Clinical Aspects of Paediatric PoTS

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Postural Tachycardia Syndrome or Postural Orthostatic Tachycardia Syndrome (PoTS) is similar physiologically in adolescents and adults. Nonetheless, the clinical presentations, diagnostic criteria [1], and, potentially, the treatment and prognosis vary by age.

Clinical Presentation of PoTS in Adolescents

The incidence of adolescent PoTS is unknown. There are data, however, about the incidence of chronic fatigue, and chronic fatigue is linked to autonomic dysfunction[2]. Approximately 31% of US early adolescent girls struggle with morning fatigue at least twice weekly [3]. In Holland, 21% of adolescent girls and 7% of adolescent boys have had significant fatigue for at least three months [4]. A community study in the UK suggested that 1.1% of adolescents have chronic disabling fatigue [5]. Thus, it could well be that at least 1% of adolescents have autonomic dysfunction, including postural orthostatic tachycardia syndrome. Clearly, there are more than the number of PoTS patients who have orthostatic intolerance to some degree since more than 25% of adolescents sometimes feel dizzy when they assume an upright posture [6].

Typically, PoTS presents during early adolescence, around the start of a growth spurt and, for girls, within a year of menarche [7–9] It is extremely rare for PoTS to present much before the onset of pubertal changes. Some older adolescents and young adults, however, report PoTS symptoms beginning separate from the time of pubertal hormone changes. About two-thirds of adolescents with PoTS are females.

It seems likely that anyone can develop PoTS, but there are clear predisposing factors in addition to potential influences of pubertal hormone changes [7]. PoTS is less common in blacks than in whites and Asians and is found in about 15% of first degree relatives of PoTS patients, indicating a probable genetic predisposition. Over half of people affected with PoTS have a significant degree of hypermobility, again suggesting either a genetic or, perhaps, a structural physical predisposing factor. Anecdotally, many patients are high achievers, hinting at a possible biochemical predisposition, however, the observation could just be due to ascertainment bias: high achievers in high achieving families getting access to the medical teams who can make the diagnosis. The actual onset of symptoms often follows a period of physical illness, such as mononucleosis or an injury, such as a concussion. Some people have suggested that immunisation, such as for human papilloma

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virus, can trigger PoTS, but that impression lacks support of controlled epidemiological studies and could be due to recall bias [10].

Symptoms of PoTS are similar in adolescents and adults. Fatigue and postural dizziness are nearly uniform. Pain is also common, usually headache and or abdominal discomfort but also sometimes extremity or back pain. Cloudy thinking and a sense of forgetfulness are common. Heat and cold intolerance are also common.

Diagnostic Criteria

The key physical finding of PoTS is postural tachycardia. Other associated findings can include abnormally large pupils and, when upright, facial pallor and mottled dusky distal extremities.

The diagnosis of adolescent PoTS is based on typical symptoms (chronic fatigue and orthostatic intolerance) along with an excessive postural tachycardia in the absence of another obvious cause of those findings (such as severe anxiety with a panic attack during postural challenge) [9]. Based on data from active standing tests (ASTs) and head-up tilt tests (HUTTs), a postural tachycardia rise of more than 40 beats per minute is considered "excessive" in adolescents [6, 11]. Standardised HUTTs may be more reliable than ASTs (due to muscle use facilitating blood flow during standing), but there is a loose correlation between results [$p = 0.04$ in one study [12]]. In the UK, there is currently no agreed consensus on whether ASTs or HUTTs are more sensitive in adolescents. In a recent unpublished survey of 61 patients under the age of 18 by the national charity, PoTS UK, 62% of patients reported receiving their diagnosis following a HUTT. There are a variety of protocols for ASTs and HUTTs in current practice (Box 1, Box 2). ASTs and HUTTs require neither medication nor venous access, however, beat-to-beat Blood Pressure (BP) and Heart Rate (HR) are essential for HUTTs.

Box 1 Example of an Active Standing Test (AST)

Resting supine 5 minutes	BP	HR
Stand up (≤ 1 min)	BP	HR
Standing up for 3 minutes	BP	HR
Standing up for 10 minutes	BP	HR

Use a common place automated sphygmomanometer that can simultaneously record BP and HR non-invasively from the brachial artery. Use largest cuff that comfortably fits around the upper arm. If BP or HR are high at baseline after 5 min supine, ask them to relax and repeat baseline in a few minutes.

In adolescents with orthostatic intolerance a rise in HR of ≥ 40 bpm without OH at the time, and with typical symptoms (chronic fatigue, orthostatic intolerance etc.), confirms the diagnosis of PoTS.

