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Causes of Chronic Fatigue Syndrome in Covid-19 Patients and Treatment Recommendations

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ABSTRACT

COVID-19 virus infection mainly affects the respiratory system and presents with the initial symptoms of fever, cough, and body aches. It has been observed that in cases of corona disease, patients show signs of chronic fatigue after the disease. Chronic Fatigue Syndrome (CFS) is referred to as chronic fatigue caused by diseases and can include long-term symptoms such as deep fatigue, difficulty concentrating, and problems in controlling the autonomic system. Studies show that the cytokine response is effective in causing this problem. The cytokine response is an over-inflammatory process that results in complications such as multiple organ failure. Delayed expression of interferons, as an essential part of the innate defense against viral infections such as COVID-19, plays a key role in creating the "cytokine storm", which is observed in patients with COVID-19. This disruption of the immune system and increased immune response in people with corona disease can lead to chronic fatigue syndrome. But the important point is that chronic fatigue, with changes in neuropsychiatric health, can affect the activity and function of the immune system of people with the disease, predisposing them to other diseases. Paying attention to effective factors and treatments can play an important role in improving the health of people with chronic fatigue syndrome.

KEYWORDS

Chronic Fatigue, Fatigue Syndrome, Coronavirus, Covid 19.

Introduction

Most of the focus on Coronavirus in 2019 (COVID-19) has been related to its acute symptoms and recovery. However, many recovered patients experience persistent physical, cognitive, and psychological symptoms. Among these symptoms, chronic fatigue is one of the most persistent and debilitating (1-7). Myalgic encephalomyelitis or chronic fatigue syndrome (ME / CFS) is a severely debilitating and complex disease of unknown cause that has affected the lives of millions of people around the world. This disease occurs with prolonged fatigue and causes physical and neurological health problems in people. The causes and mechanisms that lead to chronic debilitating muscle fatigue are unknown, and more time and research are needed to identify the factors influencing them (8).

Considering the worldwide epidemic of Covid-19 and the fact that corona disease has been associated with chronic fatigue syndrome, in this article we intend to investigate the causes of chronic fatigue syndrome in patients with Covid-19 and provide the desired treatment suggestions.

General Characteristics of Coronavirus and its Complications

Throughout history, many viral diseases have occurred that lead to severe and persistent fatigue, perhaps the most famous of which were observed in Los Angeles (1934), Iceland (1948), London (1955), and Nevada (1984). (9-12). In December 2019, cases of β-coronavirus-induced pneumonia were identified in Wuhan, China. At the beginning of the outbreak on January 12, 2020, the World Health Organization (WHO) named the virus coronavirus-2019 (8). The SARS-CoV-2 genome sequence found in bats was 96.2% similar to MERS-CoV; the findings showed that mutations in the virus genome changed the host from bats to humans and made it possible for humans to be infected. The coronavirus has infected humans in the past, but a new mutation has turned it into a dangerous virus (13). Studies on the Covid-19 genome, which is closely related to SARS-CoV and MERS-CoV, and the accumulated clinical and experimental data on previous viruses, can be used in the treatment of this disease. In addition, it is possible to predict how the host's immune system will react to this particular virus and how the host immune responses can prevent the disease (8, 14).

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SARS-CoV-2 occurs in humans, especially in the elderly and people with very severe underlying diseases, with symptoms of pneumonia. The mean age of patients is 47-59 years and 41.9-45.7% of patients are female (13). Up to February 5, 2021, more than 100 million confirmed cases have been reported worldwide, of which about 2.5 million have died. The virus mainly occurs with the initial symptoms of fever, cough, and body aches and affects the respiratory system. Fatigue is also a symptom of COVID-19 that has been widely reported in patients. However, observational evidence suggests that certain individuals continue to experience chronic and severe fatigue as they recover from the infection (15).

The site of primary infection with SARS-CoV-2 is unknown and the pathogenesis of COVID-19 is still under investigation. For most patients, COVID-19 may only affect the lungs because it is primarily a respiratory disease. The main mode of infection is human-to-human transmission through close contact, most of which is transmitted through the spread of airborne droplets in the form of cough or sneezing. For this reason, the rapid spread of SARS-CoV-2 has occurred with an original R0 of 2.2-2.6, meaning that on average each individual has the potential to spread the infection to 2.2 other people (16).

In severe cases of SARS-CoV-2 disease, the number of lymphocytes decreases, and the neutrophil to lymphocyte ratio (NLR) increases. In addition to decreasing the percentage of monocytes, eosinophils and basophils also show a decreasing trend. Helper and suppressor T cells have also been reported to decrease during SARS-CoV-2 infection (17).

Several long-term systemic consequences have been observed in patients with COVID-19, and its complications are expected to be observed even after the disease. Complications of SARS-CoV2 infection affect several organs and systems of the body. These systems include the cardiovascular, nervous, metabolic, musculoskeletal, and mental health systems (18). Paying attention to systemic injuries and reducing injuries can be possibly effective in the health of people after the coronavirus disease.

