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Review

# Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome

Anthony L. Komaroff<sup>1,\*</sup> and W. Ian Lipkin<sup>2,\*</sup>

**Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause chronic and acute disease. Postacute sequelae of SARS-CoV-2 infection (PASC) include injury to the lungs, heart, kidneys, and brain that may produce a variety of symptoms. PASC also includes a post-coronavirus disease 2019 (COVID-19) syndrome ('long COVID') with features that can follow other acute infectious diseases and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Here we summarize what is known about the pathogenesis of ME/CFS and of 'acute' COVID-19, and we speculate that the pathogenesis of post-COVID-19 syndrome in some people may be similar to that of ME/CFS. We propose molecular mechanisms that might explain the fatigue and related symptoms in both illnesses, and we suggest a research agenda for both ME/CFS and post-COVID-19 syndrome.**

## Post-COVID-19 syndrome and ME/CFS

At the time of the writing of this review, nearly 170 million people were estimated to have been infected with SARS-CoV-2 worldwide, including nearly 35 million people in the USA alone (<https://www.worldometers.info/coronavirus/worldwide-graphs/#case-outcome>). The majority of those infected are asymptomatic or have only mild disease; however, 6.4% with documented infection in the USA have required hospitalization, and the global estimated mortality rate is 2.35% (<https://www.worldometers.info/coronavirus/worldwide-graphs/#case-outcome>, <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html>).

Most people recover completely from 'acute' COVID-19. However, others develop a variety of different **postacute sequelae of SARS-CoV-2 infection (PASC)** (see [Glossary](#)). Some develop chronic damage to the lungs [1], heart [2,3], kidneys [4], brain [5], or extremities through either a cytopathic effect of viral replication an exuberant immune response or thromboembolism. The attendant tissue injury can lead to organ dysfunction and resulting symptoms including but not limited to fatigue, shortness of breath, and cognitive impairment.

In addition, up to 20% have a lingering illness that has not yet been associated with obvious organ injury: **post-COVID-19 syndrome**, also known colloquially as '**long COVID**.' People with the syndrome are referred to as 'long haulers.' The symptoms of post-COVID-19 syndrome are similar to those of **postinfectious fatigue syndromes** following other well-documented infectious diseases. They also are similar to those of **myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)**, an illness originally called just 'chronic fatigue syndrome' that is often preceded by an infectious-like illness. Finally, the symptoms of post-COVID-19 syndrome also

## Highlights

In some people, the aftermath of acute coronavirus disease 2019 (COVID-19) is a lingering illness with fatigue and cognitive defects, known as post-COVID-19 syndrome or 'long COVID.'

Post-COVID-19 syndrome is similar to postinfectious fatigue syndromes triggered by other infectious agents and to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a condition that patients often report is preceded by an infectious-like illness.

ME/CFS is associated with underlying abnormalities of the central and autonomic nervous systems, immune dysregulation, disordered energy metabolism, and redox imbalance. It is currently unclear if the same abnormalities will be identified in post-COVID-19 syndrome.

The USA and other developed nations have committed considerable support for research on post-COVID-19 illnesses.

<sup>1</sup>Division of General Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

<sup>2</sup>Center for Infection and Immunity, Mailman School of Public Health, Columbia University, New York, NY, USA

\*Correspondence: [anthony\\_komaroff@hms.harvard.edu](mailto:anthony_komaroff@hms.harvard.edu) (A.L. Komaroff) and [wil2001@cumc.columbia.edu](mailto:wil2001@cumc.columbia.edu) (W.I. Lipkin).



resemble those that develop in some people following a critical illness (severe injury or infection), variably called **post-critical illness syndrome** or post-intensive care unit syndrome [6].

People with both mild/moderate and severe ‘acute’ COVID-19 can develop the symptoms of post-COVID-19 syndrome. Although it is possible that the pathophysiology causing the chronic symptoms following severe acute COVID-19 is different from the pathophysiology causing symptoms following moderate acute illness, it also is possible that the pathophysiology following severe and moderate illness is similar. In either case, it is likely that the pathophysiology of post-COVID-19 syndrome overlaps with that of acute COVID-19, other postinfectious fatigue syndromes, and ME/CFS.