Orthostatic Hypotension (OH) is a drop in BP systolic ≥ 20 mmHg, or BP diastolic ≥ 10 mmHg, or BP systolic < 90 mmHg.

Box 2 Example of a Head-Up Tilt Test (HUTT) for PoTS

Resting supine 5 minutes	BP	HR
Resting supine 10 minutes	BP	HR
60° Head-Up Tilt (≤ 1 min)	BP	HR
60° Head-Up Tilt 3 minutes	BP	HR
60° Head-Up Tilt 10 minutes	BP	HR

Use an automated tilt table.

Use continuous beat-to-beat finger BP and HR recording, in addition to a common place automated sphygmomanometer on the opposite arm to record brachial BP and HR at these specific times.

Can be combined with continuous video-EEG, respiratory bands, and end-tidal CO_2 recording.

In adolescents with orthostatic intolerance a rise in HR of ≥ 40 bpm without OH at the time, and with typical symptoms (chronic fatigue, orthostatic intolerance etc.), confirms the diagnosis of PoTS.

A longer HUTT (up to 50 min) may be required if investigating Transient Loss of Consciousness, e.g. syncope.

Orthostatic Hypotension (OH) is a drop in BP systolic ≥ 20 mmHg, or BP diastolic ≥ 10 mmHg, or BP systolic < 90 mmHg.

Orthostatic hypotension (OH) and PoTS are both on the spectrum of autonomic dysfunction and sometimes overlap, e.g. in the same person on different occasions. Vasovagal syncope, with orthostatic hypotension (a systolic blood pressure drop of more than 20 mm Hg or a drop in diastolic pressure of more than 10 mmHg with postural challenge), is a common cause of fainting in adolescents. Patients who have hypotension prior to manifesting tachycardia during tilt likely have orthostatic hypotension rather than PoTS. Typically, PoTS patients are chronically tired and only rarely faint while patients with vasovagal syncope are not bothered by daily fatigue and "just" faint.

Treatment of PoTS in Adolescents

The treatment of adolescents with PoTS has been incompletely studied. In fact, there are very few comparative studies of various treatments in either adults or adolescents with PoTS [13, 14]. For now, management decisions are often based on personal experience of the treating physician and extrapolated adult data and expert reviews [15]. It is hoped that this current publication can serve as a sort of "expert consensus" to guide management.

1. Non-Pharmacological Measures (see also Sect. 5, Chapters 27 & 28)

   Non-pharmacologic measures are essential in managing adolescents with PoTS [7, 9] First, steps should be taken to increase the circulating blood volume. Fluid intake should be very generous; it is often suggested that adolescents should drink so much water that their urine appears clear like water, apart from an early morning urine which can be pale yellow. Salt intake should be increased since intravascular salt helps "hold on" to the fluid; if affirmation of adequate salt intake is needed, the daily output of sodium (in a 24 h urine collection) should be more than 170 mmol. In the UK, Slow sodium is available and is an easy way to add salt without disrupting the family's healthy low salt diet. For a teenager or young adult, a reasonable starting dose is 50 mmol of sodium (3 g of salt) twice a day increasing to 100 mmol of sodium (6 g salt) twice a day. For small or younger patients start at a lower dose of 2 mmol sodium/kg/day (0.12 g/kg/day salt) in 2 divided doses.

   Manoeuvers to temporarily increase BP can help with acute orthostatic symptoms, e.g. drinking a large glass of water before trying to get out of bed in the morning [16] Compression stockings can also help return otherwise pooled vascular volume to the circulation.

   Second, exercise is vitally important. Gentle morning exercises involving the contraction of large muscle groups can get blood flowing. Aerobic exercise is important to improve vascular tone and to correct any concurrent deconditioning. Patients should exercise daily, starting with a duration of aerobic exercise that does not lead to excessive post-exertional fatigue and then building the duration by a few minutes every week until reaching the target of 30 min of daily aerobic exercise. However, some patients will not be able to maintain their

previous levels of activity even though they should still get daily aerobic exercise.

Third, cognitive behavioral therapy is effective in reducing symptoms of PoTS and in facilitating functional restoration. Intensive programs can lead to quick improvement in tolerance of normal daily activities in PoTS patients who had been debilitated [17].

Regular school attendance should be facilitated wherever possible to maintain academic activity, peer interaction, and to prevent social isolation.

2. Drug therapy of PoTS in adolescents (see also Chapters 27–35)

Medications do not cure PoTS, but they can help improve blood flow and functional ability while non-pharmacologic measures are being instituted [7, 8] Beta blockers (such as metoprolol tartrate, 25 mg orally first thing in the morning and then again mid-day) are commonly used with good effect. While low-dose propranolol has proven effective in adults [18], there is anecdotal evidence that some adolescents feel more fatigued on propranolol. Various beta blockers have different receptor specificity and varying ability to cross the blood–brain barrier; thus, when one beta blocker is incompletely effective, another may be tried.

