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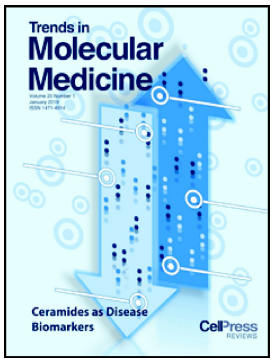

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Insights from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome May Help Unravel the Pathogenesis of Post-Acute COVID-19 Syndrome

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Abstract

SARS-CoV-2 can cause chronic and acute disease. Post-Acute 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-COVID-19 syndrome ("long COVID") with features that can follow other acute infectious diseases as well as 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 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 suggest a research agenda for both ME/CFS and post-COVID-19 syndrome.

Post-COVID-19 Syndrome and ME/CFS

At the time of writing nearly 170 million people are estimated to have been infected with SARS-CoV-2 worldwide, nearly 35 million people in the United States alone (see 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 United States have required hospitalization and the global estimated mortality rate is 2.35% (see 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 **post-acute sequelae of SARS-CoV-2 infection (PASC) (see Glossary)**. Some develop chronic damage to lungs [1], heart [2, 3], kidneys [4], brain [5] or extremities either through cytopathic effect of viral replication, and 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 **post-infectious fatigue syndromes** following other well-documented infectious diseases. They also are similar to those of **myalgic encephalomyelitis/chronic fatigue syndrome, or ME/CFS** (an illness originally called just “chronic fatigue syndrome”, and often preceded by an infectious-like illness). Finally, the symptoms of post-COVID-19 syndrome also 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. While 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 post-infectious 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, post-infectious 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 Severe Acute Respiratory Disease, 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 sp [20]. Claims that murine leukemia viruses, including a laboratory recombinant virus (XMRV), cause ME/CFS have been refuted [21, 22], as have similar claims for Borna disease virus [23]. Post-infectious 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 post-exertional malaise.

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. Pro-inflammatory Proteobacteria species tend to be increased in number, and anti-inflammatory *Faecalibacteria* and *Bifidobacteria* 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: 1) evidence of increased gut wall permeability with bacterial products entering the circulation; 2) that the abundance of various bacterial taxa correlate significantly with the severity of pain and fatigue [25, 26]; and 3) that some metabolomic findings (discussed below) 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 to 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 three 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 as well as serving 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 Daltons) that represent substrates or products of biological processes—is a relatively recent tool for insights into pathophysiology. As summarized in **Box 3**, studies have found evidence of three phenomena: 1) a *generalized impairment in energy production* from fatty acids, glucose, amino acids and oxygen; 2) a *general hypometabolic state* characterized by depressed levels of most metabolites, as occurs in hibernating animals; and 3) *redox imbalance*.

Nervous System Abnormalities

A wide variety of objective central 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.**

Since depression can cause fatigue, investigators have asked whether psychiatric disorders may be co-factors in ME/CFS. Most studies have found concomitant psychiatric disorders in 50-60% of patients with ME/CFS. However, these disorders typically developed after the onset of ME/CFS. Psychiatric disorders *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 Multi-System Pathology of COVID-19

Although it was initially thought to be primarily a pulmonary pathogen, the type 2 Severe Acute Respiratory Coronavirus Virus (SARS-CoV-2) can also cause multi-organ 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 to 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 to hospitalized influenza patients [41]

