Postural orthostatic tachycardia syndrome following SARS-CoV-2 infection and COVID-19 vaccination: A comparative review

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June 8, 2023

Abstract

The coronavirus disease 2019 (COVID-19) has shown unexpected viral infection traits. Initially thought to affect respiratory health primarily, it also involves the gastrointestinal system. However, many complications during the pandemic were caused by the virus, including neurological, cardiovascular, dermatological, and metabolic issues. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has also been linked to cardiac complications, such as myocardial infarction, in individuals without cardiovascular risk factors. SARS-CoV-2 vaccines exacerbated the situation with possible adverse events (AEs). Vaccine side effects, like thromboembolic events, can be life-threatening or simply bothersome. Postural orthostatic tachycardia syndrome (POTS) is a nonlethal cardiac complication seen with COVID-19 and its vaccines. In this review, we summarized the POTS-COVID-19 relationship comprehensively.

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic has revealed several strange features of a viral infection. At the beginning of the pandemic, it had been believed that COVID-19 is predominantly a respiratory disease with occasional gastrointestinal involvement. Nevertheless, the vast range of neurological, cardiovascular, dermatological and metabolic complications occurring during the pandemic were later discovered to be attributable to the virus[1-3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to many serious cardiac consequences, including myocardial infarction in individuals with no cardiovascular risk factors, which has subsequently been demonstrated to be the result of this viral infection. Later, the introduction of SARS-CoV-2 vaccines further complicated the condition. Despite being an essential health issue, vaccines are sometimes followed by adverse events (AEs). Some vaccine-associated AEs, like thromboembolic events, are life-threatening, while others are only bothersome without risk of death[4-7]. Postural orthostatic tachycardia syndrome (POTS) has been among the most annoying, albeit nonlethal cardiovascular complications, reported with SARS-CoV-2 infection and vaccination. Here, we have comprehensively reviewed every aspect of the relationship between POTS and COVID-19.

What is POTS?

POTS is defined as a chronic (more than 6 months) persistent heart rate increase of more than 30 beats per minute within 10 minutes of active standing, upright posture or head-up tilt without orthostatic hy-

potension in the absence of other evident causes of orthostatic tachycardia like prolonged bed rest. These medications dysregulate autonomic function (e.g. diuretics, vasodilators, and antidepressants) or chronic comorbidities which induce tachycardia (e.g. thyrotoxicosis and anemia). Women of childbearing age (13–50 years) comprise most patients with POTS[8].

Autonomic dysfunction is the underlying pathophysiologic mechanism for this condition. The autonomic nervous system, responsible for regulating respiration, digestion, heart rate and blood pressure, is impaired[9]. This autonomic dysfunction might result from autoimmunity, mast cell activation, partial sympathetic neuropathy, hyperadrenergic state or hypovolemia. More than one mechanism can be the underlying mechanism of POTS in a single patient. Epinephrine and norepinephrine release causes substantial tachycardia, dyspnea and chest discomfort, which is followed by paradoxical vasodilatation, sympathetic activity withdrawal, and vagus nerve activation manifested as hypotension, lightheadedness and fatigue[10].

This syndrome is manifested as palpitation, headache, nausea, abdominal pain, fatigue, exercise intolerance, shortness of breath, chest or abdominal discomfort, diplopia, mental clouding, memory loss, poor sleep, orthostatic intolerance, dizziness, and presyncope. However, fainting rarely occurs in the settings of POTS[11, 12]. This syndrome is usually triggered by acute stressors like viral infections, pregnancy, menstruation, major surgery, trauma, and psychological stress[13, 14].

The diagnosis of POTS is usually delayed due to the nonspecific presentations of this condition. The most sensitive method to detect POTS is a detailed medical history, physical examination with vital orthostatic signs or brief tilt table test, and a resting 12-lead electrocardiogram. Additional diagnostic testing may be warranted in selected patients based on clinical signs. Diagnosing orthostatic tachycardia requires that orthostatic hypotension (a fall in blood pressure of more than 20 mm Hg systolic or 10 mm Hg diastolic within three minutes of standing) and other precipitants of tachycardia (e.g., anemia, dehydration, fever, sepsis, endocrinological conditions such as hyperthyroidism or Addison's disease, respiratory conditions such as pulmonary embolism, and cardiac conditions) have been excluded. Hence, thorough laboratory workup including measurement of blood glucose, serum cortisol, complete blood count, renal and thyroid function tests, inflammatory biomarkers like erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), ferritin, vitamin B12, folate and calcium, in addition to chest x-ray imaging is required. However, it should be noted that cardiac ischemia, myocarditis, and pulmonary embolism must be considered in any patient presenting with possible acute cardiac symptoms, as acute conditions need to be urgently detected and managed[15-17].

