Dual Sympathetic Block (LEVEL 4)
DSB FOR Post-Acute COVID-19 Syndrome (PACS)

Introduction

Post-Acute COVID-19 Syndrome (PACS), commonly known as long-haul COVID or long COVID, is a new disease state characterized by the presence of persistent symptoms that affects patients who have recovered from acute infection by the SARS-CoV-2 virus. Some individuals infected with COVID-19 experience new, returning, or ongoing health problems following acute infection by the SARS-CoV-2 virus. Most commonly, PACS symptoms may include dyspnea, chronic fatigue, post-exertional malaise, neurocognitive issues such as difficulty concentrating (commonly referred to as "brain fog"), persistent cough, chest pain, headache, heart palpitations, joint or muscle pain, diarrhea, insomnia, fever, dizziness, anosmia, or ageusia (1).

Risk Factors for PACS

Any individual who has been infected with the SARS-CoV-2 virus can develop PACS, despite a mild or asymptomatic initial symptom presentation. The majority of patients who present with a mild initial symptom presentation recover within 7-10 days, but PACS patients experience persistent symptoms that continue beyond this typical recovery time frame. Results from clinical studies have estimated that 87% of recovered individuals who were previously hospitalized due to severe COVID-19 symptoms experience the persistence of at least one symptom for over 60 days (2). Results from a prospective cohort study of 277 adults who had recovered from mild or severe cases of SARS-CoV-2 indicated that PACS was detected in approximately half of all study participants, as measured by persistence of at least one clinically relevant symptom, and approximately 25% of study participants exhibited radiological and/or spirometric changes 77 days after disease onset (3). Despite our vastly insufficient understanding of PACS, four quantifiable risk-factors at the time of initial COVID-19 diagnosis have been recently identified: 1) type 2 diabetes 2) SARS-CoV-2 RNAemia 3) Epstein-Barr virus viremia 4) specific autoantibodies (4). In addition, persistence of chronic inflammation, some psychological symptoms, such as post-traumatic stress, may represent additional risk factors for developing PACS (1-2, 4). Although any individual infected with SARS-CoV-2 has the potential to develop PACS, data suggests that those who experience a severe initial COVID-19 infection, women and individuals with comorbidities have a higher risk of developing PACS (1).

Current PACS Treatments

As PACS has only recently been defined as a distinct disease state, targeted and effective treatment options are extremely limited. PACS can affect many different organ systems, so current treatments are often multi-disciplinary, focusing on symptomatic management and treatment of underlying health problems (6). Some symptoms, such as cough or fever, may be effectively managed using over-the-counter medications like acetaminophen, but other symptoms, such as brain fog, are difficult to treat with traditional protocols. PACS symptoms can

be functionally debilitating and can severely diminish quality of life, so developing novel management strategies that address this disease may prove to have significant implications in the wake of the COVID-19 Pandemic.

Role of Autonomic Dysfunction in PACS Pathogenesis

Autonomic dysfunction is associated with an extended symptom presence in numerous viral infections, such as human immunodeficiency virus (HIV), herpes viruses, and, more recently, SARS-CoV-2 virus (12-13). Given the widespread influence of sympathetic innervation on multiple organ systems, clinical manifestations of autonomic dysfunction may vary between acute and recovery phases of these viral infections (13). In the context of acute SARS-CoV-2 infection, clinical symptoms deriving from dysautonomia may include direct tissue damage leading to respiratory, cardiovascular or neurological symptoms (13). Alternatively, some characteristic PACS symptoms may derive from either immune-mediated or virus-mediated dysautonomia (13). Previous literature has hypothesized that some such symptoms, like orthostatic intolerance, postural orthostatic tachycardia syndrome (POTS), palpitations, chest pains/discomfort, and temperature intolerance may be attributable to PACS-related dysautonomia (13). As high levels of catecholamines can cause paradoxical vasodilation, subsequent cerebral hypoperfusion and tachycardia that occurs as a result of elevated catecholamines may account for autonomic-related PACS symptoms (14).

