, most patients have many other symptoms (Table 14-1). As a patient's history unfolds, clinicians are likely to think of a variety of disease states that fall within the range of neurological, metabolic, or psychiatric disorders to account for the patient's distress. In most cases, however, no picture of any disorder clearly emerges from history taking alone.

Table 14-1 Signs and Symptoms Reported by Patients with Chronic Fatigue Syndrome

The physical examination is also an unreliable source of diagnostic certainty. In addition to chronic fatigue, for example, patients may complain of feeling warm or having chills with normal body temperature, and others may complain of lymph node tenderness in the absence of node enlargement. These and other equivocal findings neither confirm nor rule out the disorder. The CDC diagnostic criteria for CFS, which are listed in Table 14-2, include fatigue for at least 6 months, impaired memory or concentration, sore throat, tender or enlarged lymph nodes, muscle pain, arthralgias, headache, sleep disturbance, and postexertional malaise. Fatigue, the most obvious symptom, is characterized by severe mental and physical exhaustion, sufficient to cause a 50 percent reduction in patients' activities. The onset is usually gradual, but some patients have an acute onset that resembles a flu-like illness.

Table 14-2 Centers for Disease Control and Prevention Criteria for Chronic Fatigue Syndrome

In some cases, a noticeable correlation exists between CFS and neurally mediated hypotension, an autonomic nervous system dysfunction. It has been suggested that patients presenting with CFS symptoms undergo a tilt-table test to delineate symptoms attributable to hypotension so that they may be placed on appropriate pharmacotherapy. A 55-year-old woman is referred to a neuromuscular disease specialist by her primary care physician for assessment and treatment of chronic fatigue. The symptoms have lasted for about 2 years and have worsened. Her primary complaint is a debilitating fatigue, which she calls "weakness." She also has painful sensations and aching in her muscles and joints, which is exacerbating whenever she "pushes" herself to be more active. Thorough internal medicine and rheumatological evaluations have yielded no definite findings except a persistently low-grade elevation of the sedimentation rate, at about 35 mm. She is taking prednisone, 20 mg per day, and she wishes to continue this medication, but her rheumatologist recommends against it. This caused conflict with her physician, and he refused to

see her any longer or to prescribe the prednisone. Her primary care physician wanted to refer her to a psychiatrist, but she refused. The patient had a refined manner, dressed tastefully, and spoke articulately. She was mildly obese and moved slowly, even laboriously, as she entered the consultation room. She opened the interview and controlled the early stages of the interaction by explaining that she needs to have the prednisone, or she will just “die.” Before she began the daily prednisone dosing about a year previously, she explained, she was almost immobile; sitting at home in a large chair, requiring constant care from her husband, who was a prominent attorney in town. “It almost ruined his practice,” she explained. “He couldn’t work. He had to come home to look after me several times each day.” As she spoke during the opening stages of the interview, the theme developed into

that of psychosomatics. “Don’t say this is all in my head,” she said forcefully. “Because it is not,” she says. “It is true that I had some...difficulties when I was young,” she continued. “But that has nothing to do with what is happening now.” She paused and looked squarely at the consultant. “Look at me!” she said. “Do I look depressed to you? Do I look anxious? Do I look like a psychiatry patient?” The consultant had to admit that she did not show clear and present psychiatric signs and symptoms. Judging by the patient’s clinical history, it was clear that the patient has been relatively healthy, except for the neuropsychiatric symptoms of fatigue. In addition to the prednisone, she took a selective serotonin reuptake inhibitor (SSRI) medication at a modest dose and a sleep medication each night. She also took an angiotensin-converting enzyme (ACE) inhibitor for hypertension. The patient showed no overt red flags to suggest unusual stressors or markers for psychopathology. Although she did not have a career outside the home, she was usually active in the community as a volunteer or a member of various boards. Her marriage to the attorney was her second marriage and they had been married 20 years. Her fatigue symptoms developed insidiously over the past 2 to 3 years and became so profound that she ceased all community activities and sat at home. Even with the prednisone, which the patient stated had “done miracles,” the patient had not returned to her premorbid functioning level in terms of leaving her house to continue her work as a volunteer or community board member. (Adapted from Randolph B. Schiffer, M.D., and James W. Albers, M.D., Ph.D.)

Differential Diagnosis Chronic fatigue must be differentiated from endocrine disorders (e.g., hypothyroidism), neurological disorders (e.g., multiple sclerosis [MS]), infectious disorders (e.g., acquired immune deficiency syndrome [AIDS], infectious mononucleosis), and psychiatric disorders (e.g., depressive disorders). The evaluation process is complex, and a diagnostic scheme is listed in Table 14-3.

Table 14-3 Approach to the Assessment of Persistent Fatigue

Up to 80 percent of patients with CFS meet the diagnostic criteria for major depression. The correlation is so high that many psychiatrists believe that all cases of this syndrome are depressive disorders, yet patients with CFS rarely report feelings of guilt, suicidal ideation, or anhedonia and show little or no weight loss. Also, usually, no family history of depression or other genetic loading for psychiatric disorder is found and few, if any, stressful events have occurred in patients’ lives that might precipitate or account for a depressive illness. In addition, although some patients respond to antidepressant medication, many eventually become refractory to all psychopharmacological agents. Regardless of diagnostic labeling, however, depressive comorbidity requires treatment with either antidepressants, cognitive-behavioral therapy, or a combination of both.

