A Guide for Medical Professionals

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The Postural Tachycardia Syndrome (PoTS) is a disorder of the autonomic nervous system. Although PoTS can affect both sexes, it typically affects women age 15-50 years. Signs and symptoms include tachycardia, palpitations, syncope and pre syncope and a sense of anxiety on standing. There is a cross-over with reflex or vaso-vagal type syncope.

PoTS is defined as a sustained increase in heart rate of 30 bpm within 10 minutes of standing or upright tilt (during tilt table testing) or an increase of heart rate exceeding 120 bpm on prolonged standing. A heart rate increase of greater than 40 beats per minute is required for those aged 12-19. These findings should be associated with symptoms of orthostatic intolerance, such as dizziness, fatigue, sweating, nausea, palpitations. Other dysautonomic features may occur affecting digestion, bladder control, temperature regulation and stress response.

**Presentation**

- Normally affects people between ages of 15-50 years
- Mainly affects females with a ratio 5:1
- Symptoms differ from other causes of orthostatic intolerance, tending to present with significant symptoms of sympathetic activation
- Symptoms usually have lasted longer than 6 months

Patients frequently report their symptoms following:

- Viral illness
- Pregnancy
- Trauma / major surgery
- Ingestion of toxins
- Immunization
- Sepsis

In some patients more the onset is more insidious.
In younger patients, the symptoms, often present between the ages of 12-15 especially after growth spurts.

**Frequent symptoms**

- Palpitations, often on standing or sitting, sometimes can come on at rest
- Fatigue sometimes can be disabling
- Light-headedness / dizziness / blurred or tunnel vision / pre syncope
- Inability or difficulty performing physical exercises
- Tremulousness
- Weakness especially in the legs
- Syncope
- Loss of concentration / memory loss / brain fog
Other symptoms

- Chest wall pain
- Shortness of breath
- Gastrointestinal problems, lack of appetite, nausea, early satiation, bloating, constipation, diarrhoea, abdominal pain (often diagnosed with Irritable Bowel Syndrome)
- Headaches/ migraines. Often patients complain of muscular headaches associated with upright posture which begin in the occipital region of the skull and radiate to the shoulders- the ‘coathanger headache’
- Pain or coldness of legs, fingers/ ears
- Difficulty sleeping. Patients can complain of difficulty getting to sleep, waking suddenly with a racing heart and feeling wide awake or sleeping for hours and still feeling unrefreshed when they wake.
- Hyperhidrosis or loss of sweating
- Papillary symptoms – sensitive to glare
- Myofascial pain
- Neuropathic type pain
- Sense of anxiety. Many patients who have PoTS are told that their symptoms are due to panic attacks. The anxiety and hyperventilation often happens as a result of the symptoms above and the uncertainty of diagnosis and feelings of fear related to the symptoms. It is also thought that PoTS and orthostatic intolerance can alter breathing regulation leading to deeper respirations and hyperventilation.

PoTS can be secondary to the following conditions:

- Joint hypermobility syndrome / Ehlers Danlos Hypermobility type (most common)
- Chronic Fatigue syndrome/ME
- Lupus
- Fibromyalgia
- Diabetes
- Sarcoidosis
- Amyloidosis
- Alcoholism
- Chemotherapy (esp. with vinca alkaloids)
- Sjorgens syndrome
- Heavy metal poisoning
- Lyme disease

Symptoms are often exacerbated by extremes of temperature, exercise, after meals and during or around menstruation

Some of these symptoms can profoundly affect a patient’s quality of life, making it difficult to perform the simplest activities of daily living.
Differential Diagnosis

Obtain a detailed history, examination and general medical evaluation, and evaluation of joint hyper mobility using either the Beighton Hypermobility score or the Brighton criteria.

Identify conditions that may produce orthostatic intolerance- dehydration, anaemia, Addison disease or any other endocrinopathy including pituitary disease.

Measure lying and standing heart rate and BP (lying for 3 mins, standing at 2, 5 and 10 minutes). Observe for venous pooling in both the hands and feet whilst standing, which appears as a purplish discolouration.

Underlying aetiology

The cause of PoTS is not fully understood but researchers have made important observations that provide insights in to some of the mechanism involved in this condition.

Orthostatic intolerance is central to the diagnosis of PoTS and investigators have reported abnormalities in the physiological response to standing in affected individuals.

The action of moving from a lying or sitting position to a standing position causes a redistribution of 300-800ml of blood volume from the thoracic cavity and abdomen to the lower limbs. These gravity-related effects occur within seconds of standing and trigger a compensatory response mediated by the baro-receptor reflex pathway to restore the central blood volume and maintain blood perfusion to vital organs including the brain.