Current management of POTS is predominantly dependent upon symptom therapy and lifestyle modification. The management of POTS consists of nonpharmacologic and pharmacologic therapies. Nonpharmacologic treatment includes increasing fluid and salt intake, increasing isometric and aerobic exercise, lower-limbs strengthening, the gradual elevation of intensity and duration of physical activity, psychological support and training to control pain and anxiety, rehabilitation, reassurance and family education, wearing compression socks or using compression garments extending up to the waist, and avoiding triggers like alcohol, caffeine, heavy meals, prolonged standing or upright position, warm places and hypotensive medications like diuretics, opiates, a-receptor blockers, angiotensin-converting enzyme inhibitors, nitrates, tricyclic antidepressants, monoamine oxidase inhibitors, phenothiazines, and sildenafil citrate[18-20].

Pharmacologic treatment includes heart rate control, peripheral vasoconstriction, and intravascular volume increase. Medical therapy is usually individualized but is generally consisted of β-blockers (Propranolol), channel blockers (Ivabradine), α-agonists (Clonidine), antihistamines (Diphenhydramine), mineralocorticoids (Fludrocortisone), vasopressin analogs (Desmopressin), anticholinesterase inhibitors (Pyridostigmine), CNS stimulants (Modafinil), and selective serotonin reuptake inhibitors (Sertraline). POTS may interfere with even the least energy-requiring daily activities like bathing or doing housework, significantly decreasing functional capacity. Nevertheless, it is not associated with mortality; many patients improve over time after diagnosis and proper treatment [21-24].

POTS following SARS-CoV-2 infection

The COVID-19 pandemic has led to several prolonged symptoms, sometimes annoying or debilitating for patients. These longstanding symptoms are termed "long COVID", "long-haul COVID", or "chronic COVID"[25]. Many previously-infected SARS-CoV-2 individuals complain of palpitations triggered by minimal exertion or standing. These patients experience dyspnea, lightheadedness, fatigue and sweating following palpitation. Manifestations of this syndrome, to some extent, resemble those of post-traumatic stress disorder. However, many patients fulfilled the diagnostic criteria for POTS, which seemed to result from autonomic nervous system dysfunction (dysautonomia) triggered by the virus[26]. The weight loss and hypovolemia resulting from constitutional symptoms of SARS-CoV-2 infection can increase cardiac SNS outflow and predispose to orthostatic intolerance. On the other hand, COVID-associated anxiety and sleep disturbance can lead to a hyperadrenergic state which further increases the probability of dysautonomia.

The underlying pathophysiologic mechanisms include direct autonomic nervous system damage by the virus, hyperinflammatory response and cytokine storm, hypercoagulability state, and autoimmune reactions. The direct viral effect is binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed on autonomic neurons and sometimes followed by hyperadrenergic POTS[27]. However, the most probable mechanism of post-COVID-19 POTS is SARS-CoV-2-associated induction of autoimmunity through producing cross-reacting antibodies with autonomic ganglia and nerve fibers and neuronal or cardiovascular receptors. In addition, sympathetic overactivation induced by SARS-CoV-2 infection may lead to post-COVID POTS[28, 29].

Besides POTS, SARS-CoV-2 infection has caused other autonomic dysfunctions such as orthostatic hypotension (OH), neurocardiogenic syncope (NCS), vasovagal syncope (VVS), post-COVID-19 exacerbation of paroxysmal hypothermia and hyperhidrosis, and small fiber neuropathy with orthostatic cerebral hypoperfusion syndrome[30-32].

