Medical News & Perspectives

As Their Numbers Grow, COVID-19 "Long Haulers" Stump Experts

Rita Rubin, MA

For 32-year-old Hanna Lockman of Louisville, Kentucky, it all started March 12. She was at work when she suddenly felt a stabbing pain in her chest.

"It just got worse and worse and worse, to the point I was crying from the pain," she recalled in a recent interview. At 3 AM, the pain sent her to the emergency department. "I had developed a dry cough, maybe a mild fever. I don't remember."

Five months, 16 emergency department trips, and 3 short hospitalizations later, Lockman can't remember a lot of things. She places the blame squarely on coronavirus disease 2019 (COVID-19).

"I joke, 'Well, COVID has eaten my brain, because I can't remember how to remember words, keep track of medication,'" she said. "My brain just feels like there's a fog."

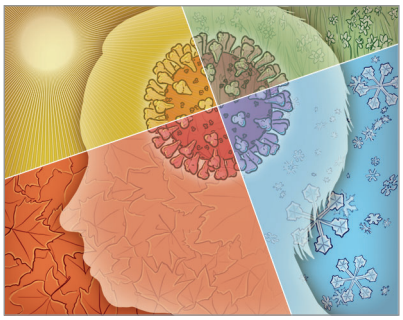
Lockman considers herself to be a "long hauler," someone who still hasn't fully recovered from COVID-19 weeks or even months after symptoms first arose. She serves as an administrator of 2 "Long Haul COVID Fighters" Facebook groups, whose members now number more than 8000.

The longer the pandemic drags on, the more obvious it becomes that for some patients, COVID-19 is like the unwelcome houseguest who won't pack up and leave.

"Anecdotally, there's no question that there are a considerable number of individuals who have a postviral syndrome that really, in many respects, can incapacitate them for weeks and weeks following so-called recovery and clearing of the virus," Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, said in July during a COVID-19 webinar organized by the International AIDS Society.

That appeared to be the case with the first severe acute respiratory syndrome (SARS), which emerged in 2002 and was also caused by a coronavirus. Some people who were hospitalized with SARS still had impaired lung function 2 years after their symptoms began, according to a prospective study of 55 patients in Hong Kong. But only 8096 people were diagnosed with SARS worldwide—a fraction of the COVID-19 cases reported each day in the US alone.

In a recent *JAMA* research letter, 125 of 143 Italian patients ranging in age from 19 to 84 years still experienced physician-confirmed COVID-19–related symptoms an average of 2 months after their first symptom emerged. All had been hospitalized, with their stays averaging about 2 weeks; 80% hadn't received any form of ventilation.



Physicians at a Paris hospital recently reported that they saw an average of 30 long haulers every week between mid-May, when the COVID-19 lockdown ended in France, and late July. The patients' average age was around 40 years, and women outnumbered men 4 to 1.

As with SARS, many COVID-19 long haulers are health care workers who had massive exposure to the virus early in the pandemic, neuroimmunologist Avindra Nath, MD, of the National Institute of Neurological Disorders and Stroke (NINDS), noted in a recent editorial.

Overall, approximately 10% of people who've had COVID-19 experience prolonged symptoms, a UK team estimated in a recently published Practice Pointer on postacute COVID-19 management. And yet, the authors wrote, primary care physicians have little evidence to guide their care.

Puzzling Persistence

Adults with severe illness who spend weeks in intensive care, often intubated, can experience long-lasting symptoms, but that's not unique to patients with COVID-19. What's unusual about the long haulers is that many initially had mild to moderate symptoms that didn't require lengthy hospitalization—if any—let alone intensive care.

"Most of the patients that I see who are suffering from [post–COVID-19] syndrome were not hospitalized," Jessica Dine, MD, a pulmonary specialist at the University of Pennsylvania Perelman School of Medicine, said in an interview. "They were pretty sick, but still at home."

Why some previously healthy, often young, adults still haven't recovered from the disease has stymied physicians.