Baro-receptors in the carotid arteries and aorta, and volume and pressure receptors in the heart are activated during the early phase of standing and orchestrate a response by the nervous system and hormone producing cells.

The autonomic nervous system comprises of two balanced opposing groups of nerves: the sympathetic nerves and the parasympathetic nerves. These exert opposing effects on heart rate and peripheral vascular resistance.

In the early phase of standing in a normal individual the sensors trigger the sympathetic nervous system to constrict the blood vessels in the peripheries, thereby increasing the central blood pool and return of blood to the heart. At the same time the parasympathetic nerve stimulation is reduced, with the net effect of an increased pulse rate and cardiac output.

The autonomic nervous system also acts with other tissues to stimulate hormone production to counter the effects of standing and reduced central blood volume pool (hypovolaemia). One of the cascades of hormones involved in this response includes renin, angiotensin and aldosterone. The
main effects of the hormone response are to further promote constriction of the blood vessels and the retention of salt and water by the kidneys to the blood volume.

PoTS is characterised by a disturbance in the auto-regulatory responses described above. The disturbed response by the autonomic nervous system, termed dysautonmia, causes impaired constriction of blood vessels in the peripheries. The precise reason for this is not clear but researchers have discovered some patients with antibodies that attack the nerve endings and many others who demonstrate blood vessels, muscles and skin that are insensitive to sympathetic nerve stimulation.

In rare cases a genetic abnormality has been detected in a transporter protein at the nerve ending which recycles the chemical stimulator (noradrenalin) released by the nerve ending. Theoretically, failure to recycle this chemical reduces the nerve stores and the nerve loses the ability to stimulate downstream tissues. It is clear that if the sympathetic nerves are unable to stimulate constriction of the blood vessels then this may also disturb heat regulation and sweating of the hands or feet – symptoms also commonly observed with PoTS. Some researchers have found high levels of norephinerine in PoTS and others disruption of the autonomic nerves in the heart. Both of these may account for the excessive heart rate observed on standing in PoTS. The hormone cascade is also abnormal. In some patients’ lower levels of rennin, angiotensin (some subtypes) and aldosterone have been measured.

Other abnormalities have been detected in the context of PoTS and more are likely to be discovered. Only some of the causes are likely to be important in any single individual and it is unknown whether individuals with different groups of abnormalities or symptoms respond differently to the various available medical therapies.

**Classification**

**Primary PoTS**

**Partial dysautonomic / neuropathic PoTS**

There is preferential denervation of sympathetic nerves innervating the lower limbs. This can also be termed peripheral adrenergic failure

A partial dysautonomia could account for the warm dry feet (loss of sudomotor nerve), the gravity-dependent dusky skin (blood suffusion of the skin), the leg vein hyper-responsiveness to norepinephrine, the reduced galvanic responses, abnormal sweating of the extremities, the excessive orthostatic blood pooling, the tachycardia, and the reduced stroke volume seen in orthostatic intolerance.
**Hypovolaemic PoTS**
Some patients are intensely sensitive to salt intake and can fine-tune their plasma volume and BP control with salt alone.

**Central Hyperadrenergic PoTS**
In many cases the hyperadrenergic state of PoTS is secondary to partial dysautonemia or hypovolaemia. However, in some cases the primary underlying problem seems to be excessive sympathetic discharge. Patients have extremely high levels of upright norepinephrine. These patients have large increases in blood pressure on standing, indicating that baroreflex buffering is somehow impaired.

The symptoms include excessive palpitations, anxiety, tachycardia and tremulousness.

This form of PoTS is much less common than neuropathic PoTS and occurs in about 5-10% of patients. Therapy should be targeted at decreasing sympathetic tone centrally and peripherally.

A specific genetic abnormality has been identified with hyperadrenergic PoTS; this is a single point mutation in the norepinephrine transporter (NET). This results in an inability to adequately clear norepinephrine and produces a state of excessive sympathetic activation in response to a variety of sympathetic stimuli.

**Deconditioning PoTS**
Deconditioning is often present in patients with prominent fatigue and fibromyalgia type symptoms. Studies have shown that PoTS with deconditioning is similar to pure deconditioning and bed rest.

The combination of hypervigilance in these patients raise the possibility that in at least some PoTS patients there was an initial event or illness that evoked orthostatic symptoms and that the symptoms were then over interpreted and followed by reduced physical activity and deconditioning.

