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Autonomic Dysfunction Related to Postacute SARS-CoV-2 Syndrome

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KEYWORDS

• PASC • Autonomic dysfunction • COVID-19 • Brain fog • Tilt table test

KEY POINTS

- Autonomic dysfunction related to postacute SARS-CoV-2 can present with dizziness, tachycardia, sweating, headache, syncope, labile blood pressure, exercise intolerance, and "brain fog."
- Nonpharmacologic management involves increased salt and water intake, compression garments, progressive aerobic exercises, and enhanced external counterpulsation.
- Pharmacologic treatment can include β-blockers, fludrocortisone, midodrine, pyridostigmine, and ivabradine.

INTRODUCTION

The SARS-CoV-2 virus, a member of the coronavirus family, has been responsible for the coronavirus disease-2019 (COVID-19) pandemic with an acute phase causing pneumonia and pulmonary disorders, but it has been shown to result in extrapulmonary manifestations including cardiovascular and neurologic diseases. Moreover, residual symptoms have been reported to persist past the acute phase. In a cross-sectional study of SARS-CoV-2–positive patients, at 48 days postdischarge the most common persistent symptoms were fatigue, difficulty breathing, and psychological distress.[1] In a cohort study of 1733 patients with COVID-19 from Wuhan, China, patients reported persistence of fatigue, muscle weakness, sleeping difficulties,

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palpitations, anxiety, or depression at 6 months after initial onset.[2] Numerous other studies now indicate the presence of persistent symptoms following COVID-19 infection, with more than 200 symptoms reported. This syndrome has been coined as the postacute SARS-CoV-2 (PASC) syndrome and has been defined as the persistence of symptoms or development of new symptoms after the time of infection, which can include fatigue, brain fog, palpitations, and a plethora of other manifestations.

BACKGROUND

Infection with SARS-CoV-2 in the acute phase can lead to extrapulmonary manifestations including fatigue, myalgias, gastrointestinal dysfunction, as well as cardiovascular complications.[3–6] It has also been reported that SARS-CoV-2 infection can have neurologic involvement in more than one-third of acute infections.[7] In a meta-analysis of patients with acute COVID-19 of more than 1585 records, acute SARS-CoV-2 infection can lead to autonomic dysfunction during the acute stages in terms of cardiovascular, sudomotor, and pupillometric functions.[8]

However, there have been growing reports that patients continue to remain unwell beyond 3 weeks.[9] In a systematic review of 57 studies, it was found that 250,351 survivors of acute COVID-19 had persistent symptoms after 6 months of initial diagnosis that could be divided into 4 major categories: neurologic symptoms, generalized symptoms, mental health disorders, and mobility impairment.[10] The same study reported common symptoms including headaches, difficulty concentrating, cognitive impairment, fatigue, functional impairment, and mobility decline. Therefore, postacute COVID syndrome continues to remain an ongoing issue that requires more examination.

Currently, there have been multiple names and criteria for this postacute phase COVID-19 syndrome. The Mayo Clinic uses the term “long COVID” to refer to long-term sequelae that occurred on or after the initial positive SARS-CoV-2 test.[11] Meanwhile, the United Kingdom National Institute for Health and Care Excellence (NICE) has defined various phases of COVID-19 including “post-COVID-19 syndrome” for symptoms that develop around the acute phase and persist for more than 12 weeks that are not explained by an alternative diagnosis and “long COVID” that describes symptomatic COVID-19 and post-COVID-19 syndrome based on the criteria.[12] In addition, a common term used has been postacute COVID-19 syndrome (PACS) and PASC and defined as the persistence of symptoms for more than 3 weeks after the initial onset of COVID-19.[13]

The mechanism of postacute COVID-19 autonomic dysfunction is thought to be multifactorial.[14] One major proposed mechanism is through direct viral effects with multiple hypotheses. Persistent viremia can lead to a persistent highly inflammatory state with cellular injury.[15–19] One of the proposed pathophysiology is cytokine- and hypoxia induced injury leading to neuronal apoptosis affecting the while matter fiber bundles causing impaired neurological function. Another hypothesis is that this inflammatory pathway could lead to autonomic and small fiber neuropathies, as previously seen in viral infections from herpes simplex and infectious mononucleosis.[20,21]

