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REVIEW

Postural Orthostatic Tachycardia Syndrome, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID as Neuroimmune Disorders

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Abstract: Postural orthostatic tachycardia syndrome (POTS), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID are heterogeneous disorders with overlapping complex, multi-factorial and multi-systemic pathophysiology. POTS and ME/CFS are the most common phenotypes of Long COVID that can lead to significant disability and functional impairment. The exact pathophysiologic mechanisms of these disorders alone or in combination are still being investigated, but important mechanistic factors have been identified, such as autonomic dysfunction, immune dysregulation, autoimmunity, mitochondrial dysfunction, cerebral hypoperfusion, and neuroinflammation. To this end, we believe that these conditions should be viewed as neuroimmune disorders and should be included in the field of neuroimmunology, with its educational curriculum, training, and clinical care pathways. Including these disorders as part of neuroimmunology subspecialty is the key to advancing the science and clinical care of this underserved patient population with these complex and disabling conditions.

Keywords: postural orthostatic tachycardia syndrome, myalgic encephalomyelitis/chronic fatigue syndrome, long COVID, neuroimmunology, dysautonomia

Postural orthostatic tachycardia syndrome (POTS) and dysautonomia in general, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID are currently viewed as heterogeneous disorders with overlapping complex, multi-factorial and multi-systemic pathophysiology.[1–3] POTS/dysautonomia and ME/CFS are common sequelae of SARS-CoV-2 infection and the most common phenotypes of Long COVID.[1–3] The exact pathophysiologic mechanisms of these disorders alone or in combination are still under investigation, but several themes emerged as frontrunners: immune dysfunction, autoimmunity, autonomic dysfunction, cerebral hypoperfusion and neuroinflammation.[1–3] In this narrative review, we discuss established and proposed pathophysiologic mechanisms of POTS, ME/CFS and Long COVID, given the existing and emerging scientific evidence. Despite the multi-factorial pathology, we believe that these syndromes should be viewed as neuroimmune disorders and should fall under the umbrella of neuroimmunology, along with multiple sclerosis, neuromyelitis optica spectrum disorders, neurologic Sjogren's disease and others.

Autonomic Nervous System

Consisting of sympathetic, parasympathetic and enteric divisions, the autonomic nervous system (ANS) is involved in vital physiologic functions, including cardiovascular control of heart rate and blood pressure, gastric motility and secretion, bladder function, respiration, temperature control and perfusion of organs and tissues. The ANS is responsible

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for the "flight or fight" response to both external and internal stimuli, and the goal is to maintain homeostasis.[4] The ANS and the immune system are connected, with the ANS playing a significant role in the process of inflammation via the vagus nerve, which carries the parasympathetic nervous system output. The vagus nerve is the critical component of the inflammatory reflex, which controls innate immune responses and inflammation during pathogen invasion and tissue injury.[5] To this end, it has been postulated that sympathetic overactivity may be associated with a pro-inflammatory state, while increased parasympathetic activity has anti-inflammatory properties.[5,6]

Postural tachycardia and orthostatic intolerance are key features of POTS, but dysautonomia more broadly may include other symptoms and manifestations, such as chronic dizziness, lightheadedness, palpitations, presyncope, syncope, exercise intolerance, heat intolerance, cognitive dysfunction, fatigue and a decline in functioning. Gastrointestinal, respiratory, and genitourinary symptoms are also common and, in some patients, may be prominent and disabling.[1,7]

Postural Orthostatic Tachycardia Syndrome

POTS, one of the most common autonomic disorders, is a frequent sequela of SARS-CoV-2 as part of Long COVID and is a common comorbidity of ME/CFS.[8,9] POTS diagnostic criteria include the following: 1) an excessive and sustained increase in heart rate (HR) of more than 30 beats per minute (bpm) within 10 minutes of standing or during a head-up tilt table test [or in individuals aged 12 to 19 years, an increase of > 40 bpm] 2) absence of orthostatic hypotension (sustained drop in systolic blood pressure of at least 20 mmHg) 3) presence of symptoms of orthostatic intolerance that are worse with standing and typically improve with lying down, such as palpitations, lightheadedness, and exercise intolerance, 4) symptom duration should be at least 3 months.[10,11] Other conditions mimicking POTS, such as anemia, anorexia nervosa, anxiety, fever, infection, dehydration, pain, hyperthyroidism, pheochromocytoma, deconditioning, or use of drugs such as anticholinergics and sympathomimetics, need to be ruled out although many of these conditions can be present alongside with POTS.[10,11]

