

PEDIATRIC LONG COVID AND MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME

Overlaps and Opportunities

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David Spodick once wrote: “We must view published material critically (if not biblically), for too often the ‘Conclusions’ giveth, but the ‘Materials and Methods’ taketh away.” In the December 2021 issue of the *Pediatric Infectious Diseases Journal*, Zimmermann et al¹ provide a masterful application of Spodick’s exhortation. Their review of the existing evidence regarding long COVID in children enumerates important methodologic challenges in interpreting this literature, including the heterogeneity of available case definitions for long COVID, differences in the time intervals in which symptoms are ascertained, variability regarding which symptoms are included under the rubric of long COVID, and whether laboratory confirmation of the initial COVID infection is required. Additionally, the authors emphasize that without control groups in many of these studies, and in light of the overlap of some long COVID symptoms with symptoms of prolonged social isolation, it is difficult to discern which symptoms are attributable to the general pandemic circumstances rather than the COVID-19 infection itself. Despite such limitations, it is clear that pediatric patients are at risk for prolonged symptoms following acute SARS-CoV-2 infection. Although many persistent symptoms, such as anosmia, dysgeusia and shortness of breath are unique to the post-COVID state, many other symptoms such as fatigue, cognitive dysfunction, lightheadedness and postexertional malaise overlap with symptoms found in myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS). In this commentary, we review case definitions for long COVID and ME/CFS, emphasize recent research findings on the biologic basis of ME/CFS, discuss the overlap with long COVID, and consider opportunities posed by the pandemic to improve the understanding of both conditions.

POST-COVID-19 CONDITION/LONG COVID

The Centers for Disease Control and Prevention guidance defines post-COVID conditions as new, persistent, or evolving symptoms that are present 4 or more weeks after an initial SARS-CoV-2 infection.² The WHO definition of post-COVID-19 condition requires persistent, new onset, or relapsing symptoms that begin within 3 months after a confirmed or suspected SARS-CoV-2 infection, lasting for at least 2 months.³ While post-COVID condition or long COVID can occur in any age group, adolescents are more commonly affected than are younger children.⁴ It can occur after asymptomatic, mild, or severe disease.¹ Common symptoms of long COVID in children and adolescents include fatigue, “brain

fog,” headache, insomnia, muscle and joint pain, cough, breathlessness and postexertional malaise.^{4,5} However, the long COVID term can also encompass multisystem inflammatory syndrome and other organ-specific complications such as pulmonary fibrosis and myocarditis. In the adult population, female sex and asthma have been associated with increased risk of developing long COVID.⁶

MODERN UNDERSTANDINGS OF ME/CFS

The lingering long COVID symptoms of fatigue and “brain fog”—often associated with considerable disability—have prompted research into whether SARS-CoV-2 virus is just one more potential trigger for ME/CFS or whether there is something fundamentally different about long COVID (in pathophysiology, clinical features, management, or other aspects). Our preliminary observations favor the former view,^{7,8} but much more work is needed before a final verdict is reached.

An extensive 2015 Institute of Medicine review of the evidence from the last 3 decades concluded that ME/CFS “is a serious, chronic, complex and systemic disease that frequently and dramatically limits the activities of affected patients. In its most severe form, this disease can consume the lives of those whom it affects.”⁹ The Institute of Medicine report proposed a new case definition which required a substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities, lasting for at least 6 months, accompanied by fatigue that is often profound, of new onset, not the result of ongoing exertion and not substantially alleviated by rest. The diagnosis also required the presence of postexertional malaise (an exacerbation of a variety of symptoms after increases in physical, cognitive, or orthostatic stresses), unrefreshing sleep and either cognitive impairment or orthostatic intolerance.

Frequently initiated by an acute infection, ME/CFS has been reported following Epstein Barr Virus, Ross River virus, Q fever and earlier coronaviruses such as SARS and MERS. In contrast to long COVID, the likelihood of developing ME/CFS from many of the associated infections, especially Epstein Barr Virus, correlates with the severity of the initial illness.¹⁰ Female sex is a risk factor for ME/CFS in adolescents and adults.