POSTACUTE AUTONOMIC MANIFESTATIONS OF CORONAVIRUS DISEASE-2019

In a systematic review involving 54 articles involving 154 cases of COVID-19, the most common clinical presentation was orthostatic intolerance (including orthostatic lightheadedness, dizziness, tachycardia, sweating, headache, and “brain fog”) and syncope (including reflex and orthostatic hypotension-related syncope) (**Fig. 1**).[22] Orthostatic intolerance has been defined as the inability to tolerate the upright position due to symptoms caused by cerebral hypoperfusion, sympathetic activation, or

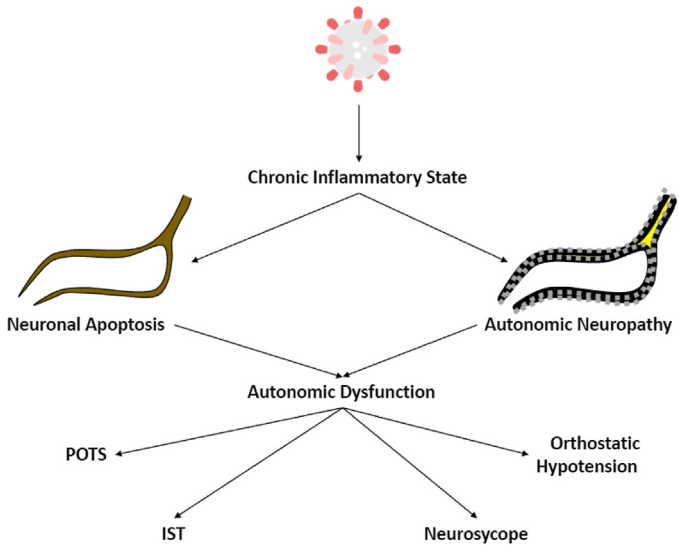

Fig. 1. Mechanism of post-acute SARS-CoV-2 autonomic dysfunction.

both and is relieved by recumbency.[23] In a prospective study of 24 patients with PASC, 23 demonstrated orthostatic intolerance based on the head-up tilt table test (HUTT).[24] In the same study, they found that these patients can present with postural orthostatic tachycardia syndrome (POTS), inappropriate sinus tachycardia, neurocardiogenic syncope (NCS), and orthostatic hypotension.

POTS, characterized by partial dysautonomia and hyperadrenergic orthostatic intolerance, typically affects young high-achieving adults, particularly Caucasian women of childbearing age who are at the beginning of their working lives.[25] POTS is heterogeneous in presentation and is associated with palpitations, dizziness, headache, fatigue, and blurry vision.[26–28] Typically, POTS is diagnosed by a tilt table test or 10-minute stand test and is characterized by an increase in heart rate of at least 30 beats per minute (bpm) from supine to standing position in the absence of orthostatic hypotension.[11,29] Before the arrival of COVID-19, approximately 50% of patients with POTS report a history of infection before symptom onset.[11,30] Most reported infections associated with POTS included mycoplasma pneumonia,[31] Epstein-Barr virus,[32,33] Trypanosoma cruzi,[34] and Borrelia burgdorferi.[35,36] Now, since the inception of the SARS-CoV-2 virus, POTS seems to be a prevalent manifestation of PASC syndrome, with this viral infection being an inciting event.

Similarly, inappropriate sinus tachycardia (IST) has been characterized by unexpected fast sinus rates (greater than 100 beats bpm) at rest and/or with minimal physical activity and can be accompanied by symptoms including palpitations, dyspnea, or dizziness.[37] Typically, IST can be diagnosed based on resting heart rate greater than 100 bpm with an average rate greater than 90 beats bpm on a 24-hour Holter monitor in symptomatic patients.[37] The underlying pathophysiology is not completely understood, although it may be related to sinus node automaticity or autonomic imbalance. It has been seen in patients with Trypanosoma cruzi antibodies that cross-react with beta receptors and stimulate tachycardia.[38,39] In a recent study of 200 patients with PASC, 20% were found to have inappropriate sinus tachycardia and can commonly affect younger women without previous comorbidities who have had a mild initial SARS-CoV-2 infection.[40] It is suggested that IST in these patients may be related to

autonomic dysfunction due to decreased heart rate variability based on 24-hour electrocardiogram (ECG) monitoring.

