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Review

Chronic Fatigue Syndrome: Risk Factors and Treatment Recommendations

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ABSTRACT

Chronic fatigue syndrome (CFS) is serious, a long-term disorder with a heterogeneous character that can be diagnosed based on clinical foundations or its symptoms. The cause or factors that lead to this condition, which lowers the patient's quality of life, cannot be fully determined, and there is no specific diagnosis. It has some triggering factors. In addition to drug therapy, cognitive-behavioral therapy, sleep therapy, exercise therapy, and nutrition also contribute to the treatment of the condition. In this review, the causes of CFS were examined.

Keywords: Chronic fatigue syndrome, depression, energy low, inflammation, weakness

Diagnosing and identifying chronic fatigue syndrome (CFS) is quite difficult to detect. Fatigue is a temporary event frequently encountered in society as exhaustion.[1] It can be classified into three categories. Prolonged fatigue is a type of fatigue that lasts at least one month. Chronic fatigue lasts at least six months and causes disability. The broadest definition of CFS is as follows: It is a serious psychiatric disorder that occurs without a clearly understood cause and lasts for at least six months, accompanied by rheumatological, infectious, and neuropsychiatric symptoms, as well as muscle and skeletal pain, headaches, sore throat, impaired concentration, and disrupted sleep patterns.[2]

Chronic fatigue syndrome is a clinical or symptomatic diagnosis independent of physical examination or routine laboratory results. Infectious, immunological, neuroendocrine, sleep, and psychiatric mechanisms have been investigated; however, a clear etiology of CFS has not yet been established. It is likely that CFS is a heterogeneous disease with different pathophysiological disorders that present with similar symptoms. Regardless of its pathogenesis, people with CFS have a significantly impaired functional status that results in significant personal and economic morbidity, similar to those with other chronic illnesses.[3]

DIAGNOSIS

In 2015, diagnostic criteria for CFS were published by the US National Academy of Medicine. According to the defined criteria, the patient must have experienced fatigue that lasts for at least six months, limits or impairs their ability to engage in educational, occupational, personal, or social activities, is not the result of exertion, and cannot be relieved by rest. Additionally, the patient must exhibit at least three of the following symptoms: post-exertional malaise, unrefreshing sleep, cognitive impairment, and orthostatic intolerance. There are no laboratory tests available to diagnose CFS.[4,5]

EPIDEMIOLOGY

Chronic fatigue syndrome has been reported to be more common in individuals aged 40-49, with white skin color, young people, successful women, and experienced employees.[6] Estimates for the prevalence of CFS vary between 0.007% and 2.8% in the general adult population and between 0.006% and 3.0% in primary care or general practice. Although

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CFS is observed in lower age groups such as children and adolescents, it is at a lower rate.[7]

CLINICAL STUDIES

Depression tendencies have been observed in patients with CFS. Studies have shown that most individuals with CFS have major depressive disorder symptoms or have experienced at least one major depressive episode in the past. Although there is some overlap in symptoms between CFS and depression, patients with CFS also experience symptoms such as throat pain, lymphadenopathy, and post-exertional fatigue, which are not typical of depression. Symptoms of guilt, anhedonia, and lack of motivation seen in depression are not observed in CFS.[8]

As the name suggests, fatigue is the distinguishing feature of CFS. In cases where CFS is observed, patients generally report sudden onset of fatigue with perfect physical fitness, energy, and typically a flu-like illness prior to the condition. After the onset of the disorder, patients report that physical exertion tends to exacerbate fatigue. In many patients with CFS, there is also a low tolerance for alcohol and other drugs that affect the central nervous system, as well as nausea, anorexia, dizziness, and night sweats. In almost all patients with CFS, a decline in social relationships is observed, in addition to other unwanted consequences of the condition. Approximately one-third of patients with CFS cannot work, while in the remaining two-thirds, only part-time work is possible. Studies on the general population have shown that women with CFS, members of minority groups, and non-working individuals may experience more functional impairment and symptom severity than men, whites, and working individuals. However, a diagnosis of CFS is not associated with increased mortality. About 70% of patients diagnosed with CFS also meet the criteria for fibromyalgia. 30-70% of fibromyalgia patients also meet the criteria for CFS.[9]

ETIOPATHOGENESIS

Although the etiopathogenesis of CFS is not fully understood, many factors have been proposed as causes, but none have been proven to cause CFS.[6]

Many theories have been put forward for the pathophysiology of CFS, with earlier theories focusing on the prominence of symptoms suggestive of an acute viral or psychiatric disorder. Subsequent research has revealed abnormalities in a wide range of areas, including immune function, brain structure and function, sleep structure, neuroendocrine responses, virological studies, exercise capacity, and different psychological profiles. Despite demonstrating these abnormalities, such findings largely remain as isolated observations, with their interactions and relationships yet to be discovered.[10] Several factors have been proposed to be effective in the etiopathogenesis of CFS.

