Long-COVID: A Chronic Fatigue Condition – Case Report

Abstract

For the growing number of patients suffering from post-COVID-19 syndrome, there is little definitive guidance for treatment protocols or prognosis. Neurologic manifestations following acute COVID-19 infection are continually surfacing in the literature, with fatigue being the most common persistent symptom. This case study follows a 44-year-old female experiencing debilitating fatigue and neurologic symptoms persisting after the resolution of an acute SARS-COV-2 infection. The complex medical history of this patient, including past Epstein-Barr Virus (EBV) infection and Myalgic Encephalomyelitis, commonly known as Chronic Fatigue Syndrome, suggests a potential predisposition for the development of neurologic long-COVID. Through investigation of current research and treatment responses, this case report aims to gain an understanding of the complicated nature of this illness, and to propose treatments that address this specific subset of post-acute SARS-COV-2 sequelae.

Keywords: COVID-19; long-COVID; chronic fatigue; myalgic encephalomyelitis; post viral conditions; Epstein-barr virus

Introduction

The persistence of symptoms following COVID-19 infection is occurring at alarming rates, with one study reporting that 87% of patients still experience at least one symptom two months after initial infection [1]. As the prevalence of patients with enduring symptoms rises, understanding of this phenomenon continually evolves. Still, the nature and development of long-COVID is not well understood.

The prevailing long-COVID symptom is fatigue [2]. Fatigue as a generalized symptom only further complicates the goal to understand the pathophysiology of the disease. While there are several presentations of long-COVID, this patient did not demonstrate common cardiovascular or pulmonary abnormalities. Therefore, this report will focus on a subset of neurologic symptoms.

Symptoms of neurologic pathology in long-COVID include headaches, vertigo, brain fog, anosmia, ageusia, insomnia, mood disturbance, nerve pain and fatigue. Several theories have been presented to explain the neurologic involvement of COVID-19, including the direct invasion of the neurological system. COVID-19 is thought to cross the blood brain barrier through the cribriform plate and olfactory nerve, which has been demonstrated through post-mortem studies. The virus has been observed as distantly as the cerebrospinal fluid [3]. Additionally, it has been evidenced to spread to the frontal lobe, resulting in abnormalities on MRI, EEG, and PET. Frontal lobe impairment can lead to reduced executive brain function, which may contribute to brain fog [4,5].

Another observed mechanism of disease is through immune impairments and inflammation. Beyond the acute virus-induced cytokine storm, there is evidence of long-term dysregulated immunologic responses [6]. COVID-19 patients have elevated levels of activated inflammasome NLRP3, which can lead to the accumulation of beta amyloid plaques, correlated with neurodegenerative illnesses such as Alzheimer's disease [6]. Other inflammatory cytokines implicated in COVID infections, IL-18 and IL-1β, have been shown to negatively impact cerebral function [6,7]. The progression of SARS-COV-2 has also been compared to studies of post-stroke depression, with elevated IL-7 and INF gamma [8]. Inflammation is a likely contributor to neurodegeneration and vasculature damage, which may be more difficult to treat than acute inflammation alone.

When inflammation and neurodegeneration of the central nervous system (CNS) occurs, impacts on cellular metabolism may be observed. Specifically, SARS-COV-2 has demonstrated selective targeting of the mitochondria of neurons [9]. Mitochondria serve to produce ATP, the primary source of cellular energy; mitochondrial damage may impact brain function. Through imaging analysis of PET scans of patients with long-COVID, hypometabolism was measured in several regions including the orbital gyrus, olfactory gyrus, temporal lobe, amygdala, hippocampus, thalamus, pons/medulla brain stem and cerebellum [6.] Mitochondria dysfunction may explain symptoms of fatigue and exertional intolerance.

With fatigue being the most common symptom of long-COVID, similarities are being drawn with another debilitating medical condition known as Myalgic Encephalomyelitis, or Chronic Fatigue Syndrome (ME/CFS) [10]. This condition is sometimes referred to as Post Viral Fatigue, or Systemic Exertional Intolerance Disease. It is typically characterized by extreme fatigue, unrefreshing sleep, mood or cognitive disturbance, and systemic decline in energy after physical or cognitive exertion. Of all proposed etiologies of ME/CFS, one of the most highly implicated pathogens is EBV [11,12]. While EBV has been observed to trigger this syndrome, like COVID-19, the virus has not been proven to be directly responsible for chronic symptoms.

The patient described not only exhibits signs of neurologic long-COVID, but also has a complex medical history including past EBV infection and ME/CFS. This case study speculates that a history of EBV or ME/CFS may be a risk factor for the development of neurologic long-COVID; this could be due to genetic or auto-immune alterations in viral mediated inflammation, pre-existing infiltration and destruction of the nervous system, mitochondrial dysfunction, or through reactivation of EBV. Those affected by neurologic long-COVID and ME/CFS alike experience debilitating fatigue, decreased ability to complete activities of daily living, a decrease in quality of life, presenting significant burden on the healthcare system. The perplexing nature of both conditions indicates a need for further research and development of effective treatments.

