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Postural Tachycardia Syndrome in Children and Adolescents

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Postural tachycardia syndrome is a chronic condition with frequent symptoms of orthostatic intolerance or sympathetic activation and excessive tachycardia while standing, without significant hypotension. Orthostatic symptoms include dizziness, lightheadedness, blurring of vision, near faints, weakness in legs, poor concentration, nausea, and headaches. Somatic symptoms include fatigue, sleep disorder, widespread pain, abdominal pain, and menstrual irregularities. Psychological problems may overlap with physical complaints. This review discusses the normal physiology of orthostatic change, different pathophysiological mechanisms of postural tachycardia syndrome, including hypovolemia, venous pooling, autonomic neuropathy, and hyperadrenergic responses. In addition, an outline for management tailored to the patient's clinical syndrome is presented, along with concluding thoughts on future research needs.
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Introduction

Orthostatic intolerance (OI) is defined as the symptoms and signs of presumed cerebral hypoperfusion or sympathetic activation while standing that are relieved by recumbence.[1,2] Orthostatic symptoms include dizziness, lightheadedness, near syncope, weakness in legs, blurred vision or transient "blackout" or "whiteout" of vision, headache, neck pain, nausea, poor concentration, and occasional syncope. Symptoms of sympathetic activation include palpitations, chest pain, vasomotor skin changes and warm feeling, tremulousness, and occasional sympathetic storms.[2]

Postural orthostatic tachycardia syndrome (POTS) is increasingly recognized in children and adolescents. POTS in adults consists of chronic OI and sustained increment in heart rate (HR) of ≥ 30 beats per minute (bpm) or an absolute HR of ≥ 120 bpm or both within 10 minutes of active standing or head-up tilt test.[3,4] A HR increment of 35 bpm,[5,6] or 40 bpm,[7-9] is considered excessive in children and adolescents. Patients with POTS may sometimes faint, but unlike OI from autonomic failure, a significant orthostatic hypotension (OH) is absent. In fact, blood pressure (BP) in POTS may increase upon standing secondary to a hyperadrenergic response.

POTS is a multisystem condition with heterogeneous clinical features and pathophysiology that can be quite disabling with significant effect on the daily quality of life.[2,4,10,11] Although POTS has been reported in adults for over a century under various names and further defined by Schondrof and Low in 1993,[3,4] the condition is rarely reported in children. Streeten et al. reported in 1972 a familial syndrome of excessive tachycardia, hypotension, and narrow pulse pressure upon standing in 5 patients, including adolescents. Patients experienced severe OI symptoms with flushing of skin. Marked improvement was reported after therapy using fludrocortisone, propranolol, or cyproheptadine.[12] Further reports of POTS in children appeared more recently.[13-15]

This review highlights our current understanding of the pathophysiology of POTS in the pediatric population, the proposed pediatric diagnostic criteria, the spectrum of clinical manifestations, the guidelines for diagnostic evaluation and management, and areas for further research.

Normal Physiological Orthostatic Responses

When we stand up, 500-1000 mL of blood moves from the upper body to the lower body below the heart, primarily into the legs and abdomen. The reduced pulse pressure activates the baroreflex, which causes the release