### ME/CFS

An illness consistent with ME/CFS (Box 1) has been described in the medical literature for over 200 years. Many people with ME/CFS report that the illness began with an ‘infectious-like’ prodrome – typically respiratory and gastrointestinal symptoms, fever, lymphadenopathy, and myalgias. In most instances, an infectious agent is neither sought nor identified. However, postinfectious fatigue syndromes that resemble or meet criteria for ME/CFS have been reported following well-documented infections. The precipitating infectious agents include herpesviruses (Epstein-Barr virus [7], human cytomegalovirus [8], and human herpesviruses 6A and 6B [9]), SARS-CoV-1 (the cause of SARS) [10], Ebola virus [11], West Nile virus [12], dengue virus [13], Ross river virus [14], *Borrelia burgdorferi* [15], enteroviruses [16], human parvovirus B19 [17], *Mycoplasma pneumoniae* [18], *Giardia lamblia* [19], *Coxiella* [14], and *Candida* species [20]. Claims that murine leukemia viruses, including a laboratory recombinant virus [XMRV (xenotropic murine leukemia virus-related virus)], cause ME/CFS have been refuted [21,22], as have similar claims for Borna disease virus [23]. Postinfectious fatigue syndromes can follow both sporadic and apparently epidemic infections [24]. The observation that such a wide variety of infectious agents are associated with ME/CFS suggests that an abnormal host response to infection may be implicated.

Two physical stressors, exercise and prolonged upright position, as well as cognitive and emotional stressors, typically produce a worsening of all of the symptoms of the illness, a condition called ‘postexertional malaise.’

#### Box 1. National Academy of Medicine case definition of ME/CFS<sup>‡</sup>

- (i) Substantial impairment in the ability to function at home or at work, lasting for more than 6 months, accompanied by profound fatigue, of new or definite onset (not lifelong), not substantially alleviated by rest; AND
- (ii) Postexertional malaise; AND
- (iii) Unrefreshing sleep;

PLUS at least one of:

- (iv) Cognitive impairment OR
- (v) Orthostatic intolerance

#### Definitions:

Cognitive impairments: problems with thinking exacerbated by exertion, effort, or stress or time pressure.

Orthostatic intolerance: symptoms worsen upon assuming and maintaining upright posture and are improved, though not necessarily abolished, by lying back down or elevating feet.

Postexertional malaise (PEM): a prolonged exacerbation of a patient’s baseline symptoms after physical/cognitive/orthostatic exertion or stress. It may be delayed relative to the trigger.

Unrefreshing sleep: feeling unrefreshed after sleeping many hours.

<sup>‡</sup>Adapted from the Institute of Medicine [89].

### Glossary

**Ageusia:** loss of taste, which can be due to damage to the tongue, to the cranial nerves that carry taste sensations from the tongue to the brain, or to the parietal lobes in the brain where taste sensations are received and interpreted.

**Anosmia:** loss of smell, which can be due to damage to the olfactory nerve that carries taste sensations from the nose to the brain or to the parietal lobes in the brain where smell sensations are received and interpreted.

**Angiotensin-converting enzyme 2 (ACE2) receptor:** the receptor originally described because of its role in the renin-angiotensin-aldosterone system, but which also is the receptor for SARS-CoV-2, the virus that causes COVID-19.

**Brain fog:** a term for the cognitive difficulties experienced by patients with both ME/CFS and postacute COVID-19 syndrome, characterized primarily by difficulty with attention and concentration.

**Microbiome:** the collective genes of all of those microbes (bacteria, viruses, fungi) that live on or in the human body and that produce molecules that affect human physiology.

**Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS):** an illness that can occur in sporadic or epidemic form; is often preceded by an infectious-like illness; and includes fatigue, cognitive problems, a flare of symptoms following physical, cognitive, or emotional stressors (postexertional malaise), disrupted sleep, and orthostatic intolerance.