Neurologic Disease During and Following Acute COVID-19

Reports of neurological signs and symptoms in in-patients 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 2-4% of patients, including young adults without known vascular disease [45, 46]. Although controversial, some observers have reported **neurogenic respiratory failure** ("Ondine's curse"). 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 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, as well as 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 cerebrospinal fluid (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% with 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 of 17 (41%) had elevated CSF levels of the interleukin-6 (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, rather than a direct cytopathic effect of SARS-CoV-2 [50]. Indeed, the vascular pathology –pro-coagulant, pro-aggregatory, anti-fibrinolytic, pro-inflammatory, vasoconstrictive, 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 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 six weeks that included cognitive dysfunction described as "**brain fog**" (81%), headache (68%), **paresthesias** (60%), dysgeusia (59%), anosmia (55%) and myalgias (55%) [59]. Surveys from the US, Europe and Scandinavia [40, 60-66] report very different frequencies of persisting symptoms at 6 months out from acute illness. This may be due to differences in methods for ascertainment, differing patient populations (hospitalized vs. 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 post-acute COVID-19 syndrome. Conversely, because ME/CFS by definition cannot be diagnosed until six 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, 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 animal models [69]. Since 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 ISR, non-essential 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, like 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, and to assess the impact of organ injury on symptoms and functional status of that injury, as well as 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 like hormones, neurotransmitters, and other factors that are essential for 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 2,770 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 suffered by 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 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, while virtually all reported studies find impairment in energy metabolism, they differ as to 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, while the findings we have summarized regarding the underlying pathology of ME/CFS are robust, they also raise questions that require further investigation, as outlined below in **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 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: 1) how frequently do debilitating symptoms and functional limitations occur following acute COVID-19, and what risk factors make them more likely; 2) how often are such symptoms and limitations due to permanent injury to the lungs, heart, kidneys or other organs; 3) 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; 4) if so, 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 to the psychosocial trauma of the illness and the impact of the pandemic on family, friends and workplace. In other patients, without evidence of such chronic organ damage—those with post-COVID-19 syndrome—it seems likely that the underlying biology is similar to that of other post-infectious fatigue syndromes, to post-critical illness syndrome and to that of ME/CFS. It also is likely that the underlying pathology involves the central and 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 suffer from ME/CFS or a similar illness, as well as 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 2,500,000 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 United States 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 Clinicians Corner). The National Institutes of Health 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, social, and economic costs of these diseases.

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Box 1. National Academy of Medicine Case Definition of ME/CFS*

1. 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
2. Post-exertional malaise AND
3. Unrefreshing sleep

   PLUS at least one of:
4. Cognitive impairment OR
5. Orthostatic intolerance

Definitions:
Post-exertional 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

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

*Adapted from the Institute of Medicine [89]

Box 2. Immunologic abnormalities in ME/CFS

Increased production of pro-inflammatory cytokines (e.g., interleukin-1A, interleukin-17a, tumor necrosis factor-α) and "anti-inflammatory" cytokines (e.g., interleukin-1 receptor antagonist, interleukin-4, and interleukin-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 $CD8^+$ cytotoxic T cells bearing activation antigens (CD38+, Human Leucocyte 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 vs. relative remission).

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

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

Box 3. Metabolomic abnormalities in ME/CFS

Reduced generation of ATP from:

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

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 magnetic resonance imaging (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], neuroinflammation characterized by widespread activation of both astrocytes and microglia [67, 68]

Down-regulation 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., α2-macroglobulin, keratin 16, orsomucoid) indicating tissue injury and repair [125]

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

Post-exertion 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]

Clinicians' 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.

Glossary

Ageusia: loss of taste, which can be due to damage to the tongue, 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 (ACE)-2 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 post-acute 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 which produce molecules that affect human physiology.

Myalgic encephalomyelitis/chronic fatigue syndrome: 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 (post-exertional 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.

Post-acute 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.

Post-acute sequelae of SARS-CoV-2 (PASC): lingering symptoms following 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.

Post-infectious fatigue syndromes: lingering and debilitating symptoms following a variety of well-documented, specific viral, bacterial, fungal and protozoal infections.

