Long Haulers Syndrome—An Integrative Approach to Etiology and Treatment

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Abstract

Many research centers, including Mount Sinai Health System's Center for Post-COVID Care in New York City, have recently been set up to investigate and treat the growing number of patients who remain persistently symptomatic after acute COVID-19 infection. Additional research is clearly necessary to properly characterize, diagnose, and treat this highly challenging condition, as well as to develop an evidence-based, systems-oriented approach for caring for post-COVID-19 syndrome patients.

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The term "Long Haulers Syndrome" broadly relates to people of all ages who have had a recent documented SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection, subsequently tested negative either once or multiple times, yet still have persistent symptoms that may include fatigue, brain fog, gastrointestinal symptoms, headaches, dyspnea, muscle aches, anxiety, reduced exercise tolerance, and heart palpitations. These symptoms persist after recovery from the initial infection and may continue for months.

Post-COVID-19 syndrome has not been definitively linked to the comorbidities commonly associated with increased severity and mortality in acute COVID-19 infection, including diabetes, obesity, and cardiovascular disease. However, while some patients report a previously asymptomatic initial infection followed by the onset of long-term symptoms, several studies have found that the severity of illness during acute COVID-19 (measured by admission to an intensive care unit and/or requirement for mechanical ventilation) has been significantly associated with the presence or persistence of symptoms (such as dyspnea, fatigue, and muscular weakness), reduction in health-related quality of life scores, pulmonary function abnormalities, and radiographic abnormalities in the post-acute COVID-19 setting.[1-4]

The prevalence of long haulers syndrome, recently termed "post-acute sequelae of SARS-CoV-2 infection (PASC)," by Dr. Anthony Fauci, is believed to be between 15%-30%. Initial theories as to the cause of persistent post-COVID-19 symptoms include direct cellular and tissue damage, a robust innate immune response with inflammatory cytokine production, and a pro-coagulant state directly induced by SARS-CoV-2 infection.[5-7]

The occurrence of a post-viral syndrome with the persistence of flu-like symptoms including fatigue is not an uncommon phenomenon. The SARS epidemic in 2003 represents the last time there was a coronavirus pandemic. Tansey et al.[8] found that fatigue persisted in more than half of their sample throughout their recovery: 64% reported fatigue at 3 months, 54% at 6 months, and 60% at 12 months.

Post-viral fatigue has also been observed in people recovering from Ebola virus infection. Wilson et al.[9] estimated that 28% of patients experienced unusual levels of fatigue post-Ebola virus. Post-Ebola Syndrome shares several common symptomologies with long haulers syndrome, most notably fatigue, muscle and joint pain, and sleep disturbances. The development of post-viral syndrome including persistent fatigue has been observed and documented in many studies throughout the literature.

A study partially funded by the CDC and performed in Australia followed 253 individuals for 12 months after developing an infection with either Epstein-Barr virus (a DNA virus) or Ross River virus (an RNA virus). The researchers found that 11% of the participants developed symptoms consistent with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) during the 12-month post-infectious period. These symptoms included fatigue, brain fog, and myalgias.[10] They also found that the strongest predictor of "post-infectious syndrome" was the severity of the initial illness, as judged by the patient's symptoms and laboratory tests. Of note, people with psychiatric illness were not more likely to develop post-infectious ME/CFS.

Post-infectious syndrome has in all likelihood been around since the day viruses began infecting eukaryotic cells approximately 2 billion years ago. When a virus infects a cell, it attempts to transform the genetic code of its host. The cell, in a struggle to repel the invader, will attempt to mount a counterattack against the virus. Cellular defenses, utilizing lysosomes which contain high concentrations of hydrogen peroxide and OH- free radicals, release chemical armaments in an effort to capture and destroy as many viral particles as possible. If the virus wins this battle, tens of thousands of virions are released, and the cell eventually dies. If the cell overcomes the virus, it may survive but collateral damage from the battle predictably results.

In the human body, millions of coronavirus particles flood the bloodstream on a quest to find their sole target, the ACE2 (angiotensin-converting enzyme 2) receptor protein. This important protein is found on the endothelial cell membranes of the lungs, kidneys, and blood vessels. When these cells are attacked, the immune system mounts a fierce battle against the virus. T cells, B cells, macrophages, and millions of antibodies swarm to the infected tissues, unleashing a barrage of free radical toxins to contain and eliminate the infection. This acute inflammatory response can also cause significant collateral damage to uninfected cells, ultimately resulting in persistent end organ dysfunction. There is also the possibility that, after the initial coronavirus infection resolves, the immune system may remain "stuck" in an activated state leading to ongoing flu-like symptoms.