Fludrocortisone, a selective mineralocorticoid, starting with 50 mcg daily and increasing to 0.1 mg twice daily according to response, is sometimes used for its ability to foster fluid and salt retention. However, there are no clear data demonstrating that this is more effective than generous oral fluid and salt intake, which should accompany its use.

Midodrine, an alpha-adrenergic receptor agonist, can improve peripheral vascular tone and increase peripheral vascular resistance, venous return and cardiac output. It may be used three times daily with the final dose at least three to four hours before lying down at night (to prevent supine headaches due to increased blood flow, and supine hypertension); starting at a low dose (2.5 mg) and increasing incrementally to as much as 10 mg can help avoid some of the bothersome side effects such as a tingling sensation in the scalp.

Selective serotonin reuptake inhibitors (SSRIs) can have a helpful adjunctive effect, presumably by increasing serotonin-mediated vascular and intestinal flow.

Ivabradine is a selective channel inhibitor which slows the sinoatrial (SA) node, the natural cardiac pacemaker. It shows some promise in adults [19] and in a UK review of 13 PoTS patients under the age of 18 treated with ivabradine, 63% reported improvement of symptoms. In these patients, mean Ivabradine dose after up titration was 0.1 mg/kg per dose [20].

Other medications have been used in small numbers of patients without proven efficacy. These include stimulants such as methylphenidate and amphetamines to decrease mental clouding, modafanil to facilitate wakefulness, and even erythropoietin to build blood volume.

Of course, concurrent comorbidities [21] should be managed while treating patients with PoTS. Nearly half of adolescents with PoTS are iron deficient with a low ferritin level (<20 ng/mL), even without anemia; iron supplementation is helpful [22, 23]. In some areas, many PoTS patients are vitamin D deficient [22]. Vitamin D deficiency has also been associated with chronic pain [24].

Anxiety and depression occur in a third or more of PoTS patients; SSRI treatment can often help these comorbidities while also helping the symptoms of PoTS. Gastrointestinal dysmotility is often part of PoTS but could be treated with motility agents such as erythromycin, metoclopramide, or, rarely, octreotide. Chronic pain in PoTS patients should not be treated with opiates but can respond to gabapentin (gradually escalating doses, as needed, up to 1200 mg three times daily), pregabalin, and amitriptyline. Hypermobility spectrum disorder and hypermobile Ehlers Danlos syndrome (hEDS) are fairly common in patients with PoTS, and require recognition and advice. The diagnostic criteria for EDS and hypermobility have recently been revised. (see https://ehlers-danlos.

com/wp-content/uploads/hEDS-Dx-Criteria-checklist-1.pdf, [25]).

Mast cell activation disorders can co-occur with PoTS: and beta blockers can worsen symptoms of mast cell activation [26].

PoTS can be debilitating for adolescents. With appropriate management, however, functional restoration is expected, even before the PoTS resolves. In complex cases fatigue and other debilitating symptoms sometimes persist when the postural tachycardia improves, and as with those with complex additional symptoms, a multidisciplinary rehabilitation approach is best, as with young people with CFS/ME. Prognosis in adolescent PoTS is unclear; In one study, over time, the vast majority of patients reported improvement of symptoms, and approximately one fifth reported full recovery [27].

