COVID-19 and postural tachycardia syndrome: a case series

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Background
Postural tachycardia syndrome (PTS) is a novel identified sequela of COVID-19 infection. This observational study describes clinical presentation, testing, and treatment response in seven patients diagnosed with PTS following COVID-19 infection.

Case summary
A total of seven active patients (three collegiate athletes, one recreational athlete, two registered nurses, one hospitality employee), age 24 ± 6 years, and six females were followed for a mean of 152 ± 105 days after contracting COVID-19. Tilt table was performed to establish the diagnosis. The most common presenting symptoms were palpitations (7/7), dyspnoea (6/7), and gastrointestinal complaints (5/7). One patient required hospitalization for symptom management. The mean latency of PTS onset following COVID-19 was 21 ± 15 days. Electrocardiograms (ECGs) demonstrated sinus rhythm in all patients, one with resting sinus tachycardia. Echocardiogram demonstrated normal systolic and diastolic left ventricular function in all patients. On tilt table testing, baseline heart rate (HR) was 72 ± 12 with maximum HR reaching 136 ± 13. Six of seven patients failed to respond to supportive therapy alone, and two patients failed medical management with ivabradine, midodrine, and/or metoprolol. Of three severely symptomatic patients, two demonstrated some degree of clinical recovery with intravenous immunoglobulin (IVIG).

Discussion
This novel case series describes the development of PTS in the context of COVID-19 infection. Severity of symptoms and response to treatment was heterogeneous. Interestingly, patients were poorly responsive to traditional PTS treatments, but IVIG showed potential as a possible therapeutic strategy for refractory PTS in two patients, particularly following COVID-19 infection.

Keywords
Severe acute respiratory syndrome coronavirus 2019 (COVID-19) • Postural tachycardia syndrome • Intravenous immunoglobulin • Autonomic dysfunction • Case series
Learning points

- Based on findings from the seven patients studied, postural tachycardia syndrome (PTS) could represent a long-standing sequela of COVID-19 infection disproportionately affecting highly active young females, refractory to supportive treatment and/or traditional PTS pharmacotherapy.
- Contrary to prior case reports, PTS did not develop selectively in patients with prolonged COVID-19 infections in our study, but rather emerged after resolution of relatively shorter-duration infections.
- As observed in two of the patients studied, intravenous immunoglobulin may represent a beneficial and well-tolerated intervention for refractory PTS, specifically following COVID-19 infection.

Introduction

Postural tachycardia syndrome (PTS) is the most common autonomic dysfunction diagnosed in the USA and is characterized by excessive increase in heart rate (HR) with postural change, specifically supine to standing, without accompanying hypotension.1 The fatigue, weakness, and exercise intolerance that characterize this disease can be debilitating in otherwise healthy patients, with a 5:1 female to male predilection. While the pathogenesis of PTS is heterogeneous, infection is a well-characterized trigger of PTS, with 28% reporting PTS onset following a viral prodrome.2 Some symptoms of autonomic dysfunction were reported in the 2002 epidemic of severe acute respiratory syndrome, but lacked the specific diagnosis of PTS.2 Few case reports and a smaller case series have described variable information on patients developing PTS after COVID-19.3–6 In response, one author analysed how COVID-19 may mechanistically give rise to PTS.7

In this case series, we detail the clinical characteristics and treatment response of seven consecutive highly active young patients who developed PTS following infection with COVID-19.

Timeline

| Patient number | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|----------------|---|---|---|---|---|---|---|
| Age            | 25| 21| 19| 24| 18| 34| 29|
| Sex            | M | F | F | F | F | F | F |
| Occupation/activity level | Hospitality employee | Collegiate athlete | Collegiate athlete | Registered nurse | Collegiate athlete | Recreational athlete | Registered nurse |
| Hospitalized for postural tachycardia syndrome (PTS) | - | - | - | - | - | - | - |
| Days since COVID-19 infection | 300| 298| 147| 118| 80| 72| 48|
| Days since PTS onset | 281| 266| 147| 79| 44| 57| 41|
| Days from COVID-19 onset to development of PTS | 19| 32| 0| 39| 36| 15| 7|
| Symptoms on presentation | | | | | | | |
| Palpitations | + | + | + | + | + | + | + |
| Dyspnoea | + | - | - | + | - | + | - |
| GI symptoms | + | - | - | + | - | + | - |
| Lightheadedness | - | + | + | + | - | + | - |
| Dizziness | - | - | + | + | - | - | - |
| Weakness | - | - | + | - | + | + | - |
| Chest discomfort | - | + | - | + | - | + | - |