**Neurogenic respiratory failure:** the failure of the brain to appropriately stimulate breathing when oxygen levels fall too low or carbon dioxide levels rise too high.

**Paresthesias:** sensations of burning, prickling, tingling, numbness, or itching that can occur in any part of the body, most often the hands, arms, legs, and feet, typically caused by damage to peripheral nerve fibers or brain hypersensitivity to signals from nerve fibers.

**Postacute COVID-19 syndrome, or long COVID:** lingering and debilitating symptoms persisting weeks or months following acute COVID-19, typically including fatigue, cognitive problems, impaired smell and taste, breathlessness, and other symptoms.

**Postacute sequelae of SARS-CoV-2 (PASC):** lingering symptoms following

### Gastrointestinal microbiome

ME/CFS has been linked not only to exogenous infectious agents but also to endogenous agents. Intestinal dysbiosis has been reported by several groups. Proinflammatory Proteobacteria species tend to be increased in number, and anti-inflammatory *Faecalibacterium* and *Bifidobacterium* species and other species that produce the anti-inflammatory compound butyrate are decreased in number [25,26]. Whether the dysbiosis is a cause of the disease or an epiphenomenon secondary to metabolic or immunologic changes or to reduced activity levels is unclear. However, these studies have also found (i) evidence of increased gut wall permeability with bacterial products entering the circulation, (ii) that the abundance of various bacterial taxa correlate significantly with the severity of pain and fatigue [25,26], and (iii) that some metabolomic findings (discussed later) appear to reflect the expression of bacterial rather than human genes [25]. These findings suggest a linkage between the **microbiome**, gut inflammation, and the symptoms of the illness in at least some people.

### Dysregulated immune responses, immune activation, immune cell exhaustion

A variety of abnormal phenotypic and functional immune responses in blood and cerebrospinal fluid (CSF), involving several arms of the immune system, have been independently reported by several research groups. The abnormalities reported by a preponderance of studies, when people with ME/CFS are compared with matched healthy control subjects, are summarized in [Box 2](#). Several of the abnormalities appear to be affected by the duration of the illness, with more pronounced abnormalities seen in the first 3 years followed by a tendency for the abnormalities to subside – a phenomenon that suggests an exuberant immune response at the onset of the illness that may then become exhausted or attenuated by counter-regulatory mechanisms as the illness becomes more chronic [27,28]. In addition, levels of several cytokines are correlated with symptom severity [29]. Cytokines may contribute to fatigue and cognitive dysfunction may serve as biomarkers for immune activation. Some patients with ME/CFS may also have autoantibodies to  $\beta$ -adrenergic and muscarinic cholinergic receptors [30].

### Metabolomic studies

Metabolomics – the simultaneous measurement of multiple small molecules (50–1500 Da) that represent substrates or products of biological processes – is a relatively recent tool for gaining insights into pathophysiology. As summarized in [Box 3](#), studies have found evidence of three phenomena: (i) a generalized impairment in energy production from fatty acids, glucose, amino acids, and oxygen; (ii) a general hypometabolic *state* characterized by depressed levels of most metabolites, as occurs in hibernating animals; and (iii) redox imbalance.

#### Box 2. Immunologic abnormalities in ME/CFS

Increased production of proinflammatory cytokines (e.g., IL-1A, IL-17a, tumor necrosis factor- $\alpha$ ) and 'anti-inflammatory' cytokines (e.g., IL-1 receptor antagonist, IL-4, and IL-13) [28,29,91], particularly in the first 3 years of illness [28].

Levels of multiple cytokines correlate significantly with severity of symptoms [29].

Decreased cytotoxicity of natural killer cells, with diminished expression of cytolytic proteins and production of cytokines [92,93].

Increased numbers of CD8<sup>+</sup> cytotoxic T cells bearing activation antigens (CD38<sup>+</sup>, human leukocyte antigen-DR isotype) [93].

T cell exhaustion [27,28], typically in illness of longer duration.

Decreased and increased numbers of regulatory T cells have been reported [93,94], although the studies did not consider the current stage of the illness (e.g., flare versus relative remission).