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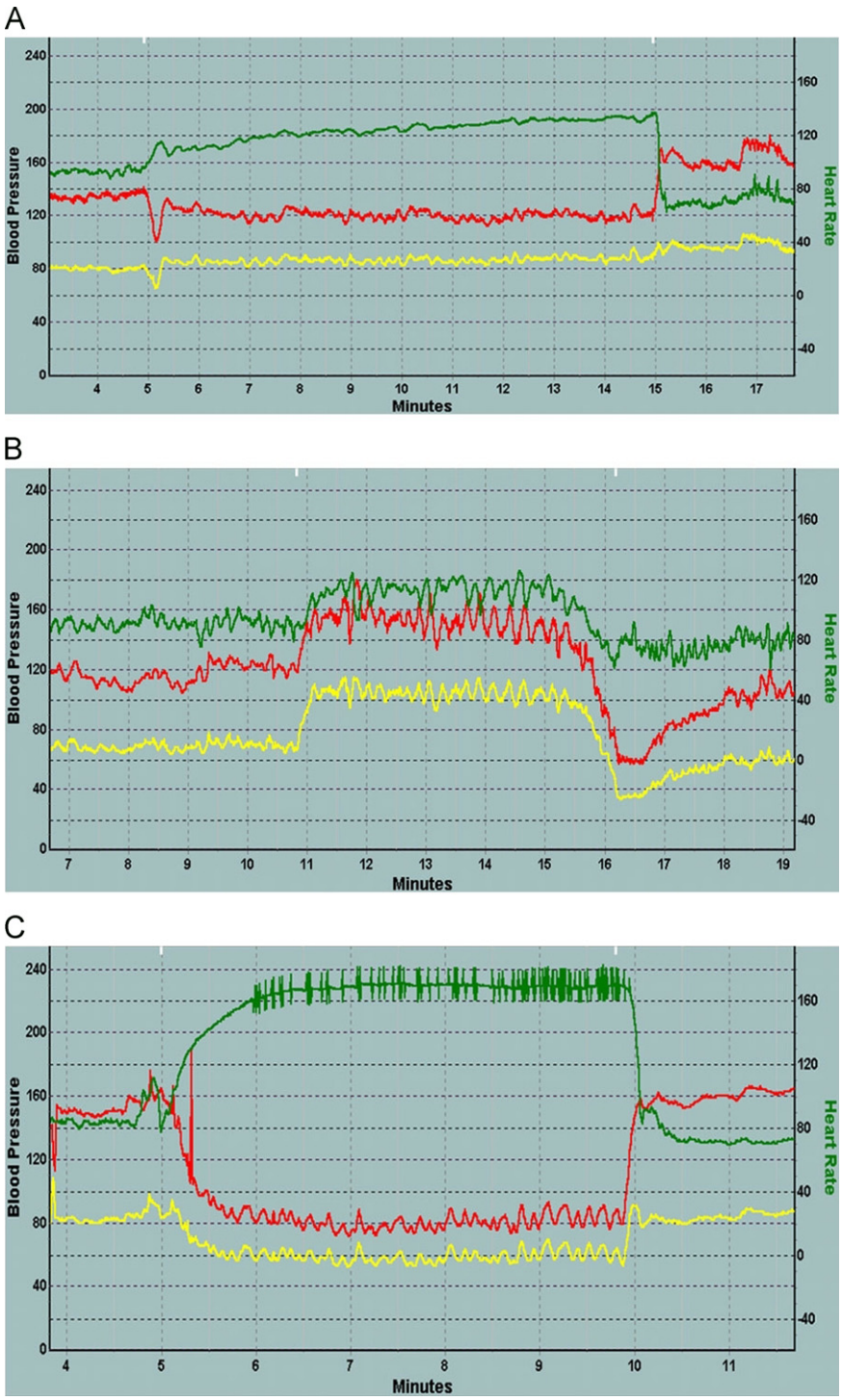

Figure 1 (A) Sustained tachycardia, narrow pulse pressure, and no hypotension in hypovolemic POTS during 10 minutes of 70° tilt. (B) Tachycardia, hypertension, oscillations in pulse, and blood pressure, followed by syncope in hyperadrenergic POTS. Tilt test stopped after 5 minutes. (C) Extreme tachycardia, hypotension, and narrow pulse pressure during 10 minutes tilt in POTS secondary to autoimmune neuropathy. (Courtesy of Dr. Phillip Low, Mayo Clinic)

of norepinephrine from sympathetic postganglionic neurons and vagal withdrawal via stimulation of medullary cardiovascular centers. The result is peripheral vasoconstriction, activation of leg muscle pump, and a mild increase in HR of 10-15 bpm. Diastolic BP may increase by up to 10 mmHg from peripheral vasoconstriction and systolic BP remains unchanged.[6,16] Prolonged standing beyond a few minutes inhibits the release of vasopressin, activates the renin-angiotensin system, and causes plasma loss into the tissues (up to 14% within 20 minutes after

standing up). The latter loss in plasma may cause a higher hematocrit in upright vs supine positions, up to a few percentage points.[17] A normal blood volume relative to vascular capacity is critically important for the maintenance of normal BP in the upright posture.