Chronic Fatigue Syndrome and Covid-19

A number of patients with COVID-19 may develop the severe post-viral syndrome. This syndrome has been reported as "Post COVID-19 syndrome", which is characterized by neuro-immune fatigue (19). Previous studies have shown that post-infection fatigue is also present in some survivors of influenza H1N1 and Ebola (19). Chronic Fatigue Syndrome (CFS) is an often debilitating condition that can feel like a persistent flu that lasts for years. Symptoms include decreased energy production, pain in the body, the need for constant sleep, and difficulty in physical and mental functioning. Among many patients and some scientists, the preferred name for chronic fatigue syndrome is "myalgic encephalomyelitis" (ME). However, among some scientists, the preferred name for this syndrome is "systemic exertional intolerance syndrome"; but the use of this term is rare. "Myalgic encephalomyelitis" basically means "muscle pain (myalgia) related to inflammation of the central nervous system (encephalomyelitis)" (20).

Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS / ME) is a disorder with an unknown prognosis that occurs due to a lack of accurate treatments and disorders of various physiological systems including the immune and nervous systems (21, 22). Approximately 53% of patients with corona disease experience chronic fatigue and there is no significant difference among patients in terms of any of the indicators of ethnicity, body mass index (BMI), and age (23).

Research shows that patients with chronic fatigue syndrome (CFS) have normal lymphocyte counts and normal erythrocyte rheology (especially accumulation and malformation). In fact, CFS leads to a deviation in the activity of red blood cells. CFS usually occurs when the immune system malfunctions and these defects may affect the activity of lymphocytes and other related immune molecules. Thus, immune cell function and phenotypes may be important diagnostic markers for CFS (24).

However, various estimates suggest that the RBC count in ME / CFS patients is significantly lower than in healthy individuals. It is speculated that larger, drier RBCs in ME / CFS patients, which is due to impaired vascular perfusion and tissue oxygenation, may partly explain the musculoskeletal pain and fatigue in the pathophysiology of ME / CFS. Whereas previously it was reported that no significant difference in moderate deformability was observed between

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erythrocytes obtained from healthy individuals and ME / CFS patients. This apparent discrepancy may be due to the low sensitivity of the measuring device, which indirectly reports the changes in ductility based on time and population average of light scattering (25).

The factors that affect fatigue after viral infections are not fully understood; recent research suggests that cytokine responses may be involved. Immune system abnormalities have been reported as an undeniable component of the CFS / ME pathologic mechanism. Also, decreased activity of cytotoxic natural killer cells (NK) and increased regulatory T cells (Tregs) in the body are the most consistent findings related to CFS / ME (26).

A study by Mehta et al. Showed that cytokine storm occurs in patients with COVID-19 and high levels of IL-2, IL-7, granulocyte colony-stimulating factor, interferon γ-induced protein, monocyte chemoattractant protein-1, macrophage inflammatory protein α, and tumor necrosis factor α have been observed in these patients (27).

In the CNS, microglial cells have the ability to secrete cytokines and act as antigen-presenting cells, causing phagocytosis. These cells may have protective pathological effects on CNS function. Cytokines produced by microglia cells include IL-4, IL-10, IL-6, IL-13, and IFN- (28-30).

Studies by Peterson et al. Have shown that the cytokine IL-10 is significantly reduced in patients with chronic fatigue. IL-10 is secreted by almost all cells of the innate and acquired immune system and protects against severe and chronic inflammatory reactions by reducing Th1 immune responses. IL-10, previously described as an inhibitor of cytokine synthesis, also regulates the immune response and immune-stimulating activities. It also prevents T-cell autoreactivity and proliferation, and autoimmunity (31). In addition, IL-10 reduces B7-2 and CD28 signaling, inhibits the secretion of nitric oxides, destroys hard cytokine-related precursors, and reduces the expression of MHC II molecules (32). Most importantly, IL-10 has positive and negative effects in several signaling pathways related to the Janus Kinase/signal transducer and activation of transcription. Thus, modulation in IL-10 may affect inflammatory signals and cellular processes in the CNS (33).

In patients with COVID -19, the inflammatory process that results from elevated cytokines in the blood is associated with complications such as multiple organ failure and disability. But the findings show that delayed secretion of interferon type I (IFN) is an essential part of the innate defense against coronavirus and influenza infections. Thus, the development of viral IFN plays an important role in the "cytokine storm" found in patients with COVID-19 (34).

These proinflammatory factors lead to cellular disturbances in various organs and it seems that these factors affect the neurological regulation of the "Golfhatic system". Accumulation of cytokines in the central nervous system may lead to symptoms after the viral infection. This is due to pro-inflammatory cytokines that cross the blood-brain barrier and affect the hypothalamus, leading to various malfunctions (19).