Increased production of multiple autoantibodies, particularly against CNS and autonomic nervous system targets [71].

Antigen-driven clonal B cell expansion (proteomic studies) [95].

infection with the virus that causes COVID-19.

#### Post-critical illness syndrome:

lingering and debilitating symptoms following severe injury and/or infection, requiring intensive care initially.

#### Postinfectious fatigue syndromes:

lingering and debilitating symptoms following a variety of well-documented, specific viral, bacterial, fungal, and protozoan infections.

### Box 3. Metabolomic abnormalities in ME/CFS

Reduced generation of ATP from:

- Glucose via the tricarboxylic acid (TCA) cycle [96], reduced levels of fatty acids and of acyl-carnitine [97], and reduced levels of amino acids via the urea cycle [96,98].
- Impaired oxidative phosphorylation [99,100].
- Glycolysis: either a compensatory increase [101] or a decrease [98].

Hypometabolic state: reduced levels of many molecules [102].

Redox imbalance [78,103]:

- Increased levels of pro-oxidants: peroxides and superoxides, correlating with severity of symptoms [104]; isoprostanes, both at rest and after exercise [105].
- Decreased levels of antioxidants: decreased levels of  $\alpha$ -tocopherol [106]; thiobarbituric acid reactive substances, or TBARS, that correlate with severity of symptoms [107].
- Increased nitrosative stress: increased levels of inducible nitric oxide synthase (iNOS), possibly secondary to increased production of NF $\kappa$ B [108]; increased nitric oxide (NO), peroxynitrite, and nitrate, particularly following exercise [109].
- Brain magnetic resonance imaging (MRI) has shown elevated levels of ventricular lactic acid consistent with oxidative stress [110,111].

### Nervous system abnormalities

A wide variety of objective central nervous system (CNS) and autonomic nervous system abnormalities have been reported in ME/CFS. Although the literature contains some contradictory reports, the preponderance of the published evidence has identified the abnormalities summarized in Box 4.

Because depression can cause fatigue, investigators have asked whether psychiatric disorders may be cofactors in ME/CFS. Most studies have found concomitant psychiatric disorders in 50–80% of patients with ME/CFS. However, these disorders typically developed after the onset

### Box 4. Neurologic abnormalities in ME/CFS

Cognitive deficits, primarily in attention and reaction time [112].

Increased pain in response to various stimuli [113–115].

White matter abnormalities on MRI [116,117].

Impaired response to cognitive, motor, visual, and auditory challenges on functional MRI testing [118].

Single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy reveal hypoperfusion and/or metabolic dysfunction of glial cells [119] and neuroinflammation characterized by widespread activation of both astrocytes and microglia [67,68].

Downregulation of the hypothalamic–pituitary–adrenal (HPA) axis [120].

Impaired connectivity (response of one region of the brain to signals from another region) [121,122], also seen in other fatigue states [123].

Disordered sympathetic and parasympathetic activity with reduced cerebral perfusion [70,124].

Proteomic studies of spinal fluid employing mass spectrometry, liquid chromatography, and peptide sequencing found increased levels of proteins (e.g.,  $\alpha_2$ -macroglobulin, keratin 16, orosomucoid) indicating tissue injury and repair [125].

Autoantibodies targeting adrenergic, muscarinic, and cholinergic receptors [30,71–73].

Postexertion neuromuscular studies reveal reduced anaerobic threshold and peak work, particularly after a second exercise challenge 24 hours later [126], as well as increased lactic acid in muscle [127] and the need to recruit additional brain regions to respond to cognitive challenges (as demonstrated by functional MRI), particularly following exertion [128].

of ME/CFS. Psychiatric disorders that manifest before the onset of CFS appear to be no more frequent than in the community at large [31]. Moreover, controlled studies of the antidepressant fluoxetine in people with ME/CFS have demonstrated no benefit [32].

## COVID-19

### The multisystem pathology of COVID-19

Although it was initially thought to be primarily a pulmonary pathogen, SARS-CoV-2 can also cause multiorgan pathology during acute illness involving many organ systems [4,33–39].

