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LETTER TO THE EDITOR

# Postural orthostatic tachycardia syndrome after mRNA COVID-19 vaccine

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## Introduction

The diagnostic criteria of postural orthostatic tachycardia syndrome (POTS) require heart rate (HR) increase of > 30 bpm in adults and > 40 bpm in patients aged 12–19 years within 10 min of assuming upright posture without orthostatic hypotension (OH) [1]. Autonomic symptoms and POTS are reported in association with coronavirus disease 2019 (COVID-19) [2, 3]; however, the association between POTS and COVID-19 vaccination is not well studied.

We report five patients who presented to SUNY Upstate Medical University autonomic clinic and dysautonomia center of excellence at UTHealth Houston to evaluate orthostatic intolerance that developed after receiving the COVID-19 vaccine. They were diagnosed with postural orthostatic tachycardia syndrome (POTS) after extensive evaluation. All patients underwent a head-up tilt table (HUTT) test [4]. Furthermore, patients 1 and 2 were examined for Q-Sweat, Valsalva, and heart rate response to deep breathing (HRDB); and patients 3, 4, and 5 underwent heart rate variability (HRV) spectral Fourier analysis [4].

## Patient 1

A 37-year-old white female presented with lightheadedness, heart racing, weakness, tiredness, difficulty concentrating, blurry vision, shakiness, vertigo, and clamminess when assuming upright posture. Her symptoms improved in the supine position. She also complained of dry eyes and mouth unrelated to medications, abnormal sweating, abnormal sensitivity to the heat, significant constipation, and numbness and tingling of the feet, legs, hands, and occasionally the face. Her symptoms started 1 week after receiving the first dose of Moderna, COVID-19 vaccine. She has no significant past medical history (PMH) apart from seasonal allergy and depression for which she is taking vortioxetine, which was held five half-lives before autonomic testing. Blood work, including morning cortisol, antinuclear antibody (ANA), ferritin level, complete blood count (CBC), thyroid-stimulating hormone (TSH), urine metanephrines, and Mayo Clinic's serum autoimmune dysautonomia panel including ganglionic acetylcholine receptors (G-AChRs) antibody, was unremarkable or negative. Electrocardiogram (EKG) and Holter monitoring showed normal sinus rhythm. Stress echocardiogram showed normal hemodynamic and chronodynamic response to exercise and no evidence of myocardial ischemia. Ten-minute HUTT showed orthostatic tachycardia without orthostatic hypotension (OH), consistent with a diagnosis of POTS (Fig. 1A, C). HRDB, Valsalva ratio, and Q-Sweat were normal. Her symptoms improved with 5 mg of ivabradine taken twice a day.

## Patient 2

A 21-year-old white female presented with light headache, palpitation, weakness, and difficulty thinking when changing position from lying to standing. Her symptoms improved in the supine position. She also complained of abnormal sensitivity to heat, excessive sweating, and numbness and tingling of