Case Report

Patient Information

Our patient presented as a 44-year-old female demonstrating persistent symptoms of brain fog, insomnia, depression, exercise intolerance, stinging nerve pain, and most notably severe fatigue, one month after recovering from an acute COVID-19 infection.

The significant medical history of this patient included asthma, chronic fatigue syndrome, EBV infection, history of B12 and iron deficiency anemia, vitamin D deficiency, Small Intestinal Bacterial Overgrowth (SIBO), and consumption of a vegan diet.

Case History

The patient reported a severe two-week COVID-19 illness, with fever, fatigue, cough, shortness of breath, anosmia, ageusia, headache, and unintentional weight loss of 10 lbs. Their PCP administered Paxlovid due to their severe presentation and significant history of asthma.

One month after resolution of acute illness, the patient presented to our clinic with persistent complaints of brain fog, insomnia, depression, exercise intolerance, stinging nerve pain, and severe fatigue that was not present before her initial SARS-COV-2 infection.

The initial assessment was geared toward ruling out red flags, including heart or lung damage. The patient denied shortness of breath, wheezing, palpitations, chest tightness or chest pain. Due to lack of significant findings, the suspicion for cardio-pulmonary damage causing symptoms was reduced. To screen for potential blood disorders, organ damage, or metabolic abnormalities, labs including CBC, CMP and TSH were tested.

Clinical Findings

Physical Exams: Heart, lung and thyroid exams were all within normal limits. The extremities examination was mostly normal, aside from sensory deficits observed with sharp-dull tests on the right distal leg (the patient reported this was retained from a past surgery). No significant new findings were revealed through physical examination.

Labs and Imaging: Initial labs ordered included CBC, CMP, and TSH; results revealed TSH and CMP within normal limits. CBC was mostly normal, aside from a slight elevation of MPV at 12.6. This finding is inconclusive but could be suggestive of an underlying process. Anemia was

ruled out. However, a historic lab value of Vitamin D was 24, reflecting an insufficiency that may impact illness.

Therapeutic Interventions

The treatment approach was aimed at supporting the immune system, reducing inflammation, promoting neuro-regeneration, restoring mitochondrial function, and correcting nutritional deficiencies.

Immune supportive therapies included nutrient-based treatments, vitamin C, vitamin D, and zinc. Low-dose naltrexone (LDN) is an immune modulator, especially indicated for this patient because she reported its historical effectiveness in treating her chronic fatigue symptoms.

Reduction of inflammation was addressed through antioxidants. Specific antioxidant treatments included Quercetin, Melatonin, and N-Acetyl Cysteine (N-AC).

Neuroprotective herbs were selected to support the CNS directly, including Bacopa Monnieri, Hericum Erinaceus, and Ginkgo Biloba.

Mitochondrial dysfunction, fatigue and neuropathy are thought to be associated with nutritional deficiencies. Correcting these deficiencies was attempted through IV therapy, prioritizing B Complex and Carnitine nutrients.

Figure I. Treatment Timeline

August 15th, 2022	**Acute Infection**
September 30th, 2022	**Treatment Initiation**
October 14th, 2022; October 20th, 2022	**IV Therapy Visits**
January 20th, 2023	**LDN Initiation**

Supplements	Vitamin D 2000 IU/day Vitamin C 1000 mg/day Zinc glycinate 25-50 mg/day N-AC 1200 mg/day Quercetin 1000 mg/day Melatonin 6-7 mg/night
Herbs	Curcumin 5 mg/day Nootropics: Bacopa, Hericium, Ginkgo
IV Nutrients	B complex, B12, Vitamin C, Calcium Gluconate, Magnesium Sulfate, Selenium, Carnitine
LDN Titration	1.5 mg x7 days, then 3 mgx7 days, then 4.5 mg daily

Outcomes

This patient presented without significant abnormalities on physical exam or serologic markers; therefore, assessment was based on reported symptoms.

One week after initiating herbs and supplements, the patient reported mild improvement in nerve pain and brain fog. After the first IV treatment, she reported a slight increase in energy and quality of sleep, and a decrease in nerve pain lasting for two to three days. However, after exertion of energy, she reported the return of exhaustion and increased pain. At the last visit, one week after LDN initiation, she reported improved sleep quality and reduction in pain severity.

A mild improvement in symptoms just two weeks after initial assessment suggests the efficacy of at least one aspect of treatment. The return of symptoms after physical exertion is an expected response in cases of mitochondrial dysfunction. Her symptoms will be continually monitored as she titrates LDN to the target dose.