### Chronic pulmonary, cardiac, and renal damage following COVID-19

The majority of patients recover from COVID-19 and resume normal activities. Nonetheless, many report persistent symptoms at least 6 months after acute infection [40]. Over 70 000 COVID-19 patients who remained alive 30 days after the onset of symptoms were compared with nearly 5 million matched non-COVID control subjects. Four months later, patients with COVID-19 had persistent respiratory, cardiovascular, nervous system, metabolic, and gastrointestinal system disorders significantly more often than the control subjects. The same was true when hospitalized COVID-19 patients were compared with hospitalized influenza patients [41].

### Neurologic disease during and following acute COVID-19

Reports of neurological signs and symptoms in inpatients with acute COVID-19 vary: 36% of patients in Wuhan, 57% of inpatients in Spain, and 82% of patients in Chicago [42–44]. The most commonly reported manifestations are myalgia, headache, dysgeusia, **anosmia**, encephalopathy, and neuropsychiatric disorders. Seizures and movement disorders are uncommon. Acute ischemic events and intracranial hemorrhage have been reported in 1–4% of patients, including young adults without known vascular disease [45,46]. Some observers have reported **neurogenic respiratory failure** ('Ondine's curse'), although this is controversial. Demyelinating events involving the brain and spinal cord have been reported, as have Guillain-Barré syndrome and leukoencephalopathies [47,48].

Autopsy reports of COVID-19 patients with neurologic disease may vary in findings in accordance with signs and symptoms of disease. Some report low levels of SARS-CoV-2 RNA and protein in the brain as well as astrogliosis and microglial activation [49–51]. In others, the primary pathology may reflect ischemia. One study found viral RNA, protein and particles in olfactory epithelial cells, dendritic projections of olfactory neurons that extended into the mucosa and the brainstem, and microthrombi and infarcts [52]. The distribution of virus in olfactory mucosa and neural processes that extend into the nasopharynx provides a mechanism for understanding anosmia and dysgeusia and for invasion of the CNS. However, in another study, single-cell sequencing of the olfactory epithelium indicated that whereas the requisite viral receptor, the **angiotensin-converting enzyme 2 (ACE2) receptor**, is expressed in support cells, stem cells, and perivascular cells, it is not present in olfactory sensory neurons [53]. It is unclear, therefore, whether COVID-associated anosmia reflects direct neuronal damage due to infection, loss of some factor that is essential to olfactory signal transduction or transmission, or a deleterious inflammatory response.

Footprints in CSF of active infection are uncommon. SARS-CoV-2 RNA was not detected in CSF of 30 patients with a wide range of neurological complications [54]. In another study of 58 patients, 81% of whom had encephalopathy, the presence of virus RNA in CSF was also infrequent (7%); however, 40% had elevated CSF albumin, a finding interpreted to represent trafficking of proteins from the systemic circulation to the CSF due to a breakdown of the blood–brain barrier. Seven (41%) of 17 had elevated CSF levels of the IL-6 cytokine [55].



Taken in concert, autopsy and CSF studies suggest that at least some of the neuropathology of COVID-19 is more likely to represent a host response to the virus and microvascular damage than a direct cytopathic effect of SARS-CoV-2 [50]. Indeed, the vascular pathology – procoagulant, proaggregatory, antifibrinolytic, proinflammatory, vasoconstrictive, and pro-oxidant – seen in the lungs, heart, brain, and other organs may all indicate that primary endothelial dysfunction is central to the pathology of both acute COVID-19 and its long-term consequences [56]. There is ample precedent for infarcts resulting in dementia and cognitive dysfunction in the elderly [57]. The wide distribution of microinfarcts in COVID-19 suggests they may be one cause of cognitive dysfunction. Magnetic resonance imaging of the brain in 37 individuals with severe disease revealed multifocal white matter hemorrhages [58].