Summary of clinical data for seven patients infected with COVID-19 who were subsequently diagnosed with PTS. Mean age ± standard deviation was 24.3 ± 5.7. Six patients were female, one male. Occupations are described, and whether PTS required hospitalization is labelled. Mean days since COVID-19 infection as of time of analysis was 151.9 ± 105.5; since onset of PTS was 130.7 ± 105.5, with a latency between the former and the latter of 21.1 ± 15 days. Symptoms described by patient on initial cardiology outpatient visit are listed by most to least common. All patients were in sinus rhythm on initial appointment electrocardiogram, with only Patient 3 demonstrating resting sinus tachycardia. All seven patients had recent transthoracic echocardiograms prior to this appointment, demonstrating normal LV systolic and diastolic function across the board, with two patients demonstrating trivial valvular disease including two with mild TR and one with mild MR as listed. On tilt table testing, mean baseline HR was 71.9 ± 11.6 and maximum HR was 131.6 ± 13. Average postural change in SBP was -8.9 ± 15.4 mmHg; DBP was -1.1 ± 10.3 mmHg. Regarding treatment, all seven patients were recommended lifestyle interventions including compression socks, aggressive hydration, and electrolyte repletion, which included a suggested sodium consumption of ~5 g/day. Supplemental medical

Continued
therapies with metoprolol, ivabradine, and midodrine were trialled as listed. IVIG was administered to three patients, as listed. Only Patient 2 improved with conservative management. With no improvement after metoprolol, Patient 4 demonstrated robust improvement of PTS symptoms without complete resolution. Patient 1 demonstrated some improvement in PTS symptoms, but reports some degree of symptoms returned. Patient 3 demonstrated no improvement with sequential trials of ivabradine, midodrine, and IVIG.

**Case presentation**

**Cases 1–7**

In a clinical cardiology outpatient setting, we evaluated 10 patients with a medical history notable for prior COVID-19 infection who described symptoms characteristic of autonomic dysfunction, such as postural dizziness/lightheadedness, tachycardia discordant to perceived level of exertion, and presyncope. COVID-19 diagnosis was confirmed via PCR in all patients, and patients self-reported COVID-19 symptom clearance date. Tilt table testing confirmed a diagnosis of PTS in seven patients. These seven patients completed 2-week ambulatory rhythm monitoring to exclude pathologic arrhythmias as a cause for symptoms. Among these seven patients, six were female and one was male, and the mean age ± standard deviation was 24.3 ± 5.7 years. Three patients were collegiate athletes, one patient was a recreational athlete, two patients were registered nurses, and one patient was a hospitality employee. One patient required hospitalization for symptom management. Length of time from COVID-19 infection to their most recent follow-up visit with a cardiologist ranged from 48 to 300 days, mean of 151.9 ± 105.5 days, and all seven

| Patient number | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|----------------|---|---|---|---|---|---|---|
| Anxiety        | - | - | - | - | + | + | - |
| Diaphoresis    | - | - | + | + | - | - | - |
| Syncope        | - | - | - | + | - | - | - |
| ECG on presentation | | | | | | | |
| Heart rate (HR) | Sinus | Sinus | Sinus | Sinus | Sinus | Sinus | Sinus |
| Rhythm         | Sinus | Sinus arrhythmia | Sinus tachycardia | Sinus | Sinus | Sinus arrhythmia | Sinus |
| Echocardiograms on presentation | | | | | | | |
| Left ventricular (LV) ejection fraction | 58 | 60 | 62 | 69 | 59 | 65 | 66 |
| LV diastolic dysfunction | - | - | - | - | - | - | - |
| Valvular disease | - | 1+ tricuspid regurgitation (TR) | 1+ TR | - | - | - | - |
| Tilt test | | | | | | | |
| Baseline HR | 74 | 58 | 59 | 87 | 70 | 69 | 86 |
| Max HR | 126 | 125 | 120 | 123 | 137 | 158 | 132 |
| Postural Increase in HR | 52 | 67 | 61 | 36 | 67 | 89 | 46 |
| Baseline systolic blood pressure (SBP) | 110 | 110 | 108 | 117 | 105 | 115 | 121 |
| End SBP | 113 | 98 | 68 | 112 | 102 | 103 | 128 |
| Postural change in SBP | +3 | -12 | -40 | -5 | -3 | -12 | +7 |
| Baseline diastolic blood pressure (DBP) | 74 | 71 | 67 | 62 | 65 | 80 | 80 |
| End DBP | 77 | 68 | 45 | 69 | 66 | 77 | 89 |
| Postural change in DBP | +3 | -3 | -22 | +7 | +1 | -3 | +9 |
| Treatment | Conservative/lifestyle | + | + | + | + | + | + | + |
| Intravenous immunoglobulin (IVIG) | + | - | + | + | - | - | - |
| Metoprolol | - | - | - | + | - | - | - |
| Ivabradine | - | - | + | - | - | - | - |
| Midodrine | - | - | + | - | - | - | - |
| Symptom improvement | Transient | Yes | No | Yes | No | No | No |
patients reported ongoing symptomatic PTS at this visit (Figure 1A). On average, latency of symptomatic PTS onset following COVID-19 infection varied between 0 and 39 days, 21.1 ± 15 days.

