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REVIEW

CHRONIC FATIGUE SYNDROME – A NOT YET FULLY UNDERSTOOD ENTITY

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Abstract. The chronic fatigue syndrome (CFS) is characterized by an intense fatigue state, which is not relieved by bed rest, has duration of at least 6 months and is responsible for impairment of the subject's capacity of fulfilling daily activities. The diagnosis is difficult because besides fatigue, the syndrome associates symptoms common for many other diseases, such as – muscle pain, memory and concentration disorders, headaches, multiple joint pain, sleep disorders, tender lymph nodes. The causes are unknown; the syndrome affects more often the female sex, during the fourth and fifth decades of life. Usually it lasts for years. An important feature is represented by worsening of the symptoms after intense physical or mental activity, lasting for more than 24 hours. Although this does not cover the whole polymorphism of the syndrome, in 1994 two diagnostic criteria were established: 1. extreme fatigue, lasting for at least 6 months, without other medical condition; 2. at least 4 of the following symptoms: severe impairment of short term memory and/or of the concentration capacity; muscle pain; multiple joint pain; sore throat; unresting sleep; headaches displaying a new pattern or severity; tender lymph nodes; post-exertional fatigue, lasting more than 24 hours. More than one million people were diagnosed with the syndrome in the USA, but tens of millions of people have similar syndromes, without fully satisfying the diagnosis criteria. It is estimated that only 20% of the cases are diagnosed. CFS may be as disabling as multiple sclerosis, lupus, rheumatoid arthritis, congestive heart failure, etc. Although a cause hasn't been isolated yet, possible etiologies include viral infections, stress and exposure to toxins. Immune data did not reveal immune factors involved in the genesis of the syndrome, besides a predisposition to developing allergic reactions. The hypothalamus-pituitary-adrenal axis showed no changes useful for diagnosis or therapy. Overlapping CFS and neurally mediated hypotension were investigated with no results in treating all cases. The syndrome shows a cyclic evolution with remission and relapse periods. After the apparent recovery, a relapse is usual. The earlier the diagnosis and therapy initiation, the better the chances of full and rapid recovery. The therapy targets each patient's symptoms – pain, sleep disorders, memory and concentration problems. Many patients may overreact to medication, especially to sedatives. Usually, the therapeutic benefits are obtained with lower doses than usual. The medication's side effects may aggravate the symptoms of the syndrome. The patients usually display high sensitivity to caffeine, alcohol and nicotine. Alternative therapies, such as acupuncture, massage, yoga are used for relieving the symptoms. There is need for more studies focused on the causes of the chronic fatigue syndrome.
Keywords: chronic fatigue syndrome (CFS)

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Definition and history

The chronic fatigue syndrome (CFS) is a disorder mainly characterized by a state of extreme fatigue. The fatigue is not improved by bed rest, has a long duration in time and it impairs one's capacity of fulfilling daily tasks. Historically known under other names, CFS was first described during the eighteenth century. In 1934, at the Los Angeles County Hospital the first cases of a disease then called atypical poliomyelitis were documented; this disease highly resembled the chronic fatigue syndrome, affecting a large number of nurses and doctors. In 1955, at the Royal Free Hospital in London, another outbreak affected the staff; it was called benign myalgic encephalomyelitis, based on the description of Achenson, Ramsay and others. The name chronic fatigue syndrome was established in 1988 – the Holmes definition, replacing the chronic Epstein-Barr virus syndrome (Holmes, 1988, Jorgensen 2008). The syndrome includes: a state of fatigue with duration of at least 6 months, muscle pain, memory and concentration disorders, headaches, multiple joints pain, sleep disorders, sore throat, tender lymph nodes. As long as a variety of diseases may cause similar symptoms, the syndrome is difficult to diagnose. Two criteria for definition were established in 1994, by an international group of CFS research specialists: 1. severe chronic fatigue of six months or longer duration without association of another medical condition;

2. at least four of the following symptoms: serious impairment of short-term memory and/or concentration; sore throat; tender lymph nodes; muscle pain; multiple joint pain with no swelling or redness; headaches of a new pattern or severity; unresting sleep; post-exertional fatigue lasting more than 24 hours. A number of other symptoms may be associated in CFS patients, with an occurrence rate varying from 20 to 50 %, such as: abdominal pain, bloating, chest pain, alcohol intolerance, chronic cough, diarrhea, dizziness, earaches, dry eyes or mouth, jaw pain, irregular heartbeat, nausea, morning stiffness, night sweats, psychological problems (depression, irritability, anxiety, panic attacks) shortness of breath, skin sensations and weight loss (Gallagher, 2004).

