A dizzying diagnosis

Sadhvi SS Naresh, Bosco Wu, Tim Tse, Amy Kwan

CASE

A university student, aged 20 years, presented to her general practitioner (GP) with a one-year history of fatigue, palpitations, tachycardia and postural dizziness. This was on a background of insomnia, hyper-mobility, tension headaches and chronic constipation. The patient had developed worsening fatigue, now triggered with minimal exertion, as well as worsening heat intolerance, difficulty concentrating and daily recurrent orthostatic dizziness. These persistent symptoms markedly limited her mobility and functional capacity to complete activities of daily living. Prior examination findings included a resting heart rate (HR) fluctuating between 160–180 beats per minute (bpm) and a standing HR of 200–220 bpm without orthostatic hypotension. Her baseline bloods and electrocardiogram (ECG) were unremarkable. The patient was subsequently referred and diagnosed with postural orthostatic tachycardia syndrome via a tilt table test (TTT).

QUESTION 1

What is postural orthostatic tachycardia syndrome (POTS)?

QUESTION 2

What is the pathophysiology of POTS?

QUESTION 3

What are the diagnostic criteria for POTS?

QUESTION 4

What is involved in the initial work-up of a patient suspected to have POTS?

ANSWER 1

POTS is a multi-system disorder characterised by symptoms of orthostatic intolerance, particularly a rise in HR when standing, without marked orthostatic hypotension or concomitant cause for tachycardia.[1,2] Patients often experience palpitations, weakness or lightheadedness, which improve upon being seated.[1] Common co-existing conditions include, but are not limited to, hyper-mobility spectrum disorder, fibromyalgia and migraines.[1,3] Symptom onset can be precipitated by a stressful event, commonly viral infections.[2] Up to 80% of POTS patients are female, often from a White background. The most common age of symptom onset is 14 years (mean age 21±12 years).[3]

ANSWER 2

Three main pathophysiologies that underlie POTS are: (1) autonomic neuropathy; (2) hypovolemia; and (3) a hyperadrenergic state.[4] Often, the aetiology is mixed and complicated by comorbid autoimmune conditions or genetic mutations.[5] Addressing these pathophysiologies underlies the management of POTS.[4]

Autonomic neuropathy of small postganglionic sudomotor fibres, mainly in the feet, have been reported in up to 50% of POTS patients. Consequent impairment of sympathetic tone causes reduced venoconstriction and venous pooling in the abdomen, pelvis and lower extremities.[6] Hypovolemic POTS is characterised by low plasma blood volume and a 24-hour urine sodium concentration ≤100 mmol/L, caused by a dysfunctional renin-angiotensin-aldosterone system. Hyperadrenergic POTS is characterised by a rise in systolic blood pressure (BP) of ≥10 mmHg during a 10-minute TTT and a plasma noradrenaline level ≥600 pg/mL.[4,7] A subset of patients also have autoantibodies to adrenergic receptors, or deficiency in noradrenaline transporters.[4]

ANSWER 3

As per the 2015 consensus statement by the Heart Rhythm Society,[7] the following four features must be met to diagnose POTS:

- sustained HR increase of ≥30 bpm (or ≥40 bpm if the patient is aged 12–19 years) within 10 minutes of upright posture
- absence of orthostatic BP drop ≥20/10 mmHg
- symptoms of orthostatic intolerance that are worse while upright, with rapid improvement upon return to a supine position for ≥6 months
- absence of other conditions that could explain sinus tachycardia.

ANSWER 4

Initial investigation of suspected POTS should include orthostatic vital sign measurements to confirm postural tachycardia, and a 12-lead electrocardiogram and a 24-hour Holter monitor to exclude an arrhythmia. Pathology tests should screen for other causes of tachycardia/presenting symptoms, including a full blood count, iron studies, active vitamin B12, electrolytes, renal function,

Table 1. Non-pharmacological options for management of POTS[5]

Strategy	Effectiveness
Exercise training and gradual reconditioning	Class IIa recommendation[A]
Sodium intake >10 g/day and fluid intake of at least 2.5 litres/day	Class IIb recommendation[A]
Class 2 compression garments >30 mmHg of pressure	Class Ib recommendation[A] for venous insufficiency; shown to have symptomatic improvement in POTS

POTS, postural orthostatic tachycardia syndrome.