On review of systems during the initial evaluation (Figure 1B), 7/7 patients endorsed palpitations. Other common symptoms included dyspnoea (6/7), gastrointestinal complaints (5/7), and lightheadedness (4/7). Dizziness, weakness, and chest discomfort were each reported in 3/7 patients, and 2/7 experienced anxiety. Only one patient experienced a true syncopal episode, which was her presenting symptom of PTS and occurred 30 days after resolution of acute COVID-19 infection symptoms.

The initial resting electrocardiogram (ECG) in supine positioning revealed four patients in sinus rhythm with normal rate, two had sinus rhythm with sinus arrhythmia, and one with sinus tachycardia, without pathologic ECG findings. Transthoracic echocardiogram demonstrated normal systolic and diastolic left ventricular function in all patients, mild tricuspid regurgitation with structural normal tricuspid valves in two patients, and mild mitral regurgitation with a structurally normal mitral valve in one patient.

Postural tachycardia syndrome was diagnosed via tilt table testing, defined as an increased HR of ≥30 beats per min (b.p.m.) within 10 min of assuming an upright posture and in the absence of orthostatic hypotension [blood pressure (BP) fall >20/10 mmHg]. The mean HR at baseline was 71.9 ± 11.6 b.p.m., with a maximum of 131.6 ± 13.0 b.p.m. and an average postural increase by 59.7 ± 17.2 b.p.m. within the first 10 min of upright positioning (Figure 1C). When upright, the mean postural change in systolic blood pressure was -8.9 ± 15.4 mmHg, and the mean diastolic blood pressure change was -1.1 ± 10.3 mmHg. It is worth noting that one patient, Patient 3, did experience a drop in BP and presyncope with upright positioning, which was attributed to a vasovagal episode. However, this patient was diagnosed with PTS due to maintenance of BP prior to vasovagal episode, due to subsequent bedside orthostatic vitals consistent with PTS, and due to the chronicity of her orthostatic intolerance which is more characteristic of PTS than vasovagal syncope.

Other investigations of tachycardia included thyroid-stimulating hormone, haemoglobin, white blood cell count (WBC), and review of medications. Thyroid-stimulating hormone, haemoglobin, and WBC were within normal limits for all patients. Patient 4 infrequently used inhaled albuterol for mild intermittent asthma, and Patient 7 used dextroamphetamine daily for attention deficit hyperactivity disorder, but both of these medications had been prescribed for years.
prior to development of PTS symptoms. There were otherwise no past medical histories nor other prescribed medications for all seven patients.

The initial treatment strategy for all patients consisted of supportive care with compression socks, aggressive hydration, and electrolyte repletion, which included a suggested sodium consumption of ~5 g/day. Despite an average of 130.7 ± 104.0 days from PTS diagnosis, at the time of this writing, only one patient showed improvement with supportive therapy alone. Metoprolol was used in one patient; ivabradine and later midodrine were utilized in another patient. Neither showed symptomatic improvement on these medications and so they were discontinued after ~2 months of treatment. In order to provide symptomatic relief in these two patients who failed to respond to medication, along with one patient who failed to respond to prolonged supportive care (280 days), we infused intravenous immunoglobulin (IVIG) based upon prior preliminary studies suggesting possible symptomatic improvement in individuals with autonomic dysfunction.10,11 One of these patients, who required hospitalization for severe symptoms, reported some symptom resolution and improving exercise tolerance within 1–2 weeks of the infusion. Another patient endorsed acute symptomatic improvement with a slight increase in exercise tolerance, although there was only a small degree of benefit 1 week after infusion. The third patient noted no improvement in symptoms 1 month after the IVIG infusion.

