E- Global Congress
Hosted online from Dubai, U. A. E., E - Conference.
Date: 29th October 2024
Website: https://eglobalcongress.com/index.php/egc
ISSN (E): 2836-3612

ME/CFS AND LONG COVID – SIMILARITIES AND DIFFERENCES IN THE BACKGROUND OF THE WORLD SITUATION: A REVIEW

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Abstract:

The global prevalence of COVID-19 and chronic fatigue syndrome (CFS) highlights the substantial health burden these conditions pose individually and in combination. COVID-19, caused by SARS-CoV-2, continues to affect millions worldwide, with post-acute sequelae, known as Long COVID, impacting an estimated 5-43% of recovered individuals. Among these, chronic fatigue is a prominent and persistent symptom, with 42.5% of Long COVID patients experiencing fatigue that can resemble CFS. Chronic fatigue syndrome (CFS), affecting an estimated 0.4% to 2.5% of the global population, is marked by enduring, debilitating fatigue often triggered by infections. Emerging data suggest that SARS-CoV-2 may exacerbate or reveal latent CFS-like symptoms, linking these conditions biologically and symptomatically. Given the shared features of immune dysregulation and

ISSN (E): 2836-3612

fatigue in both conditions, this paper reviews their epidemiological profiles and underscores the need for enhanced diagnostic criteria, research, and support systems. Improved understanding of these overlapping syndromes is crucial for global health strategies to mitigate their societal and economic impacts.

Keywords: CFS; Long COVID; Global prevalence of Long COVID.

Introduction

Coronavirus Disease 2019 (COVID-19) is a highly contagious respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Prolonged recovery, commonly referred to as Long COVID-19, has been observed even in individuals who experienced mild symptoms and did not require hospitalization. Studies indicate that at least one in ten symptomatic COVID-19 patients develop Long COVID-19.

Although there are no evidence-based clinical guidelines or a clear understanding of its aetiology, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the World Health Organization (WHO) have proposed a clinical definition for post-COVID-19 conditions. Long COVID-19 is characterized by a history of probable or confirmed SARS-CoV-2 infection, typically manifesting three months after the onset of COVID-19, with symptoms lasting at least two months and not attributable to another diagnosis. Patients often exhibit a wide range of non-specific symptoms that can fluctuate or recur over time. Commonly reported symptoms include fatigue, pain, dyspnea, sleep disturbances, physical sequelae, psychological distress, and cognitive impairment, all of which significantly impact quality of life. Symptoms may persist from the initial illness or appear anew after recovery from the acute phase of COVID-19. These manifestations can resemble those seen in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). [1]

Methodology

Exploring the potential connection between ME/CFS and Long COVID-19 is complicated by the significant heterogeneity in clinical presentation and the lack of sensitive screening tools and standardized diagnostic criteria.

ISSN (E): 2836-3612

Based on the hypothesis that post-COVID-19 patients may develop a post-viral fatigue syndrome closely resembling ME/CFS, the researches propose subgrouping individuals with Long COVID-19 into two distinct clinical phenotypes.

The first cluster consists of patients who experienced mild COVID-19 symptoms and did not require hospitalization (outpatient care) but developed persistent symptoms after the acute phase, referred to as post-COVID-19 fatigue syndrome (PCFS). There may be many clinical similarities and shared pathophysiological features between patients with ME/CFS and those with PCFS (ME/CFS-like).

The second cluster includes patients who required hospitalization for severe COVID-19 (either in the ICU or a non-ICU ward) and subsequently developed persistent symptoms after discharge, termed post-acute COVID-19 syndrome (PACS). It is important to differentiate ICU-PACS patients from those experiencing post-intensive care syndrome (PICS), which is defined as "new or worsening impairment of cognition, mental health, or physical function following critical illness, lasting beyond the acute hospital stay." Although there are some differences between ICU-PACS and PICS—likely reflecting the varied impacts of critical illness—the symptoms of both conditions may share underlying factors such as immune alterations, neurological involvement, adverse effects of treatment, prolonged immobilization, and mitochondrial dysfunction.