OI Syndromes

According to Wieling and van Lieshout, the orthostatic response upon quick standing in a few seconds from a supine position on the examination table can be divided into 3 stages while the subject is upright: the initial response (the first 30 seconds), the early phase of circulatory stabilization (1-2 minutes), and prolonged orthostasis (more than 5 minutes).[18] At Texas Children's Hospital we measure supine BP and HR at 5 minutes, then ask the patient to stand up and remain still with feet together and measure BP and HR again at 3, 5, 7, and 10 minutes of standing. We document any symptoms, their timing, and acral coldness or cyanosis. A careful review of history for various symptoms related to orthostatic dysfunction or excessive sympathetic activation and the active standing test allow clinicians to classify orthostatic syndromes accurately in most patients. More prolonged standing or tilt testing, or testing after exercise, heat stress, or food intake, may be needed in some patients.[4] There are 4 possible orthostatic syndromes:

1. Initial OH (IOH):
   This is perhaps one of the most common acute OI syndromes in otherwise healthy adolescents and young adults. It is characterized by complaints of feeling dizzy and lightheaded, seeing black spots, transient vision loss, and even presyncope or neurally mediated syncope (NMS) within 5-10 seconds after getting up to stand, especially after being supine for a while or arising from bed in the morning or from a squatting position. The symptoms disappear within 20-30 seconds without having to lie down.[16,18,19] Continuous BP monitoring while the subject arises is needed to document IOH. The diagnosis is based on a drop in systolic BP >40 mmHg or diastolic BP >20 mmHg or both within 15 seconds of standing up, with reproduction of OI symptoms upon standing up, along with absence of OH at 3 minutes of standing. Only an active standing test, not tilt testing, can detect IOH.[19]
2. OH:
   This is defined as a decrease in systolic BP of ≥ 20 mmHg or diastolic BP of ≥ 10 mmHg or both within 3 minutes of standing.[20,21] Acute OH is often due to hypovolemia and is usually associated with compensatory tachycardia, and may be associated with near syncope or syncope. Delayed OH does occur beyond 3 minutes of standing or tilt tests.[22] Chronic OH is rare in children and is a key feature of autonomic failure in adults with autonomic neuropathy, pure autonomic failure, multiple system atrophy, and Parkinson disease. Sustained tachycardia with OH and narrow pulse pressure (Fig. 1C) can be seen with secondary POTS.[12,23]
3. Excessive postural tachycardia and POTS:
   Documented sustained HR increment of ≥ 30 bpm in adults, or ≥ 35-40 bmp in children <19 years of age, and absolute HR of ≥ 120 bpm within 10 minutes of standing up, or tilt, with no or only modest hypotension (<30 mmHg drop in systolic BP), should be diagnosed as excessive postural tachycardia, not POTS (Fig. 1A).[3-9] Diagnosis of POTS is based on postural tachycardia plus chronic symptoms of OI and excessive sympathetic activation (Table 1).
4. Excessive orthostatic tachycardia with hypotension and syncope:
   Some patients may not tolerate the standing or tilt table tests, and develop a gradual drop in BP and start reporting symptoms of near faint, and the standing test or tilt test would have to be aborted (Fig. 1B). Most patients with recurrent NMS do not have POTS, and children with POTS never faint, rarely faint, or only have near fainting. It helps to think of NMS as an acute OI disorder in contrast to POTS, a chronic OI syndrome.[24] It is noteworthy that many of the principles of management of POTS are the same for treating NMS.

Diagnostic Criteria in Pediatric POTS

There is no consensus to date on the diagnostic criteria of pediatric POTS. This is a work in progress, given the absence of a gold standard diagnostic testing.

