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Brief Report

Postural orthostatic tachycardia syndrome-like symptoms following COVID-19 vaccination: An overview of clinical literature

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Abstract.
BACKGROUND: Postural Orthostatic Tachycardia Syndrome (POTS) is a common condition affecting more than 170 people per 100,000 population. However, POTS following COVID-19 vaccination remains a rare reporting in the medical literature.
OBJECTIVE: We, herein, summarize and highlight the evidence that has been reported regarding POTS-like symptoms following COVID-19 vaccination.
METHODS: We conducted a literature search and summarized the findings in the form of a narrative commentary. All types of publications (case reports/series, original articles, letters to editors, brief communications etc.) in English language were included.
RESULTS: Whilst the exact pathogenetic mechanism behind POTS is yet to elucidated, there has been increasing evidence pointing towards an autoimmune dysfunction. Females were found to be predominantly affected (72%) with age range from 17 years to 52 years. Additionally, it seems that POTS-like symptoms could be triggered after immunization with Pfizer- BioNTech, Moderna, and Oxford-AstraZeneca COVID-19 vaccines. The symptoms typically appear within the first week, depending upon previous exposure to the virus and presence of other systemic conditions. In some patients, the condition is self-resolving. However, in others, non-pharmacological interventions coupled with negative ionotropic medications can be used for symptomatic management of the patients.
CONCLUSIONS: Timely diagnosis and proper treatment are quintessential for ensuring early alleviation (and in some cases complete resolution) of symptoms. Furthermore, there may be episodes of relapse. Overall prognosis of the new-onset POTS-like symptoms is difficult to predict based on current literature.

Keywords: Autoimmunity, COVID-19, mRNA vaccine, POTS, SARS-COV-2

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1. Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) is defined as the presence of chronic symptoms of orthostatic intolerance for six months or longer, associated with an increased heart rate $\geqslant$ 30 bpm within 10 minutes of assuming an upright posture, in the absence of orthostatic hypotension [1,2]. It is estimated to affect approximately 170 people per 100,000 population and presents with cardiac symptoms such as chest pain, breathlessness, palpitations, dizziness, and loss of consciousness. Some patients may also experience associated symptoms including fatigue, headache, sleep disturbance, nausea, and bloating. Since the disease typically manifests with a broad spectrum of symptoms, each with varying severity, it is extremely difficult to achieve the correct diagnosis [3]. Additionally, the lack of definitive testing and the lack of familiarity of most healthcare providers with POTS raises questions about its misdiagnosis and subsequent under-reporting. In fact, the median time to accurately diagnose POTS is estimated to be up to two years [3].

POTS following COVID-19 vaccination is considered as an extremely rare event. However, a recent increase in reports of its incidence in the medical literature has attracted the attention of the medical community [4–11]. Although the association and pathophysiological relationship between these two events remain to be fully elucidated, a variety of mechanisms have been proposed including neuroendocrine dysfunction, neuropathy, and autoimmunity [12]. Therefore, in the present paper, we summarize and highlight the relevant evidence that has been reported in the literature to assist and enlighten physicians, nurses, and healthcare providers in the diagnosis and management of such patients.

2. Pathophysiology of POTS

Standing in an upright position results in a gravitational shift of blood (approximately 500–800 mL) from the upper body to the abdomen and legs. This causes a drop in the systemic blood pressure [13]. In healthy individuals, there are regulatory feedback pathways between the musculoskeletal, nervous, and cardiovascular systems that compensate for this shifting of vascular volume. When a lower blood pressure is sensed by the baroreceptors in the aortic arch and atrial wall, sympathetic outflow increases (with concomitant depression of parasympathetic signals), leading to increased heart rate and peripheral vasoconstriction. This increases both the cardiac output and systemic vascular resistance, thereby preventing a fall in the blood pressure. In addition, muscular contraction (mainly of the calf muscles) pushes the blood upwards into the inferior vena cava, providing an upstream flow of blood to the heart [13].