Given the strong evidence supporting multidisciplinary treatment programs for ME/CFS, which combine pharmacological approaches tailored to symptoms, education, physical exercise, and cognitive behavioral therapy, we believe that implementing a similar follow-up program could be beneficial for patients with Long COVID-19.

Long COVID-19 should be treated as a public health emergency. Further well-conducted studies are essential to determine the true prevalence, phenotypes, risk factors, potential treatments, and the differences between Long COVID-19 and ME/CFS, as well as other overlapping conditions like PICS. [3]

Discussion

ME/CFS is a complex, long-term, multisystem disorder first defined in 1988 by Holmes et al. as a post-viral fatigue syndrome. Diagnosis can be made using the 1994 Fukuda criteria, the Canadian consensus document from 2003, or the more recent international consensus criteria from 2011, which detail its pathophysiology, symptoms, and treatment.

The disorder is marked by prolonged and abnormal fatigue after exertion, which does not improve significantly with rest, as well as recurrent headaches and concentration and memory problems that have emerged within the past six months. Other accompanying symptoms include tender lymph nodes, musculoskeletal pain, sleep disturbances, and psychiatric issues.

Although the exact cause of ME/CFS remains unclear, ongoing research is investigating its aetiopathogenesis. Known predisposing factors include female sex, type A personality, and family history. Various infectious agents (such as those from the human herpesvirus family), toxic exposures, and psychological and social experiences are associated with its onset. Factors such as older age, delays in diagnosis, severe initial symptoms, comorbidities, and adaptive disorders may contribute to the persistence of the illness. Emerging data suggest a link between redox imbalance, mitochondrial dysfunction, and oxidative stress pathways in ME/CFS patients, which have also been observed in individuals with Long COVID-19, indicating that the two conditions may share similar pathophysiological characteristics. [2] [6]

Clinical manifestations and pathophysiological features

Immune dysregulation is a prominent feature in both LC and ME/CFS. While the onset of ME/CFS often follows an infection, historical research has inadequately addressed the multifactorial nature of infectious triggers. Recent advancements in technologies, such as digital PCR and multiplex MassTag PCR, have facilitated the detection of low-abundance viral loads and multiple pathogen regions, revealing a higher incidence of active viral infections in ME/CFS patients. This correlates with fatigue and neurocognitive dysfunction and highlights the role of proinflammatory cytokines, particularly TNF-α. Reactivation of latent viruses post-SARS-

ISSN (E): 2836-3612

CoV-2 infection suggests a contribution to the persistence or exacerbation of ME/CFS symptoms.

- Rituximab: This anti-CD20 monoclonal antibody has shown promise in early trials but did not yield significant differences in response rates in a Phase 3 trial.
- Immunoadsorption: Currently undergoing a randomized trial (NCT05710770), examining its effects on ME/CFS patients over multiple sessions.
- Rintatolimod: A Phase 3 trial (NCT00215800) demonstrated notable improvements in exercise tolerance and quality of life in a subset of patients.
- N-acetylcysteine: A Phase 2 trial (NCT04542161) is investigating varying dosages of this compound to assess its effects on ME/CFS symptoms.
- Despite inconclusive results regarding innate immune cell involvement, emerging evidence indicates potential quality-of-life improvements from targeting these cells. Further longitudinal studies are essential for understanding the molecular changes associated with ME/CFS.
- Both LC and ME/CFS share central symptoms of fatigue linked to metabolic dysfunction. Studies reveal significant reductions in glycolysis and mitochondrial respiration in peripheral blood mononuclear cells (PBMCs) from ME/CFS patients. Enhanced mTORC1 activity suggests dysregulated protein synthesis in mitochondrial functions.
- The gut microbiota's interactions with immune responses and metabolic processes have drawn increasing scrutiny in ME/CFS. While prior studies indicated contradictions in microbial diversity, recent investigations highlight the presence of markers of intestinal damage and altered immune responses in cohorts of ME/CFS patients, underscoring the necessity of geographical and demographic considerations in microbiota research.
- Central nervous system (CNS) dysfunction is implicated in both ME/CFS and LC, characterized by cognitive disturbances, fatigue, and autonomic disruption. Evidence indicates that viral infections and immune abnormalities lead to chronic neuroinflammation, evidenced by increased translocator protein binding in brain regions and neuroimaging studies revealing structural and functional abnormalities.