Autonomic signaling has been evidenced to facilitate the activity of various mechanisms, including inflammatory processes, involved in coordinating immune responses (14-15). For example, SNS-mediated catecholamine release from nerve terminals in secondary lymphoid organs has been shown to regulate the proliferation, differentiation and activity of immunocompetent cells (10). As such, catecholamines and other SNS signaling molecules are essential to the body's ability to elicit a rapid immune response to infection (10). Tight regulation of sympathetic signaling is crucial for maintaining normal communication between the immune and nervous systems. Many pathologies, such as SARS-CoV-2 infection, can disrupt this relationship, promoting sympathetic responses (e.g. elevated cytokine and catecholamine levels) and subsequent inflammation (10, 14-15). In such pathologies, the vagus nerve, which is partly responsible for counteracting sympathetic responses, communicates information about pro-inflammatory biomarkers to the brainstem (14). When sympathetic signaling becomes dysregulated, the brainstem integrates this information into behavioral responses (i.e. sickness behaviors), which closely resemble PACS symptoms (14). Persistent hyperactivation of the SNS can physically alter the synaptic connections between the vagus nerve and the brainstem, leading to prolonged dysautonomia (10, 14). Research suggests that continued hyperactivation of the sympathetic nervous system may be at least partially responsible for persistent inflammation-related PACS symptoms (14). Similarly, prolonged dysautonomia is associated with impaired cerebral blood flow (CBF) in many conditions (e.g., myalgic encephalitis/chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome) which have clinical presentations that parallel many symptoms of PACS (14). In

general, impaired CBF can cause a range of clinical symptoms such as cognitive dysfunction, impaired memory and attention, and reduced visual, gustatory or olfactory function (14).

Sustained SNS hyperactivity can lead to neuronal adaptation, which may present clinically as persistent dysautonomia (14-15). SARS-CoV-2 has been demonstrated to elicit long-term microstructure and cerebral blood flow changes in recovered individuals (16). During active SARS-CoV-2 infection, SARS-CoV-2 promotes and sustains microglial activation in the central nervous system, leading to a potent neuroinflammatory response (16-17). It has been hypothesized that SNS hyperactivity following acute SARS-CoV-2 infection may sustain this inflammatory response, leading to increased oxidative stress, dysfunctional vascular endothelium, neuronal cell death, and ultimately reduced CBF and decreased cortical thickness (17). Such alterations in brain structures and function may contribute to the neurological sequelae of PACS (17).

Dual Sympathetic Blockade

Stellate ganglion blocks (SGB) are minimally-invasive procedures used to treat various sympathetic nervous system-related disorders, including post-traumatic stress disorder (PTSD), complex regional pain syndrome, ventricular arrhythmia, and, more recently, PACS (19-22). Paired SGB procedures are referred to as Dual Sympathetic Blockades (DSBs) and are hypothesized to elicit clinical relief of these conditions by anesthetizing the physical source of sympathetic overdrive, the stellate ganglion (SG) The DSB procedures involve injecting the anesthetic agent bupivacaine under ultrasound guidance into the SG, a nerve bundle that runs bilaterally along the cervical spine region at the C4 and C6 levels. As these nerve bundles are highly involved in the regulation of the SNS, anesthetizing the SG may effectively "reset" the sympathetic signaling and restore normal biological function, providing rapid and significant symptom relief of even the most severe dysautonomic symptoms. DSBs have been shown to provide significant and long-lasting relief for patients with PTSD who experience symptoms related to sympathetic overdrive, with an estimated 70-80% success rate (19-26). Results from a recent randomized sham-controlled clinical study indicated that study participants who received SGB reported PTSD symptom relief twice as large as those receiving the sham procedure, as measured through PCL-5 scores, and that over 70% of the patients who received SGB experienced clinically significant symptom relief that persisted beyond 3- to 6-months post-procedure (25). PTSD is associated with overactive sympathetic reactivity and activity under resting conditions and during mental stress, and many characteristic PTSD symptoms may represent clinical manifestations of autonomic dysfunction (i.e. hyperarousal, heightened stress responses) (27-31). DSBs have also been used to treat sympathetic nervous system-related conditions of the head, neck and upper body ranging from cardiac applications to complex regional pain syndrome (32-33). Although the exact mechanisms by which DSBs provide relief of dysautonomia-related symptoms are not completely understood, numerous studies have reported that DSBs may stimulate an increase in cerebral blood flow (34-36). As cerebral vasculature is under the control of sympathetic signaling via neural pathways with the stellate ganglion and impaired CBF is commonly implicated in sympathetic-related pathologies, utilizing