These factors include food intolerance, non-specific infections such as herpes virus, enterovirus, Epstein-Barr virus (EBV), infectious mononucleosis (+), retroviruses (+), immunological factors such as decreased lymphocyte proliferation and natural killer cell cytotoxicity, decreased serum immunoglobulin-G and subtypes, increased prevalence of atopy, positive autoantibodies, and sicca symptoms. These factors also can be neuroendocrine system factors such as hypothalamic-pituitary-adrenal (HPA) axis dysfunction, decreased insulin-like growth factor-1 levels, autonomic dysfunction, increased sensitivity to serotonin and dopamine receptor antagonists, and abnormalities in central cortisol levels are thought to be related to corticotropin-releasing hormone and serotonin levels and function. Furthermore, these can include neuromuscular system factors such as muscle fiber atrophy in Type II fibers with tubular and mitochondrial dysfunction, changes in urinary excretion of protein metabolites, and normal muscle strength and endurance. Brain structure and function show an increase in abnormalities in brain white matter on magnetic resonance imaging an increase in regional cerebral blood flow on single-photon emission computed tomography, and can cause walking and motor abnormalities. Finally, with regard to cognitive performance, factors such as attention, concentration, and other cognitive dysfunctions, as well as visual and auditory memory deficits, can be mentioned.[1,11]

ROLES OF VIRUSES

Viral infections, particularly herpes viruses, especially EBV, are considered the main factors among the causes of CFS. In studies in this field, evidence has been found for 13 types of viruses that are effective in CFS, while it has been reported that EBV seronegative individuals have been observed despite being diagnosed with CFS. The presence of neurocognitive findings in infections caused by polioviruses, as well as changes in activity in the HPA axis and endocrine disorders such as increased adrenocorticotropic hormone secretion and prolactin increase in post-polio fatigue, and electrophysiological findings

such as electroencephalogram, slowing have been evaluated as areas where the two pictures overlap. In research on the relationship between immunity and stress, decreased natural killer cells in students under exam stress and reactivation findings in latent herpes viruses have been detected. The heterogeneous structure of CFS has been suggested to be due to stress making the pathology of the immune system visible.[12]

PROGNOSIS

According to research, 17-64% of patients with CFS show improvement, while less than 10% fully recover, and 10-20% of patients are observed to worsen while under follow-up.[7] The clinical picture varies individually. Chronic fatigue syndrome generally follows a cyclic course with remission and relapse periods. Factors that cause relapse include intense activity such as maximum exercise for eight to ten minutes, stress, inadequate rest, infection, and any kind of immune stimulation. Prolonged disease duration, severe fatigue, psychiatric comorbidity, and old age are risk factors for a poor prognosis.[13]

TREATMENT

Due to reasons such as CFS having an uncertain etiology and lack of diagnostic certainty, there are no treatment options that can be definitively stated. Current treatment options, whether pharmacological or non-pharmacological, generally aim to relieve symptoms. The basis of CFS treatment is to create an individualized treatment plan, support education, and social life, and establish stages for regularly monitoring new symptoms or worsening functions.[14]

Drugs

Although many pharmacological studies have been conducted for CFS, the desired result has not yet been achieved. Drugs prescribed for CFS include anticonvulsants, antidepressants, narcotics, antivirals, nonsteroidal anti-inflammatory drugs, and immunomodulators. Nonsteroidal anti-inflammatory drugs such as ibuprofen and naproxen can be prescribed for patients with muscle, joint, and headache pain. Narcotics such as tramadol, codeine, and morphine are prescribed for short-term severe pain complaints. Gabapentin and pregabalin can help with sleep disorder symptoms.[15,16] There is no strong evidence supporting the use of antiviral drugs and medications such as hydrocortisone or fludrocortisone. Although most studies conducted are not at the desired level, the number of cases is limited. In another clinical study, it was shown that the use of methylphenidate, melatonin, citalopram, and galantamine did not improve symptoms.[17]

Cognitive Behavioural Theraphy

Cognitive behavioral therapy is a non-pharmacological and increasingly important psychological and social support treatment method that shows patients with CFS how to cope with their own beliefs and thoughts about their condition and how certain thoughts and behaviors can affect symptoms. In a randomized controlled study conducted on adult patients with CFS, cognitive behavioral therapy has been shown to have positive effects on fatigue levels, work and social adjustment, depression, and anxiety.[17]