ISSN (E): 2836-3612

- Cardiovascular dysfunction, including orthostatic intolerance and postural tachycardia syndrome (PoTS), is prevalent among ME/CFS patients. Notably, reduced cerebral blood flow and other vascular pathologies pose additional risks for cardiovascular health in this population. [5]
- The heterogeneity of symptoms and long-term outcomes complicates the understanding of ME/CFS and LC. Enhanced awareness of LC could catalyze research and improve management strategies for both conditions. Longitudinal studies focusing on risk factors and clinical phenotypes are vital for tailored interventions, integrating clinical data with biological analyses.
- There are three broad categories of PASC: tissue injury of multiple organs, new onset of major diseases (diabetes mellitus, cardiovascular diseases, pulmonary failure) and long COVID.
- The CDC states that in the "post-COVID condition" symptoms can continue for four or more weeks after infection with SARS-CoV-2. According to The World Health Organization this condition is defined by continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, lasting for at least 2 months with no other explanation.

Some evidence indicates that Long COVID is more likely to develop in people with prior medical history of sickness, previous inflammation with acute COVID-19; were PCR positive; female; and have a premorbid history of asthma, chronic obstructive pulmonary disease and depression. But many patients had none of these symptoms.

The severity of the symptoms, and the functional impairment, can be various. The functional impairment in people with ME/CFS may be even greater than in those with Long COVID. Some people are able to live normally, some may stay bed-ridden. The symptoms are often cyclic, worsening by stressors—exercise, prolonged upright position, cognitive and emotional upset. It should be noted that attempts to identify a single and possibly novel infectious agent as the cause of most cases of ME/CFS have been unsuccessful.

Magnetic resonance imaging (MRI) has shown abnormalities involving both gray matter and white matter have been found in both illnesses. Myalgic

ISSN (E): 2836-3612

encephalomyelitis/CFS often follows in the wake of an "infectious-like" illness while Long COVID follows acute infection with SARS-CoV-2. a variety of immunological parameters distinguish people with ME/CFS from healthy patients The same is true of Long COVID, abnormalities in redox balance, and in the kynurenine pathway has been seen in both illnesses. It has been studied less extensively but growing number of cardiopulmonary abnormalities have been noted. Not only is a common core of symptoms shared by ME/CFS and Long COVID: these same symptoms also are also reported following multiple infectious illnesses and major non-infectious injury such as post-critical illness syndrome or post-intensive care unit syndrome, including heat stroke.

Both of this diseases clearly are systemic illnesses, involve multiple organs and physiological systems. ME/CFS more likely represents a dysfunctional response to infection. Both illnesses share abnormalities involving the central and autonomic nervous systems, the immune system, reactivation of latent infectious agents (primarily herpesviruses), the gut microbiome, energy metabolism, a hypometabolic state, redox imbalance, and various cardiac, pulmonary and vascular abnormalities.

Many of which influence each other and crate a vicious cycle. But the process may be different in one person with the illness from another. The often-similar findings suggest that insights into each disorder will have implications for the other. They may also enhance our understanding of evolutionarily preserved biological responses that fight infection. [4] [7]

Conclusions

The global prevalence of COVID-19 and chronic fatigue syndrome (CFS) presents a complex public health challenge due to their overlapping symptoms and shared mechanisms, such as immune dysregulation and persistent fatigue. The widespread impact of COVID-19, particularly through Long COVID, has led to an increase in CFS-like conditions, underscoring the importance of developing clear diagnostic criteria and improved understanding of these syndromes. Enhanced research efforts and public health strategies are needed to address the growing burden of these conditions, supporting both prevention and patient care while aiming to mitigate their economic and social impacts globally.

ISSN (E): 2836-3612

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