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A PROMISING METHOD FOR POST-COVID/LONG-COVID SYNDROME: NONINVASIVE VAGUS NERVE STIMULATION

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INTRODUCTION

The SARS-CoV-2 (COVID-19) pandemic has caused unprecedented morbidity, mortality and global disruption.Post-acute COVID(known colloquially as long COVID) refers to persistent symptoms 3 weeks after COVID-19 infection, while ‘Chronic COVID’ describes symptoms lasting more than 12 weeks (1).Autonomic symptoms of acute infection are common and are being described with increasing frequency. While most patients have mild symptoms and recover within several weeks, more than 50% are left with ongoing symptoms several months later many of which appear autonomic in nature (2). Disorders affecting the central or peripheral autonomic pathways, or both, can manifest with autonomic failure (including orthostatic hypotension, anhidrosis, impaired reaction to light, dry mouth, dry eyes, gastrointestinal dysmotility, neurogenic bladder, erectile dysfunction) or autonomic hyperactivity (primary hypertension, tachycardia, hyperhidrosis) (3). In autonomic dysfunction, there is a deterioration in the balance between the sympathetic and parasympathetic systems, which creates a load on the body (4). Pre-existing sympathetic hyperactivity may increase the morbidity and mortality of COVID-19 infection, but the disease itself may impair autonomic nervous system (ANS) function due to emotional stress, hypoxia, etc. The disease progresses more severely in people with significant autonomic dysfunction before COVID-19. Autonomic dysfunction, measured with heart rate variability (HRV), is more pronounced in patients with more disease severity during the active infection period (e.g. O2 saturation ≤93%, lung infiltration >50%). In those whose autonomic dysfunction persists, the course of the disease is worse and autonomic dysfunction is more common in the 3 months follow-up after discharge. Post COVID autonomic dysfunction rate is higher in patients with pre-disease autonomic dysfunction (5,6).

In the observational study of Stella et al, the incidence of autonomic dysfunction after symptomatic COVID-19 infection is ¼ at 9 months follow-up and more common in women (7). Several investigators have reported dysautonomia persisting for nearly a year following initial infection. Hyperactivity states such as tachycardia (tonic activity) and postural orthostatic tachycardia syndrome (POTS)(phasic activity) are more common than autonomic insufficiency states such as hypotension (tonic activity) and orthostatic hypotension (phasic activity) (8,9).In fact, the above-mentioned hyperactivity states may be due to parasympathetic hypoactivity (sympathetic activity may not be altered), so it can be stated that it is somehow written according to end-organ responses. As Berntson et al declared, hypotension may have developed because of parasympathetic hyperactivity (4). In their retrospective study, Shouman et al mentioned that orthostatic intolerance without significant hemodynamic changes is the most common finding in autonomic dysfunction after COVID-19 infection (10).

ANS Dysfunction

An autonomic dysfunction can be expected during the COVID-19 infection to fight or flight, as in other symptomatic infections. Acute, coordinated alterations in homeostatic settings (allostasis) can be crucial for surviving stressors such as infectious diseases and sepsis however, autonomic dysfunction in chronically decreased homeostatic efficiencies (dyshomeostasis) may cause debilitating or lethal vicious cycles (11). Sympathetic hyperactivation is an important component of autonomic dysregulation in infections and is associated with hyperinflammatory states (12). It can be stated that the dysfunctional state in the ANS activity (increased sympathetic activity, suppressed parasympathetic activity) contributes to morbidity and mortality in COVID-19 patients, and the solution of this problem can be a goal in treatment. In animal studies, surgical vagotomy increases alveolar damage due to overproduction of inflammatory cytokines such as IL-6 (13). Electrical or pharmacological vagal nerve activation attenuates lung injury by modulating the inflammatory response and tissue damage (14). In rat models of sepsis, vagus nerve stimulation (VNS) has been shown to reduce the release of proinflammatory cytokines, prevent hypotension, regulate coagulation, inhibit fibrinolysis activation, reduce organ dysfunction, and increase survival (15).

Many underlying mechanisms have been proposed for post covid/long covid autonomic dysfunction; direct invasion of the ANS by the COVID-19 (autonom neuropathy),

autoimmunity disorder against ANS, prolonged bed rest, microangiopathy, secondary to another pathology such as covid-induced stroke or encephalitis, both psychological and physiological stress caused by the disease itself (in adaptive, compensatory context) (2,16). New-onset POTS and other autonomic disorders can follow COVID-19 in previously healthy non-hospitalized patients who experience persistent neurologic and cardiovascular symptoms after resolution of acute infection (17-21). Orthostatic hypotension with recurrent falls, tachycardia, chronic fatigue, brain fog, muscle soreness, anxiety, irritable bowel syndrome can be seen in post covid/long covid (1,22). Inflammatory demyelinating polyneuropathies, transverse myelitis characterized by autonomic dysfunction after COVID-19 have also been reported in the literature (23,24).Heart rate and blood pressure instability, pupillary dysfunction, urinary retention, dizziness, orthostatic intolerance may accompany COVID-19 related Guillain-Barré syndrome (25).