DSB in the treatment of such pathologies may serve as an effective management strategy for restoring normal cerebral blood flow (35-38).

Dual Sympathetic Blockade for PACS

Many PACS symptoms, such as chronic dyspnea, impaired memory and concentration, chronic fatigue, and olfactory and gustatory dysfunction, have been hypothesized to be a consequence of sympathetic overdrive and dysautonomia. By targeting the root cause of dysautonomia in PACS patients, DSBs may reduce sympathetic hyperactivity and increase cerebral blood flow, providing patients with significant symptom relief. Anesthetizing the physical source of sympathetic hyperactivation (the SG) via DSB recalibrates the communication network between the immune and nervous systems toward a pre-COVID balance and may effectively reduce PACS symptoms (18). DSBs may alleviate some neurocognitive symptoms of PACS by increasing CBF and improving perfusion to brain structures involved in sensory perception or processing (18). Indeed, successful reports of DSBs in the treatment of anosmia have been published years prior to the COVID-19 pandemic (38). As the results of a recently published case series (18) support a significant clinical benefit of DSBs in restoring olfactory function and improvement in other PACS symptoms, these procedures may emerge to be an effective treatment for dysautonomia-related PACS symptoms (18).

Although it still remains unclear how SGB may produce clinically meaningful symptom relief in PACS patients, it has been hypothesized that the beneficial effects of SGB on CBF (i.e. increasing CBF without affecting the capacity of the cerebral vessels to autoregulate) may be partly responsible for relief of symptoms which are associated with impaired CBF (18, 35-38). A recent study investigating long-term dynamic brain changes in COVID-19-recovered patients found numerous recoverable and unrecovered changes in cortices, subcortical nuclei, and white matter tracts of study participants (41). Notably, the peak hypoperfusion value was observed in the insula, which is a cortical structure closely involved with autonomic signaling control (41). As such, SARS-CoV-2-induced reduction of CBF to the insula may, at least in part, explain some of the sensory, affective, and cognitive abnormalities observed in PACS. Thus, it may be possible that SGB-mediated increases in CBF allows for enhanced perfusion of brain structure involved in neurological symptoms of PACS which subsequently results in alleviation of such symptoms. At present, there are currently two ongoing clinical trials investigating the impact of DSBs on SARS-CoV-2-related pathologies (39-40).

Limitations

Further insight into the pathophysiology contributing to PACS is needed to accurately describe the alleviation of symptoms observed following DSBs. Similarly, the exact mechanisms by which DSBs “reset” hyperactive sympathetic signaling remains unclear and requires further investigation prior to determining if DSBs are a suitable treatment option for PACS. Although the safety and efficacy profile for DSBs in PTSD management has been well-documented, additional clinical studies are required for a comprehensive review of the safety implications of SGB for PACS treatment. Similarly, further clinical data supporting appropriate procedure

frequency and duration of symptom relief are necessary to justify the use of DSBs for PACS management.

Conclusion

The significant improvement of PACS symptoms following DSBs as described in these case studies indicate an important role of dysautonomia and cerebral blood flow in the pathophysiology of PACS. As such, the application of DSBs for PACS symptom management is extremely promising. DSBs have a well-established safety profile in numerous clinical applications and current research suggests that DSBs may effectively reduce dysautonomia and neurocognitive symptoms in at least a subset of PACS patients. While additional studies are required to discern the exact mechanisms involved in PACS pathogenesis and the effect of DSBs on PACS symptoms, the data available at present provides sufficient evidence to warrant further studies investigating DSBs as a potential targeted PACS treatment.

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