"We in the medical field are very accustomed to taking care of respiratory syncytial virus and other pneumoviruses in young adults," Wesley Self, MD, MPH, an emergency medicine physician at Vanderbilt University Medical Center, said in an interview. With those infections, "people feel pretty sick for 2 to 3 days, and then they feel markedly better."

But COVID-19 is another matter, Self and his coauthors found in a recent study of 292 individuals with the disease who did not require hospitalization. "One of the goals of this particular study was to understand those with mild symptoms," Self said. "This was an understudied group."

More than a third of them hadn't returned to their usual state of health 2 to 3 weeks after testing positive, the researchers wrote in the *Morbidity and Mortality Weekly Report*. The older the patients, the more likely they were to say they their pre–COVID-19 health hadn't come back. But even a quarter of the youngest, those aged 18 to 34 years, said they had not yet regained their health.

"That certainly was a surprise to us," Self's coauthor and Vanderbilt colleague William Stubblefield, MD, an emergency medicine specialist, said in an interview.

Self and others say they suspect that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection triggers long-lasting changes in the immune system. In some organs, especially the lungs, those changes persist far past the point at which patients have stopped shedding the virus, Self said. "Frankly, we don't know how long that lasts." To help answer that question, Self and his coauthors are conducting a follow-up study to assess

outpatients' health 6 months after their COVID-19 diagnosis.

Sorting Through Symptoms

Just as acute COVID-19 has been found to affect every part of the body, so, apparently, do its persistent symptoms.

In the study of Italian patients, the most common symptoms reported at follow-up were fatigue, shortness of breath, joint pain, and chest pain, in that order. None of the patients had a fever or other sign or symptom of acute illness, but about 44% of them had a worsened quality of life. As the authors pointed out, though, patients with community-acquired pneumonia can also have persistent symptoms, so the findings might not be exclusive to COVID-19.

Less formal surveys have also turned up wide-ranging lingering effects. When the Body Politic COVID-19 Support Group conducted an online survey in the spring, about 91% of 640 respondents said they hadn't fully recovered and were on day 40 of symptoms, on average. Most reported ongoing fatigue, chills and sweats, body aches, headaches, brain fog, and gastrointestinal issues. Anecdotally, some people have reported feeling better for days or weeks before relapsing with old or new symptoms, according to the organization, which started as a small Instagram group chat and has grown to more than 14 000 members.

Francis Collins, MD, PhD, director of the National Institutes of Health (NIH), blogged about the survey in September. "Because COVID-19 is such a new disease, little is known about what causes the persistence of symptoms, what is impeding full recovery, or how to help the long-haulers," Collins wrote, noting that the Body Politic and its international Patient-Led Research for COVID-19 group are now conducting a second survey of long haulers.

A recent survey by the grassroots group COVID-19 "Survivor Corps" found that fatigue was the most common of the top 50 symptoms experienced by the more than 1500 long haulers who responded, followed by muscle or body aches, shortness of breath or difficulty breathing, and difficulty concentrating.

Cough is the most common persistent symptom seen at the new COVID-19 Recovery Clinic (CORE) at Montefiore Medical Center in New York, codirector Aluko Hope, MD, MSCE, said in an interview. Between Hope, a pulmonary and critical care specialist, and the clinic's other director, general internist Seth Congdon, MD, the clinic sees a wide range of patients, including some who were never hospitalized. What the CORE patients have in common is that they haven't yet returned to their pre–COVID-19 health. At least a few of them have been sick for 4 or 5 months, Hope said. Besides the persistent cough, which can also occur with other viruses, loss of taste and smell lingers for many long haulers.

Many of the clinic's patients are also still short of breath. This could be due to the deconditioning seen with any lengthy illness, Hope said, or to infection-specific conditions, such as postviral reactive airways disease, lung fibrosis, or viral myocarditis. Hope said that he's seen at least one patient with no history of heart disease who developed postviral heart failure.