Course and Prognosis Spontaneous recovery is rare in patients with CFS, but improvement does occur. At present, most reports on the course and prognosis are based on small samples. In

study, 63 percent of patients with the syndrome, followed for up to 4 years, reported improvement. Patients with the best prognosis have had no previous or concurrent psychiatric illness, are able to maintain social contacts, and continue to work, even at reduced levels. Treatment of CFS is mainly supportive. Physicians must first establish rapport and not dismiss patients' complaints as being without foundation. The complaints are not imaginary. A careful medical examination is necessary, and a psychiatric evaluation is indicated, both of which are geared to rule out other causes for the symptoms. No effective medical treatment is known. Antiviral agents and corticosteroids are not useful, although a few patients have shown a lessening of fatigue with the antiviral drug amantadine (Symmetrel). Symptomatic treatment (e.g., analgesics for arthralgias and muscular pain) is the usual approach, but nonsteroidal anti-inflammatory drugs (NSAIDs) are not effective. Patients must be encouraged to continue their daily activities and to resist their fatigue as much as possible. A reduced workload is far better than absence from work. Several studies have reported a positive effect from graded exercise therapy (GET). Psychiatric treatment is desirable, especially when depression is present. In many cases, symptoms improve markedly when patients are in psychotherapy. Cognitivebehavioral therapy is especially useful. Therapy is geared toward helping patients overcome and correct mistaken beliefs, such as fear that any activity causing fatigue worsens the disorder. Pharmacological agents, especially antidepressants with nonsedating qualities, such as bupropion (Wellbutrin), may be helpful. Nefazodone (Serzone) was reported to decrease pain and improve sleep and memory in some patients. Analeptics (e.g., amphetamine or methylphenidate [Ritalin]) may help reduce fatigue. Table 14-4 contains recommendations for a general approach to pharmacotherapy. Table 14-4 Recommendations for a Logical Pharmacotherapy of Chronic Fatigue

Self-help groups have helped patients with CFS. They derive benefit from the group dynamic of instilling hope, offering identification, sharing experiences, and imparting information. The cohesion of members in such groups also raises self-esteem, which is usually impaired in these patients, who often feel that their physicians are not taking them seriously. For this reason, many persons with the syndrome rely on vitamins, minerals, and miscellaneous herbal products or treatment methods that fall under the rubric of alternative medicine. Neither these nor other unidentified general tonics have been peer reviewed in the medical literature, and they are of little or no benefit. FIBROMYALGIA Fibromyalgia is characterized by pain and stiffness of the soft tissues, such as muscles, ligaments, and tendons. Local areas of tenderness are referred to as "trigger points." The cervical and thoracic areas are affected most often, but the pain may be located in the arms, shoulders, low back, or legs.

Comorbidity There is a significant overlap and comorbidity between patients with fibromyalgia and other psychiatric disorders, such as depression, panic and anxiety, and posttraumatic stress disorder (PTSD). Fibromyalgia is often present in CFS and depressive disorders. The onset of the psychiatric comorbidity most often occurs over a year before the onset of fibromyalgia. There is also significant comorbidity between patients with fibromyalgia and rheumatologic disorders, such as rheumatoid arthritis, systemic lupus, and others. The symptomatology of fibromyalgia does not correlate well with disease activity of associated medical diseases, however, when such diseases are present. Epidemiology Fibromyalgia most commonly affects women (3 percent) more than men (1 percent), particularly those of working age. In fact, the diagnosis of fibromyalgia is associated

with work disability at rates approaching 50 percent in primary care settings. There are about 5 million Americans age 18 or older with the disorder. Etiology The etiology of fibromyalgia remains unclear. However, it is often precipitated by stress that causes localized arterial spasms that interfere with perfusion of oxygen in the affected areas. Diagnosis and Clinical Features The diagnosis of fibromyalgia is made after excluding rheumatic disease or hypothyroidism. According to the 2010 American College of Rheumatology criteria, patients must have widespread pain for at least 3 months at predefined tender points upon palpation. The symptoms of fibromyalgia are almost always broader than pain alone and include complaints of fatigue, muscular weakness, sleep disturbance, and impairment of certain cognitive domains such as concentration (Table 14-5). Table 14-5 American College of Rheumatology Fibromyalgia Diagnostic Criteria

Treatment Varieties of psychotropic drugs are commonly prescribed for fibromyalgia, especially antidepressants. Pregabalin (Lyrica), an antiepileptic agent, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain associated with fibromyalgia. A typical dosing for pregabalin is 150 mg three times a day. A wide spectrum of other analgesics, including aspirin and acetaminophen, is prescribed for such patients. Some patients may respond to NSAIDs. Patients with more severe cases may respond to injections of an anesthetic (e.g., procaine) into the affected area; steroid injections are usually not warranted. The SSRI and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant duloxetine (Cymbalta) has been reported to be effective in treating patients with this disorder. Experience suggests, however, that benefits from such therapies are neither long lasting nor associated with return to employment. Nonpharmacologic treatment plans have generally included GET regimens and rehabilitation programs, with modest symptomatic benefits. Massage of trigger points may also be of use. Psychotherapy is of help to enable patients to gain insight into the nature of the disorder and also to help them identify and deal with psychosocial

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