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

ME/CFS can be diagnosed via a number of diagnostic criteria, and orthostatic intolerance is one of the minor diagnostic criteria of ME/CFS according to the CDC.[12] Both POTS and autonomic dysfunction without tachycardia (termed "dysautonomia") are major pathophysiologic mechanisms of ME/CFS and Long COVID.[12] There is emerging evidence that abnormalities in the neuroimmune pathways and neuroinflammation may be among the mechanisms of ME/CFS.[13] Numerous neuroimaging studies highlighted important brain regions with hypoactivity, including insula, thalamus, and limbic cortex and suggested that cortical-limbic disconnection, impacting metabolites and brain waves, contributes to ME/CFS symptoms.[14] Extensive phenotyping and studies on serum and cerebrospinal fluid markers demonstrated distinct abnormalities in patients with ME/CFS compared to healthy controls suggesting immunologic and autoimmune pathophysiologies.[15,16]

Long COVID

Long COVID is defined as "an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems".[17] Both ME/CFS and POTS are major phenotypes associated with Long COVID, and autonomic dysfunction is present in nearly 70% of patients with Long COVID, making it a major pathophysiologic mechanism.[18,19] Other major pathophysiologic mechanisms of Long COVID include autoimmune, inflammatory and immune dysregulations, which are similar to the pathophysiology of POTS. Elevated serum autoimmune and inflammatory markers have been found in patents with POTS and in patients with Long COVID.[20,21] Neuroimaging studies suggest that neuroinflammation at the brainstem, specifically at the dorsolateral inferior medulla, may be a possible central nervous system localization for both POTS and Long COVID, which is where the vagal nuclei and vestibular pathways are located.[22] While clinical presentation of patients with these disorders are complex and diverse, consensus guidance statements on assessment and treatment of post-COVID autonomic dysfunction have been developed. Diagnostic evaluation and therapeutic options for patients with post-COVID dysautonomia closely parallel those that are available for patients with POTS and other common autonomic disorders.[23]

The Immune System in POTS, ME/CFS and Long COVID

The innate immune system acts as the body's first line of defense against infections and stressors, operating in a preprogrammed manner. Its key role in the pathophysiology of central and peripheral neurologic manifestations involves recruiting immune cells through cytokine production, activating the complement system, and initiating adaptive immune responses via antigen presentation.[24]

Studies have implicated abnormalities in dysregulated immunity in ME/CFS patients, including increased naïve B-cell numbers with switched memory B-cells in the blood, along with peripheral T-cell exhaustion, activation in the cerebrospinal fluid and decreased cytolytic expression.[16] The immunologic abnormalities in ME/CFS are numerous and beyond the scope of this review, but include increase in CD21+, CD19+, and CD5+ B cells, and antigen-driven clonal B cell expansion; an increase in activated CD8+ T cells, a reduction in CD11b levels; decreased CD8 suppressor cell population; reduced NK cell functioning and many others.[25] NK cells are innate IFN-γ-producing cells that, in conjunction with CD8 T cells, are critical for controlling viral infections. Similar to ME/CFS, the immune system in Long COVID has been found to have significant alterations, including chronic activation of a subset of CD8+ T cells, exhausted T cells, hyperactivated mast cells and elevated interleukin (IL)-1beta, IL-6, and tumor necrosis factor (TNF), as well as elevated intermediate (CD14+, CD16+) and non-classical monocyte (CD14Lo, CD16+) with SARS-CoV-2 S1 protein.[3,26,27] Unlike the studies on ME/CFS and Long COVID, the assessment of immunologic profile in patients with POTS and dysautonomia has been extremely limited, aside from the autoimmune etiology. One study demonstrated elevations of IL1β, IL21, TNFα, INFγ, and CD30 in patients with POTS, and another study showed an association with human leukocyte antigen DQB1*06:09 in Korean population with POTS.[28,29]

T-cell exhaustion represents an aspect of immunologic dysregulation that can result from prolonged responses to chronic infections or inflammatory conditions, such as certain viral infections or autoimmune diseases.[30] In this state, T-cells lose their full ability to eliminate pathogens or dysfunctional cells, leading to a suppressed immune response. Studies exploring immunologic profile and potential presence of T-cell exhaustion are urgently needed to identify an immunologic phenotype of POTS and other forms of dysautonomia that may be especially responsive to immunotherapies.

