April 17, 2020

What does COVID-19 portend for ME/CFS?

Mady Hornig, MA, MD
Columbia University Mailman School of Public Health
New York, NY

The COVID-19 pandemic has brought unprecedented suffering to our shores and around the globe. We struggle to fathom the scope of critical acute illness and loss of life commanded by this novel coronavirus. Amidst a dizzying array of ever-shifting estimates of when numbers of new infections – and deaths – will peak, we begin to allow ourselves to consider how we might inch back into some semblance of life as we knew it. But for far too many Americans, surviving infection with the SARS-CoV-2 virus may leave more than a post-traumatic scar and economic disruption. If history is a guide, those infected with this novel coronavirus may be at risk for a profound, disabling disease known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

ME/CFS affects up to 2.5 million Americans and is characterized by persistent severe malaise after exertion, musculoskeletal pain, headaches, gastrointestinal problems, autonomic nervous system instability and extreme memory and concentration problems ("brain fog").[1] It is often heralded by a viral-like illness – but one from which one never recovers. Although no strong evidence suggests a single infectious agent at the root of all ME/CFS,[2] nearly 75% of patients describe episodes of infection as triggers.[3] Up to 12% of patients contracting infectious mononucleosis (most often caused by Epstein-Barr virus) go on to be diagnosed with ME/CFS, with similar findings with other infections.[2] In follow-up studies, severe acute illness appears to add greater risk for later ME/CFS. Although immune/autoimmune, metabolic, gut microbiome and other factors are proposed, the disorder's causes remain unresolved.

Why should we be concerned about ME/CFS after COVID-19? One reason is that prior studies of SARS, MERS, West Nile virus and even Ebola show long-term symptoms akin to those seen in ME/CFS in the aftermath of acute infection, ranging from 11%-90%.[4,5,6,7] Because these viral outbreaks involved fewer total numbers, fewer longitudinal investigations were launched. As a result, the factors putting individuals at risk of persistent ME/CFS-type sequelae are unknown. Ever-growing numbers of those infected with the novel coronavirus creates a unique opportunity to invest proactively in research designed to stave off long-term consequences for COVID-19 survivors. This research would be extraordinarily well-leveraged; clues obtained would also benefit the millions of Americans already diagnosed with ME/CFS.

Another reason for concern is that for an illness first described just 4 months ago, evidence has already accrued of ***persistent neurological problems*** – well beyond that expected after prolonged ICU stays or ventilator use. According to one study, a third of COVID-19 patients still had disorientation, serious difficulties with attention or problems responding to motor commands when discharged from the hospital.[8]

Perhaps the most compelling reasons are the unusually ***high proportions of COVID-19 patients with neurological symptoms during acute infection*** – 36% in one study. Those with more severe acute COVID-19 illness had more neurological problems.[9] COVID-19's neurological features range from disturbed sense of smell or taste[10] to agitation, confusion, altered level of consciousness, slowing of brain waves (EEG evidence of global brain dysfunction), seizures and ischemic strokes.[8,9] One study showed virus in the cerebrospinal fluid and evidence of brain inflammation (encephalitis). Another notes possible association with Guillain-Barré syndrome, an autoimmune condition that attacks peripheral nerves, affects ability to control one's muscles, and has occurred with other viruses.[11] Syncope – a fall typically related to a blood pressure drop – is also reported.[12] Syncope is particularly concerning, as the ACE2 receptor used by SARS-CoV-2 to infect our cells may underlie a frequent problem in ME/CFS called Postural Orthostatic Tachycardia Syndrome. COVID-19 gastrointestinal symptoms – diarrhea, appetite loss, pain – are also reminiscent of common ME/CFS symptoms. While it is

possible that the novel coronavirus directly contributes to these clinical phenomena by infection of cells present in the nervous system, indirect processes are already known to be associated with the severity and mortality of COVID-19, including stimulation of aberrant immune molecule production ("cytokine storm")[13] and disruption of blood clotting mechanisms (coagulopathy, vasculopathy).[14] Answers to these questions of mechanism are therefore not only important for long-term COVID-19 consequences and ME/CFS risk but also have great potential utility for identifying novel treatments that may reduce the severity of the acute disease.

A quarter of individuals with ME/CFS are confined to their homes or completely bedbound.[3] Few recover. The personal cost to individuals and their families is profound. ***The economic toll of ME/CFS is up to $51 billion per year***, with as much as $14 billion in medical costs and $37 billion in lost productivity annually.[15] Given the unprecedented impact of the COVID-19 shutdown on our economy, and the toll ME/CFS takes on quality of life, it behooves us to do what we can to avert this disease.

ME/CFS is an understudied, persistent, severe disease with a huge individual and societal toll. It is often triggered by acute viral-like episodes and is reported after other severe coronavirus infections. ***Investment in research into the association of SARS-CoV-2 infection with ME/CFS has never been more timely or well-leveraged.*** Because case numbers are so highly concentrated over a short period of time, such research is extraordinarily well-positioned to help us rapidly understand why some individuals may be vulnerable to ME/CFS after novel coronavirus infection whereas others are resilient. While learning how to avoid devastating long-term consequences such as ME/CFS, we would also be poised to uncover how we might boost our resiliency to potentially lethal viral infections.

References

1. Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington (DC); 2015.
2. Hickie I, Davenport T, Wakefield D, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ 2006;333:575.
3. Pendergrast T, Brown A, Sunnquist M, et al. Housebound versus nonhousebound patients with myalgic encephalomyelitis and chronic fatigue syndrome. Chronic Illn 2016;12:292-307.
4. Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax 2005;60:401-9.
5. Garcia MN, Hause AM, Walker CM, Orange JS, Hasbun R, Murray KO. Evaluation of prolonged fatigue post-West Nile virus infection and association of fatigue with elevated antiviral and proinflammatory cytokines. Viral Immunol 2014;27:327-33.
6. Lee SH, Shin HS, Park HY, et al. Depression as a Mediator of Chronic Fatigue and Post-Traumatic Stress Symptoms in Middle East Respiratory Syndrome Survivors. Psychiatry Investig 2019;16:59-64.
7. Wilson HW, Amo-Addae M, Kenu E, Ilesanmi OS, Ameme DK, Sackey SO. Post-Ebola Syndrome among Ebola Virus Disease Survivors in Montserrado County, Liberia 2016. Biomed Res Int 2018;2018:1909410.
8. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020.
9. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020.
10. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol 2020.
11. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020.
12. Tape C, Byrd KM, Aung S, Lonks JR, Flanigan TP, Rybak NR. COVID-19 in a Patient Presenting with Syncope and a Normal Chest X-ray. R I Med J (2013) 2020;103:50-1.
13. Vaninov N. In the eye of the COVID-19 cytokine storm. Nat Rev Immunol 2020.
14. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med 2020.
15. Bae J, Lin JS. Healthcare Utilization in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Analysis of US Ambulatory Healthcare Data, 2000-2009. Front Pediatr 2019;7:185.

FOR MORE INFORMATION CONTACT:

Emily Taylor
Director of Advocacy and Community Relations
Solve ME/CFS Initiative
c: (714) 296 – 1661
e: ETaylor@solvecfs.org

Stuart Chapman
Partner
Thorn Run Partners
p: (202) 510-1996
e: schapman@thornrun.com