**Developmental PoTS**
This is a distinct form of partial dysautonomic PoTS and occurs in young people. The onset of symptoms is usually around the age of 14 years, and often follows a growth spurt. The majority of these patients are young women. Developmental PoTS can affect some patients so badly that they are severely disabled with it. Many patients will have urinary and gastrointestinal problems as well. However, the majority of the patients with this type of PoTS will eventually improve over time. Around 80% of patients recover by the time they are in their mid 20's.
PoTS secondary to other causes

PoTS like symptoms which occur due to other illnesses. The most common cause is Diabetes mellitus, but another important cause of secondary PoTS is Joint Hypermobility Syndrome (JHS). JHS is a genetic condition which means that there is a collagen or other connective tissue defect. This makes the joints hypermobile and the skin soft, almost velvet like. Patients can complain of varicose veins and a lot of patients complain of muscle and joint pain. Patients with JHS and PoTS tend to have earlier symptoms and have a significantly higher incidence of syncope and migraine.

Patients with JHS may have veins that are overly elastic and cannot maintain a good degree of vasoconstriction when a person stands. This causes venous pooling in the extremities with a compensatory tachycardia. It has been postulated that the venous pooling causes a secondary hyperadrenergic state or receptor dysregulation predisposing to autonomic dysregulation. Abnormal vascular reactivity within the cerebral vasculature is thought to be the reason for the association with migraine. Approximately 70-80% of patients with JHS may suffer form some form of dysautonomia related symptoms.

Investigations

The following tests should usually be undertaken:

**ECG** - to rule out presence of an accessory pathway or any other abnormality of cardiac conduction

**U&E’s, TFT’s, FBC**

**Ferritin** – as often low

**Vit B12 / folate** - rule out deficiency

**Basic Endocrine tests** including **Thyroid function testing**

**Short synacthen testing with ATCH to assess the adrenal axis**

**Echocardiography** – to exclude structural or functional heart disease

**24 hr Holter monitor** –

In order to ascertain that the palpitation symptom of PoTS are mediated by sinus tachycardia and not an arrhythmia; to determine mean heart rate and heart rate fluctuation due to any activity, and correlate any symptoms to rate and rhythm

Some patients may need additional heart rate monitoring with event recorders.

**CXR**
24hr urinary catecholamines and free metanephrines.
Used to exclude pheochromocytoma, this can be confused with PoTS especially in patients with Hyperadrenergic PoTS. Patients with pheochromocytoma are more likely to have symptoms when lying down.

24hr urinary sodium
This will provide documentation that the patient is taking sufficient fluids and sodium. The goal is a volume of 1,500–2,500 mL and sodium excretion of 170 mmol/24 hours. The latter indicates that the patient is taking adequate sodium and probably has a normal plasma volume.

Head up tilt table test (HUTT) and Active Stand Test
During the HUTT baseline measurements of heart rate and BP are taken whilst the patient is supine. The patient is then inclined to a 70-degree head up angle. BP and heart rate are measured continuously. This is a passive test, and the physiology is slightly different to active standing where the patient needs to support his or her own weight and maintain balance.

An Active Stand Test requires the use of the skeletal muscle pump and mimics real life.

Both HUTT and an Active Stand Test are sensitive for the diagnosis of PoTS with a 30 bpm threshold for orthostatic tachycardia; an active stand has a specificity of 79% compared to a tilt test of 23%.

Some centres offer plasma adrenaline levels that are taken before and during tilt, or simply on lying and standing to assist with the diagnosis of Hyperadrenergic PoTS. Supine norepinephrine is often high normal in subjects whilst supine but on standing can be elevated (>600pg/ml).

Some further tests may be performed:

Further autonomic function tests, including thermoregulatory sweat test typically show an intact or exaggerated autonomic reflex response.

Autonomic function tests usually show preserved vagal function and there is often a vigorous pressor response to the Valsalva manoeuvre.

Treatments

No therapy is successful in all patients with PoTS, and large-scale prospective controlled trial data is unavailable.

Initially efforts should be made to identify and treat any reversible causes.

Withdraw if possible any medications which may contributing to symptoms. Pharmacologic agents that may cause or worsen orthostatic intolerance:

- ACE inhibitors
• Alpha receptor blockers
• Calcium channel blockers
• Beta blockers (although some may be useful in the treatment of PoTS)
• Phenothiazines
• Tricyclic anti depressants
• Bromocriptine
• Ethanol
• Opiates
• Diuretics
• Hydralazine
• Drugs that decrease or block peripheral activities of SNS- Prazosin or reserpine/ ganglionic blockers
• Nitrates
• Sildenafil citrate
• MAO inhibitors
• L-dopa
• Methyldopa
• Barbiturates

If the patient has been immobile or bed-bound their symptoms may gradually improve with reconditioning to the upright posture.