While many long hauler patients may have similar and overlapping symptoms, we should be careful not to assume that all cases of post-COVID-19 syndrome are due to the same etiology. While some symptoms, such as ongoing dyspnea, may be due to direct tissue damage caused by the SARS-CoV-2 virus, other symptoms may be due to an acute or ongoing hyper-immune response. Some researchers also believe that symptoms such as brain fog and attention deficits may occur because the virus attacks the endothelial lining of blood vessels in the brain causing minute, undetectable hemorrhages and microthrombi. A recent meta-analysis of COVID-19 post-mortem brain dissections identified focal microhemorrhage in 23 of 146 cases (16%); intravascular microthrombi in 12 of 146 cases (8%); and moderate to intense microglial activation, suggestive of severe inflammation, in 73 of 146 cases (50%), particularly in the brainstem.[11]

Post-infectious mitochondrial dysfunction may also play a role in post-COVID-19 syndrome. If a patient's cells are not in a well-nourished state, or if they have not inherited a robust mitochondrial genome that is highly compatible with their nuclear genome, they may not have the energy reserves necessary to repair the free radical-induced damage caused by a significant viral infection. In this case, the cell would limp along in a dysfunctional state attracting an inflammatory response or die an apoptotic death. If a large number of brain cells, gut cells, or adrenal cells are left in a hypometabolic, dysfunctional state, attracting a persistent inflammatory response, many of these patients would be assumed to exhibit phenotypic symptoms such as fatigue, myalgias, and brain fog.

In SARS-CoV-2 infection, increased levels of tumor necrosis factor-alpha and interleukin-6 can impede mitochondrial oxidative phosphorylation and associated ATP production, resulting in a progressive buildup of reactive oxygen species (ROS) that may result in the activation of an apoptotic process. Miller et al. recently reported that SARS-CoV-2 reduced the expression of nuclear-encoded mitochondrial (NEM) genes related to cellular respiration, particularly involving Complex I activity, across multiple cell and tissue types.[12] Complex I is known to be a "choke-point" in the electron transport chain where a buildup of excess electrons readily leads to "electron leak" which can increase levels of ROS, thereby degrading mitochondrial resilience.

Pinchas Cohen, professor of gerontology, medicine and biological sciences and dean at the USC Leonard Davis School of Gerontology, and an author of the aforementioned Miller paper, suggests that, "since SARS-CoV-2 leads to a downregulation of respiratory efficiency in the electron transport chain, future work should consider mitochondrial biology as a primary intervention target for SARS-CoV-2."

The mitochondria inside platelets may also be affected by this ROS-fueled apoptotic process. When oxidative phosphorylation within platelet mitochondria is impaired, and sufficient ATP is unavailable for proper platelet functioning, viral-induced platelet dysfunction can lead to microhemorrhages and intravascular microinfarcts.[13]

Evidence also suggests that SARS-CoV-2 infects human enterocytes in the gastrointestinal tract leading to the detection of viruses in fecal samples and alterations in gut microbiome composition. Yeoh et al. found that gut microbiome composition is significantly altered in patients with COVID-19 compared to the general population.[14] This study found that several gut commensal organisms with known immunomodulatory potential, including bifidobacteria, were underrepresented in COVID-19 patient samples and remained low for up to 30 days after disease resolution. The authors concluded that gut dysbiosis after disease resolution could contribute to persistent symptoms and might provide a target for future therapeutic interventions.

When I see a patient with long-standing symptoms of fatigue and brain fog for the first time, the most common observation I hear is, "I was perfectly fine, exercising regularly, raising my kids and living a full life, until I came down with a bad flu. Since that infection, I've never been able to recover my health nor regain my previous level of activity."

When I dig deeply into a person with post-viral syndrome's history, there is often evidence of a person who

was not eating properly, was not sleeping well, had been over-extending themselves, and was under high stress. They usually had no idea that their health was becoming progressively out of balance. I call this the "house of cards" scenario.

In this scenario, a depleted state has gradually been evolving over several years. Contributing factors include age-related progressive mitochondrial dysfunction, a gradual imbalance of brain neurotransmitters, a progressively unhealthy gut microbiome, and/or an immune system that has been subject to multiple previous infections or to antibiotic treatment. All of these factors can promote the loss of immune resilience and a more generalized inflammatory state.

As observed by myself and many other specialists in the field of ME/CFS, addressing a patient's individual symptoms, both pharmacologically and non-pharmacologically, can help some individuals return to a functional, less symptomatic state.

Symptoms that can be effectively addressed with an integrative medical approach include insomnia, anxiety, depression, gastrointestinal symptoms, myalgias, and brain fog. It is also important to rule out several treatable contributing factors to fatigue including thyroid abnormalities, adrenal dysfunction, anemia, allergies, and nutritional deficiencies.

Key components of a post-viral syndrome treatment program include:

1. Mitochondrial support with key supportive micronutrients
2. Microbiome support guided by comprehensive stool testing
3. Adrenal support with micronutrients and botanicals
4. Deep, restorative sleep is an absolute necessity
5. Avoiding excessive stress is important
6. Medications to relieve symptoms so natural therapies have time to work
7. Strategic pacing is very beneficial to help conserve energy
8. Rule out exposure to mold and chemical toxins that might contribute to the patient's lack of immune resilience

Where to go from here? Dr Steven Deeks, an infectious disease specialist at the University of California, San Francisco, thinks researchers first need to create a widely accepted definition of this syndrome. It is the only way for researchers to get on the same page when diagnosing this condition. A medical syndrome is defined as a group of patients who possess the same symptoms and meet an agreed upon set of diagnostic criteria. Nevertheless, it does not require that all patients meeting those criteria arrived there due to the exact same mechanism.

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