#### Chronic fatigue, sensory, and cognitive deficits following COVID-19

The primary persistent symptoms following COVID-19 include chronic fatigue, impaired smell (anosmia) and taste (**ageusia**), cognitive problems (e.g., difficulty with concentration and attention, and possibly memory), and breathlessness. These symptoms may occur in people who have had only mild or no respiratory disease. A post-COVID-19 clinic reported that even patients never hospitalized for pneumonia or hypoxemia reported neurologic complaints persisting for more than 6 weeks that included cognitive dysfunction described as '**brain fog**' (81%), headache (68%), **paresthesias** (60%), dysgeusia (59%), anosmia (55%), and myalgias (55%) [59]. Surveys conducted in the USA, Europe, and Scandinavia [40,60–66] reported very different frequencies of persisting symptoms at 6 months after acute illness. This may be due to differences in methods for ascertainment, differing patient populations (hospitalized versus not hospitalized), different definitions of COVID-19 (confirmed by nucleic acid, antigen, or antibody testing or not), and different methods for collecting symptoms (medical records, patient self-report, formal surveys).

#### Pathogenesis of ME/CFS

The frequency of an infectious prodrome in patients with ME/CFS suggests that, in many cases, infection triggers host responses that culminate in disease. It is plausible that SARS-CoV-2 infection might induce a similar syndrome and that insights from ME/CFS research may be helpful in developing a research agenda for postacute COVID-19 syndrome. Conversely, because ME/CFS by definition cannot be diagnosed until 6 months after symptom onset, studies of PASC may yield insights into early manifestations and biomarkers for ME/CFS.

#### Neuroinflammation

Several studies have reported widespread activation of both astrocytes and microglia in people with ME/CFS [67,68]. Cognitive dysfunction ('brain fog') may reflect cytokines produced by immune activation (either peripherally or in the CNS) that are known to cause fatigue and cognitive and mood disorders. For example, elevated peripheral levels of proinflammatory cytokines such as IL-6 can have profound effects on mood, cognition, and behavior in humans and in animal models [69]. Because this has been well documented for cytokines detected in the circulation, it is at least as likely when cytokines are generated in the brain by neuroinflammation.

#### Energy metabolism

The sensation of fatigue experienced by people with ME/CFS is not relieved by rest and becomes more pronounced hours to days after physical or cognitive exertion. ME/CFS is characterized by a generalized impairment in energy production, a general hypometabolic state, and redox imbalance (Box 3) that may contribute to the pathogenesis of fatigue.

### Dysautonomia

Many patients report postural hypotension and tachycardia. Dysautonomia and cerebral hypoperfusion have been documented in ME/CFS patients by various autonomic nervous system tests [70].

### Autoantibodies

Many ME/CFS patients have autoantibodies that target adrenergic and muscarinic cholinergic receptors [30,71–73]. Autoantibodies against neural targets may contribute to cognitive dysfunction, depression, weakness, and autonomic instability.

### Mechanisms that may link these abnormalities

ME/CFS may represent the unchecked persistence of a response that occurs when various stressors (e.g., infection, injury, cold temperatures, lack of sufficient nutrients) threaten the viability of a cell or of an organism. At the cellular level, it is called the ‘cell danger response’ (CDR) [74]. At the level of the organism, such as in the extreme case of a hibernating animal, it has been called the ‘integrated stress response’ (ISR) [75]. In both the CDR and the ISR, nonessential energy-consuming processes are throttled down, allowing the available energy molecules to be used for processes essential to maintaining viability. A hypothalamic ‘torpor’ nucleus (a group of neurons dedicated to a particular function) has been identified in rodents [76]; we speculate that such a nucleus also may mediate the ISR. We speculate that a similar nucleus of neurons may be implicated in human sickness symptoms and associated physiologic phenomena, such as fever. The nucleus may be triggered by neuroinflammation. Neuroinflammation can occur directly through injury to or infection of the brain. It also can occur indirectly in response to humoral and retrograde neural signals generated by inflammation elsewhere in the body [77] or by autoantibodies against specific neural or immune system targets. The redox imbalance that is a central feature of ME/CFS [78] may be a marker for systemic inflammation in response to infection or injury.