Occurrence and etiology

The chronic fatigue syndrome affects over one million people in the United States and at least 150 thousands in the United Kingdom. Tens of millions of people display similar syndromes without satisfying the complete adopted definition of the CFS. CFS affects women four times more often than men and is more common in the fourth and the fifth decades of life, although it can be found in children and teenagers as well. It is estimated that only 20% of the cases are diagnosed (Reeves, 2003, Ranjith, 2005). The symptoms and their consequences may be severe; CFS may be as disabling as multiple sclerosis, lupus, rheumatoid arthritis, congestive heart failure and other similar chronic conditions. Even if a certain cause for the development of CFS was not identified, the possible etiology of the syndrome includes virus infection, stress and toxins.

Infectious hypotheses. CFS was first believed to be caused by a virus infection (Epstein-Barr, EBV, mononucleosis). It is now apparent that CFS is not exclusively caused by any known infectious disease agent (Reid, 2000). No association was found between CFS and infection with EBV, human retroviruses, human herpesvirus 6, Candida albicans, enteroviruses, bornaviruses or Mycoplasma. It is possible that CFS has multiple causes leading to a common endpoint, in this case viruses or other infectious agents may be involved to a certain degree in the etiology of CFS. Recent data show that infection with Epstein-Barr virus, Ross River virus and Coxiella burnetti are followed by a post-infective condition that includes the criteria for CFS in approximately 12% of cases. The severity of the acute infectious disease was found to predict which subjects would display symptoms of CFS, at six-months and one-year period after infection (Patarca-Montero, 2004).

Immune data. The inappropriate production of cytokines, such as interleukin-1 and other inadequate function of different immune factors were considered possible causes for the development of CFS. However, no specific immune disturbances were found to be associated with CFS. Autoantibodies and immune complexes suggestive of autoimmune disease were observed in many CFS patients, but no specific tissue damage was found. No increased risk of cancer or opportunistic infections was observed in CFS patients. Several studies showed that CFS patients often had a history of allergies, compared to healthy controls; it is considered that the allergic status is a predisposing condition for CFS (Prins, 2006).

Hypothalamic-Pituitary-Adrenal Axis. Physical or emotional stress is usually reported as a pre-onset situation in CFS patients. Stress will

lead to increased cortisol and other hormones release. Cortisol and corticotropin-releasing hormone (CRH) influence many body systems and the immune functions, as well as different aspects of behavior. Recent studies have shown that CFS subjects often produce lower levels of cortisol compared to healthy controls. However, the level of cortisol cannot be used as diagnostic marker in CFS, because the low cortisol levels are found in the accepted range of normal (the difference was only noticed between cases and controls). A trial in which replacement therapy with hydrocortisone or a placebo was used, conducted for 12 weeks, found that low levels of cortisol by itself cannot be incriminated for CFS and that hormonal replacement is not an effective therapy. Additional studies are needed to elucidate the neuroendocrine patterns of CFS (Sharpe, 1991).

Neurally mediated hypotension Studies were conducted to establish if neurally mediated hypotension is usual in CFS patients (Rowe and co.) because an overlap was observed in patients with CFS and those with hypotension. Neurally mediated hypotension can be induced using tilt table testing, when neurally mediated hypotension patients will develop low blood pressure and characteristic symptoms such as visual dimming, lightheadedness or a slow response to verbal stimuli. Most of the CFS patients develop lightheadedness or worsened fatigue when standing for prolonged periods of time or when exposed to heat (for example a hot shower). The studies tried to determine if the medication used for neurally mediated hypotension patients is beneficial for CFS patients. A subset of CFS patients improved strikingly, but not all of them (Salit, 1997).

