LETTER TO THE EDITOR

Postural orthostatic tachycardia syndrome after mRNA COVID-19 vaccine

Ahmed M. Eldokla1,2 · Mohammed T. Numan3

Received: 29 May 2022 / Accepted: 11 July 2022 / Published online: 23 July 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany 2022

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 chromodynamic 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, abnormal symptoms...
### A.

| Sex | Age | COVID-19 Vaccine to autonomic Sx (Days) | Vaccine type | Sx to HUTT (days) |
|-----|-----|----------------------------------------|--------------|------------------|
| F   | 71  | 7                                      | Moderna      | 209              |
| F   | 19  | 12                                     | BioNTech-Pfizer | 129              |
| F   | 21  | 12                                     | BioNTech-Pfizer | 14              |
| F   | 12  | 14                                     | BioNTech-Pfizer | 18              |
| F   | 17  | 21                                     | BioNTech-Pfizer | 21              |

### B.

| Autonomic Sx                  | HUTT                                                                 |
|-------------------------------|----------------------------------------------------------------------|
| orthostatic lightheadedness    | Dizziness, chest tightness, nausea, heat intolerance and fatigue     |
| Palpitation, Blurry vision,    |                                                                      |
| Shakiness, weakness,          |                                                                      |
| Difficulty thinking,          |                                                                      |
| Tiredness, clamy,             |                                                                      |
| Vertigo, Dry eye,             |                                                                      |
| Dry mouth, Sensitivity to heat, |                                                                  |
| ES, Constipation, Numbness,   |                                                                      |
| Tingling.                     |                                                                      |

### 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                  | Autonomic Dx |
| orthostatic lightheadedness    | POTS |
| Palpitation, Blurry vision,    | POTS |
| Shakiness, weakness,          | POTS |
| Difficulty thinking,          | POTS |
| Tiredness, clamy,             | POTS |
| Vertigo, Dry eye,             | POTS |
| Dry mouth, Sensitivity to heat, ES, Constipation, Numbness, Tingling. | POTS |

### HUTT

| HR max systolic BP (mmHg) | 130 | 166 | 10 | 18 |
|--------------------------|-----|-----|----|----|
| Max diastolic BP (mmHg)   | 130 | 10  | 18 |
| Max HR (bpm)             | 153 | 136 | 110| 130| 123 |
| CBC                      | NL  | NL  | NL | NL |
| TSH                      | NL  | NL  | NL | NL |

### Possible markers of autoimmunity

| Negative | Positive G-AChR; Titer=0.87 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 < 2.3 pg/mL) |
|----------|----------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
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-19 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. 1B, C). 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.

**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 (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.

**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-19 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 responded fairly to salt tablets and propranolol with improvement of the syncope and fatigue.

---

**Note:**

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-19 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. 1B, C). 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-19 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.
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]. Another 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.

References

1. Sheldon RS, Grubb BP 2nd, Olshansky B et al (2015) 2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm 12(6):e41–63. https://doi.org/10.1016/j.hrthm.2015.03.029
2. Eldokla AM, Ali ST (2022) Autonomic function testing in long-COVID syndrome patients with orthostatic intolerance. Auton Neurosci 241:102997. https://doi.org/10.1016/j.autneu.2022.102997
3. Eldokla AM, Mohamed-Hussein AA, Fouad AM et al (2022) Prevalence and patterns of symptoms of dysautonomia in patients with long-COVID syndrome: a cross-sectional study. Ann Clin Transl Neurol. https://doi.org/10.1002/acn3.51557
4. Cheshire WP, Freeman R, Gibbons CH et al (2021) Electrodiagnostic assessment of the autonomic nervous system: a consensus statement endorsed by the American Autonomic Society, American Academy of Neurology, and the International Federation of Clinical Neurophysiology. Clin Neurophysiol 132(2):666–682. https://doi.org/10.1016/j.clinph.2020.11.024
5. McKeon A, Lennon VA, Lachance DH, Fealey RD, Pittock SJ (2009) Ganglionic acetylcholine receptor autoantibody: oncologic, neurological, and serological accompaniments. Arch Neurol 66(6):735–741. https://doi.org/10.1001/archneur.2009.78
6. Li Y, Jammoul A, Mente K et al (2015) Clinical experience of seropositive ganglionic acetylcholine receptor antibody in a tertiary neurology referral center. Muscle Nerve 52(3):386–391. https://doi.org/10.1002/mus.24559
7. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA (2000) Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med 343(12):847–855. https://doi.org/10.1056/nejm200009213431204
8. Reddy S, Reddy S, Arora M (2021) A case of postural orthostatic tachycardia syndrome secondary to the messenger RNA
COVID-19 vaccine. Cureus 13(5):e14837. https://doi.org/10.7759/cureus.14837

9. Park J, Kim S, Lee J, An JY (2022) A case of transient POTS following COVID-19 vaccine. Acta Neurol Belg. https://doi.org/10.1007/s13760-022-02002-2

10. Segal Y, Shoenfeld Y (2018) Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol 15(6):586–594. https://doi.org/10.1038/cmi.2017.151

11. Brinth LS, Pors K, Theibel AC, Mehlsen J (2015) Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus. Vaccine 33(22):2602–2605. https://doi.org/10.1016/j.vaccine.2015.03.098

12. Chandler RE, Juhlin K, Fransson J, Caster O, Edwards IR, Norén GN (2017) Current safety concerns with human papillomavirus vaccine: a cluster analysis of reports in VigiBase(®). Drug Saf 40(1):81–90. https://doi.org/10.1007/s40264-016-0456-3

13. Li Y, Heuser JS, Cunningham LC, Kosanke SD, Cunningham MW (2006) Mimicry and antibody-mediated cell signaling in autoimmune myocarditis. J Immunol 177(11):8234–8240. https://doi.org/10.4049/jimmunol.177.11.8234

14. Lyons-Weiler J (2020) Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. J Transl Autoimmun 3:100051. https://doi.org/10.1016/j.jtauto.2020.100051

15. Organization WH. Causality assessment of an adverse event following immunization (AEFI), 2019 update. Available online: https://www.who.int/publications/i/item/9789241516990 (accessed on 25 June 2022)

16. Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N (2022) Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. Clin Microbiol Infect 28(2):202–221. https://doi.org/10.1016/j.cmi.2021.10.005