Larsen et al define orthostatic intolerance, palpitations/tachycardia, temperature intolerance, labile blood pressure, new-onset hypertension, gastrointestinal symptoms (e.g., abdominal pain, bloating, nausea) as symptoms suggestive of autonomic dysfunction. However, fatigue, headache, cognitive impairment (brain fog) were not associated with autonomic dysfunction in the study (2). Similarly, Townsend et al, in their evaluation of post-covid patients with and without chronic fatigue, stated that fatigue was not associated with autonomic dysfunction but was associated with anxiety. They applied heart rate variability (HRV), 24-hour blood pressure monitoring, prefrontal cortex oxygenation with infrared spectroscopy to evalute ANS activity (26). Lo argue that COVID-19 related chronic fatigue may be due to hypotension but Barizien and colleagues directly linked fatigue to autonomic dysfunction in long COVID-19 patients (27,28). In fact, fatigue may accompany conditions with autonomic dysfunction such as bradycardia or tachycardia, in which hypoactivity or hyperactivity of the branches of the ANS can be seen (21).

Neuromodulation and VNS

Neuromodulation methods can improve and regulate the activites of the sympathetic and parasympathetic branches. VNS is approved for the treatment of drug refractory epilepsy and depression. Also it has been shown to attenuate hyperinflammation and it carries the potential for correction of the imbalance in ANS. So it can be said that noninvasive VNS can be used as an adjunct therapy in COVID-19 patients (29). In COVID-19 viral pneumonia cases transcutaneous auricular VNS can reduce markedly elevated interleukin-6 levels (30). In

addition, VNS appears to be useful in COVID-19 related respiratory symptoms (31). However, selective VNS is important to decrease unwanted side effects like bronchoconstriction in COVID-19 caused acute respiratory distress syndrome. VNS can further decrease airway passage by increasing mucus secretion. To prevent this, organ/function-specific stimulation will be better for regulation of the ANS (32). VNS is also recommended for the treatment of cytokine storm in severe COVID-19 patients and again monitoring of the ANS is suggested for more accurate treatment (33,34).Cytokine storm is strongly correlated with sympathetic overactivity and ANS dysfunction. So it can be said that PNS-mediated anti-inflammatory effect is diminished in hyperinflammatory status. Chronic ANS dysfunction in post-COVID patients probably continues in a vicious circle. Disease-related stress also aggravates the condition (35). As a safe treatment method, auricular VNS can be preferred as an adjuvant therapy in Covid-19 and similar infectious diseases with hyperinflammation (36). The ability of VNS to modulate the immune system without impairing specific immunity to infectious agents is highly advantageous in the treatment of inflammatory conditions due to COVID-19 and other infectious agents.

Non-invasive neuromodulation methods can be preferred for the management of COVID-19 symptoms both in the active disease period or after it to control long COVID (37). Non-invasive cranial microcurrent stimulation can reduce vascular dysregulation and improve visual/cognitive impairment in long COVID patients (38). VNS can be accepted as a cranial neurostimulation and moreover it can regulate the ANS dysfunction. Vagus nerve signal disorder and ANS dysfunction are most likely to occur in long COVID. This is often accompanied by an immune system disorder. Fatigue, malaise, brain fog, headaches, sleep problems, muscle pain, tachycardia are commonly seen in long COVID and all are related with ANS dysfunction (39). VNS is a method that has been recognized as safe and it can be beneficial for the treatment of postural orthostatic tachycardia syndrome and other symptoms related with long COVID (40).

Conclusion

The COVID-19 pandemic has had devastating health and socioeconomic impacts on people. Although the effects of the disease decreased with the use of vaccines, some people who had the disease continued to experience symptoms such as fatigue, brain fog, and tachycardia that impair their quality of life. Post-COVID/Long-COVID seems likely to occur as the virus itself or the clinical condition it causes affects the ANS. Noninvasive VNS may be an additional treatment option to control symptoms seen in Post-COVID/Long-COVID.

The applications so far in different indications show that noninvasive VNS is an effective and safe treatment method.

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Authors' Contributions

A.V.Ö.: provided the conception and design of the study, revised it critically for important intellectual content; A.P.: provided the revised the article critically for important intellectual content and gave final approval of the version to be submitted.

Conflict of Interest

All authors have no conflict of interest to report.

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