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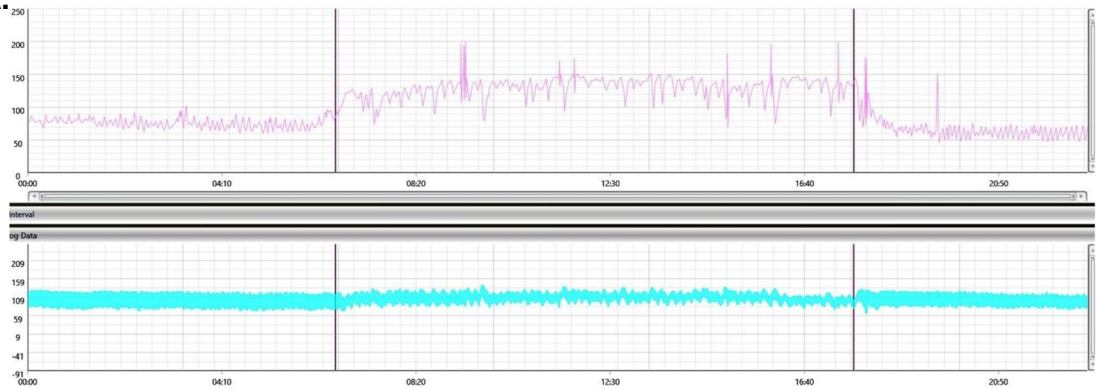
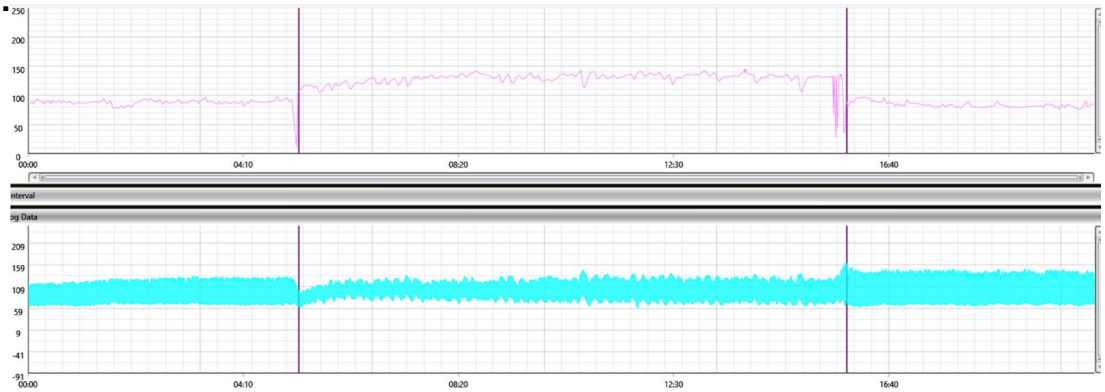
**A.**




**B.**




**C.**

| Patient | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Sex | F | F | F | F | F |
| Age | 37 | 21 | 46 | 19 | 17 |
| COVID-19 Vaccine to autonomic Sx (Days | 7 | 12 | 14 | 18 | 21 |
| Vaccine type | Moderna | BioNTech-Pfizer | BioNTech-Pfizer | BioNTech-Pfizer | BioNTech-Pfizer |
| Sx to HUTT (days) | 209 | 129 | 168 | 98 | 135 |
| Autonomic Sx | orthostatic lightheadedness Palpitation, Blurry vision, Shakiness, weakness, Difficulty thinking, Tiredness, clammy, Vertigo, Dry eye, Dry mouth, Sensitivity to heat, ES, Constipation, Numbness, Tingling. | orthostatic lightheadedness, Palpitation, weakness, Difficulty thinking, Sensitivity to heat, ES, Numbness, Tingling | orthostatic lightheadedness, palpitations, nausea, brain fog and fatigue | Dizziness, orthostatic lightheadedness, nausea and bloating, fatigue, palpitations, tingling, excessive sweating | Syncope, Dizziness, chest tightness, nausea, heat intolerance and fatigue |
| Autonomic Dx | POTS | POTS | POTS | POTS | POTS |
| **HUTT** | | | | | |
| *-Sx* | Nausea, Shakiness, Sweating | Palpitation | Nausea and short of breath | Hot, nausea, palpitations, chest tightness, leg numbness | Dizzy, light headed, nausea, short of breath, poor concentration. |
| *-Max systolic BP Δ* | 13 | 16 | 24 | 16 | 30 |
| *-Max diastolic BP Δ* | 20 | 14 | 12 | 10 | 18 |
| *-Max HR Δ* | 75 | 47 | 38 | 62 | 53 |
| *-Max HR* | 153 | 136 | 110 | 130 | 123 |
| CBC | NL | NL | NL | NL | NL |
| TSH | NL | NL | NL | NL | NL |
| Possible markers of autoimmunity | Negative | Positive G-AchR; Titer=0.07 nmol/L (normal <0.02 nmol/L). | Positive serum peroxidase antibody (65 IU/ml, normal < 9 IU/ml) | ANA: 1:80. Elevated tumor necrosis factor alpha (12.8 pg/ml, normal ≤ 7.2 pg/mL) and interleukin 10 (6.2 pg/ml, normal ≤ 2.8 pg/ml) | Increased titer of interleukin 2 (9.4 pg/ml, normal < 2.1 pg/ml), interleukin 10 (5.6 pg/ml, normal < 2.8 pg/ml) and interleukin 13 (10.4 pg/ml, normal < 2.3pg/ml) |

