



CHRONIC FATIGUE SYNDROME IS AN OBSCURE INFLAMMATORY DISEASE LACKING THERAPY WHICH ALSO AFFECTS COVID-19

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ABSTRACT

Chronic fatigue syndrome (CFS) is characterized by physical and mental tiredness with muscle fatigue, headache, and joint pain. This disease can additionally present mental disorders such as depression, mood swings, and "brain fog". CFS affects women more than men with an incidence 4 times higher in women, and the diagnosis is often difficult to assess. The cause of CFS is still unknown, and the disease can last for years and can cause neurological disorders. Patients affected by this dysmetabolic syndrome do not improve with rest and the therapy does not make use of specific markers because they do not exist. CFS is often correlated with humoral immune dysfunction. Patients with SARS-CoV-2-induced COVID-19 were recently observed to present with CFS. The inflammatory disease is mediated by the pro-inflammatory cytokines IL-1, TNF, and IL-6 which are released by microglial cells activated by the SARS-CoV-2 virus. Laboratory tests that aid in the diagnosis of CFS are blood cytometry and urinalysis, measurements of thyroid hormones T3 and T4, C-reactive protein, and blood phosphorus levels, and metabolic panel analysis. More in-depth future studies may lead to a better diagnosis and therapy that takes into account specific biomarkers.

KEYWORDS: *chronic fatigue syndrome, immunity, COVID-19, SARS-CoV-2, inflammation, CNS*

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by severe tiredness that can worsen with physical and/or mental activity (1). In addition to chronic fatigue, patients affected by this disorder may also present headache, light sensitivity, muscle and joint pain, difficulty concentrating, depression, and mood swings (2,3) (Table I). Additionally, CFS can produce sleep disturbances, mental cloudiness, and worsening of symptoms with physical activity (4). Patients with CFS experience persistent tiredness that can be combined with other disorders, and the diagnosis is often difficult since symptoms are often underestimated or poorly understood. The disease affects more women than men (with women affected about 4 times more often than men) and usually occurs between the ages of 20 and 40, even though it can also occur in children and adolescents (5). Fatigue can be acute or chronic, can be triggered by stress, and can manifest itself in various forms (6). Sometimes symptoms can be alleviated or resolved with rest and by improving the diet or doing physical exercises (7). A healthier lifestyle can help to alleviate the symptoms of CFS. Chronic diseases, such as

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rheumatoid arthritis, multiple sclerosis, stroke, systemic lupus erythematosus, some psychiatric disorders, and tumors, can induce chronic fatigue (8).

Table I. *Symptoms that may accompany chronic fatigue syndrome (CFS).*

• Severe fatigue	• Difficulty concentrating
• Polyarthralgia	• Chills and night sweats
• Sleep disturbances	• Tender lymph nodes in the neck or armpits
• Sore throat	• Depression
• Muscle weakness and pain	• Digestive issues, like irritable bowel syndrome
• Joint pain	• Allergies and sensitivities to foods, odors, chemicals, light, or noise
• Headache	• Shortness of breath
• Irregular heartbeat	

DISCUSSION

In subjects suffering from CFS, tiredness remains even after resting, and it can appear suddenly and can last for years (9). The disease has an unknown cause and can affect individuals of any age, although it usually appears at middle-age. CFS initially appears like a cold, with typical cold-like symptoms, that can be different from person to person (10). Afterwards, patients go on to experience tiredness, effort fatigue, cognitive problems, and other dysfunctions such as disorders in which the sympathetic, parasympathetic, and enteric systems of the autonomic nervous system are affected. CFS is not relieved by rest and may be accompanied by other pathological symptoms including dysfunction of cellular metabolism, and abnormalities with the endocrine system and ion transport (8).

Fukuda et al. described some clinical diagnostic criteria for this neurological disorder, where it was highlighted that for the disease to be such it had to have at least a 50% reduction in physical activity (11). This neurological diagnostic procedure was approved by the scientific community since there are no specific biomarkers or particular methods to reveal the disease (9).

The pathogenesis of CFS appears to be related to the humoral immune system (12). It has been noted that CFS can be triggered by infectious diseases, including viral ones, exposure to toxic substances, and stressful living conditions (13). The diagnosis should always consider both the severity and duration of the disease. Individuals suffering from CFS should undergo laboratory tests such as blood cytometry, urine analysis, T3 and T4 thyroid hormone tests, measurement of C-reactive protein and phosphorus blood levels, and metabolic panel analysis (14). However, laboratory tests by themselves are not satisfactory, even if they serve to exclude other pathologies, since the symptoms of CFS may look like other medical conditions (15). Affected patients should closely monitor their health to help perform a more accurate diagnosis.