References

1. You, J. et al. (2020) Anormal pulmonary function and residual CT abnormalities in rehabilitating COVID-19 patients after discharge. J Infect 81 (2), e150-e152.
2. Lindner, D. et al. (2020) Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiol 5 (11), 1281-1285.
3. Puntmann, V.O. et al. (2020) Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 5 (11), 1265-1273.
4. Chan, L. et al. (2021) AKI in Hospitalized Patients with COVID-19. J Am Soc Nephrol 32 (1), 151-160.
5. Lee, M.H. et al. (2021) Microvascular Injury in the Brains of Patients with Covid-19. N Engl J Med 384 (5), 481-483.
6. Stanculescu, D. et al. (2021) Hypothesis: Mechanisms That Prevent Recovery in Prolonged ICU Patients Also Underlie Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Front Med (Lausanne) 8, 628029.
7. Jones, J.F. et al. (1985) Evidence for active Epstein-Barr virus infection in patients with persistent, unexplained illnesses: elevated anti-early antigen antibodies. Ann Intern Med 102 (1), 1-7.
8. Wray, B.B. et al. (1993) Detection of Epstein-Barr virus and cytomegalovirus in patients with chronic fatigue. Ann Allergy 71 (3), 223-6.
9. Komaroff, A.L. (2006) Is human herpesvirus-6 a trigger for chronic fatigue syndrome? J Clin Virol 37 Suppl 1, S39-46.
10. Moldofsky, H. and Patcai, J. (2011) Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurol 11, 37.
11. Epstein, L. et al. (2015) Post-Ebola Signs and Symptoms in U.S. Survivors. N Engl J Med 373 (25), 2484-6.
12. Sejvar, J.J. et al. (2008) Neurocognitive and functional outcomes in persons recovering from West Nile virus illness. J Neuropsychol 2 (2), 477-99.
13. Seet, R.C. et al. (2007) Post-infectious fatigue syndrome in dengue infection. J Clin Virol 38 (1), 1-6.
14. Hickie, I. et al. (2006) Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ 333 (7568), 575-578.
15. Sigal, L.H. (1990) Summary of the first 100 patients seen at a Lyme disease referral center. Am J Med 88 (6), 577-81.
16. Chia, J.K. and Chia, A.Y. (2008) Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach. J Clin Pathol 61 (1), 43-8.
17. Kerr, J.R. et al. (2010) Antibody to parvovirus B19 nonstructural protein is associated with chronic arthralgia in patients with chronic fatigue syndrome/myalgic encephalomyelitis. J Gen Virol 91 (Pt 4), 893-7.
18. Salit, I.E. (1985) Sporadic postinfectious neuromyasthenia. CMAJ 133 (7), 659-63.
19. Mørch, K. et al. (2013) Chronic fatigue syndrome 5 years after giardiasis: differential diagnoses, characteristics and natural course. BMC Gastroenterol 13, 28.