In patients with POTS however, there are disruptions in these feedback pathways. Excessive sympathetic outflow (causing orthostatic hypertension), downregulated venous receptors (causing decreased venous return), decreased plasma aldosterone-to-renin ratio (causing reduced sodium retention and plasma volume expansion), and elevated angiotensin II without concomitant hypertension (decreased sensitivity to vasoconstrictive effects) are some of the mechanisms that have been identified in the pathophysiology of POTS [13]. Other factors that have been identified as precipitating POTS include hypovolemia, deconditioning, neuroendocrine dysfunction (central hyperadrenergic state), neuropathy, infection, medications (antihypertensives, antipsychotics), surgery, pregnancy, concussion, and autoimmunity [14].

3. Autoimmunity and POTS

Despite the apparent lack of detectable antibodies in POTS patients, there are several features that POTS patients showcase which are indicative of an underlying autoimmune pathophysiology. Like other autoimmune conditions (lupus, rheumatoid arthritis), POTS predominantly affects women, has post-viral onset, and showcases elevated autoimmune markers [15,16]. Additionally, some reports have suggested that symptoms and biomarkers tend to respond well to a high-dose corticosteroid treatment [17]. It is also interesting that POTS is reported as a common complaint in patients suffering from other autoimmune conditions [1].

It is thought that given the role of autoimmune system in POTS, it could also be classified as an inflammatory disorder [18]. Indeed, studies have shown an increased levels of pro-inflammatory cytokines including IL-1β, IL-21, TNFα, INFα, TNF receptor [18], and IL-6 [19], which are usually coupled with elevated levels of autoantibodies adrenergic and cholinergic muscarinic receptors [18]. It has been reported that one in seven POTS patients have been found to be positive for ganglionic A3 acetylcholine receptor antibodies [11,20]. Furthermore, the role of platelets has been theorized whereby chronic inflammation due to underlying au-

toimmune condition causes acquired platelet delta granule storage pool deficiency (δ-SPD), an autosomal dominant disorder characterized by bleeding, epistaxis, and heavy menstrual bleeding [18,21].

However, it should be noted that concerns have been raised about the ability of these autoantibody assays (ELISA-based; enzyme-linked immunosorbent assay) to discriminate between healthy controls and individuals with POTS [22]. Differences in assay sensitivity and method of quantification of autoantibodies limit their utility. In addition, the detection of these autoantibodies in healthy controls complicates the interpretation of these assays [22].

4. POTS-like symptoms following COVID-19 vaccination

We identified 18 cases of reported POTS following COVID-19 vaccination from the available literature (Table 1). Females were found to be predominantly affected (72%) with an age range of 17 to 52 years. Most cases were reported from the United States (US) followed by the United Kingdom (UK), Australia, and South Korea. 11 cases (61%) were found to develop POTS-like symptoms after the first dose of COVID-19 vaccine, while seven cases developed symptoms after the second dose of the COVID-19 vaccine. A single case was reported to develop the symptoms twice – after the second and the third vaccine doses (Patient 10; Table 1). We further found that most of the cases (83%) were associated with mRNA vaccines – six cases post-vaccination with Moderna, and nine cases post-vaccination with Pfizer-BioNTech. The remaining three cases were reported post-vaccination with Oxford-AstraZeneca.

The onset of POTS-like symptoms varied from a few hours to three weeks after vaccination. In most cases, patients complained of dizziness, tachycardia, brain fog, headache, nausea, weakness, paraesthesia, and episodes of syncope while standing. Improvement in symptoms has been reported with recumbency or sitting. In addition, it appears that many patients who developed these symptoms post-vaccination, also developed vitamin B12 (cobalamin) deficiency. Correcting this deficiency seemed to improve patient's symptoms. Hypovitaminosis, including vitamin D, B1, B12, and iron deficiency, has been previously reported in a subset of POTS patients [23–25]. However, the exact relationship between hypovitaminosis and POTS is still not clear. Moreover, included studies didn't report baseline vitamin B12 levels and dietary intake. Pregnant patients, vegetarians, the older individuals, and those living in developing countries have been shown to have higher risk of vitamin B12 deficiency [26,27].