To date, there is no cure for CFS, although some treatments can help to alleviate the symptoms in some cases. Treatments must consider the patient's overall health, medical history, and drug tolerance. To date, there is no specific therapy for this disease and therefore, non-specific treatments are utilized, which can include the use of non-steroidal anti-inflammatory drugs, antidepressants, physical exercise, psychotherapy, and in some cases, cortisone (16). Additionally, vitamin supplements and antioxidants can alleviate the symptoms in some cases (17). The rate of clinical depression in CFS patients is between 36% to 70% and affected subjects should undergo an examination of their general mental state (18). To date, drug therapy is limited, but cognitive therapy and exercise therapy often improve fatigue, anxiety, and quality of life (19).

CFS is a very complex disease and may involve dysfunction of the immune system. Some studies report that patients may have decreased antibodies with abnormal changes in B cells, T cells, and cytokines and chemokines (20). The symptoms of CFS often overlap with those of viral infections and the etiology of the disease is unclear (21).

CFS is a disease involving the CNS that is similar to fibromyalgia (22). The difference between these two nervous system disorders is that in fibromyalgia, the diagnosis is made by recognizing the inflammatory trigger points, while in CFS, there can be a low degree of systemic inflammation mediated by inflammatory cytokines induced by a specific agent such as a virus, including SARS-CoV-2.

Chronic fatigue syndrome and COVID-19

Certain viral infections can trigger CFS post-infection, including infection by SARS-CoV-2 that induces COVID-19 (23). COVID-19 first appeared in China and caused an international pandemic emergency with over five million deaths globally. This disease can provoke severe acute respiratory syndrome and flu-like symptoms. It has been reported in biomedical literature that after a few weeks or months of infection with the SARS-CoV-2 virus, some patients presented fatigue and other symptoms, called long COVID (23). Long COVID is a multisystem pathology that can be very serious, is associated with the age of the patient, and mainly affects non-hospitalized subjects.

After an acute phase, COVID-19 can cause fatigue and physical tiredness that persist even with rest, characteristic symptoms of CFS (24). Patients with this disorder can suffer from severe mental fatigue called “brain fog”, muscle pain and weakness, migraines, palpitations, anxiety, dyspnea, and sleep disturbances (25). These symptoms appear after COVID-19 and in extreme cases, can even last for a few years.

Other post-infectious virus phenomena such as Borrelia Burgdorferi, Epstein-Barr virus, and cytomegalovirus can also cause CFS (26). These infections are increased in patients previously infected with SARS-CoV-2. CFS occurs with much less incidence in vaccinated patients. Vaccination, cognitive therapy, and exercise therapy often improve fatigue, anxiety, and quality of life.

Bacterial infections can also trigger CFS, although the biochemical and molecular mechanisms are still being studied (27). The clinical and neuropsychiatric diagnosis of the disease, which includes cognitive aspects, often relies on the help of a neurologist and a psychologist. CFS is often associated with depression and anxiety, serious symptoms that can even lead to suicide (7). The acute phase of COVID is accompanied by manifestations of muscle weakness and tiredness and can cause damage to organs such as the lungs and heart (23). In CFS, the ability to generate energy is lost and breathing capacity can also be reduced (28).

CFS patients have less energy than healthy people and should exercise more to improve their condition. However, exercise increases levels of IL-1, a pro-inflammatory cytokine that mediates the increase in corporeal temperature (10). In addition, CFS is mediated by high levels of lactate with defective metabolism (increased acidosis in the peripheral circulation, and muscles) (29). In severe cases of the disease, a defect in glycolysis may also occur (30). In CFS, patients show cognitive impairment with verbal difficulty and slowed cognitive functioning. These effects are due to low grade brain inflammation caused by pro-inflammatory cytokines such as IL-1, TNF, and IL-6 that are produced by microglial cells after activation with SARS-CoV-2 through the TLR receptor (24). These effects may decrease with physical exercise as the patient's physiological condition improves. Therefore, CFS must be diagnosed accurately and quickly to avoid serious complications.

CONCLUSIONS

At the moment, there are no specific treatments for CFS. Non-specific pharmacological treatments can reduce inflammation and pain and can be useful. Furthermore, exercise can help improve memory and cognitive functioning, and the use of light and noise protection devices, and the consumption of healthy and easily digestible foods, may help alleviate symptoms. However, drug therapy is limited and vaccination against COVID-19, cognitive therapy, and exercise therapy can improve fatigue, anxiety, and quality of life for the patient.

Conflict of interest

The author declares that they have no conflict of interest.

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