Historically, there has been medical neglect of patients with ME/CFS due in part to the incorrect assumption that the etiology of the illness was behavioral or psychiatric in nature. This assumption relied heavily on claims that the physical examination was normal, and initially was supported by trials suggesting that cognitive behavioral therapy (CBT) was helpful and possibly curative for this condition.¹¹ Subsequent work has demonstrated that a number of abnormalities are present on the physical examination, most notably dysfunctional circulatory control that affects over 95% of pediatric ME/CFS patients, most of whom have heart rate and blood pressure abnormalities consistent with neurally mediated hypotension or postural tachycardia syndrome on orthostatic testing, often associated with acrocytosis.¹² The risk of joint hypermobility is 3-fold higher in adolescents with ME/CFS, and a variety of tests commonly employed by physical therapists identify abnormalities in range of motion in the limbs and spine in over 80%.¹² Thus, it can no longer be claimed that the examination in ME/CFS is normal.

Methodologic problems abound in the published CBT studies in pediatrics and adults. Reported improvements are modest and unsustained after the trials have been completed. The large PACE trial, for instance, claimed that CBT and graded-exercise therapy (GET) caused a significant portion of their patients to “recover” and clinically improve compared with standard medical care alone. The proposed study outcome measures were changed

midway through the trial, which artificially inflated the reported rates of improvement. Independent analysis of the PACE trial data using the original study plan showed few if any clinically important differences; reaching “recovery” as defined by the study authors did not represent a true restoration of health, and in some instances, it was possible for participants who had worse outcome scores on quality-of-life measures than at study entry to be considered recovered.¹³

The situation has not been much better in pediatric ME/CFS. One study from the Netherlands found that 10 weeks of CBT was helpful in improving fatigue, functional impairment and school attendance in children with ME/CFS.¹⁴ However, the control group in this study consisted of people on the waiting list for CBT who received no therapy or care at all, and thus no method of controlling for the level of attention that the CBT group was receiving. In describing this study, journalist David Tuller provided a pithy commentary: “Here’s what this BMJ study proved: Ten sessions of something lead to more reports of short-term benefits than no sessions of anything. But 10 sessions of what? Maybe 10 sessions of poker-playing or 10 sessions of watching Seinfeld reruns while holding hands with the therapist and singing ‘The Girl from Ipanema’ in falsetto would have produced the same results. Who knows?”¹⁵

A 2014 literature review of ME/CFS studies by the US Agency for Health Care Research and Quality (AHRQ) found that harms from treatment were overall not well-reported in trials examining CBT/counseling and GET as options for ME/CFS treatment with some of the GET trials suggesting increased harm associated with this intervention.¹⁶ Anecdotally, when advanced in fixed intervals, increases in exercise intensity can trigger postexertional malaise in patients with ME/CFS. As a result of these and other critiques, CBT and rigid GET are no longer recommended as primary treatments of ME/CFS.¹¹

Physiologic studies from the last 30 years have also identified abnormalities over which patients would not have conscious control, including reductions in cerebral blood flow. When tilted upright to 70° for 30 minutes, adults with ME/CFS experience a 26% reduction in cerebral blood flow compared with supine values, whereas healthy controls experience only a 7% reduction; similar reductions in cerebral blood flow have recently been reported in adults with long COVID.^{8,17} ME/CFS adults have significantly lower maximal oxygen uptake and workload measurements on the second day of a consecutive-day cardiopulmonary exercise test.⁹ After 25 minutes of moderate exercise to 70% of the maximal expected heart rate, those with ME/CFS develop elevations in the expression of adrenergic, sensory and immune genes, and the gene expression changes correlate with the intensity of symptoms of postexertional malaise, among other ME/CFS symptoms.¹⁸ Patients with ME/CFS have been shown to perform worse at cognitive tasks compared with healthy controls while in a position of orthostatic stress compared with when they are supine, where performance between ME/CFS and healthy patients is similar.⁹ Experimental interventions to increase brain blood flow have been shown to improve cognitive ability in ME/CFS patients.⁹ Additionally, fMRI studies in adults have shown that patients with ME/CFS recruit more areas of the brain to complete the same task with the same proficiency compared with healthy controls.⁹ Pediatric quality-of-life scores in adolescents with ME/CFS are worse than for patients being treated in clinics for cystic fibrosis, sickle cell disease, eosinophilic gastroenteritis and diabetes.¹⁹ Why, then, are there not specialty clinics for ME/CFS in every Department of Pediatrics to deal with such a substantial level of morbidity?