Autoimmunity

Traditionally, POTS has been classified as neuropathic, hypovolemic and hyperadrenergic although clinically, these subtypes may be indistinguishable from one another due to their overlapping and compensatory pathophysiologies.[31] Despite the notion that POTS has heterogeneous and diverse pathophysiology, autoimmunity has emerged as one of its major mechanisms in the past decade. One study of 100 patients with POTS found a higher prevalence of various non-specific autoimmune markers, including antinuclear antibodies, and comorbid autoimmune disorders than in the general population.[20] Subsequently, multiple studies identified a variety of antibodies important to the autonomic nervous system and vascular control, including ganglionic N-type and P/Q type acetylcholine receptor antibodies, alpha 1, beta 1 and beta 2 adrenergic antibodies, muscarinic M2 and M4 antibodies, angiotensin II type 1 receptor antibodies and opioid-like 1 receptor antibodies in patients with POTS and other forms of dysautonomia.[32–36] Interestingly, many of these antibodies have been also found in overlapping or comorbid conditions with POTS, such as ME/CFS, small fiber neuropathy, complex regional pain syndromes and cardiovascular disorders.

Similar to POTS, autoimmunity is considered to be one of the major mechanisms of Long COVID, with an associated increased risk, overall incidence and range of autoimmune conditions after SARS-CoV-2 infection.[21,37] Autoantibodies to inflammatory cytokines such as IgG to IL-2, D8B, thyroglobulin, and IFNδ and others have been identified in patients with Long COVID, and these autoantibodies have been associated with anti-SARS CoV2 IgG antibodies.[21,26,37] Similar to patients with POTS, G protein-coupled receptor antibodies, including against alpha- and beta-adrenergic antibodies and muscarinic antibodies, as well as autoantibodies to antinuclear and extractable nuclear antigens, were also found in patients with Long COVID.[38] The pro-inflammatory mediators, non-specific antibodies and antibodies relevant to the function of the autonomic nervous system are thought to be important in Long COVID and in post-COVID autonomic disorders, more specifically.[26,37,39]

Similarly to POTS and Long COVID, evidence of autoimmunity has been found in some patients with ME/CFS. A positive ANA has been identified in 68% of ME/CFS patients with the majority directed against nuclear envelope,[40] while dsDNA antibodies were found in 12% of patients.[41] Anti-ganglioside antibodies, anti-phospholipid antibodies and antibodies against cardiolipin were described in a large subset of patients with ME/CFS[42] Additionally, G-coupled protein receptor antibodies, which include anti-muscarinic and anti-adrenergic receptor antibodies, that have been found in patients with POTS and Long COVID, have been also identified in patients with ME/CFS, suggesting that receptors mediating autonomic nervous system transmission are highly relevant and might be a unifying mechanism in all three disorders.[36,38,42]

Mitochondrial Dysfunction

Mitochondrial dysfunction has been recognized as a pathophysiologic substrate in ME/CFS and its comorbidities and as a mediator in inflammation and autoimmunity.[43,44] While many potential abnormalities in mitochondrial genes, protein structure and function and the influence of external factors on mitochondrial function, such as infection or toxic clearance, are being investigated, its role in the pathogenesis of fatigue has been established.[43] Chronic fatigue is one of the defining features and most disabling symptoms of ME/CFS, POTS, Long COVID and is associated with many other systemic disorders. Patients with ME/CFS, POTS and Long COVID experience chronic fatigue, both physical and mental, which is likely the most disabling and most limiting feature of these conditions, resulting in significant functional impairment and reduced quality of life.[45] Importantly, most patients with POTS have chronic fatigue with at least 20% satisfying the diagnostic criteria of ME/CFS.[45] Immune dysfunction, including cellular exhaustion and persistent inflammation, has been linked to mitochondrial function.[43] Thus, it is possible that POTS is associated with mitochondrial and immune dysfunction, which then impacts the function of every cell, alters homeostasis and affects energy production and consumption at the cellular level.

Recently, a study of twenty POTS patients following time-restricting eating for six months demonstrated improvements in upright heart rate, energy, and mitochondrial/metabolic function.[46] Additionally, several case reports on mitochondrial disorders in patients with POTS have been published,[47,48] but further studies on mitochondrial structure and function in POTS and other forms of dysautonomia are needed to determine whether mitochondrial dysfunction is present in most patients with POTS and chronic fatigue and how it ties into autonomic dysfunction and immune dysregulation.