Discussion

Definitive treatment protocols for long-COVID chronic fatigue have yet to be established. Therefore, rationale for selected therapies was based on consideration of neurologic pathophysiology of long-COVID, the patient's presentation and past medical history. There is evidence to support the efficacy of these interventions based on short term studies of COVID-19, historical use of the interventions, and biochemical mechanisms reported in the literature. Treatment goals included: immune support, reduction of inflammation, neuroregeneration, restoring mitochondrial function, and correcting nutritional deficiencies.

Each immune supportive supplement has demonstrated antioxidant and anti-inflammatory abilities. Specifically, Vitamin C is protective against infectious respiratory conditions, and may shorten the duration of illness [13]. Vitamin D is an immune modulator and protective of respiratory epithelium; Insufficiency is associated with increased severity (hospitalization and mortality) of COVID-19 disease [13]. Zinc has been shown to reduce viral replication of SARS-CoV-2 [13]. This patient is at increased risk for Zinc and Vitamin D deficiency due to historical values, SIBO diagnosis and consumption of a vegan diet.

Reduction of inflammation was addressed through antioxidants, which reduce the effects of widespread oxidative stress. Antioxidant treatments including Quercetin, Melatonin, and N-Acetyl Cysteine (N-AC), have specific effects on the nervous system and mitochondria. For example, Quercetin has been demonstrated to reduce neuroinflammation, and stimulate biogenesis of mitochondria through activation of SIRT1-PGCQ α pathway [14,15]. Melatonin (recommended to support sleep through circadian rhythm regulation) has been shown to promote energy metabolism, and other mitochondria-related effects [16.] Lastly, N-AC, a precursor to glutathione, aids in detoxification, neuroprotection, and promotion of mitochondrial function [17].

Neuroregeneration was targeted through herbal medicine. Bacopa demonstrates abilities to inhibit neural cell death, delay brain aging, and improve executive brain function [18]. Hericium improves cognition, stimulates neurotransmission and growth [18]. Ginkgo has been studied to block neural cell death, improve mitochondrial function, stimulate neurogenesis and cerebral

blood flow [18]. Increased cerebral perfusion may further promote healing and integration of nutrients into the CNS for repair.

The nutrients prioritized in IV therapy, particularly B complex and Carnitine, have been studied to have effects on the neurologic system and mitochondrial function. Carnitine is involved in transporting fatty acids to the mitochondrial matrix, contributing to the production of ATP [16]. B vitamins have a wide range of activities on mitochondria. For example, riboflavin inhibits the mitochondrial release of reactive oxygen species and mtDNA, preventing activation of the NLRP3 inflammasome [16]. Niacin is a precursor to NAD and NADP, co-substrates in pathways of fatty acid oxidation and energy synthesis [16]. Products of thiamine enhance the electron transport chain, and deficiency is associated with abnormal ATP synthesis [16]. Pyridoxine, folic acid and cobalamin have been shown to lower neurotoxic homocysteine, and impact energy production of the CNS [16].

The last therapy initiated was low-dose naltrexone. Naltrexone is a prescription medication used to treat substance use disorders. It is an opiate receptor antagonist at higher doses, however at lower doses (1-4.5 mg) it acts uniquely as an immune modulator [19], with specific indications in neuroinflammation [20]. LDN has been shown to benefit conditions including Crohn's disease, rheumatoid arthritis, fibromyalgia, multiple sclerosis, chronic fatigue syndrome (ME/CFS) and long-COVID [19,20]. One study of long-COVID patients treated with LDN demonstrated improvement in energy, pain, concentration, sleep disturbance, activities of daily living and overall recovery [19].

Conclusion

Challenges of this investigation stem from the lack of understanding of long-COVID. Literature still lacks clear terminology, diagnostic criteria, pathophysiology, treatment guidelines or prognosis.

Although the patient retained symptoms at her most recent visit, she did report an improvement in pain, brain fog, energy, and quality of sleep throughout the treatment duration. This presents hope for recovery. The strengths of treatment protocols embody a holistic approach: addressing nutritional deficiencies, supporting mitochondria, reducing inflammation, promoting neuro-regeneration and circulation with herbs, IV therapy, and LDN. Immune support beyond acute infection confronts potential reactivation of EBV, persistent viral reservoirs [20], and prevents re-infection before full recovery is achieved.

The patient’s extreme fatigue and neurologic symptoms of long-COVID are further complicated by a significant medical history including EBV infection and chronic fatigue (ME/CFS). This case study supports a current hypothesis that a history of EBV or ME/CFS may be a risk factor for the development of neurologic long-COVID. The devastating nature of these symptoms indicates a need for further research and development of effective treatments.

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