1. Chronic OI:
   Based on various published reports,[9,13,15,25] an essential criterion is chronic, frequent daily or near daily symptoms of OI for ≥ 3 months.

Table 1 Symptoms of Orthostatic Intolerance and Sympathetic Overactivation in Postural Tachycardia Syndrome

Orthostatic Symptoms
Dizziness and lightheadedness
Near faint
Blurred vision
Blackout or ''whiteout'' of vision
Weakness in legs
Poor concentration
Headache
Nausea
Sympathetic Overactivation
Palpitations
Chest pain
Migraine
Tremulousness
Anxiety
Pallor
Excessive sweating

2. Excessive postural tachycardia:
   This involves an excessive and sustained HR increment or absolute HR or both, within 10 minutes of standing or tilt. An increment of ≥30 bpm and absolute HR of ≥120 bpm are excessive at age ≥19 years. Published pediatric normative orthostatic HR data show higher values for orthostatic HR increments of either ≥35 bpm[5,6] or ≥40 bpm.[7-9] Moreover, a single study using tilt test found a cutoff absolute HR of ≥120 bpm in adolescents who were 13-19 years of age and ≥130 bpm for ages 6-13 years.[9] These pediatric studies lacked standardization of orthostatic tests and enrolled different range of ages of subjects in various countries and ethnic groups.
3. Absence of significant OH:
   There is either no OH in POTS or only modest OH (<30 mmHg systolic BP change). It is noteworthy that cutoff values for orthostatic BP are the same in children and adults (systolic BP ≥20 mmHg and diastolic BP ≥10 mmHg).[6,8]
4. Absence of reversible cause, such as medications.

Clinical Manifestations of POTS

Patients with POTS experience chronic and daily symptoms of OI and overactive sympathetic nervous system (Table 1). Additionally, they may have a myriad of other somatic symptoms,[11,26] including migraine,[27,28] nausea, abdominal pain,[29] widespread pain, cognitive dysfunction,[30] fatigue,[13,31] insomnia and nonrefreshing sleep,[32] sweating abnormalities,[10,26] vasomotor skin dysfunction, and poor exercise tolerance (Table 2). Moreover, anxiety, depression, and other psychiatric disorders add to the complexity of this syndrome and contribute to the disability and poor quality of life in patients with POTS.[33,34]

The prevalence of POTS in adults is estimated at 170 per 100,000,[1] and it is not known how many children and teens have POTS. It is most likely underrecognized because pediatric patients may not volunteer to report orthostatic symptoms. Moreover, orthostatic vital signs may not be checked or are measured inaccurately, with patients rising up from supine to sitting then standing positions, without adequate baseline supine BP and HR data, or after standing up for only 2-5 minutes.

Table 2 Frequency (%) of Nonorthostatic, Somatic, and Gastrointestinal Symptoms in 57 Adolescents With POTS Evaluated at Texas Children's Hospital

Chronic fatigue	79
Nausea	60
Sleep disorder	56
Sweating disorder	49
Migraine	46
Cognitive dysfunction	44
Abdominal pain	42
Chronic daily headache	30
Vomiting	26
Weight loss	26

Patients are typically females (4:1 ratio), in the age group of 12-40 years, mostly Caucasian, and have either acute or subacute onset of orthostatic and sympathetic activation symptoms (Table 1), with extreme fatigue even at rest and a feeling of low energy, with severe gastrointestinal (GI) dysfunction. There may be a history of prior infection with virus or rickettsia, trauma, surgery, or extreme athletic activity. Diagnosis of POTS is often delayed by 2 or more years. Most pediatric patients with POTS have a syndrome rather than a disease, in which no etiology is found in spite of extensive diagnostic testing. The pathophysiology of POTS varies according to dynamic physiological, neural, humoral, or fluid balance states, as well as possible genetic or acquired disorders. Patients with POTS may belong to one of several phenotypes based on mechanisms for potential pathophysiology, and these phenotypes may overlap:

1. Hyperadrenergic POTS:
   In addition to OI symptoms (Table 1), patients with this subset of POTS complain of prominent symptoms of sympathetic activation, such as palpitations, fast HR, chest pain, tremulousness, migraine-like headaches, anxiety, and vasomotor skin changes, including cold sweaty extremities. They have an increment of ≥10 mmHg in systolic BP within 10 minutes of standing up or tilt and an orthostatic plasma norepinephrine ≥600 pg/mL.[1,35] The magnitude of absolute orthostatic HR increment is often ≥120 bpm, and prominent oscillations in BP with tilt test are common (Fig. 1B). Compared with normal controls, supine BP is not different, but supine diastolic BP and HR are higher than controls.[36] Quantitative sudomotor axon test is typically normal. Hyperadrenergic outflow emanates from the brain and traverses baroreflex mechanisms.[37] Moreover, there is increased sympathovagal index and marked increase of HR response to isoproterenol.[1] Autonomic, sympathetic storms may occur in this subset of patients, with extreme rise in BP, anxiety, headache, and other features of sympathetic activation. Potential causes of this subtype are norepinephrine transporter deficiency,[38] pheochromocytoma,[39] mast cell activation disorders,[40] and baroreflex failure, which may result from trauma or irradiation to the neck.[41]
2. Hypovolemic and deconditioned POTS:
   Patients with POTS have reduced plasma volume. A study of 152 patients with POTS conducted by Thieben et al. estimated that nearly 30% had hypovolemia.[10] Venous pooling in the legs and mesenteric bed, during standing up or tilt, results in modest increments of HR to increase cardiac output (Fig. 1A). This redistribution of blood to the legs may be associated with postural swelling and edema in POTS.[42] Patients with hypovolemic POTS complain

of extreme chronic fatigue and fibromyalgia-type symptoms, with decreased exercise tolerance.[43]
Deconditioning may coexist with POTS as the primary etiological factor or may be secondary to POTS symptoms. There may be a preceding viral illness or trauma or surgery, followed by reduced physical activity and OI symptoms with marked somatic hypervigilance. An indirect marker for hypovolemia is a low concentration of urinary sodium (24-hour Na $<$ 100 mEq).
OI syndromes, such as POTS and NMS, are very common in children and adolescents with chronic fatigue and the 2 syndromes may overlap or share a common pathophysiology in a subgroup of patients.[13,33,44-46] Young adult female patients with POTS and chronic fatigue syndrome have higher markers for sympathetic activation.[47] A history of chronic fatigue in a child with syncope has a high positive predictive value pointing to NMS as the cause.[48] We found a high prevalence of low iron stores and mild anemia in patients with POTS and NMS,[25,49] as well as hypovitaminosis D in patients with POTS.[50] Similar observations were reported in adolescents with chronic fatigue and OI.[51] Prospective case control studies are needed to confirm these preliminary findings.

3. Neuropathic POTS:
Patients with this subtype of POTS have partial distal autonomic neuropathy, a length-dependent pattern affecting mostly longer fibers, with adrenergic and sudomotor denervation, especially in the distal legs. This is demonstrated on autonomic function tests as abnormal quantitative sudomotor axon test and thermoregulatory test, with distal anhidrosis, and abnormal Valsalva BP waves with loss of late phase II.[1] Further evidence supporting adrenergic denervation of the legs in POTS is an impaired norepinephrine spillover in the legs, with preserved response in the arm.[52] Modest delayed orthostatic reductions in systolic BP may occur in this subtype, with occasional prominent OH (Fig. 1C). Such cases should be considered a POTS with OH variant.
An acute or subacute autonomic neuropathy may be caused by autoimmunity, such is the case with autonomic ganglionopathy due to antibodies directed against the nicotinic ganglionic acetylcholine receptor.[23] Symptoms develop over days or few weeks and involve OH, significant GI dysfunction, sicca complex, bladder retention, and anhidrosis. This autoimmune disorder may be associated with cancer in adults.[53] This form of POTS is rare in children.[54]
4. POTS with joint hypermobility:
Joint hypermobility syndrome may be associated with autonomic dysfunction and is seen frequently in patients with POTS.[4,55,56] Hypermobility of joints can be measured using the Beighton score.[57] Genetics may play a role in this type of POTS, with significant family history.