Cerebral Hypoperfusion

Cerebral hypoperfusion emerged as one of the major mechanisms of POTS, dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome and probably Long COVID.[49,50] Cerebral and brainstem hypoperfusion together with neuroinflammation, specifically at the dorsolateral medulla, may be the CNS mechanisms in POTS and Long COVID and need to be investigated further.[22,51,52] Why brainstem hypoperfusion occurs is unclear: multiple hypotheses exist, including a possibility that small penetrating arteries coming off the vertebrobasilar arterial system and supplying the brainstem may be damaged from endothelial dysfunction, hypercoagulable state and possible microclots, all of which have been suggested as playing a role in the pathogenesis of POTS and Long COVID.[53] Other possible mechanisms may include alterations in the glymphatic system, which can lead to inadequate venous drainage of the medulla, venous congestion and toxin accumulation, all of which can result in neuroinflammation. Finally, abnormalities in the connective tissue itself, which could be caused by neuroinflammatory and immune-mediated pathways that include hyperactivated mast cells, may damage the venous and arteriolar walls and the blood-brain barrier. In turn, the altered blood-brain barrier can result in abnormal permeability and vascular contractility, thereby causing decreased perfusion of the brainstem.[22,53]

Neuroinflammation

Emerging evidence suggests that neuroinflammation plays an important role in the pathophysiology of Long COVID. The neuroinflammation has been identified at specific regions of the brain and brainstem that are critical to the autonomic nervous system control of the organs and vital physiologic processes, including respiration, heart rate, blood flow, digestive system, bladder function and probably immunologic response.[52,54,55] Additionally, neuroinflammation might affect other brain regions, such as the insular cortex, basal ganglia and hypothalamus.[3] Using advanced neuroimaging

techniques and 7T MRI, structural abnormalities at the dorsolateral medulla were observed in patients with Long COVID.[52] The multisystemic and diverse symptoms experienced by patients with Long COVID correlate with the structural abnormalities of the brainstem seen on 7T MRI,[52] which could also be the localization for POTS and autonomic dysfunction more broadly, unrelated to SARS-CoV-2 infection.[22] Importantly, systemic abnormalities consisting of central hypovolemia, hyperadrenergic response and downstream autonomic neuropathy resulting from central autonomic network dysregulation may correlate to the hypovolemic, hyperadrenergic and neuropathic POTS phenotypes and may localize to the dorsolateral medulla and hypothalamus via nucleus tractus solitarius, dorsal motor nucleus of the vagus and dorsal longitudinal fasciculus traversing near the floor of the fourth ventricle.[22,52]

To delineate the structural and function abnormalities in the central nervous system further, future studies should utilize advanced neuroimaging techniques and animal models with immunohistochemical brainstem tissue assessments. These studies would need to focus on the underlying mechanisms and precise localization of neuroinflammation that are likely to affect patients with Long COVID, POTS and other autonomic disorders that involve cerebral hypoperfusion. Studies demonstrate that chronic cerebral hypoperfusion can induce excessive inflammatory response that precedes neuronal dysfunction and that TRPM2 channel aggravates neuroinflammation via activation of microglia in a state of chronic cerebral hypoperfusion.[56] TRMP2 channels are involved in the production of proinflammatory cytokines in macrophages and inflammation-related disorders as well as neuropathic pain.[56] Clearly, the relationship between cerebral hypoperfusion and neuroinflammation as it relates to Long COVID, POTS and ME/CFS needs to be explored, and it might be modulated by the microglia and other factors that regulate perfusion, neurotransmitter concentration, metabolism and connectivity between the brain regions.