20. Evengård, B. et al. (2007) Increased number of Candida albicans in the faecal microflora of chronic fatigue syndrome patients during the acute phase of illness. Scand J Gastroenterol 42 (12), 1514-5.
21. Simmons, G. et al. (2011) Failure to confirm XMRV/MLVs in the blood of patients with chronic fatigue syndrome: a multi-laboratory study. Science 334 (6057), 814-7.
22. Alter, H.J. et al. (2012) A multicenter blinded analysis indicates no association between chronic fatigue syndrome/myalgic encephalomyelitis and either xenotropic murine leukemia virus-related virus or polytropic murine leukemia virus. mBio 3 (5), e00266-12.
23. Evengård, B. et al. (1999) Absence of evidence of Borna disease virus infection in Swedish patients with Chronic Fatigue Syndrome. J Neurovirol 5 (5), 495-9.
24. Poskanzer, D.C. et al. (1957) Epidemic neuromyasthenia; an outbreak in Punta Gorda, Florida. N Engl J Med 257 (8), 356-64.
25. Nagy-Szakal, D. et al. (2017) Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome 5 (1), 44.
26. Giloteaux, L. et al. (2016) Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome 4 (1), 30.
27. Mandarano, A.H. et al. (2020) Myalgic encephalomyelitis/chronic fatigue syndrome patients exhibit altered T cell metabolism and cytokine associations. J Clin Invest 130 (3), 1491-1505.
28. Hornig, M. et al. (2015) Distinct plasma immune signatures in ME/CFS are present early in the course of illness. Sci Adv 1 (1), e1400121.
29. Montoya, J.G. et al. (2017) Cytokine signature associated with disease severity in chronic fatigue syndrome patients. Proc Natl Acad Sci U S A 114 (34), E7150-E7158.
30. Sotzny, F. et al. (2018) Myalgic Encephalomyelitis/Chronic Fatigue Syndrome - Evidence for an autoimmune disease. Autoimmun Rev 17 (6), 601-609.
31. Hickie, I. et al. (1990) The psychiatric status of patients with the chronic fatigue syndrome. Br J Psychiatry 156, 534-40.
32. Smith, M.E. et al. (2015) Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 162 (12), 841-50.
33. Ellul, M.A. et al. (2020) Neurological associations of COVID-19. Lancet Neurol 19 (9), 767-783.
34. Baral, R. et al. (2020) COVID-19: a pan-organ pandemic. Oxf Med Case Reports 2020 (12), omaa107.
35. Topol, E.J. (2020) COVID-19 can affect the heart. Science 370 (6515), 408-409.
36. Galván Casas, C. et al. (2020) Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol 183 (1), 71-77.
37. Koralnik, I.J. and Tyler, K.L. (2020) COVID-19: A Global Threat to the Nervous System. Ann Neurol 88 (1), 1-11.
38. Lechien, J.R. et al. (2020) Loss of Smell and Taste in 2013 European Patients With Mild to Moderate COVID-19. Ann Intern Med 173 (8), 672-675.

39. Varatharaj, A. et al. (2020) Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 7 (10), 875-882.
40. Carfì, A. et al. (2020) Persistent Symptoms in Patients After Acute COVID-19. JAMA 324 (6), 603-605.
41. Al-Aly, Z. et al. (2021) High-dimensional characterization of post-acute sequalae of COVID-19. Nature, In press.
42. Liotta, E.M. et al. (2020) Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 7 (11), 2221-2230.
43. Romero-Sanchez, C.M. et al. (2020) Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology 95 (8), e1060-e1070.
44. Mao, L. et al. (2020) Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 77 (6), 683-690.
45. Nannoni, S. et al. (2021) Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke 16 (2), 137-149.
46. Fridman, S. et al. (2020) Stroke risk, phenotypes, and death in COVID-19: Systematic review and newly reported cases. Neurology 95 (24), e3373-e3385.
47. Uncini, A. et al. (2020) Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. J Neurol Neurosurg Psychiatry 91 (10), 1105-1110.
48. Scheidl, E. et al. (2020) Guillain-Barré syndrome during SARS-CoV-2 pandemic: A case report and review of recent literature. J Peripher Nerv Syst 25 (2), 204-207.
49. Solomon, I.H. et al. (2020) Neuropathological Features of Covid-19. N Engl J Med 383 (10), 989-992.
50. Lee, M.H. et al. (2020) Microvascular Injury in the Brains of Patients with Covid-19. N Engl J Med 384 (5), 481-483.
51. Matschke, J. et al. (2020) Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol 19 (11), 919-929.
52. Meinhardt, J. et al. (2020) Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 24 (2), 168-175.
53. Brann, D.H. et al. (2020) Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 6 (31), eabc5801.
54. Neumann, B. et al. (2020) Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms. J Neurol Sci 418, 117090.
55. Lersy, F. et al. (2020) Cerebrospinal fluid features in COVID-19 patients with neurologic manifestations: correlation with brain MRI findings in 58 patients. J Infect Dis 223 (4), 600-609.
56. Libby, P. and Lüscher, T. (2020) COVID-19 is, in the end, an endothelial disease. Eur Heart J 41 (32), 3038-3044.
57. Kapasi, A. and Schneider, J.A. (2016) Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. Biochim Biophys Acta 1862 (5), 878-86.
58. Kremer, S. et al. (2020) Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology 297 (2), E242-E251.