Clinical and Diagnostic Evaluations

The most important part of the evaluation of patients with suspected POTS is a careful and detailed history. Exploring potential triggers at the onset, early manifestations at presentation, course of illness, various test results, intake of prescription and nonprescription drugs and other therapy, aggravating factors, nutritional and fluid intake, menstrual history, and psychosocial stressors and school history, is key to an effective understanding of this multisystem syndrome. Moreover, the history should include special attention to OI and document how severe it is and what the aggravating factors are. Further, a full autonomic nervous system review should help identify any symptoms and signs of autonomic neuropathy.

The physical examination is typically normal except for excessive postural tachycardia on active standing test. Data from a standing test and a careful history does help make the diagnosis of POTS in the majority of patients. Tilt table testing may be necessary to establish the diagnosis in some patients. Other clinical signs on examination include the presence of hypermobile joints with high Beighton score, Gorlin sign where the tongue may touch the nose, and lax and paper-thin skin.[4,57]

Diagnostic studies of suspected POTS should be guided by the medical history and findings on clinical examination. Initial testing includes complete blood count, serum ferritin, C-reactive protein, electrolytes, blood urea nitrogen, creatinine, glucose, 25-hydroxy vitamin D, thyroid-stimulating hormone and free T4, and plasma metanephrines in hyperadrenergic POTS, and an electrocardiogram. Further testing for Addison disease or a glucose tolerance tests should be done where appropriate. Tests for paraneoplastic autoantibodies, including ganglionic acetylcholine receptor antibody titers, should be considered in patients with neuropathic POTS, pandysautonomia, and severe GI dysautonomia. Measuring urine methyl histamine within 4 hours of a flushing episode helps diagnose mast cell activation disorder.[40] Further cardiac testing after a cardiology consultation may include echocardiography, exercise stress tests, tilt tests with use of medications to induce syncope, and electrophysiological studies including holter monitoring. Inappropriate sinus tachycardia and POTS may have overlapping clinical manifestations.[58] Neuroimaging is rarely useful in suspected POTS, but may be necessary depending on the clinical presentation, such as in suspected Chiari malformation or in intracranial hypotension from cerebrospinal fluid leaks. Referral to a gastroenterologist should be considered to help evaluate and manage severe GI dysfunction and gastroparesis. Genetic consultation may help in familial cases, such as POTS with hypermobile joints and Ehlers-Danlos syndrome.

Autonomic function tests provide valuable information in the evaluation of POTS.[26,59,60] These tests are described in greater detail by Dr Kuntz in this issue. Tilt testing with 60°-70° angle does generally yield similar

results to an accurately performed active standing test, unless the 2 tests are done on different days or times of the day,[61] after therapeutic interventions, or under different testing conditions (such as time of meals, exercise, heat, and medications), when the results may differ. Quantitative sudomotor axon reflex testing is abnormal in distal legs in nearly 2 of 3 patients with POTS, and distal anhidrosis is suggestive but not diagnostic of partial autonomic neuropathy.[1,26] Valsalva maneuver may show normal or reduced ratio (HR variability) and BP response may be normal or show an increased late phase II and phase IV in hyperadrenergic POTS. A markedly increased early phase II with absent late phase II and phase IV is seen in patients with OH due to autonomic failure, which may be seen in secondary POTS due to autonomic autoimmune neuropathy (Fig. 1C).[62] Sinus arrhythmia with deep breathing is preserved in most patients with POTS.