◂**Fig. 1** **A** Hemodynamic profile of the head-up tilt study in patient 1. Note prominent orthostatic tachycardia (above), HR Δ75 bpm, max HR 153 bpm with no significant orthostatic hypotension (below). **B** Hemodynamic profile of the head-up tilt study in patient 2. Note prominent orthostatic tachycardia ( above), HR Δ47 bpm, max HR 136 bpm with no significant orthostatic hypotension (below). **C** Patient characteristics and testing results. *F* female, *Dx* diagnosis, *Sx* symptoms, *ES* excessive sweating, *POTS* postural orthostatic tachycardia syndrome, *max BP Δ* maximum blood pressure changes mmHg, *max HR Δ* maximum heart rate changes bpm, *HUTT* head-up tilt table, *NL* normal, *G-AChR* acetylcholine receptor ganglionic antibody, *ANA* antinuclear antibody, *CBC* complete blood count, *TSH* thyroid-stimulating hormone

the face and extremities. Her symptoms started about 12 days after receiving the first dose of BioNTech-Pfizer, COVID-19 vaccine. She has no significant PMH and takes no medication. Blood work, including, CBC, TSH, and serum Lyme screening, was normal. Mayo Clinic's serum autoimmune dysautonomia panel was unremarkable apart from mildly positive G-AChRs antibody with a titer of 0.07 nmol/L (normal < 0.02). EKG and Holter monitoring showed normal sinus rhythm. Echocardiogram showed normal biventricular size and function. Autonomic testing showed orthostatic tachycardia without OH, consistent with a diagnosis of POTS (Fig. 1B, C). HRDB, Valsalva ratio, and Q-Sweat were normal. The patient felt she was almost back to normal after she was started on metoprolol XR 25 mg and fludrocortisone 0.2 mg daily.

## Patient 3

A 46-year-old Hispanic female developed new onset of lightheadedness, nausea, fatigue, poor concentration, palpitations, and brain fog about 2 weeks after receiving the first dose of BioNTech-Pfizer COVID vaccine. She has no significant PMH and takes no medication. Her echocardiogram, EKG, and Holter were normal. TSH and CBC were normal. HUTT showed orthostatic tachycardia without OH, consistent with a diagnosis of POTS (Fig. 1C). Heart rate variability (HRV) spectral Fourier analysis showed a significant increase in sympathetic activity after the head-up position. Autoimmune panel showed mildly elevated serum antiperoxidase antibodies. The patient responded well to the combination of fludrocortisone and propranolol.

## Patient 4

A 19-year-old white female-developed dizziness, headache, nausea, bloating, excessive sweating, and fatigue after 18 days of receiving a second dose of BioNTech-Pfizer COVID vaccine. She has no significant PMH and takes no medication. Her echocardiogram, EKG, and Holter were within normal. Autoimmune panel showed elevated ANA 1:80, elevated tumor necrosis factor-α 12.8 pg/ml (normal ≤ 7.2 pg/mL), and interleukin 10 6.2 pg/mL (normal ≤ 2.8 pg/mL). HUTT showed orthostatic tachycardia without OH, consistent with a diagnosis of POTS (Fig. 1C). HRV spectral Fourier analysis showed a significant increase in sympathetic tone after the head-up position. She responded fairly to salt tablets and propranolol.

## Patient 5

A 17-year-old white female developed syncope, fatigue, chest tightness, nausea, and heat intolerance 3 weeks after receiving a second dose of BioNTech–Pfizer COVID vaccine. She has no significant PMH and takes no medication. She had a normal echocardiogram, EKG, and TSH. Her autoimmune panel showed increased titer levels of interleukins 2, 10, and 13 (Fig. 1C). HUTT showed orthostatic tachycardia without OH, consistent with a diagnosis of POTS (Fig. 1C). HRV spectral Fourier analysis showed an increased sympathetic activity with occasional spikes of vagal tone after the head-up position. She was treated with scopolamine patches for nausea, and received salt tablets and propranolol with improvement of the syncope and fatigue.