References

1. Sheldon RS, Grubb BP II, Olshansky B, Shen WK, Calkins H, Brignole M, et al. 2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope. Heart Rhythm. 2015;12(6):e41–63.
2. Wyller VB, Godang K, Mørkrid L, Saul JP, Thaulow E, Walløe L. Abnormal thermoregulatory responses in adolescents with chronic fatigue syndrome: relation to clinical symptoms. Pediatrics. 2007;120:e129–37.
3. Ghandour RM, Overpeck MD, Huang ZJ, Kogan MD, Scheidt PC. Headache, stomachache, backache, and morning fatigue among adolescent girls in the United States: associations with behavioral, sociodemographic, and environmental factors. Arch Pediatr Adolesc Med. 2004;158:797–803.
4. ter Wolbeek M, van Doornen LJ, Kavelaars A, Heijnen CJ. Severe fatigue in adolescents: a common phenomenon? Pediatrics. 2006;117:e1078–86.
5. Rimes KA, Goodman R, Hotopf M, Wessely S, Meltzer H, Chalder T. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics. 2007;119:e603–9.
6. Skinner JE, Driscoll SW, Porter CB, Brands CK, Pianosi PT, Kuntz NL, et al. Orthostatic heart rate and blood pressure in adolescents: reference ranges. J Child Neurol. 2010;25:1210–5.
7. Johnson JN, Mack KJ, Kuntz NL, Brands CK, Porter CJ, Fischer PR. Postural orthostatic tachycardia syndrome: a clinical review. Pediatr Neurol. 2010;42:77–85.
8. Kizilbash SJ, Ahrens SP, Bruce BK, Chelimsky G, Driscoll SW, Harbeck-Weber C, et al. Adolescent fatigue, PoTS, and recovery: a guide for clinicians. Curr Probl Pediatr Adolesc Health Care. 2014;44(5):108–33.
9. Stewart JM, Boris JR, Chelimsky G, Fischer PR, Fortunato JE, Grubb BP, et al. Pediatric Writing Group of the American Autonomic Society. Pediatric disorders of orthostatic intolerance. Pediatrics 2018;141:e20171673.
10. Butts BN, Fischer PR, Mack KJ. Human papillomavirus vaccine and postural orthostatic tachycardia syndrome: a review of current literature. J Child Neurol. 2017;32:956–65.
11. Singer W, Sletten D, Opfer T, Brands CK, Fischer PR, Low PA. Postural tachycardia in children and adolescents: what is normal? J Pediatr. 2012;160:222–6.
12. Fischer PR, Brands CK, Porter CJ, Kuntz NL, Mack KJ, Risma JM, et al. High prevalence of orthostatic intolerance in adolescents in a general pediatric referral clinic. (abstract) Clin Autonom Res. 2005;15:340.
13. Wells R, Elliott AD, Mahajan R, Page A, Iodice V, Sanders P, et al. Efficacy of therapies for postural tachycardia syndrome: a systematic review and meta-analysis. Mayo Clin Proc. 2018;93:1043–53.
14. Hasan B, Almasri J, Marwa B, Klaas KM, Fischer PR. treatment of postural orthostatic tachycardia syndrome with medication: a systematic review. J Child Neurol. 2020 (in press)
15. Miller AJ, Raj SR. Pharmacotherapy for postural tachycardia syndrome. Autonom Neurosci: Basic Clin. 2018;215:28–36.
16. Ma J, Hu W, Wu D. Drinking cold water increases blood pressure in healthy young students. Blood Press Monit. 2014;19:118–9.
17. Bruce BK, Weiss KE, Ale CM, Harrison TE, Fischer PR. Development of an interdisciplinary pediatric pain rehabilitation program: the first 1000 consecutive patients. Mayo Clin Proc Inn Qual Out. 2017;1:141–9.
18. Raj SR, Black BK, Biaggioni I, Paranjape SY, Ramirez M, Dupont WD, et al. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more. Circulation. 2009;120:725–34.
19. Barzilai M, Jacob G. The effect of ivabradine on the heart rate and sympathovagal balance in postural tachycardia syndrome patients. Rambam Maimonides Med J.2015 Jul 30;6(3).
20. Donne GD, Roses-Noguer F, Til J, Salukhe T, Prasad S, Daubeney P. Ivabradine in the pediatric population: preliminary findings. J Am Coll Cardiol. 2016;67(13):774.

21. Ojha A, Chelimsky TC, Chelimsky G. Comorbidities in pediatric patients with postural orthostatic tachycardia syndrome. J Pediatr. 2011;158:20–3.
22. Antiel RM, Caudill JS, Burkhardt BE, Brands CK, Fischer PR. Iron insufficiency and hypovitaminosis D in adolescents with chronic fatigue and orthostatic intolerance. South Med J. 2011;104:609–11.
23. Jarjour IT, Jarjour LK. Low iron storage and mild anemia in postural tachycardia syndrome in adolescents. Clin Auton Res. 2013;23:175–9.
24. Turner MK, Hooten WM, Schmidt JE, Kerkvliet JL, Townsend CO, Bruce BK. Prevalence and clinical correlates of vitamin D inadequacy among patients with chronic pain. Pain Med. 2008;9:979–84.
25. Tinkle B, Castori M, Berglund B, Cohen H, Grahame R, Kazkaz H, et al. Hypermobile Ehkers-danlos syndrome: clinical description and natural history. Am J Med Genet (Seminars in Medical Genetics). 2017;175C:48–69.
26. Seneviratre SL, Maitland A, Afrin L. Mast cell diseases in Ehlers-danlos syndrome. Am J Med Genet (Seminars in Medical Genetics). 2017;175C:226–36.
27. Bhatia R, Kizilbash SJ, Ahrens SP, Killian JM, Kimmes SA, Knoebel EE, et al. Outcomes of adolescent-onset postural orthostatic tachycardia syndrome. J Pediatr. 2016;173:149–53.