Other investigations may be considered. A 24-hour urinary sodium test is helpful to assess adequacy of fluid and salt intake, with a goal of 1500-2500 mL of urine and sodium excretion >170 mmol/24 h.[1,63] Measurements of norepinephrine while the patient is supine and after 15 minutes of standing help confirm a diagnosis of hyperadrenergic POTS.[37]

Treatment Guidelines

One of the important aspects of managing patients with POTS is an accurate diagnosis and elimination of secondary causes, such as medications. The available scientific evidence for treatment of POTS is based mostly on studies in adults, with case series and few nonrandomized, controlled trials. Pediatric POTS is a relatively new entity with heterogeneous clinical presentations, a wide spectrum of symptoms, varying degrees of disability, and premorbid comorbidities, such as migraine, attention deficit disorders, and anxiety. Moreover, family dynamics and ability of patients and parents to handle the challenges in treatment, and adaptation to functional disabilities and school attendance play an important role in effective treatment. Furthermore, a comprehensive initial clinical assessment should help identify possible somatic complaints and psychiatric comorbidity and cognitive dysfunction and prompt referral to appropriate other specialists in cardiology, gastroenterology, psychiatry, and gynecology. A multidisciplinary approach is needed to address a multisystem, severely disabling condition. Careful education of patients and their family is essential to any successful therapy, whether nonpharmacologic or pharmacologic. Therapy must be individualized according to the findings of clinical assessment and laboratory tests.

Nonpharmacologic Treatment

Therapy of OI with daily fluid intake increased to 2-2.5 L, salt intake of 4-5 g/d, healthy nutrition, avoidance of excessive standing and heat, raising the head of the bed by 10° (2-4 in), and a program of lower-body isometric exercises can be a great help as the initial management of POTS. Moreover, drinking 500 mL of water prior to rising in the morning rapidly helps raise the BP within 5 minutes and can further help patients with morning OI symptoms.[64] Patients with poor exercise tolerance and deconditioning may benefit from a progressive exercise program.[65] Reconditioning is very important in patients with hypovolemic POTS, and compression stockings or abdominal binder of 30-40 mmHg pressure may be helpful, however, most patients do not wear them. Some patients with POTS faint under certain conditions, such as prolonged standing in warm temperatures with relative hypovolemia. Physical counter maneuvers, such as crossing legs, stooping, squatting, and tensing muscles in the lower body can help abort an impending faint by reducing peripheral pooling of blood, which increases venous return to the heart and thus improves cardiac output.

Extreme fatigue can be a major symptom in POTS, and may be difficult to treat, because patients are "too tired" to exercise and "have no energy". Iron deficiency, with or without mild anemia, is common in POTS and iron supplementation may help improve fatigue and exercise tolerance.[25,49,66]

Pharmacologic Treatment

Given the multisystem complaints in POTS and the positive response to nonpharmacologic therapy in some patients, it is important to target major symptoms, such as OI and sympathetic overactivation for a trial of medications. There is currently no Food and Drug Administration–approved pharmacologic therapy in children with POTS. There are no longitudinal long-term follow-up data on any pharmacologic therapy in POTS. It is important to be careful when using sympathomimetic drugs, calcium channel blockers, phenothiazines, β-blockers, and tricyclic antidepressants, because patients with POTS may be oversensitive to these drugs and they may worsen OI. Thus, "start low and go slow," is good advice when using new medications in POTS.

Fludrocortisone acetate, a synthetic mineralocorticoid when administered at a low dose of 0.1-0.2 mg daily helps OI in hypovolemic POTS if increased salt and fluid intake are ineffective, by increasing the sensitivity of peripheral α-adrenergic receptors and promoting vasoconstriction. Higher doses (0.4 mg/d) are more likely to cause side effects with long-term therapy, such as hypertension, due to expansion of intravascular volume with retention of water and salt. Fludrocortisone may help improve chronic idiopathic nausea in children with chronic OI.[67] Fludrocortisone requires time to work, so 2 or more weeks should be allowed between dose increases. One side effect is hypokalemia and increased potassium intake in diet is encouraged.