## Discussion

We report five patients with POTS after receiving the mRNA COVID-19 vaccine. Age ranged from 17 to 47 years, and time to develop symptoms after receiving the mRNA COVID-19 vaccine ranged from 7 to 21 days, with a median of 14 days. HUTT test showed orthostatic tachycardia with symptoms of orthostatic intolerance and without OH, consistent with a diagnosis of POTS, heart rate changes ranged from +38 to +75 bpm, with a median of +53, and systolic blood pressure changes ranged from +13 to +30 mmHg with a median of +16.

All patients met the diagnostic criteria for POTS [1]. No other causes of sinus tachycardia were identified, including hyperthyroidism, anemia, dehydration, inappropriate sinus tachycardia, or medications (e.g., sympathomimetics, anticholinergics).

One of our patients had a weakly positive G-AChRs antibody with a titer of 0.07 nmol/L. Low levels of G-AChRs antibody, especially < 0.2 nmol/L, are quite nonspecific, and the majority of low-positive G-AChRs antibody titers are unlikely to be associated with neurological diseases [5, 6]. However, high levels of G-AChRs antibody titers > 1.0 nmol/L are quite specific for autoimmune autonomic ganglionopathy (AAG) [5, 6]. The patient also did not have the typical findings seen in AAG associated with positive G-AChRs antibody given the absence of OH, significant constipation, and prominent cholinergic dysfunction

such as dry mouth and eyes, urinary retention, and impaired pupil responses [7]; therefore, we believe that the low titer of G-AChRs seen in our patient is nonspecific and it is unlikely to be the cause of orthostatic intolerance and POTS.

In the initial case report of POTS, after approximately 1 week of receiving the first dose of the BioNTech–Pfizer mRNA COVID-19 vaccine, the patient had episodes of sinus tachycardia. However, HUTT and other autonomic testing were not performed to confirm the diagnosis of POTS [8]. Anther case of POTS was reported 7 days after receiving the first dose of Moderna COVID-19 vaccine. The patient improved after receiving propranolol, and her symptoms were nearly resolved after 5 months without medication [9].

Interestingly, four of our patients had serum markers of possible autoimmunity (Fig. 1C). Vaccine-induced autoimmunity through molecular mimicry between certain pathogenic elements contained in the vaccine and human proteins can lead to immune cross-reactivity and possible harm of the similar human protein by reaction of the immune system causing autoimmune disease [10]. Furthermore, POTS has been reported after vaccination, especially human papilloma viruses (HPV) vaccine [11]. Moreover, cluster analysis of reports from international database for adverse drug reactions, showed HPV vaccines, compared with other vaccines, to be associated with an increased proportion of reports clinically consistent with the POTS [12]. The exact mechanism of vaccine-induced POTS is not clear, however; for example, antibody induced by molecular mimicry between HPV L1 peptides and cardiac myosin/adrenergic receptors was suggested as a possible mechanism for POTS after receiving HPV vaccine [10, 13]. Several severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) peptide sequences, with the largest number being those of the SARS-CoV-2 spike protein, shared homology with human proteins involved in the adaptive immune response [14].

Although vaccine-induced autoimmune response is suggested as a possible mechanism, all our patients responded well to the treatment for POTS and did not require immune therapy or intravenous immunoglobulin (IVIG) treatment. This is in agreement with a recent report of significant improvement seen in a patient who developed POTS after COVID-19 vaccine [9].

We used the World Health Organization (WHO) guidelines to evaluate the causality of the adverse events following immunization (AEFI) after COVID-19 vaccination [15]. On the basis of the available evidence, we could conclude that the classification is consistent and it seems likely that the vaccine caused the event. There is evidence, although not strong, in the published peer-reviewed literature that the COVID-19 vaccine may cause POTS [8, 9], there is biological plausibility that the vaccine could cause POTS, and the development of POTS occurred within a plausible time window after vaccine administration.

The COVID-19 vaccine appears to be a safe and effective way to protect against COVID-19, reduce the hospitalization, and prevent severe SARS-CoV-2 complications, including death [16]. We want to stress that, although POTS can occur after COVID-19 vaccination, we speculate that the incidence is extremely low. Finally, we can only report an association between the POTS and COVID-19 vaccine, and we cannot report a solid conclusion regarding the causative relationship or the underlying mechanism.

## Declarations

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethical approval** All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments; the specific national laws have been observed.

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