### Discussion

This is one of the first case series describing the relationship between COVID-19 and PTS,6 and the first highlighting the disease of a uniquely young and active population. By observing a cross-section of seven patients, we were able to appreciate the heterogeneity of disease progression in this long-standing sequela of COVID-19. Rubin12 suggests autonomic dysfunction may selectively target patients who have had delayed resolution of COVID-19 viral infection. In contrast, all patients in this series had resolution of their initial infectious symptoms of COVID-19 within 1–3 weeks following COVID-19 diagnosis, and six of the seven patients developed symptoms of PTS after clearing the virus (Figure 1A). Our patients ranged from 18 to 34 years old and demonstrated female predilection analogous to PTS in the general population.1 Interestingly, while all seven patients had physically active lifestyles inclusive of collegiate and recreational athletes, nursing, and hospitality pre-dating COVID-19 infection onset, they all developed debilitating symptoms that markedly reduced their exercise tolerance, suggesting that the severity of autonomic dysfunction may be unrelated to exercise tolerance prior to COVID-19 infection.

‘Post-acute COVID-19 syndrome’ is a term gaining increasing attention as more patients demonstrate symptoms well after the acute phase of COVID-19 infection.13 Nalbandian et al. published a unifying review article summarizes many symptoms and diseases following COVID-19 infection, and mentions PTS and other autonomic dysfunction disease such as inappropriate sinus tachycardia as a possible component of this broader syndrome. As of now, however, there is no literature tying PTS to specific other long-term sequelae of the syndrome, and it therefore becomes hard to group PTS with this broader diagnosis.

Current evidence guiding treatment of PTS is limited mostly to small studies with disparate diagnostic criteria and to expert opinion,14 and these treatment strategies are summarized in Table 1. Despite a relatively long follow-up of >150 days, only one observed patient reported improvement with supportive management alone (without complete symptomatic resolution). Taken together, these data may challenge the public narrative that young patients suffer substantially less long-term consequences of COVID-19 than older patients, as PTS represents a protracted and debilitating disease mostly affecting youth.5,12

Liu et al.,10 initially proposed IVIG as a therapy for autonomic dysfunction including PTS with the underlying assumption that autoimmune small-fibre polyneuropathy constituted a major aetiology of autonomic dysfunction, analogous to Guillain–Barré and chronic inflammatory demyelinating polyneuropathy. Analysis of patients in that study and another study authored by Schofield and Chemali demonstrated significant clinical improvement in patients with autonomic dysfunction treated by IVIG.10,11 While IVIG is still under investigation, two of three patients in this case series noted relative improvement in symptoms shortly after its administration. Importantly, all three patients tolerated the IVIG treatment without complication. The two patients who benefitted from IVIG had progressive PTS symptoms for 80 and 280 days, respectively. Thus, IVIG could show potential as a possible therapeutic strategy for refractory post-viral PTS, particularly following COVID-19 infection. Although IVIG overall improved quality of life in this small cohort, this potential treatment strategy warrants further longitudinal investigation, to better comprehend the mechanisms of a possibly beneficial effect and to ultimately identify the ideal candidates for treatment. Remarkably, as tens of millions of patients across the world are now recovering from acute COVID-19 infection, we will see more cases of post-viral PTS, a disease with heterogeneous presentation and variable response to therapy.

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**Table 1** Postural tachycardia syndrome treatment options

| Mechanism                        | Therapy               |
|----------------------------------|-----------------------|
| Conservative management          | Sodium chloride supplementation |
|                                  | Incremental exercise program |
|                                  | Compression garments   |
| Rate control                     | Metoprolol            |
|                                  | Propranolol            |
|                                  | Ivabradine             |
| Adrenergic agonism               | Midodrine             |
|                                  | Pyridostigmine         |
|                                  | Droxidopa              |
|                                  | Methylphenidate        |
| Intravascular volume expansion   | Fludrocortisone        |
| Investigational/unknown          | IVIG                  |

Current evidence guiding treatment of PTS is limited. These treatment strategies and mechanisms of action are summarized in this table.

IVIG, intravenous immunoglobulin; PTS, postural tachycardia syndrome.
Lead author biography

William H. Parker is an internal medicine resident at the Cleveland Clinic in Cleveland, Ohio. He aspires to a career in cardiovascular medicine and critical care medicine.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patients in line with COPE guidance.

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