NCS has been reported as the most common cause of syncope, with a median of 3 episodes in a lifetime and a recurrence rate of 30% within 30 months.[41] There have been case reports of NCS.[42,43] There may be some overlap between neurogenic syncope with POTS, as NCS can occur in up to 38% of patients with POTS.[35,44–46]

Orthostatic hypotension, defined as a drop of systolic blood pressure by at least 20 mm Hg or drop of diastolic blood pressure by at least 10 minutes within 3 minutes of standing from a supine position, has been accompanied by similar symptoms of dizziness and syncope. It often involves excessive pooling of blood into the splanchnic and leg circulation, leading to decreased venous return with change to standing position and resulting in decreased cardiac output.[47] Typically, the autonomic nervous system can compensate with changes in vascular tone, heart rate, and cardiac contractility. However, in neurogenic orthostatic hypotension, there may be a defective or delayed response.[47] Similarly, there have been case reports of orthostatic hypotension as a presenting symptom of autonomic dysfunction in patients with PASC.[22]

EVALUATION AND MANAGEMENT

The initial evaluation should begin with a detailed history and physical examination with particular attention to symptoms including dizziness, lightheadedness, fatigue, dyspnea, diarrhea or constipation, presyncope, anxiety, panic attacks, and brain fog.[48] Vital signs evaluation should include a review of blood pressure, heart rate, breathing rate, oxygen saturation, and pain scale. Physical examination should include a full neurologic examination (involving cranial nerve evaluation, sensory and motor function, deep tendon reflexes, and coordination), pulmonary evaluation, cardiovascular examination, musculoskeletal tone and range of motion, skin exam for rashes, and psychiatric evaluation.

The Composite Autonomic Symptom Scale (COMPASS-31) questionnaire, originally developed as an 84-question scoring instrument for autonomic symptoms,[49] has been growing in use for patients with PASC.[50] The survey has been validated in patients with autonomic dysfunction and seems to be a quick and efficient method to have patients with PASC screened.

Initial laboratory evaluation should include a complete blood cell count, renal function panel, B-type natriuretic peptide, electrolytes, thyroid stimulating hormone, morning cortisol, and resting 12-lead ECG. Based on the history, physical examination, and clinical evaluation, further laboratory testing may be warranted. There has been a high prevalence of G-protein–coupled receptor antibodies and ganglionic neuronal nicotinic acetylcholine receptor antibodies in patients with PASC and POTS.[51] POTS itself has also been reported to be associated with antinuclear, antithyroid, anti-NMDA glutamate receptor, antiphospholipid, and Sjogren antibodies and may be reasonably considered in patients with PASC with POTS if clinically appropriate.[51]

The 3-minute standing test, involving patients going from the supine position to the standing position, has been recommended by the Centers of Disease Control and Prevention and can be used as a quick and easy method for evaluating autonomic dysfunction in patients with PASC.[52] In addition to the standing test, the HUTT uses a similar concept but requires patients to be on a table with restraining belts, and the table moves into supine and upright vertical positions that can leave patients feeling uncomfortable. Despite this, the HUTT has been the most used autonomic testing mechanism in patients with PASC with concerns for cardiac autonomic dysfunction.[22]

In addition, Holter ECG monitoring and 24-hour ambulatory blood pressure monitoring can also be used in patients with PASC to evaluate for autonomic dysfunction[53]; this would particularly allow close examination for heart rate variability (HRV) in sitting and standing positions. Before COVID-19, reduced HRV has been associated with chronic fatigue syndrome and myalgic encephalomyelitis[54] and has been a tool used to evaluate autonomic nervous system functions.[8]

If further testing is needed, an examination can involve skin biopsy for intraepidermal nerve fiber density evaluating for small fiber (aδ and C fiber) neuropathy and quantitative sudomotor axon reflex test to evaluate postganglionic sympathetic cholinergic sudomotor function by evaluating sweat response time.[55] Similarly, the thermoregulatory sweat test evaluates the central and peripheral sympathetic sudomotor pathways from central nervous system to the sweat glands.[56] Electrochemical skin conductance (ESC) is a noninvasive test of sudomotor function. It is an indirect index of sympathetic nonmyelinated C-fiber activity and be estimated with ESC, due to the lack of parasympathetic innervation in the skin.[57] An abnormal ESC result can also suggest autonomic small fiber neuropathy and autonomic dysfunction in patients with PASC.