Nevertheless, the role of vitamin B12 in neurologic dysfunction is well documented [26]. A deficiency of cobalamin may result in a peripheral neuropathy that produces autonomic manifestations that would tend to be like orthostatic hypotension. This may partially explain the relief of symptoms reported by patients upon correction of cobalamin deficiency. The treatment approach generally, varied between studies (mostly due to differences in symptoms, medical history, and national guidelines). Most patients reported improvement in symptoms with the therapy they received.

5. COVID-19 vaccination induced autoimmunity

Autoimmunity may be the key pathogenetic pathway of post-vaccination POTS-like symptoms, particularly with adjuvanted mRNA vaccines. However, given the small number of reports published in the literature describing POTS-like symptoms after vaccination, concerns have been raised that patients are either being undiagnosed or misdiagnosed, leading to underreporting and underappreciation of its true incidence [1]. Consider the difficulty faced by clinicians in distinguishing POTS from postural vasovagal syncope, a transient loss of consciousness caused by reduced cerebral blood flow. This leads to difficulties in determining the exact pathogenetic mechanism responsible for the phenomenon.

It has been postulated that autonomic dysfunction following COVID-19 infection could be modulated by cross-reaction of anti-SARS-COV-2 antibodies with components of autonomic nervous system, including ganglia, nerve fibres, and receptors [12]. A similar argument could also be advanced in the context of the antibodies generated in response to COVID-19 vaccination [11]. Furthermore, it is possible that these autoantibodies remain undetected in patients who developed autonomic neuropathies post-vaccination [11].

In the case of mRNA-based immunizers, the vaccine triggers host cells to translate the genetic code of the virus and produce the viral spike protein target, which acts as an intracellular antigen. The immune system then mounts its adaptive response, producing and releasing neutralizing antibodies that block viral entry [28]. Given the possibility of autonomic cross-reactivity of vaccine-generated antibodies, several pathways have been proposed. Reactivity with α1-adrenergic recep-

Table 1
Characteristics of patients reported to have developed POTS-like symptoms following COVID-19 Vaccination

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	40 years	42 years	46 years	37 years	21 years	46 years
Gender	Male	Male	Female	Female	Female	Female
Country	South Korea	USA	USA	USA	USA	USA
First dose	Moderna	Pfizer-BioNTech	Pfizer-BioNTech	Moderna	Pfizer-BioNTech	Pfizer-BioNTech
Second dose	–	–	–	–	–	–
Third dose	–	–	–	–	–	–
POTS Symptom onset	7-days post first dose	24 hours post first dose	1.5 hours post first dose	1 week post first dose	12 days post first dose	2 weeks post first dose
Symptoms	Intermittent headache, palpitation, fatigue, and dyspnoea	Generalized fatigue, headache, and myalgia. On day 7 also developed sinus tachycardia and presyncope episodes	Erythema, urticaria, paraesthesia, light-headedness, tremors, rapid heart rate, Raynaud's Phenomenon, and marked fatigue	Light-headedness, racing heart, weakness, tiredness, difficulty concentrating, blurry vision, shakiness, vertigo, and clamminess	Light headache, palpitation, weakness, and difficulty thinking	Lightheadedness, nausea, fatigue, poor concentration, palpitations, and brain fog
Other medical conditions	None	Hypothyroidism and B12 vitamin deficiency (both are controlled using medications)	None	Seasonal allergy and depression. Patient takes vortioxetine (serotonin reuptake inhibitor)	None	None
Past medical history	Not significant	Left-sided orchiectomy for cryptorchidism	Allergic rhinitis, COVID-19 infection (9 months before vaccination)	Not significant	Not significant	Not significant
Previously known reactions to other vaccines	None	None	–	–	–	–
Medical Interventions	Propranolol for 2 months	Lifestyle modification (compression stocking, increased sodium intake)	Lifestyle modification and Ivabradine	Ivabradine	Metoprolol and Fludrocortisone	Fludrocortisone and Propranolol
Resolution	Five months from symptom onset	Patient suffers from symptoms at time of publication	Patient suffers from mild symptoms still 8 months post treatment start	Patient reported improvement in symptoms	Patient reported improvement in symptoms	Patient reported improvement in symptoms
Reference	Park et al., [4]	Reddy et al., [5]	Hermel et al., [6]	Eldokla and Numan [7]	Eldokla and Numan [7]	Eldokla and Numan [7]