The main principle of cognitive behavioral therapy is generally similar to rehabilitation principles. During cognitive behavioral therapy, not only the patient but also the patient's family and/or children, if any, should be consulted and provided with the necessary support. Especially if the patient is an adolescent, it is important to communicate with their family and teachers and provide necessary psychological and social support. It has been observed that these young cases respond positively to cognitive behavioral therapy treatment, showing an improved prognosis within an average of between two and four years.[18]

Exercise

Although it is often perceived that less movement is more beneficial for patients with CFS, it has been observed that mild exercise reduces patients' pain and improves their daily quality of life. The mild exercise should be planned to gradually increase while being monitored for up to a maximum of 30 minutes and using a maximum of 60% oxygen at a submaximal heart rate. In a study, gradually increasing exercise therapy was found to be more effective than relaxation and flexibility exercises in patients with CFS who did not have accompanying sleep disorders or psychiatric disorders, and these effects were reported to continue up to one year after exercise therapy. In another study, it was observed that fatigue symptoms in patients with CFS decreased with gradually increasing exercise therapy. The intensity of exercise should be determined by evaluating the patient's physical and mental condition on a daily and weekly basis.[19,20]

Sleep

In CFS, a normal sleep pattern can be chronically disrupted. This condition brings symptoms such as

fatigue, concentration problems, and muscle pain. The goal of sleep therapy in CFS is to regulate sleep in an uninterrupted manner and to improve sleep quality. Sleep therapy strategies include sleeping at the same time every night, using non-steroidal anti-inflammatory drugs for muscle pain, avoiding naps lasting less than 30 minutes during the day, doing light daily exercise, using sedative and hypnotic drugs, and addressing sleep hygiene.[1,21,22]

Nutrition

The treatment of CFS is generally symptomatic, and in addition, the role of nutrition in symptomatic treatment is very important. It has been observed that deficiencies in some nutrients can also worsen the symptoms of CFS. Nutrient deficiencies can prolong the recovery process of CFS and lead to an increase in clinical symptoms. Changes in diet and the use of dietary supplements are thought to contribute to the recovery of patients with CFS. Many nutrients have been found to have therapeutic benefits in studies. Considering all these, the diets of patients with CFS should be monitored and missing nutrients should be replaced.[23]

Essential Fatty Acids

In patients with CFS, low levels of essential fatty acids are commonly observed. In a study, patients with CFS who had low plasma levels of essential fatty acids at the beginning were given capsules containing 36 mg of gamma-linolenic acid, 17 mg of eicosapentaenoic acid, 11 mg of docosahexaenoic acid, 255 mg of linoleic acid or placebo for three months. After three months, those who received essential fatty acid supplementation reported a decrease in symptoms of CFS such as pain, fatigue, and unhappiness compared to those who received a placebo.[24]

Coenzyme Q10

Coenzyme Q10 is a natural powerful antioxidant, a co-factor that enhances mitochondrial function, and a substance that plays an important role in cellular metabolism homeostasis by participating in adenosine triphosphate (ATP) production. Additionally, it acts as a strong free radical scavenger that can prevent lipid peroxidation and deoxyribonucleic acid damage. It has been found that plasma levels of coenzyme Q10 are low in patients with CFS. Coenzyme Q10 has been found to increase energy metabolism, which plays a role in reducing fatigue and in the physiopathology of CFS.[25-28]

Vitamines

Symptoms such as fatigue and depression, which are common in CFS, are caused by folate deficiency. However, it has been observed that 800 mcg/day of folic acid supplementation is not sufficient to improve fatigue in patients with CFS who have folate deficiency, and it is emphasized that long-term and high-dose folate supplementation may be necessary.[23]

Minerals

Magnesium (Mg) is one of the most studied elements in CFS. Studies began after it was observed that patients with CFS had lower levels of Mg in their erythrocytes. It is thought that low Mg levels may be related to symptoms such as decreased ATP and muscle weakness, and fatigue.[15] In a study, oral Mg supplementation of 10 mg/kg/day was given to 93 CFS patients with low serum Mg levels, and the increase in total antioxidant capacity was found to be higher compared to the control group.[17]

In conclusion, CFS is a serious, long-term medical condition in the population but it significantly decreases the patient's quality of life. It is a condition diagnosed without the need for laboratory settings. Patients diagnosed with CFS can be treated using various methods, including cognitive behavioral therapy, exercise therapy, sleep therapy, and nutrition-related treatments.

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