59. Graham, E.L. et al. (2021) Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". Ann Clin Transl Neurol 8 (5), 1073-1085.
60. Tenforde, M.W. et al. (2020) Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. MMWR Morb Mortal Wkly Rep 69 (30), 993-998.
61. Garrigues, E. et al. (2020) Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect 81 (6), e4-e6.
62. Carvalho-Schneider, C. et al. (2021) Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect 27 (2), 258-263.
63. Stavem, K. et al. (2020) Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. Thorax 76 (4), 405-407.
64. Goërtz, Y.M.J. et al. (2020) Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res 6 (4), 00542-2020.
65. Townsend, L. et al. (2020) Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One 15 (11), e0240784.
66. Davis, H.E. et al., Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact, medRxiv, 2020.
67. Nakatomi, Y. et al. (2014) Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An (11)C-(R)-PK11195 PET Study. J Nucl Med 55 (6), 945-50.
68. Mueller, C. et al. (2020) Evidence of widespread metabolite abnormalities in Myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy. Brain Imaging Behav 14 (2), 562-572.
69. Felger, J.C. (2018) Imaging the Role of Inflammation in Mood and Anxiety-related Disorders. Curr Neuropharmacol 16 (5), 533-558.
70. van Campen, C.L.M.C. et al. (2020) Cerebral Blood Flow Is Reduced in Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients During Mild Orthostatic Stress Testing: An Exploratory Study at 20 Degrees of Head-Up Tilt Testing. Healthcare (Basel) 8 (2), 169.
71. Loebel, M. et al. (2016) Antibodies to beta adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome. Brain Behav Immun 52, 32-39.
72. Fujii, H. et al. (2020) Altered Structural Brain Networks Related to Adrenergic/Muscarinic Receptor Autoantibodies in Chronic Fatigue Syndrome. J Neuroimaging 30 (6), 822-827.
73. Shoenfeld, Y. et al. (2020) Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy. Clin Immunol 214, 108384.
74. Naviaux, R.K. (2019) Metabolic features and regulation of the healing cycle-A new model for chronic disease pathogenesis and treatment. Mitochondrion 46, 278-297.
75. Costa-Mattioli, M. and Walter, P. (2020) The integrated stress response: From mechanism to disease. Science 368 (6489), eaat5314.
76. Saper, C.B. and Machado, N.L.S. (2020) Flipping the switch on the body's thermoregulatory system. Nature 583 (7814), 34-35.