tor could impair the vasoconstrictor response, leading to increased sympathetic activation [5]. Alternatively, the role of angiotensin-converting enzyme 2 (ACE2) receptor dysfunction has been shown to be causative in POTS [29], which is intriguing since ACE2 receptor plays a key role in COVID-19 viral pathogenesis. COVID-19 is thought to reduce the activity of ACE2 receptor, consequently resulting in increased sympathetic activation [30].

A recently posted preprint showed that following COVID-19 vaccination, a third of the patients who underwent skin biopsy had subthreshold nerve fibre density, thereby fulfilling the pathological criteria for new onset small fibre neuropathy [11]. Other study patients had demonstrated either borderline low density or axonal swelling with reduced conduction velocities in distal leg [11]. The authors also reported increased C4d deposition on endothelial cells in skin biopsy samples and the presence of oligoclonal bands in cerebrospinal fluid (CSF). Interestingly, most of the study participants were females and responded to immunotherapy, potentially pointing towards the role of the autoimmune system [11].

Since the reports indicated that patients received different vaccines (Pfizer-BioNTech, Moderna, and Oxford-AstraZeneca), we could potentially rule out the

Table 1, continued

	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Age	19 years	17 years	29 years	43 years	30 years	52 years
Gender	Female	Female	Male	Male	Female	Male
Country	USA	USA	Australia	UK	UK	USA
First dose	Pfizer-BioNTech	Pfizer-BioNTech	Oxford-AstraZeneca	Pfizer-BioNTech	Oxford-AstraZeneca	Pfizer-BioNTech
Second dose	Pfizer-BioNTech	Pfizer-BioNTech	–	Pfizer-BioNTech	–	Pfizer-BioNTech
Third dose	–	–	–	Pfizer-BioNTech	–	–
POTS Symptom onset	18 days post second dose	3 weeks post second dose	4 days post first dose	1 to 2 weeks post second dose; 2–3 days post third dose	6 hours post first dose	After second dose
Symptoms	Dizziness, headache, nausea, bloating, excessive sweating, and fatigue	Syncope, fatigue, chest tightness, nausea, and heat intolerance	Intermittent paraesthesia, palpitations, racing hearbeat, dizziness, and worsening of paraesthesia and skin colour	Dizziness, leg weakness, light-headedness, brain fog, word-finding difficulties	Dizziness, nausea, weakness, bradykinesia, brain fog, early waking, fatigue, “jelly-legs”, changes to walking gait,	Burning and stabbing feeling, orthostatic intolerance, syncope, supraventricular tachycardia, tinnitus
Other medical conditions	None	None	None	None	Patient uses Naproxen, Lansoprazole, Dihydrocodeine, Melatonin	–
Past medical history	Not significant	Not significant	Not significant	Suspected COVID-19 infection (8 months before vaccination)	Fatigue and sleep disturbances	–
Previously known reactions to other vaccines	–	–	–	–	–	–
Medical Interventions	Salt tablets and Propranolol	Scopolamine patches, Salt tablets and Propranolol	5-week course of steroid (no effect); lifestyle modifications	Intramusular hydroxocobalamin followed by oral cyanocobalamin	Intramusular hydroxocobalamin therapy	Nadolol, Gabapentin, Amitriptyline, and trazodone (no effect); Five plasma exchange sessions
Resolution	Patient reported improvement in symptoms	Patient reported improvement in symptoms	Patient has some improvement still 6 months post treatment start	Eight weeks from treatment	Patient reported improvement in symptoms	Patient reported improvement in symptoms
Reference	Eldokla and Numan [7]	Eldokla and Numan [7]	Karimi [8]	Carroll et al., [9]	Carroll et al., [9]	Schelke et al., [10]