TREATMENT

With autonomic dysfunction, initial treatment can include conservative and nonpharmacological measures including increased water consumption of up to 2 to 3 L per day, increased sodium consumption of up to 10 to 12 g per day, lower limb compression stockings, and progressive aerobic exercise training programs that start in supine or sitting position for physical reconditioning. It is also important to review the existing medication and supplementation list to remove agents that can worsen the symptoms of autonomic dysfunction (anticholinergics, antihypertensives, and so forth)

Multidisciplinary care can play an essential role in the treatment and management of these patients. Primary care, neurology, physical medicine and rehabilitation, cardiology, neuropsychologists, psychiatrists, occupational therapists, physical therapists, speech therapists, and dietitians may be part of the care team to assist with the complex syndrome of PASC autonomic dysfunction.[10,58,59] Rehabilitation therapeutics include breathwork exercises, yoga/pranayama, autonomic reconditioning, symptom-titrated physical activity/movement, and functional restoration.

If symptoms persist despite the above measures, pharmacologic management may be considered. The Heart Rhythm Society recommends medical management with fludrocortisone, midodrine, pyridostigmine, β-blockers (specifically propranolol), or ivabradine.[37] However, ivabradine is still being studied for safety and efficacy in patients with a specific subtype of POTS.[60] These therapies can theoretically help with volume expansion (fludrocortisone), heart rate inhibition (propranolol, ivabradine, and pyridostigmine), and vasoconstriction (midodrine) that may help with autonomic dysfunction response (**Table 1**).

There have been case reports where enhanced external counterpulsation (EECP), a noninvasive therapy that involves retrograde aortic flow to decrease the number of inflammatory cytokines, has been added as a suitable treatment method for patients with PASC.[61,62] EECP has been approved by Food and Drug Administration and shown to improve morbidity and mortality for patients with chronic stable angina or ischemic heart failure. The benefit has been theorized to be due to vascular changes and improve endothelial function by affecting vasodilation and proinflammatory agents.[63] Therefore, EECP may improve response to PASC autonomic dysfunction.

Blitshteyn and colleagues made additional multidisciplinary recommendations for evaluating and treating PASC-related autonomic dysfunction, and their consensus

Table 1
Options for pharmacologic treatment

Drug	Mechanism of Action	Dosing	Side Effects
Propranolol	Reduces HR by beta-adrenergic blockade	10–20 mg up to 4 times a day	Bradycardia, hypotension, fatigue, bronchospasm
Fludrocortisone	Volume expansion	0.1–0.2 mg daily	Hypokalemia, edema, headache
Desmopressin (DDAVP)	Volume expansion	0.1–0.2 mg daily	Hyponatremia, edema
Midodrine	Vasoconstriction	2.5–15 mg 3 times a day	Headache, scalp tingling, hypertension
Pyridostigmine	Cholinergic, reduces HR	30–60 mg 3 times a day	Nausea, abdominal cramps, diarrhea
Ivabradine	Reduces HR	2.5–7.5 mg twice a day	Headache, palpitations, hypertension, visual disturbance

Abbreviation: HR, heart rate.

guidance was published in 2022 and is now accessible.[64] In the authors' preliminary study looking at 42 patients with PASC-related autonomic dysfunction, despite treatments, they continue to be symptomatic at 1 year since PASC onset with mild to moderate improvement of their symptoms. Long-term follow-up and studies are needed to bring the much-needed respite for these symptoms.

CLINICS CARE POINTS

- There are several subtypes of autonomic dysfunction related to postacute SARS-CoV-2 including postural orthostatic tachycardia syndrome (POTS), inappropriate sinus tachycardia, neurocardiogenic syncope (NCS), and orthostatic hypotension.
- Evaluation beyond a history and physical, should be inclusive of a Composite Autonomic Symptom Scale (COMPASS-31) questionnaire and a 3-minute standing test. The head-up tilt table test (HUTT) can be done when there is concern for cardiac autonomic dysfunction and stand test is nondiagnostic.
- Treatment for autonomic dysfunction should include both conservative and nonpharmacological management to start. It is also imperative to consider pharmacologic management to help treat symptoms.

DISCLOSURES

None related to this work.

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