The Brain and the Immune System

The association between the brain and the immune system has been an emerging and exciting area of research, which may uncover how the brain modulates and regulates the immune system and, alternatively, how systemic immunologic response to an infection, allergen, major trauma or another trigger translates into a variety of neurologic and psychiatric manifestations.[57,58] Jin et al showed that a peripheral immune insult strongly activates the body–brain axis to regulate immune responses, which is accomplished via pro-inflammatory and anti-inflammatory cytokines in communication with vagal neurons.[57] Additionally, the gut-brain axis via the vagus nerve and the connection to spleen, lymph nodes and other organs activates T and B cells, macrophages, dendritic cells, plasma cells, production of antibodies, and release of pro-inflammatory cytokines.[57,58] Trabanelli et al showed that anticipation of approaching infection via virtual reality activates infection-sensing brain regions and the hypothalamus and connect these effects to the hypothalamic–pituitary–adrenal axis, suggesting an integrated neuro–immune reaction in humans toward infection threats, not solely following physical contact, but through the perception of a threat.[59]

Besides the vagal nuclei and the hypothalamic-pituitary-adrenal axis, neurons in the insular cortex have been shown to activate during peripheral inflammation. These insular cortex neurons project to autonomic nervous system control sites: reactivation of these neurons can retrieve specific immune responses demonstrating immunological memory to neuronal representations of inflammatory information.[60] Finally, the importance of meningeal lymphoid tissue, glymphatic system, cytokines produced by T cells and their impact on behavior, cognition, learning and memory have been acknowledged.[61]

Furthermore, microglia, the resident immune cells of the central nervous system, participate in the complex communication with other brain cells under steady-state conditions as well as with infiltrating peripheral immune cells during perturbations. Microglia are critical for maintaining the homeostasis and to overcome pathology leading to neuroinflammation.[62] Importantly, microglial activation was found to be associated with the development of neurocognitive symptoms in Long COVID via specialized PET scan that used a protein ligand expressed by activated microglia as part of the neuroinflammatory response of the brain.[63] Increased microglial activation was found specifically in the ventral striatal and dorsal putamen of patients with Long COVID and may identify possible CNS correlates of neurocognitive symptoms after COVID-19 infection. Microglia hyperactivation has been also considered in the CNS pathophysiology of ME/CFS;[64,65] however, detailed studies on microglial activation in ME/CFS, POTS and dysautonomia more broadly are lacking. Specialized PET scans able to quantify microglial activation and immunohistochemistry of brain biopsy in the existing animal models for ME/CFS and POTS are needed to determine if microglial activation is present in these disorders.[66,67]

Neuroimmunology and POTS, ME/CFS and Long COVID

For many decades patients with POTS, ME/CFS and, more recently, with Long COVID, were largely neglected or misdiagnosed with a host of psychiatric disorders, including somatization, generalized anxiety disorder, depression, conversion or functional neurologic disorder, panic disorder and others. The assumption was that an infection or another acute event took place, then led to deconditioning, debility, faulty coping mechanisms and psychological disturbance with persistent sick behavior, which implied that the acute event resolved, the expected physiologic recovery occurred, but the patient's psyche or mind continued to perpetuate the sick behavior, avoidant patterns and minimal effort preference. Physicians were erroneously taught that since all routine diagnostic tests returned as "normal," then there should be no biological basis for the patient to remain sick. This false narrative neglected chronic inflammation, immune dysregulation, viral persistence, autonomic dysfunction, mast cell hyperactivation and other pathophysiologic mechanisms underlying post-acute infectious syndromes.[3,12] Furthermore, education and training on autonomic disorders are lacking, which similarly leads to a lack of recognition and diagnostic accuracy in patients with dysautonomia and misdiagnosis with psychiatric or psychologically-based disorders. Diagnosing dysautonomia requires specialized training as patients typically present with complex neurologic, cardiovascular, rheumatologic, allergic and psychiatric symptoms. Nevertheless, as in most medical conditions, diagnosis relies on clinical skills, which includes obtaining a detailed history, performing a 10-minute stand test instead of a vital sign check while sitting only, and conducting a thorough neurologic and medical physical examination.[1] Additional diagnostic tests include a tilt table test in conjunction with complete autonomic function testing if available, a skin punch biopsy to test for comorbid small fiber neuropathy, a serum panel with autoimmune and inflammatory markers, a cytokine panel if available, and other neurologic and immunologic tests as dictated by personalized case history.[1,23]

Similarly to POTS, patients with ME/CFS experience significant difficulty in obtaining medical care given the stigma, inadequate education and misdiagnosis with psychiatric conditions[68] while patients with Long COVID appear to follow the same difficult and inadequate diagnostic and therapeutic journey. Long COVID is a major public health issue with long-lasting adverse health effects and impact on the individual and public health risks.[69] Neurologic, autonomic and cognitive sequelae of SARS-CoV-2 infection represents a major healthcare burden and a threat to brain health, which would necessitate well-trained physicians and neurologists capable of diagnosing and treating Long COVID, POTS and ME/CFS.[67,68] Many known and unknown adverse effects of SARS-CoV-2, including repeated infections on the developing brain of children and adolescents, the carcinogenic effects of the virus and its deleterious effects on aging and neurodegeneration, suggest that neurologists would be undoubtedly involved in the healthcare of these patients.[69]