Diagnosis

The chronic fatigue syndrome is accompanied by fatigue, but this is not the kind of fatigue we experience after a busy day or week, after a sleepless night or after a stressful event. It's a severe and incapacitating fatigue not improved by bed rest and worsened by physical or mental activity; it is of new onset (not lifelong) and it is not provoked by ongoing exertion. People with CFS function at a significantly lower level of activity than that which they were priorly capable of. This results in significant reduction of occupational, social, personal and educational activities. A CFS diagnosis is considered in subjects who show at least six months of unexplained fatigue, accompanied by other characteristic symptoms (at least four of these symptoms are needed to be associated with fatigue for the diagnosis of CFS, according to 1994 established diagnosis criteria): impaired memory or concentration; exhaustion and increased symptoms lasting more than 24 hours, following physical or mental exercise; unrefreshing sleep; multiple joint pain (without redness or swelling); muscle pain; headaches of a new pattern or severity; recurrent sore throat; tender cervical or axillary lymph nodes. Besides these eight primary symptoms, some other symptoms were found in CFS patients. The frequency of these symptoms varies among patients. These symptoms are: irritable bowel, abdominal pain, bloating, nausea, diarrhea; chills and night sweats; brain fog; chest pain; shortness of breath; chronic cough; visual problems (blurring, sensitivity to light, eye pain or dry eyes); allergies or sensitivities to foods, alcohol, odors, chemicals, medications, noise; difficulty to maintain upright position (orthostatic instability, irregular heartbeat, dizziness, balance problems or fainting); psychological problems (depression, irritability, mood swings, anxiety, panic attacks); jaw pain; weight loss or gain (Clark, Craig, 2002).

A CFS diagnosis is possible only when other morbid conditions were excluded. CFS may resemble many other diseases, such as: mononucleosis, Lyme disease, lupus, multiple sclerosis, primary sleep disorders, fibromyalgia, severe obesity, major depressive disorder and side effects of different medications (Wyler, 2007). Because CFS is sometimes found in members of the same family, there might be a familial predisposition or a genetic link; further studies are needed in this direction (Walsh, 2001). Diagnosis of CFS is peculiarly difficult because there is no specific diagnostic laboratory test or biomarker for CFS, and fatigue and other symptoms are common for many diseases; CFS does not show objective symptoms and patients do not appear to be sick; the syndrome has a characteristic pattern of remission and relapse; symptoms show variety from person to person regarding type, number, severity (not even two patients show exactly the same symptoms). These factors explain the low diagnosis rate; for example, out of four million Americans with CFS, only less than 20% were diagnosed (Aslakson, 2006).

Clinical course. The severity of the chronic fatigue syndrome differs from one patient to another; some of them being able to maintain active

lives. Usually, however, CFS reduces school, work and personal activities. Even if symptoms vary a lot from person to person, in number, type and severity, all CFS patients are functionally impaired to some degree. A small percent of patients are so disabled that they are bed-linked, and even daily toilet and the use of the bathroom seem to be problematic. CFS often follows a cyclical course – periods of illness alternating with periods of relative well-being. Sometimes patients experience partial or complete remission of symptoms, but usually they relapse. This characteristic evolution of CFS with remissions and relapses makes CFS difficult to manage. The percentage of recoveries is unknown, but it seems that the sooner the treatment is started, the better the chances for recovery. Early diagnosis and therapy are of utmost importance; delays in establishing the diagnosis and follow-up of the treatment may complicate the disease and delay the recovery (Cairns, 2005, Chambers, 2006).

Treatment options

The pharmacologic therapy aims to relieve specific symptoms experienced by each patient. Many over-the-counter and prescription drug therapies are used in treating sleep disorders, pain, cognitive difficulties and other symptoms of CFS. A problem is that many CFS patients are sensitive to medications, especially sedating drugs. The therapeutic benefits are often obtained at doses lower than the normal ones. The medication can cause side effects which may develop new symptoms or worsen the existing ones. There are drugs which act on several symptoms, allow the use of fewer drugs addressing multiple symptoms and limit side effects; an example are the tricyclic antidepressants, which improve mood, but may also help with sleep and pain (Friedberg, 2001). Depression may be part of the symptoms of CFS, but it may also appear as consequence of the syndrome. If depression develops, it must always be treated, because it can aggravate the evolution of chronic fatigue syndrome; serotonin reuptakers are used for treating depression. Food supplements and vitamins are largely used in CFS, for symptoms' relief. Patients should avoid herbal remedies which may be potentially dangerous, such as – ephedra, comfrey, kava, germander, chaparral, bitter orange, licorice root, yohimbe. Usually, sensitivities to caffeine, alcohol and tobacco are present in CFS patients (Rimes, 2005). Alternative therapies such as acupuncture, aquatic therapy, massage, deep breathing, yoga, have been found to help some of the CFS patients. Progressive exercise programs were used with good results in the treatment of CFS patients (Mc Cully, 1996).

The priority remains finding the real triggering factor of the chronic fatigue syndrome.

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