differences in vaccine platforms as a potential cause of POTS following vaccination. This is also evident from the fact that POTS has also been widely reported following Human Papillomavirus (HPV) and Influenza (H1N1) vaccinations [1,31,32].

6. POTS-like symptoms or usual side-effects of vaccination

Diagnosis for POTS in a suspected patient requires fulfilment of clinical criteria, identification of comorbid conditions, medication use, and exclusion (along with severity assessment) of conditions that could cause or mimic the autonomic syndrome. A thorough physical, cardiologic, and neurologic examination is needed to differentiate between exaggerated orthostatic tachycardia in the absence of orthostatic hypotension and to rule out any gross structural pathology. A basic workup should include a complete blood count, serum electrolytes, thyroid and cardiac function tests, and electrocardiogram (ECG). For a more accurate diagnosis, it is essential to perform clinical examinations before vaccination and several weeks after vaccination [33].

A recent large study cohort showed that the odds

Table 1, continued

	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18
Age	31 to 40 years	31 to 40 years	31 to 40 years	41 to 50 years	31 to 40 years	31 to 40 years
Gender	Female	Female	Female	Female	Female	Female
Country	USA	USA	USA	USA	USA	USA
First dose	Oxford-AstraZeneca	Moderna	Pfizer-BioNTech	Moderna	Moderna	Moderna
Second dose	–	Moderna	Pfizer-BioNTech	–	–	Moderna
Third dose	–	–	–	–	–	–
POTS Symptom onset	2 hour post first dose	2 days post second dose	10 days post second dose	2 days post first dose	6 days post first dose	5 days post second dose
Symptoms	Severe paresthesia in limbs, tachycardia, blood pressure fluctuation, intermittent internal tremor, cognitive complaints	Orthostasis, fluctuation in heart rate and blood pressure, nausea, diarrhea, Paresthesia in face, upper and lower limbs; internal tremor	Severe orthostatic tachycardia, paler, diarrhea, fluctuation in blood pressure	Intermittent paresthesia, burning and numbness in face, hands and feet. Mild right-hand weakness and episodic positional palpitation	Exercise intolerance; fasciculations in all limbs; internal tremor, facial paresthesia; band like tightness in chest; cognitive changes; episodic positional palpitations	Paresthesia and burning sensation in V1 distribution of trigeminal nerves; positional palpitation and dizziness with activity
Other medical conditions	–	–	–	–	–	–
Past medical history	Probable history of COVID-19 and family history of Sjrogen's disease	Family history of psoriasis	Family history of rheumatoid arthritis	Not significant	Not significant	Not significant
Previously known reactions to other vaccines	–	–	–	–	–	–
Medical Interventions	–	–	–	–	–	–
Resolution	–	–	–	–	–	–
Reference	Sayafi et al., [11]	Sayafi et al., [11]	Sayafi et al., [11]	Sayafi et al., [11]	Sayafi et al., [11]	Sayafi et al., [11]

of developing POTS and POTS-associated diagnoses (dysautonomia, mast cell disorder, fatigue, and Ehlers–Danlos syndrome) were higher three months after COVID-19 vaccination than three months preceding vaccination [34]. In addition, POTS and POTS-associated diagnoses were among the top five disease diagnoses and were generally similar across age groups, sex, ethnicities, types of vaccine, and the dose number received. Since the diagnosis of POTS requires 3–6 months of symptoms, it is not possible to classify the symptoms noted immediately after vaccination as POTS. Rather it may be appropriate to describe them as "POTS-like".