### Pathogenesis of post-COVID-19 syndrome

Studies are underway to identify the type and frequency of permanent organ injury caused by COVID-19, to assess the impact of organ injury on the symptoms and functional status of that injury, and to identify the frequency and underlying pathogenesis of post-COVID-19 syndrome. Viruses can cause damage directly and indirectly [79]. They can invade and kill cells by diverting resources and processes required for viability. They can also compromise cells without killing them and reduce their capacity to express products such as hormones, neurotransmitters, and other factors that are essential for the function of the infected organism [80]. Infection can also induce immune responses that result in damage or dysfunction, even at sites where the virus may not be replicating. Infection-induced cytokine expression can have profound effects on energy metabolism and cognition [81,82]. Adaptive immune responses may result in damage to adjacent, uninfected cells or a break in tolerance to self that culminates in autoimmunity [83].

There is evidence that, as in ME/CFS, autoantibodies may be contributing to post-COVID illness symptoms. Investigators looked for autoantibodies against 2770 extracellular and secreted proteins in 194 acute COVID-19 patients. They found autoantibodies against cytokines, chemokines, lymphocyte receptors, endothelial targets, and multiple CNS targets, including the orexin receptor (important in fatigue and sleep) – autoantibody profiles that correlated with the severity of illness [84].

There also is evidence that autonomic dysfunction may contribute to post-COVID illness [85] as it does in ME/CFS [70,86,87]. Given the emotional, social, and financial trauma experienced by

### Clinician's corner

Although many subjects with ME/CFS report a prodrome consistent with infection, no single agent is consistently implicated. A diagnosis of ME/CFS is based on symptoms; no diagnostic test with adequate sensitivity and specificity has yet been developed, although a number are being tested. Even though the diagnosis is based just on symptoms, multiple underlying biological abnormalities have been identified, as summarized in this article.

There is no specific therapy for ME/CFS, and few if any therapies have yet been studied with large randomized controlled trials.

Although respiratory tract infection may be considered the *sine qua non* of acute COVID-19, SARS-CoV-2 can also cause injury to multiple organs, including the heart, kidney, and brain, through parenchymal infection as well as the immune response and vascular damage.

Following COVID-19, some individuals have lingering illness with features of ME/CFS that may not be explained by obvious organ pathology: post-COVID-19 syndrome.



many people with COVID-19, in some people, it is possible that mood disorders also contribute to the symptoms of post-COVID-19 syndrome. Much remains unknown about its pathogenesis.

### A proposed research agenda for ME/CFS and post-COVID-19 syndrome ME/CFS

In this review, we have summarized the preponderance of the evidence as reflected by multiple prospective, controlled studies conducted by multiple laboratories. As is often true in the literature on most topics, some studies involve fewer patients than one would like. Whereas peer-reviewed studies of ME/CFS patients typically include matched healthy control subjects, very few also include comparison groups with other fatiguing illnesses. Despite this weakness in the literature, inconsistencies in findings most commonly entail differences in the details rather than in general conclusions.

For example, although virtually all reported studies find impairment in energy metabolism, they differ regarding which mechanisms of energy production are most impaired and which metabolites have the most aberrant levels. This is neither surprising nor disturbing: Metabolomics measures 'dynamic' processes rather than 'fixed' defects, such as polymorphic change in gene structure. The moment in a dynamic process when a blood sample is obtained affects the results of any measurement. The first movement and the third movement of the same symphony do not sound the same.

In summary, although the findings we have summarized regarding the underlying pathology of ME/CFS are robust, they also raise questions that require further investigation, as outlined later in the Outstanding questions (see [Outstanding questions](#)).

In addition to defining individual components in the pathogenesis of ME/CFS – chronic inflammation, redox imbalance, defective energy metabolism – we also need to understand how these components interact. Several are bidirectionally related. For example, inflammation can create redox imbalance that, in turn, can damage mitochondrial DNA and membranes. Conversely, mitochondrial dysfunction can generate inflammation, as can redox imbalance sufficient to damage tissue. Thus, the precipitating event may be different in different individuals, but it may lead to the same self-reinforcing vicious cycles that generate the symptoms of the illness.