The historical development of multiple sclerosis pathophysiology, biomarkers, diagnostic criteria and therapeutic options – and the treatment of patients, a majority of whom are also women as is the case with POTS, ME/CFS and Long COVID – closely parallels the patterns of POTS, ME/CFS and Long COVID.[70,71] Although our understanding of these disorders is still evolving, along with the knowledge of how the brain is involved in the regulation of the immune system, we must designate POTS, other forms of dysautonomia, ME/CFS and Long COVID as an important category of neuroimmunology (Figure 1). Furthermore, we must develop educational materials, consensus guidance statements and clinical care pathways for neurologists and neuroimmunologists to gain knowledge and skills necessary for delivery of effective patient-centered care.[23] For this to happen, the first step would be to abandon an outdated notion that these patients have psychiatric or psychological disturbances (or functional neurologic disorder, previously known as hysteria)[70,71] – a critical change that transformed a disorder known in the past as hysterical paralysis to multiple sclerosis - a neuroimmune disease.

Future Direction

Neuroimmunology is a neurologic subspecialty that traditionally encompasses multiple sclerosis and other demyelinating disorders as well as neuroimmune manifestations of systemic autoimmune disorders. The field has been undergoing rapid transformation and paradigm shifts with neuroimmune aspects being identified in many neurologic and psychiatric disorders that have been traditionally viewed as not associated with neuroimmunology.[72] The SARS-CoV-2 pandemic and Long COVID, with its prominent neurologic, immunologic and autonomic manifestations, further highlighted the