Previously, autonomic dysfunction had been reported following infection with bacteria (Borrelia burgdorferi, Mycoplasma pneumonia, Mycobacterium lepra, Clostridium tetani and Clostridium botulinum), viruses (HIV, HTLV-1, influenza virus, Epstein-Barr virus, West Nile virus and Rabies virus), and parasites (Trypanosoma cruzi)[33-36]. Hence, viral infections, including SARS-CoV-2, are established triggers for POTS and patients with POTS usually report a recent viral infection[16].

The incidence of dysautonomia in the settings of long COVID is estimated to be up to 25% and has presented up to several months after infection. It has affected females more than males and has been more common in the young population. Most cases have been reported to occur within one month of SARS-CoV-2 infection[37, 38]. The relationship between the severity of the causative SARS-CoV-2 infection and the incidence of POTS is not yet determined. Even mildly SARS-CoV-2 infected patients have experienced COVID-related dysautonomia; nonetheless, it has occurred more commonly in COVID patients with hypertension, obesity, or immunocompromise. It should be acknowledged that post-COVID patients presenting with tachycardia should be evaluated for meeting the associated criteria, as all of them do not necessarily have POTS[39-41].

The mentioned condition is not life-threatening but affects daily function and mood. Like long COVID, POTS severity can fluctuate unpredictably, making rehabilitation and return to work challenging[42]. It should be noted that since POTS is quite common in COVID-19 survivors, clinicians should be aware of the condition and refer any patient with compatible manifestations to a specialist to be screened for POTS and also exclude life-threatening events like myocardial injury[43].

POTS following COVID-19 vaccination

Postural orthostatic tachycardia syndrome has not only occurred as a part of the "long COVID" syndrome following SARS-CoV-2 infection but has also been reported after COVID-19 vaccination. However, the incidence rate is multiple times higher after infection than after vaccination[44, 45]. POTS is among the wide range of cardiovascular and neurological complications imposed by SARS-CoV-2 vaccination[5-7, 46].

Previously POTS had been rarely reported following vaccination, except for HPV vaccination[47-49]. With the introduction of SARS-CoV-2 vaccines, the reported cases of new-onset POTS have increased[45, 50].

Most cases of vaccine-associated POTS occurred within one month of receiving COVID vaccines. Vaccine-induced phenomena are usually of autoimmune origin; thus, autoimmunity is the most probable explanation for this autonomic dysfunction disorder following SARS-CoV-2 vaccination. The vaccine is believed to trigger. This results from molecular mimicry between certain vaccine components and human proteins in the above receptors [51, 52]. Besides POTS, other autonomic dysfunctions caused by SARS-CoV-2 include sympathetic adrenergic and postganglionic sympathetic pseudomotor dysfunction[53, 54]. This COVID vaccine-related adverse event has been more reported after receiving mRNA vaccines, compared with other vaccine platforms[55-57]. Management of vaccine-related POTS is the same as the one due to other causes; however, its autoimmune origin suggests that unresponsive cases can be successfully treated with intravenous immunoglobulin (IVIG)[58].

Conclusion

After several months passing from the dreadful surges of SARS-CoV-2 infection, many manifestations of long COVID are still evident in the survivors. Moreover, the COVID vaccination has also brought about many adverse events, leading to vaccination hesitancy. POTS has been among the vast range of SARS-CoV-2 infection- and SARS-CoV-2 vaccination-induced complications, which should be considered incompatible settings. Clinicians should be aware of the manifestations and seek the criteria to diagnose and subsequently treat the condition. Moreover, they should advise the patients to receive vaccines despite the probability of adverse events like POTS, since its incidence is quite low after vaccination and the benefits outweigh the potential harms.

Acknowledgments

The authors wish to thank the Clinical Research Development Center of Imam Reza Hospital of Kermanshah University of Medical Sciences and Infectious Diseases and Tropical Medicine Research Center of Babol University of Medical Sciences.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

Conflict of interest disclosure

All authors have no relevant financial interests to be declared.

Author Contributions

- **ZMA:** Data collection and writing of the manuscript.
- **HM:** Data collection and writing of the manuscript.
- **HNR:** Data collection and writing of the manuscript.
- **AB:** Data collection and writing of the manuscript.
- **EH:** Data collection and writing of the manuscript.
- **MB:** Helped with manuscript writing and contributed substantial revisions to the manuscript's content.
- **SE:** Design of the research study and supervision.

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