77. Poon, D.C. et al. (2015) Sickness: From the focus on cytokines, prostaglandins, and complement factors to the perspectives of neurons. Neurosci Biobehav Rev 57, 30-45.
78. Paul, B. et al. (2021) Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. Proc Nat Acad Sci USA, In press.
79. Lipkin, W.I. (2010) Microbe hunting. Microbiol Mol Biol Rev 74 (3), 363-77.
80. Oldstone, M.B. (1989) Viruses can cause disease in the absence of morphological evidence of cell injury: implication for uncovering new diseases in the future. J Infect Dis 159 (3), 384-9.
81. Malik, U.R. et al. (2001) Interferon-mediated fatigue. Cancer 92 (6 Suppl), 1664-8.
82. Valentine, A.D. et al. (1998) Mood and cognitive side effects of interferon-alpha therapy. Semin Oncol 25 (1 Suppl 1), 39-47.
83. Getts, D.R. et al. (2013) Virus infection, antiviral immunity, and autoimmunity. Immunol Rev 255 (1), 197-209.
84. Wang, E.Y. et al. (2021) Diverse Functional Autoantibodies in Patients with COVID-19. Nature, online ahead of print.
85. Dani, M. et al. (2021) Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond) 21 (1), e63-e67.
86. Nelson, M.J. et al. (2019) Evidence of altered cardiac autonomic regulation in myalgic encephalomyelitis/chronic fatigue syndrome: A systematic review and meta-analysis. Medicine (Baltimore) 98 (43), e17600.
87. Lee, J. et al. (2020) Hemodynamics during the 10-minute NASA Lean Test: evidence of circulatory decompensation in a subset of ME/CFS patients. J Transl Med 18 (1), 314.
88. Komaroff, A. and L, B. (2021) Will COVID-19 Lead to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome? Front. Med. 7 (606824), 1-4.
89. Institute of Medicine. (2015) Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness, National Academies Press.
90. Cutler, D.M. and Summers, L.H. (2020) The COVID-19 Pandemic and the $16 Trillion Virus. JAMA 324 (15), 1495-1496.
91. Fletcher, M.A. et al. (2009) Plasma cytokines in women with chronic fatigue syndrome. J Transl Med 7, 96.
92. Eaton-Fitch, N. et al. (2019) A systematic review of natural killer cells profile and cytotoxic function in myalgic encephalomyelitis/chronic fatigue syndrome. Syst Rev 8 (1), 279.
93. Rivas, J.L. et al. (2018) Association of T and NK Cell Phenotype With the Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Front Immunol 9, 1028.
94. Ramos, S. et al. (2016) Regulatory T, natural killer T and γδ T cells in multiple sclerosis and chronic fatigue syndrome/myalgic encephalomyelitis: a comparison. Asian Pac J Allergy Immunol 34 (4), 300-305.
95. Milivojevic, M. et al. (2020) Plasma proteomic profiling suggests an association between antigen driven clonal B cell expansion and ME/CFS. PLoS One 15 (7), e0236148.
96. Yamano, E. et al. (2016) Index markers of chronic fatigue syndrome with dysfunction of TCA and urea cycles. Sci Rep 6, 34990.

97. Reuter, S.E. and Evans, A.M. (2011) Long-chain acylcarnitine deficiency in patients with chronic fatigue syndrome. Potential involvement of altered carnitine palmitoyltransferase-I activity. J Intern Med 270 (1), 76-84.
98. Armstrong, C.W. et al. (2015) Metabolic profiling reveals anomalous energy metabolism and oxidative stress pathways in chronic fatigue syndrome patients. Metabolomics 11, 1626-1639.
99. Missailidis, D. et al. (2020) An Isolated Complex V Inefficiency and Dysregulated Mitochondrial Function in Immortalized Lymphocytes from ME/CFS Patients. Int J Mol Sci 21 (3), 1074.
100. Tomas, C. et al. (2020) The effect of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) severity on cellular bioenergetic function. PLoS One 15 (4), e0231136.
101. Lawson, N. et al. (2016) Elevated Energy Production in Chronic Fatigue Syndrome Patients. J Nat Sci 2 (10), e221.
102. Naviaux, R.K. et al. (2016) Metabolic features of chronic fatigue syndrome. Proc Natl Acad Sci U S A 113 (37), E5472-80.
103. Nijs, J. et al. (2014) Altered immune response to exercise in patients with chronic fatigue syndrome/myalgic encephalomyelitis: a systematic literature review. Exerc Immunol Rev 20, 94-116.
104. Maes, M. et al. (2011) Increased plasma peroxides as a marker of oxidative stress in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Med Sci Monit 17 (4), SC11-5.
105. Robinson, M. et al. (2010) Plasma IL-6, its soluble receptors and F2-isoprostanes at rest and during exercise in chronic fatigue syndrome. Scand J Med Sci Sports 20 (2), 282-90.
106. Miwa, K. and Fujita, M. (2009) Increased oxidative stress suggested by low serum vitamin E concentrations in patients with chronic fatigue syndrome. Int J Cardiol 136 (2), 238-9.
107. Fenouillet, E. et al. (2012) Association of biomarkers with health-related quality of life and history of stressors in myalgic encephalomyelitis/chronic fatigue syndrome patients. J Transl Med 14, 251.
108. Morris, G. and Maes, M. (2014) Oxidative and Nitrosative Stress and Immune-Inflammatory Pathways in Patients with Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS). Curr Neuropharmacol 12 (2), 168-85.
109. Suarez, A. et al. (2010) Nitric oxide metabolite production during exercise in chronic fatigue syndrome: a case-control study. J Womens Health (Larchmt) 19 (6), 1073-7.
110. Natelson, B.H. et al. (2017) Multimodal and simultaneous assessments of brain and spinal fluid abnormalities in chronic fatigue syndrome and the effects of psychiatric comorbidity. J Neurol Sci 375, 411-416.
111. Shungu, D.C. et al. (2012) Increased ventricular lactate in chronic fatigue syndrome. III. Relationships to cortical glutathione and clinical symptoms implicate oxidative stress in disorder pathophysiology. NMR Biomed 25 (9), 1073-87.
112. Cockshell, S.J. and Mathias, J.L. (2010) Cognitive functioning in chronic fatigue syndrome: a meta-analysis. Psychol Med 40 (8), 1253-67.