It appears that the symptoms of POTS-like syndrome post-vaccination are usually recorded as late reactions, usually within the first seven days after vaccination. This temporal association maybe noteworthy in distinguishing between common vaccine side effects and vaccine-induced POTS-like syndrome. Although the most common side effects of the COVID-19 vaccines are fatigue and headache, the duration of symptoms is usually one to three days and patients don't experience episodes of presyncope or syncope and sinus tachycardia [35,36]. Thus, the onset of symptoms and duration of approximately one week after vaccination with the mRNA vaccine may prove to be indicative for the diagnosis of POTS-like symptoms, especially in patients with no prior noticeable medical history. Nonetheless, a few cases have been described in which the patients developed POTS-like symptoms within hours to two days after COVID-19 vaccination. What distinguishes these cases are the prior history of COVID-19 infection and/or other chronic conditions, which could potentially explain the accelerated immune response in these cases (Table 1).

7. Patient management

Treatment for these patients is aimed at alleviating symptoms, improving blood volume, and lifestyle

changes. Symptoms could be eased by wearing compression stockings to improve venous return in the lower extremities and increasing sodium intake [37]. Given the multifactorial pathogenesis of POTS itself, several studies have compared and evaluated the efficacy of various treatment approaches, including intravascular volume expansion, vasopressor therapy, heart rate reduction, and miscellaneous therapies [38]. Based on current evidence, the Canadian Cardiovascular Society recommends non-pharmacological therapy as the first line management approach – withdrawal of exacerbating medications, increasing blood volume with dietary interventions, use of compression stockings, adoption of head-up tilt sleeping position, and semi-recumbent exercises [39]. For pharmacological therapy, the society recommends midodrine (α-adrenergic agonist) and low-dose propranolol (nonselective β-blocker) for symptom relieve. It is further suggested to consider pyridostigmine (peripheral acetylcholinesterase inhibitor), fludrocortisone (mineralocorticoid), ivabradine, clonidine (central sympatholytic agent), and intermittent intravenous (I.V.) normal saline infusions for further relieve based on individual patient assessment [39].

8. Prognosis

An evaluation of the risk-benefit ratio shows that there is currently no evidence to support the propaganda against vaccination because of its adverse effects, with its benefits far outweighing its drawbacks. POTS-like symptoms after COVID-19 vaccination could be controlled by a combination of lifestyle changes and medications (if necessary). The prognosis of patients is difficult to predict based on the available literature. According to a Mayo Clinic study of adolescents with POTS symptoms (possibly different mechanism than vaccine induced symptoms), 37% of patients no longer met the tilt criteria for POTS after one year [40]. However, to formulate risk factors and accurate prognosis for POTS-like symptoms after vaccination, longer follow-up studies are needed.

9. Conclusions

POTS-like symptoms following COVID-19 vaccination is a heterogeneous condition characterized by prolonged episodes of tachycardia, syncope, or presyncope. The onset of symptoms appears to be independent of the type of vaccine administered, although the onset may vary depending on previous history of COVID-19 infection or systemic diseases. These symptoms usually appear on the first day of injecting the vaccine and worsen within seven days. The pathophysiology of the symptoms could possibly relate to many mechanisms, with the predominant role potentially being hypothesized as autoimmune. Although orthostatic intolerance is very uncomfortable for patients, it does not significantly increase the risk of mortality. If patients seek timely diagnosis and appropriate treatment, their symptoms may relieve over time.

Ethical approval

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Conflict of interest

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Author contributions

PTV, NJ, TTT, THT, and NTHH conceptualized the present perspective paper whilst all authors were involved in data collection and preparation of the initial draft of the manuscript. PTV and NJ were responsible for revising the manuscript. Supervision was done by AR. All authors have read and agreed to the final version of the paper for publication.

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