Research on SARS also shows that the virus crosses the blood-brain barrier in the hypothalamus through the olfactory pathway and follows the path previously seen in patients with chronic fatigue syndrome. This pathway involves impaired lymphatic drainage of microglia in the brain. One of the main routes of the lymphatic drainage of the brain is through the perivascular spaces along the olfactory nerves and through the cribriform plate to the nasal mucosa. If the pathogenesis of the coronavirus affects a similar pathway, the observed anosmia in some COVID-19 patients is also justified (35-37).

CFS / ME disorder leads to the accumulation of proinflammatory agents, especially post-infection cytokines such as gamma interferon and interleukin-7, and this hypothesis is due to its effect on the neurological control of the "glymphatic system", which is observed in patients with CFS / ME. Accumulation of cytokines in the central nervous system (CNS) may lead to the transmission of viral signals through the blood-brain barrier to brain organs such as the hypothalamus, leading to dysfunction and severe-prolonged fever. Sleep/wake cycle disorders, cognitive dysfunction, and deep uninterrupted energy are all marks of CFS / ME (38).

Treatment Recommendations

Fatigue is one of the most common symptoms of coronavirus; it reduces a person's motivation to continue activities,

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which means that the patient often avoids activities. This condition can lead to less energy and more fatigue. If this behavior becomes a habit, it is often difficult to break this cycle. There are several methods that can be used to control excessive fatigue (39).
In 2020, Mark et al. Conducted an extensive study on cognitive-behavioral therapy (CBT) affecting chronic fatigue syndrome in Covid-19 patients. In this review study, contradictory results were obtained. Rehabilitation clinics currently offer cognitive-behavioral therapy (CBT) as an effective treatment for COVID-19 and post-COVID-19 chronic fatigue syndrome, and accordingly, claim that this type of treatment is effective for myalgic encephalomyelitis/Chronic fatigue syndrome. However, re-analysis of these studies showed that CBT did not lead to an objective improvement in heterogeneous groups of ME / CFS patients and did not restore the ability to work (40).

An analysis by Qure showed that the use of CBT in a homogeneous group of patients with chronic fatigue syndrome could be effective. CBT is potentially an effective and long-term treatment for CFS after COVID-19 infection. However, the re-analysis showed that the Qure study suffers from serious methodological problems, which include relying on an initial mental outcome in a study without a control group. In addition, only 10% of participants experienced clinically significant mental improvements as a result of CBT. Thus, CBT has no clinically significant effect on nine out of ten patients treated. In addition, the mental recovery of fatigue did not correspond to the improvement of disability, even if this disability was related to fatigue. CBT did not lead to objective physical function improvement. Therefore, it cannot be said that CBT is also an effective treatment for fatigue syndrome. Therefore, CBT is unlikely to reduce disability or lead to an objective improvement in patients experiencing COVID or post-COVID-19 fatigue syndrome (40).

There is also a hypothesis about the presence of the D-lactate microbiome in the intestines of patients with CFS, which produces cases such as D-lactate acidosis, and, therefore, prescription of synbiotics may be a possible treatment (41, 42). Also, probiotics are considered a therapeutic possibility for CFS as well as fibromyalgia. However, because intestinal-brain axis disorders include microbiota and intestinal immunity, several CFS therapies have been considered to target the immune system, including B cell clonal degradation and the use of human antibodies (43, 44).

A systematic review has suggested a positive effect of dietary supplements such as D-ribose, with particular regard to omega-3 fatty acid supplements, in reducing symptoms and improving recovery, since blood levels of omega-3 may also be associated with symptoms relief (45). However, another review by analyzing 27 studies showed that there is still little data to provide a promising hypothesis on the effective role of mineral and vitamin supplements in the pathophysiology and treatment of CFS (46).

Conclusion

It is important to confirm that the effects of COVID-19 are not acute in many cases, but it does have long-term consequences. Increasing awareness, knowledge, research, and multilateral participation by physicians and biologists will be the cornerstone for effective management of the long-term consequences of COVID-19. There are no established biomarkers in CFS, but there has been a long interest in the role of the immune system in the pathogenesis and pathophysiology of CFS and the role that cytokines may have. This focus on the immune system came from several findings. Firstly, CFS may be caused by an infection; then, the role of cytokines in acute diseases is well described, and some symptoms are similar to those of CFS. Finally, the interaction between the nervous and endocrine systems and the immune system is well documented and there is evidence of mismatch in hypothalamic-pituitary regulation in CFS.

In general, the immune system is impaired in patients with chronic fatigue syndrome, and cellular proteins play an important role in this problem. On the other hand, chronic fatigue with changes in physical, mood, and neurological health can affect the activity and function of the immune system of patients and predispose their bodies to other diseases. This issue indicates the need to provide treatment strategies for chronic fatigue syndrome, and paying attention to affective factors and treatments can play an important role in reducing the problems of people with this disease.

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