COVID-19-induced postural orthostatic tachycardia syndrome treated with ivabradine

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SUMMARY

A 22-year-old woman was referred with exertional dyspnoea and chest tightness 3 weeks following a diagnosis of COVID-19. Evaluation revealed a resting sinus tachycardia and criteria for postural orthostatic tachycardia syndrome were met. After non-pharmacological interventions failed to yield symptomatic improvement, ivabradine was commenced. This intervention was followed by a substantial improvement in the patient's exercise tolerance and energy levels and an objective reduction in supine and standing heart rate.

BACKGROUND

Postural orthostatic tachycardia syndrome (POTS) is a common debilitating condition characterised by a sustained heart rate (HR) increment of ≥30 beats/min within 10 min of standing or head-up tilt in the absence of orthostatic hypotension. Associated symptoms typically include chest pain, palpitations, exercise intolerance, orthostatic intolerance and fatigue, gastrointestinal disturbance, headache, fibromyalgia and sleep disturbance. It commonly affects young women.

It has been noted that POTS may develop in susceptible individuals after an acute viral illness[1–3] with a viral prodrome preceding symptom onset in 28%–41% of cases.[4 5] Autonomic dysfunction has previously been observed in cohorts of patients affected by the 2002 SARS epidemic.[6] Dysautonomia has already been observed in hospitalised patients with COVID-19.[7 8] However, there may be a significant number of individuals who do not experience severe symptoms in the acute phase of the illness but for whom dysautonomic postacute COVID-19 or 'long COVID-19' results in substantial morbidity.

CASE PRESENTATION

An asymptomatic 22-year-old nurse working on a COVID-19 ward tested positive for SARS-CoV-2 on routine hospital surveillance testing. Two days later, she developed a dry cough, interscapular back pain and fatigue. Symptoms had completely resolved in 1 week. Ten days following diagnosis, she began to experience chest tightness, palpitations, dyspnoea and fatigue on mild exertion. She sought medical attention on day 21 when symptoms had not resolved and a home pulse oximeter showed a normal oxygen saturation with HR of 150 beats per minute (bpm).

She had no significant medical history. Her only medication was the contraceptive pill. She was a non-smoker with no recent alcohol consumption.

Cardiovascular and respiratory examinations were normal apart from a resting (supine) sinus tachycardia of 100 bpm. Standing provoked a reproducible increase in HR to 130–140 bpm which was sustained at 10 min. Symptoms were reproduced on walking 10 m on the flat, associated with HR 140–150 bpm, and resolved with rest. She did not have orthostatic hypotension (blood pressure 140/86 mm Hg lying, 136/80 mm Hg standing). There were no signs of deep venous thrombosis and no evidence of joint hypermobility.

INVESTIGATIONS

Haemoglobin, thyroid function tests, ferritin, d-dimer and troponin were normal. ECG demonstrated sinus tachycardia. Chest X-ray showed a normal cardiac silhouette without pulmonary infiltrates. Echocardiography revealed a hyperdynamic left ventricle and was otherwise normal.

DIFFERENTIAL DIAGNOSIS

Supraventricular tachycardia
Pulmonary embolism
Atrial fibrillation
Thyrotoxicosis

TREATMENT

She was educated regarding adequate fluid intake, avoidance of caffeinated products and counter-pressure manoeuvres. When symptoms failed to resolve following these interventions, she was commenced on ivabradine 5 mg two times per day.

OUTCOME AND FOLLOW-UP

Within 24 hours of treatment with ivabradine, her symptoms had significantly improved. She was advised to engage in daily exercise, building effort tolerance in an incremental manner. Two weeks later, she was reviewed at clinic. Resting (supine) HR was 82 bpm. This rose to and was sustained at 96 bpm on standing. Two months following diagnosis, the patient reported near complete resolution of symptoms with restoration of exercise tolerance to close to premorbid status. Ivabradine was thus downtitrated to 2.5 mg two times per day as a trial but the patient became symptomatic once more. As a result, the higher dose was reinstituted, to good effect.