β-Blockers may help improve orthostatic symptoms by blocking adrenergic dilator effects on veins. Low doses of propranolol, 10 mg daily, are recommended as initial therapy, titrating the dose up to 10 mg t.i.d.[1] Another option is using more β-selective blockers, such as metaprolol. β-Blockers are useful in hyperadrenergic POTS, once pheochromocytoma and mast cell activation are excluded as likely causes. Midodrine, an α-1 adrenergic agonist, is an effective therapy for OI in POTS. Saline infusion or midodrine improved the orthostatic tolerance with tilt.[68] A study of Chinese children with POTS found decreased symptoms with midodrine therapy to a greater extent than metaprolol, with or without conventional therapy.[69] Midodrine effects start within 30-60 minutes and last for 2-4 hours. It is given every 4 hours, but not after 6 PM (or less than 4 hours before sleep) to avoid supine hypertension. Other side effects include parasthesias (scalp tingling and itching) and goose bumps. Midodrine is useful in neuropathic POTS in combination with fludrocortisone. Starting dose is 2.5 mg b.i.d. or t.i.d. up to 10 mg t.i.d. Another medication that helps decrease hyperadrenergic effects in POTS, especially those with sympathetic storms, is the α-2 receptor agonist clonidine, which works by inhibiting central venous system sympathetic outflow.

Pyridostigmine, a cholinesterase inhibitor, increases orthostatic BP while the patient is standing without worsening the supine BP. Starting dose is 30 mg twice daily. Side effects are excessive cholinergic activity such as abdominal cramps and diarrhea.[70] Other therapies with anecdotal evidence for use in pediatric POTS include erythropoietin, octreotide, selective serotonin reuptake inhibitors, methylphenidate, serotonin-norepinephrine reuptake inhibitors (venlafaxine), and analog of vasopressin (desmopressin).

Patients with neuropathic type of POTS who are seropositive for autoimmune autonomic ganglionopathy or neuropathy may respond well to immunotherapy.[71] There are case reports of good treatment response to intravenous immunoglobulin followed by immunosuppressive combined therapy or plasma exchange. This is a new era in neuroscience and prospective, well-designed studies are needed. Moreover, patients who develop POTS following viral infections with neuropathic features and who test negative for known autoantibodies may be considered putative cases of autoimmune neuropathy and some centers choose to treat them with immunotherapy. There are no long-term follow-up data in pediatric or adult patients with POTS with respect to the efficacy of various interventions on quality of life or specific aspects of the syndrome, such as chronic pain, OI, fatigue, and gastroparesis.

Concluding Remarks and Future Research

Although chronic OI symptoms and excessive tachycardia upon standing up or tilt are the essential clinical features of POTS, they may represent only the tip of an iceberg of numerous symptoms. Other features, including sympathetic overactivation, somatic and GI dysfunction, widespread pain, and psychological complaints, may cause significant functional disability. Moreover, heterogeneity in presentation and pathophysiology and absence of any disease state in the majority of patients add to the complexity in evaluation and treatment of this chronic and potentially incapacitating syndrome.

POTS is common among adolescents and early diagnosis is key to starting effective nonpharmacologic and, if needed, pharmacologic therapy. Moreover, management should include education, empowering of patient, addressing physical, psychological, and social issues, and tailoring therapy to address the greatest needs first.

There are many questions surrounding pediatric POTS. First, a consensus should be reached on a diagnostic criteria and a classification paradigm. Second, defining the phenotype paves the way to multicenter, prospective, randomized clinical trials to evaluate short-term and long-term effectiveness and safety of pharmacologic and nonpharmacologic interventions targeting specific symptoms of POTS. Third, identifying the biological and behavioral basis for psychosocial and educational challenges would help us manage a major source of functional disability in POTS. Fourth, stratifying the diagnostic evaluation based on clinical presentations and subtypes would improve the yield of useful results. Finally, it is important to provide the patients and families with hope. We need more data on the long-term outcome in pediatric POTS. Outcome studies in adults show very good outcomes in the majority of patients.[10] Despite our limited scientific knowledge in pediatric POTS, whenever science fails compassionate care must prevail.

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