[A]Ib, strong recommendation where benefits clearly outweigh risks, based on moderate-quality evidence; IIa, weak recommendation where benefits are closely balanced with risks, based on high-quality evidence; IIb, weak recommendation where benefits are closely balanced with risks, based on moderate-quality evidence.

thyroid function tests, plasma noradrenaline and morning cortisol. A patient might also be referred for a TTT to confirm postural variability in HR between supine and standing without significant postural changes in BP.[1,5]

CASE CONTINUED

The patient was commenced on Fludrocortisone and Propranolol. She was advised to increase her daily fluid and salt intake, wear compression stockings and see a physiotherapist and dietitian to aid in reconditioning.

Table 2. Pharmacological options for management of POTS[5,6]

Goal	Examples of medications	Mechanism of action	Effectiveness	Possible adverse effects
Reducing upright sinus tachycardia/ sympathetic tone	BBs (eg propranolol, 10–40 mg tid; bisoprolol, 2.5–5 mg bid; metoprolol, 25–100 mg daily; atenolol, 12.5–50 mg daily)	β-AR antagonist[8]	• Class IIb recommendation[10] • Especially useful for hyperadrenergic phenotype	• Bradycardia, hypotension, fatigue, syncope • Caution recommended for patients with asthma
	Ivabradine (2.5–5 mg bd)	Inhibits selective cardiac pacemaker current (*If*) slowing sinoatrial node firing[9]	• Not currently part of first- or second-line guidelines, shown to improve symptoms with very few side effects • Effective when BBs not well tolerated	• Bradycardia, hypertension, atrial fibrillation, visual brightness
Enhancing vasoconstriction/ venoconstriction	Midodrine (2.5–10 mg bd)	Direct α1-AR agonist	• Class IIb recommendation,[10] might be especially useful for hypovolemic subtype or patients with pronounced orthostatic intolerance	• Supine hypertension, paresthesias, urinary retention
	Clonidine (0.2–0.6 mg bd)	Direct centrally acting 2-AR agonist	• Class IIb recommendation,[10] recommended for hyperadrenergic phenotype or for patients with hypertension on standing	• Headache, generalised rash, fatigue and sedation
	Pyridostigmine (30–60 mg bd/tds)	Acetylcholinesterase inhibitor	• Class IIb recommendation,[10] can be considered in possible neuropathic phenotype	• Abdominal pain, diarrhoea, vomiting
Augmenting blood volume	Fludrocortisone (0.1–0.2 mg one daily)	Increases sodium reabsorption and enhances sensitivity of α-AR	• Class IIb recommendation, might be especially useful for hypovolemic subtype	• Hypertension, hypokalaemia
	Desmopressin (0.1–0.4 mg bd)	Vasopressin analogue	• Limited evidence but symptomatic improvement in tachycardia reported[6]	• Hyponatremia

α-AR, alpha adrenoreceptor; β-AR, beta adrenoreceptor; BBs, beta blockers; IIb, weak recommendation where benefits are closely balanced with risks, based on moderate-quality evidence; POTS, postural orthostatic tachycardia syndrome.

QUESTION 5

What are the principles of management of POTS?

ANSWER 5

Management for patients with autonomic neuropathy aims to promote venous return via compression garments or increasing peripheral vasoconstriction, commonly with midodrine. Management of hyperadrenergic POTS is two-fold: (1) sympathetic suppression (commonly with beta blockers); or (2) parasympathetic stimulation (often with pyridostigmine). Management of hypovolemic POTS focuses on volume expansion. Increasing daily sodium and fluid intake, as well as Fludrocortisone or Desmopressin, can be considered.[5,6] Suggestions for non-pharmacological and pharmacological management are given in Tables 1 and 2.

Key points

- POTS is a multi-system syndrome characterised by symptoms of orthostatic intolerance, usually seen in young women.
- Diagnosis is on a combination of orthostatic intolerance for ≥6 months and increase in HR ≥30 bpm within 10 minutes of upright posture in the absence of orthostatic hypotension or other explanatory diseases.
- Management is both non-pharmacological and pharmacological, and is aimed at expanding blood volume, enhancing venous return and reducing tachycardia.

Authors

Sadhvi SS Naresh BClinSci, Medical Student, Macquarie University, Sydney, NSW

Bosco Wu MBBS, BMedSci (Hons), FRACGP, General Practitioner, MQ Health General Practice, Discipline of Primary Care, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW

Tim Tse BMed, MD, MMed, FRACGP, General Practitioner, MQ Health General Practice, Discipline of Primary Care, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW

Amy Kwan MBBS, DCH, FRACGP, General Practitioner, MQ Health General Practice, Discipline of Primary Care, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW

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Correspondence to:
sadhvinaresh@gmail.com

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