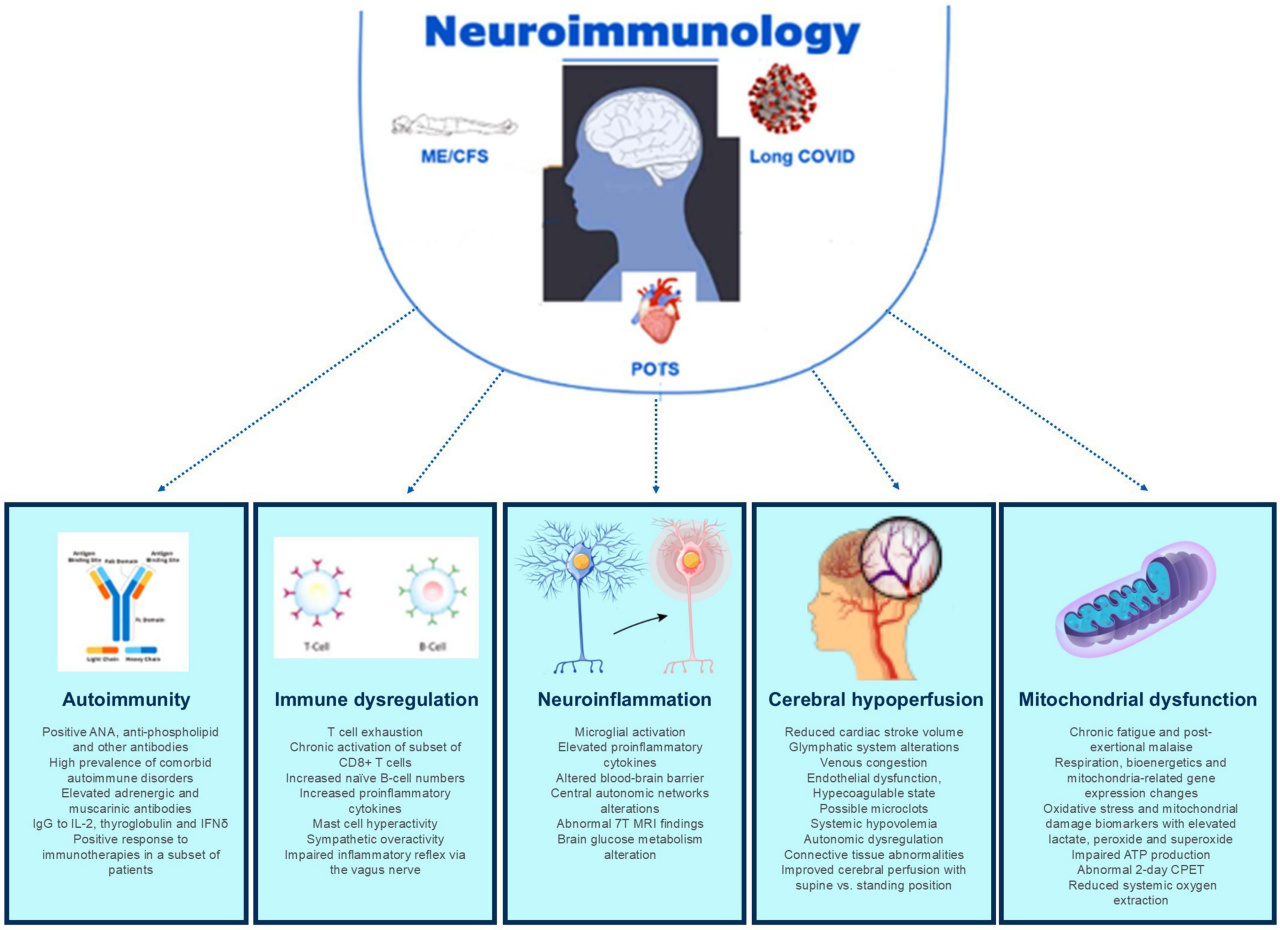

Figure 1 POTS, ME/CFS and Long COVID as Neuroimmune Disorders with shared pathophysiologic mechanisms.
Abbreviations: POTS, postural orthostatic tachycardia syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; ANA, anti-nuclear antibodies; IgG, immunoglobulin G; 7T MRI, 7 Tesla magnetic resonance imaging.

importance of studying the brain-immune system interplay and the need to merge immunology and neuroscience research with clinical neurology going forward.

Although our knowledge of the neuroimmune mechanisms of POTS, ME/CFS and Long COVID is still expanding, along with our understanding of how the brain is involved in the modulation and regulation of the immune system, there is clinical and scientific evidence to suggest that POTS, ME/CFS and Long COVID fall into a broad category of neuroimmune disorders (Figure 1) and that immunotherapies may present an effective therapeutic option.[73] Other complex disorders with significant neuropsychiatric manifestations that may fit into this category are pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), neuropsychiatric manifestations of acute and chronic infections in adults and neuropsychiatric manifestations of systemic autoimmune, immunologic and allergic disorders, including mast cell activation syndrome.[74]

Neurologists, neuroimmunologists and autonomic specialists are uniquely positioned to understand and lead the scientific effort and clinical care of complex disorders involving the brain, the peripheral nervous system, the autonomic nervous system and the immune system. Expanding the scale and scope of neuroimmunology as a field would be critical from the diagnostic, therapeutic, scientific and public health perspectives. Validated and clinically available diagnostic tests, including 7T MRI, functional MRI, specialized PET scans, MR spectroscopy, autonomic function testing, skin biopsy, transcranial dopplers, wearable technology and devices that can accurately assess cerebral perfusion, as well as serum cytokine, antibody and inflammatory markers panels, would need to become available as routine diagnostic tests. There is unprecedent opportunity and an urgent call for action to improve the care of many millions of patients with

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complex disorders involving the brain and the immune system and to promote brain health by developing neurotherapeutics consisting of new and repurposed immunomodulating, anti-inflammatory, and, potentially, antimicrobial therapies.

Conclusion

In summary, POTS, ME/CFS and Long COVID demonstrate overlapping pathophysiologies rooted in immune-mediated and neuroinflammatory pathways involving the interplay between the brain and the immune system with mechanistic factors, such as T cell exhaustion, autoimmunity, proinflammatory cytokines, autonomic dysfunction, mitochondrial dysfunction, cerebral hypoperfusion, microglial activation and probably many other factors that remain to be identified. As neurology, neuroscience and neuroimmunology are advancing and evolving, so is our understanding of complex disorders involving the brain, the immune system and the autonomic nervous system. Once considered obscure and elusive, POTS, ME/CFS and Long COVID emerged as neuroimmune disorders, each with its own diagnostic criteria, but all three with overlapping pathophysiologies and therapeutic considerations. Classifying these disorders as neuroimmune and including them in neuroimmunology education and training is imperative to advancing the science and clinical care of millions of patients living with these complex and disabling conditions.

Disclosure

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