#### Post-COVID-19 syndrome

Large, longitudinal studies of post-COVID-19 syndrome are underway around the world to collect detailed data on the natural course of symptoms, functional status, and underlying biological aberrations. In our opinion, the most important questions are the following: (i) How frequently do debilitating symptoms and functional limitations occur following acute COVID-19, and what risk factors make them more likely? (ii) How often are such symptoms and limitations due to permanent injury to the lungs, heart, kidneys, or other organs? (iii) In patients with symptoms and limitations but without such permanent organ injury (i.e., those with post-COVID-19 syndrome), is there a detectable pathophysiology? (iv) If the answer to question (iii) is yes, is that pathophysiology similar to what has been found in ME/CFS?

#### Concluding remarks

Lingering symptoms after acute COVID-19 may be due in some patients to chronic damage to the lungs, heart, and kidneys, and in other patients, they may be due to the psychosocial trauma of the illness and the impact of the pandemic on family, friends, and the workplace. In other patients without evidence of such chronic organ damage, such as those with post-COVID-19 syndrome, it seems likely that the underlying biology is similar to that of other postinfectious

#### Outstanding questions

Will multicenter studies of people with ME/CFS in different geographic areas, including people with both early and late disease, consistently confirm the previously described immunologic, neurologic, and metabolomic/redox abnormalities?

Do the molecular, proteomic, and metabolomic tests that discriminate people with ME/CFS from healthy control subjects also discriminate ME/CFS from comparison groups of people with other fatiguing illnesses, such as post-COVID-19 syndrome, multiple sclerosis, systemic lupus erythematosus, and major depression?

Will abnormalities that distinguish people with ME/CFS and post-COVID-19 syndrome at baseline become worse after physical, cognitive, and emotional stressors that typically worsen symptoms and thereby suggest that they may be directly connected to the disease process that generates the symptoms?

Will larger studies using noninvasive imaging techniques confirm the presence of neuroinflammation in people with ME/CFS and post-COVID-19 syndrome?

Will newer anti-inflammatory therapies targeting neuroinflammation specifically, such as therapies to suppress inflammasome activation in glial cells, ameliorate symptoms in people with both ME/CFS and post-COVID-19 syndrome?

Because a redox imbalance has been consistently documented in people with ME/CFS, will trials of therapies to restore redox balance ameliorate symptoms in people with both ME/CFS and post-COVID-19 syndrome?

fatigue syndromes, to post-critical illness syndrome, and to that of ME/CFS. It also is likely that the underlying pathology involves the CNS; the autonomic nervous system; and a persistent, dysregulated immune and metabolic response to any of multiple infectious agents.

The COVID-19 pandemic is likely to greatly increase the number of people who develop ME/CFS or a similar illness and other post-COVID illnesses (e.g., chronic hypoxia from impaired lung function, congestive heart failure from post-COVID cardiomyopathy) [88]. Before the pandemic, ME/CFS was estimated to impact 836 000 to 2.5 million Americans and to cost as much as \$24 billion annually [89]. An estimated 10 million people may be affected worldwide [88]. It is too early to know the ultimate health impact of post-COVID chronic illnesses; however, senior economists have estimated that the cumulative future costs in the USA may be as high as \$4.2 trillion [90].

These human and economic costs underscore the importance of investing in rigorous research into the epidemiology and pathogenesis of ME/CFS and post-COVID chronic illnesses (see Outstanding questions and [Clinician's corner](#)). The National Institutes of Health (NIH) announced in early 2021 that it would invest \$1.15 billion in studies of these illnesses. In addition, an NIH-supported biorepository of plasma, serum, and cells from well-characterized patients, with detailed clinical information on each patient, is available to investigators (<https://searchmecfs.org/>). We anticipate that this investment will lead to fundamental answers about the underlying biology of both post-COVID-19 syndrome and ME/CFS, diagnostic and prognostic tests, and new strategies for intervention that reduce the morbidity and the social and economic costs of these diseases.

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### Declaration of interests

The authors have no interests to declare.

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