113. Van Oosterwijck, J. et al. (2010) Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. J Intern Med 268 (3), 265-78.
114. Nijs, J. et al. (2012) In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. Eur J Clin Invest 42 (2), 203-12.
115. Meeus, M. et al. (2010) Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. J Rehabil Med 42 (9), 884-90.
116. Buchwald, D. et al. (1992) A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. Ann Intern Med 116 (2), 103-13.
117. Barnden, L.R. et al. (2018) Hyperintense sensorimotor T1 spin echo MRI is associated with brainstem abnormality in chronic fatigue syndrome. Neuroimage Clin 20, 102-109.
118. Cook, D.B. et al. (2007) Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. Neuroimage 36 (1), 108-22.
119. Schwartz, R.B. et al. (1994) SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndrome, AIDS dementia complex, and major unipolar depression. AJR Am J Roentgenol 162 (4), 943-51.
120. Tak, L.M. et al. (2011) Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol 87 (2), 183-94.
121. Wortinger, L.A. et al. (2016) Aberrant Resting-State Functional Connectivity in the Salience Network of Adolescent Chronic Fatigue Syndrome. PLoS One 11 (7), e0159351.
122. Gay, C.W. et al. (2016) Abnormal Resting-State Functional Connectivity in Patients with Chronic Fatigue Syndrome: Results of Seed and Data-Driven Analyses. Brain Connect 6 (1), 48-56.
123. Wylie, G.R. et al. (2020) Using functional connectivity changes associated with cognitive fatigue to delineate a fatigue network. Sci Rep 10 (1), 21927.
124. Biswal, B. et al. (2011) Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. J Neurol Sci 301 (1-2), 9-11.
125. Baraniuk, J.N. et al. (2005) A Chronic Fatigue Syndrome - related proteome in human cerebrospinal fluid. BMC Neurol 5, 22.
126. Davenport, T.E. et al. (2020) Properties of measurements obtained during cardiopulmonary exercise testing in individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Work 66 (2), 247-256.
127. Jones, D.E. et al. (2012) Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study. Eur J Clin Invest 42 (2), 186-94.
128. Cook, D.B. et al. (2017) Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Brain Behav Immun 62, 87-99.

Outstanding Questions

Will multi-center 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 controls* also discriminate ME/CFS from comparison groups of people with *other fatiguing illnesses*, such as post-COVID-19 syndrome, MS, 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?

Since 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?

Highlights

In some people, the aftermath of acute 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 post-infectious 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 system, 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 US and other developed nations have committed considerable support for research on post-COVID illnesses.