Dine first noticed that some patients weren't getting better through Penn's COVID Watch outreach program, which texts those who are home sick with the disease twice a day until they've been symptom-free for a week to 10 days. She now sees so many people with persistent issues that she's developed a flowchart to try to narrow down the reasons for their ill health: Is this a new symptom unrelated to COVID-19? Is it a complication of the disease, like a blood clot? Or is it a side effect of treatment? If she rules those out, she said there are just 2 options left: Either the patient is still infected with SARS-CoV-2 or they have postviral syndrome.

When the Fog Doesn't Lift

Lockman and many other long haulers describe their most debilitating persistent symptom as impaired memory and concentration, often with extreme fatigue.

The effects are different from the cognitive impairment patients might experience after a critical illness, according to Hope. When it comes to COVID-19, "I do think there's a subset of patients [who] weren't even in the hospital who have a postviral brain fog," he said.

At the end of May, Lockman took a 6-week leave of absence from her job at a human resources management company. Since that ended, she has been working part-time—4 hours on a good day. She moved her home office to her living room so she can rest on the couch. After a recent trip to the emergency department, she was so exhausted that she slept all but 3 hours the next day.

An intriguing idea is taking shape. During the July webinar, Fauci noted that some long haulers' symptoms like brain fog and fatigue are "highly suggestive" of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

New York–based psychiatrist Mady Hornig, MD, a member of Columbia University Medical Center's epidemiology faculty, has long studied the role of microbial, immune, and toxic factors in the development of brain conditions such as ME/CFS, whose etiology and pathogenesis are unknown. Now she's looking at these relationships not only as a physician and scientist but also as a long hauler.

Hornig wrote off a throat tickle and cough in March as allergies. And she assumed that walking around her home shoeless caused the chilblains that later developed on her toes. It wasn't until a 4 AM fever awoke her on April 24 that she suspected she had contracted COVID-19. Although she takes 650 mg of aspirin daily for another condition, the fever persisted for 12 days, a longer stretch than any she had experienced since she had her tonsils removed at age 14, nearly 50 years ago.

Despite all the indicators, Hornig's April 27 nasal swab test was negative for SARS-CoV-2. That's likely because it was performed either too soon or too late—depending on whether the late April fever or the earlier cough or "COVID toes" were the first sign.

Her doctors told her they didn't have a better explanation than COVID-19 for her symptoms, which have also included oxygen saturation levels as low as 88% and 8- to 10-minute tachycardia episodes that still send her heart rate to 115 to 135 beats per minute at least once a day and leave her breathless, even if she's sitting down. Before COVID-19, Hornig was used to working 12- to 14-hour days. For weeks after becoming ill, tachycardia would leave her so fatigued that "I felt like I could not do anything further—my brain was just empty," she said in an interview.

About 3 out of 4 people diagnosed with ME/CFS report that it began with what appeared to be an infection, often infectious mononucleosis caused by Epstein-Barr virus (EBV), Hornig noted. One ME/CFS *International Classification of Diseases* diagnosis code even calls the condition "post-viral fatigue syndrome." Although EBV is a herpesvirus, not a coronavirus, Hornig speculated

that SARS-CoV-2 infection might reactivate latent EBV, triggering the fatigue.

To explore the idea, she has designed prospective studies with the Solve ME/CFS Initiative. The nonprofit in July launched a registry and biobank, funded in part by the NIH, to collect data from COVID-19 long haulers, as well as people diagnosed with ME/CFS and healthy controls.

"Because of the large number of COVID-19 cases occurring simultaneously, we have a unique scientific window and a huge responsibility to investigate any long-term consequences and disabilities that COVID-19 survivors may face," Hornig said in a statement announcing the registry and biobank. "Doing so will provide clues and potential treatment candidates for the millions of Americans already diagnosed with ME/CFS."