OVERLAPS BETWEEN LONG COVID AND ME/CFS

The overlap of symptoms between long COVID and ME/CFS is substantial and includes fatigue, postexertional malaise, cognitive impairment, sleep disturbance and lightheadedness. Both conditions are more frequent in females than males. Neither condition can be reliably diagnosed with laboratory findings, although such testing can help exclude other similar conditions.^{2,12} Diagnosis for both consists of a thorough history to elicit symptoms along with a full physical exam^{2,12}; to identify orthostatic intolerance, we recommend at least a 10-minute period of orthostatic stress, such as with a passive standing test.¹² Treatment focuses on symptom management.^{2,12} While no single pharmacologic agent is effective for all long COVID or ME/CFS patients, this should not encourage therapeutic nihilism, as many effective treatments exist for the common features such as orthostatic intolerance, pain, headaches and insomnia.¹²

More work will be needed to identify whether the prevalence of orthostatic intolerance is as high in long COVID as it is in ME/CFS, and whether the risk factors for pediatric ME/CFS (including allergic inflammation, female sex, peak onset in adolescence and heritable risk factors such as joint hypermobility) apply to post-COVID conditions.

OPPORTUNITIES FOR IMPROVED UNDERSTANDING AND TREATMENT

SARS-CoV-2 enters human cells through the widely expressed ACE-2 receptors, which are present in the entire respiratory system, heart, brain, vascular endothelium and smooth muscle cells, GI tract, kidney, spleen, pancreas and liver.⁴ How chronic symptoms develop is unclear, but proposed mechanisms include direct tissue damage, RNA persistence in body tissue, reactivation of dormant noncoronaviruses due to immune dysregulation, autoimmunity and molecular mimicry, brainstem infection or inflammation and underlying genetic predisposition.²⁰ Mast cells, which contain ACE-2 receptors and are known to remain at a heightened state of activation after an infectious insult in patients with mast cell activation syndrome, have also been hypothesized as potential triggers for long COVID as well as for severe acute COVID-19 in certain predisposed individuals.²¹ Any discoveries regarding the mechanisms for long COVID have the potential to bring insight into the pathogenesis of postinfectious ME/CFS.

It will be important to examine which symptoms persist after acute SARS-CoV-2 infection at different time points (1, 3, 6, 12 and 24 months). To disentangle the degree of distinctiveness or overlap of long COVID and ME/CFS, studies will need to include improved ascertainment of orthostatic symptoms and the other cardinal features of ME/CFS. Since most SARS-CoV-2 virus-specific symptoms are expected to have resolved by the 6-month time point, it might be reasonable to categorize long COVID based on the time since acute infection. Prolonged postviral fatigue consists of symptoms consistent with ME/CFS that last from 1 to 6 months; ME/CFS is diagnosed only after symptoms have persisted for 6 months or longer.

The absence of an organized and robust clinical infrastructure for managing pediatric and adult ME/CFS has adversely affected the care of those with ME/CFS in the United States and elsewhere. Patients with ME/CFS at all ages have reported difficulty obtaining direct care. Unlike the situation in HIV and pediatric cancer, there is no coordinated network of centers that could participate in ME/CFS clinical trials. A corollary of this underdevelopment has meant that resources for managing the many people who have developed long COVID were scarce from the start of the pandemic. While post-COVID clinics are starting to emerge, it will be an important part of managing this and planning for future pandemics that we ensure these clinical efforts succeed. It would

only be just and equitable to ensure that those with nonpandemic ME/CFS have similar access to care.

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