DISCUSSION

As our attention shifts to understanding the long-term sequelae of SARS-CoV-2 infection, we have collectively begun to recognise a multisystem postacute COVID-19 syndrome often characterised

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by dysautonomia. The UK COVID-19 symptom study, based on self-input of symptoms into a smartphone app, reported that approximately 10% of patients who test positive for SARS-CoV-2 remain unwell beyond 3 weeks.[9] For some of these patients, an orthostatic intolerance syndrome may be the cause of their symptoms.

The underlying pathophysiological mechanisms resulting in autonomic dysfunction in POTS are not mutually exclusive and may include peripheral neuropathy, increased serum norepinephrine, baroreceptor dysfunction and hypovolaemia.[1 2] Autoimmune-mediated autonomic nervous system dyshomeostasis in response to a viral infection is posited as a mechanism though to date there is insufficient evidence of pathogenicity.

In patients presenting with postacute COVID-19 symptoms consideration should be given to other significant diagnoses such as pericarditis, myocarditis, pneumonia and pulmonary embolism. In those with tachycardia, it is also important to outrule thyroid disorder and iron deficiency. An active stand test wherein one measures resting HR and blood pressure after 5 min lying supine and repeats measurements after 3 min of standing should be performed to determine if orthostatic intolerance in the form of tachycardia and/or hypotension is present.

Non-pharmacological interventions for treatment of POTS include consumption of 2–3 L of water per day and 10–12 g/day of sodium, lower limb compression stockings and regular and progressive exercise. Beyond this, the guidelines suggest consideration of fludrocortisone, midodrine, pyridostigmine, low dose propranolol or ivabradine, depending on the specific underlying mechanism presumed or proven responsible in an individual case of POTS.[10] In spite of this, the use of ivabradine for POTS is currently off-label. A trial published in February 2021 by Taub *et al* showed ivabradine to be safe and effective in significantly improving HR and quality of life in patients with predominantly hyperadrenergic POTS.[11]

Ivabradine was approved for use in the treatment of chronic stable angina pectoris and chronic stable heart failure with reduced ejection fraction by the European Medicines Agency in 2005. In a dose dependent manner it selectively inhibits the I_f current, which is highly expressed in sinoatrial (SA) nodal cells. This results in slowed diastolic depolarisation of SA node cells causing a negative chronotropic response in sinus rhythm. It does this without significantly impacting blood pressure as it does not affect myocardial contractility and is generally well tolerated.

As symptoms are diverse and patients may present to various specialists, it is imperative that all physicians are equipped to recognise post-acute COVID dysautonomia and are aware of the non-pharmacological and pharmacological interventions that may lead to an improvement in quality of life. One group with a high incidence of SARS-CoV-2 infection worldwide throughout this pandemic has been healthcare workers. In Ireland, 78% of healthcare staff are female,[12] many of whom are in the highest incidence age bracket for the development of POTS. Since our evaluation of this patient we have seen a number of other young female healthcare workers present with COVID-19 mediated POTS. We believe it is a significantly under-recognised entity. Early recognition and proper management will allow intervention to improve symptoms and earlier return to normality.

Learning points

- COVID-19-mediated postural orthostatic tachycardia syndrome (POTS) is an evolving troublesome disorder that predominantly affects young females.
- The predominant symptoms of COVID-19 POTS are tachycardic palpitation, chest tightness and dyspnoea on exertion.
- Management of POTS has been traditionally difficult and many patients have a chronic disorder.
- Ivabradine represents a very useful drug to ameliorate symptoms of tachycardia in COVID-19 POTS.

Contributors AL reviewed the patient in the first instance and identified the patient as having symptoms consistent with a post-COVID phenomenon. He referred the patient to CV who reviewed the patient with JSO, diagnosed postural orthostatic tachycardia syndrome and advised commencement of ivabradine. JSO collated the data and undertook literature review prior to writing up the case report. CV edited the case report. AL has conducted follow-up reviews of the patient.

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