Hornig and other scientists point to autonomic nervous system dysregulation as the possible explanation for long-haulers' tachycardia, extreme fatigue, and other persistent symptoms. The system controls involuntary physiologic processes such as heart rate, blood pressure, respiration, and digestion.

Stanford University neurologist Mitchell Miglis, MD, who specializes in autonomic nervous system disorders such as postural orthostatic tachycardia syndrome (POTS), recently coauthored a case report about a previously healthy, 26-year-old emergency department nurse who developed classic POTS symptoms—fatigue, tachycardia—that hadn't resolved 5.5 months after she was diagnosed with COVID-19 in March.

"One of the most common symptoms of POTS is brain fog," Miglis noted. "It's not clearly related to blood flow to the brain. It's something else."

With Lauren Stiles, JD, president of Dysautonomia International and research assistant professor of neurology at Stony Brook University School of Medicine, Miglis has developed an online survey that is being shared with COVID-19 survivor social media groups to gather more information about autonomic symptoms. He plans to resurvey respondents every 3 months for the next year to see how they progress. Miglis speculated that POTS, ME/CFS, and persistent COVID-19 may be different names for the same disorder, and patients' diagnoses depend on their physicians' subspecialty.

Nath, chief of the Section of Infections of the Nervous System at NINDS, is planning a prospective study of persistent ME/CFS-type symptoms among people who've had COVID-19. "I think we need to assure the public that we are aware of the syndrome," he said in an interview. "We're very keen to understand what it's about."

"Medical Gaslighting"

Many long haulers never had laboratory confirmation of COVID-19, which, they say, adds to some health care professionals' skepticism that their persistent symptoms have a physiological basis.

Only about a quarter of the Body Politic survey's respondents had tested positive for COVID-19, while nearly half were never tested—often because their request was denied. But everyone's answers were included in the analysis. The main difference between those who received a positive or negative result was how early in their illness they were tested. "We believe future research must consider the experiences of all people with COVID-19 symptoms, regardless of testing status, in order to better understand the virus and underscore the importance of early and widespread testing," the report's authors wrote.

Lockman was not one of the survey respondents, but she exemplifies the Body Politic's point. At her first trip to the emergency department, she was diagnosed with pneumonia and admitted to the hospital, where she received supplemental oxygen and intravenous antibiotics for 3 days. She suspected it was COVID-19 from the beginning. But she was told she wasn't sick enough or old enough to get one of the then-scarce tests for SARS-CoV-2.

Three weeks after her symptoms began, and after testing negative for influenza and respiratory syncytial virus, Lockman was finally given a SARS-CoV-2 nasal swab test. She tested negative, likely because she had low virus levels by then, she said. In June, she was hospitalized again, this time with pulmonary emboli. A physician who reviewed her chart said she had no doubt that COVID-19 explained her symptoms.

Body Politic has acknowledged that its survey sample wasn't representative of all people with COVID-19. But the organization expressed hope that the findings would inform public health professionals and future research. Toward that end, the founders of the Long Haul COVID Fighters recently launched a Medical and Scientific Collaboration group on Facebook, giving patients and researchers a place to exchange information.

One thing that's clear, Miglis said, is that "these mystery diagnoses are real, and they're not just in patients' heads."

Long haulers say they aren't always taken seriously, though, especially if they're women, harkening back to the era when "female troubles" were written off as hysteria.

"There is definitely gender bias," Dine said. Women with persistent symptoms are more likely than men to be viewed as "dramatic and anxious," she said. "One of the first steps is believing them and making them feel heard. That alone helps."

"We've experienced so much medical gaslighting, basically doctors telling us, 'That's not what you have. It's just anxiety,'" Lockman said. Despite her frustrations, she remains hopeful that her health will continue to improve, although she recognizes that there likely will be bumps along the way.

"I definitely feel better than I did a month ago," she said in early August. "But I still wake up not knowing what I'm going to deal with today." ■

Note: Source references are available through embedded hyperlinks in the article text online.