Optimise treatment for any chronic condition.

If there is any evidence of re entrant tachycardia this must be treated

Radiofrequency of the SA node is not recommended

Educate patient about nature of disorder

Avoid aggravating factors

**Non pharmacological treatments**

• **Water** - at least 2-3 litres per day. Some studies have reported that drinking at least 400-500mls before rising in the morning can be helpful
• **Salt** at least 150-250 mEq daily
• **Compression stockings.** To deliver at least 30 mmHg of compression at the ankles. Anecdotally the use of abdominal compression in the form of ‘magic pants’ or ‘spanx’ pants can also be useful.
• **Sleeping with head of the bed elevated**
• **Countermanoeuvres.** Pumping calves before rising, using countermanoeuvres if feeling lightheaded or dizzy
• **Rising slowly** from a lying down to sitting or standing position
• **Exercise** - both aerobic and resistance training should be encouraged and has shown to be beneficial. It is important that patients start slowly and build up exercise tolerance as too much vigorous exercise can aggravate symptoms and then discourage patients from undertaking it.
It is recommended that the patient undertake aerobic exercise 3 times a week for 20 minutes at a time if they can tolerate it. Use of the recumbent bicycle or swimming may be better tolerated initially. Leg exercises (resistance) and use of ankle weights to build up muscles in legs will help the skeletal muscle pump.

- **Avoiding** – alcohol, recreational drugs. Some patients find avoiding caffeine helps with symptoms, some patients find having caffeine helps with symptom relief!
- **Keep cool**
- **Eat regular meals**

### Pharmacological treatments

**Beta blockers** – Often Labetalol 100-200mg twice daily is used. Other beta blockers may be tolerated by some patients.

Beta-blockers are usually used successfully in patients with Hyperadrenergic PoTS. The combined alpha and beta blocking agent labetalol (carvedilol can also be used) is often used. Pure beta blockers can exacerbate symptoms in hyperadrenergic PoTS, because of unopposed alpha receptor stimulation.

Beta blockers would not usually be used in patients with a PoTS reflex syncope overlap.

Side effects: low BP, slow heart rate, fatigue, CCF, impotence

**Clonidine** -0.1-0.4 mg twice daily

In the hyperadrenergic form of PoTS, patients often respond best to agents that block norepinephrine or its effects. Clonidine is an alpha 2 agonist which acts to inhibit sympathetic outflow; this can result in low blood pressure.

Side effects include dry mouth, slowed heart rate, low BP due to slowed heart rate, constipation, blurred vision.

**Fludrocortisone** - (50-200 mcg once daily Max dose can be up to 400 mcg daily)

Used with patients with partial dysautonomic PoTS and patients in whom hypovoleamia is known or strongly suspected. Fludrocortisone should expand plasma volume by enhancing sodium retention. It also appears to sensitize peripheral alpha adrenergic receptors to the patients own catecholamines.

It is important for the patient to carry on taking increased amount of salt and fluids and also to be aware that it will not work immediately, and the effects will last for a while after stopping the medication. Fludrocortisone can deplete potassium and magnesium and supplements may be required. Regular monitoring of U&E’s and magnesium is required.
Side effects: worsening headaches, depression, hypokalaemia, hypomagnesemia, acne and fluid retention. Numerous symptoms of sympathetic over activity can be enhanced.

**Ivabradine - 2.5 – 5 mg twice daily**
A sinus node blocker has reportedly helped some PoTS patients experience less symptoms. Ivabradine is sometimes used as an alternative to beta-blockers because it results in heart rate reduction without vasodilatation, sexual disturbances, or negative inotropic effects.

Side effects: muscle cramps

**Midodrine - 2.5 – 10 mg 3-4 times daily**
Alpha 1 agonist used for its vasoconstrictor properties in neuropathic PoTS.

It is taken 3, sometimes 4 times daily. Each dose should be taken 3-4 hours apart and the last dose no later than 3 hrs before bedtime. The effect is felt very soon after taking it, but is short lived. Patients usually start to feel the effects after about 20 minutes, the effects begin to wear off after 2.5 to 3 hours.

Midodrine needs to be taken with an increased salt and water intake.

Side effects: Piloerection, dilation of pupils, goose bumps, tingling, itching especially of the scalp, supine hypertension, nausea.

**Octreotide- 25 mcg bd or tds by subcutaneous injection (can be increased if necessary to 100-200 mcg tds)**
Usually given to patients who are refractory to other treatments, Octreotide is used for its potent vasoconstrictor effects.

Side effects: nausea, abdominal pain, muscle cramps, hypertension

**Slow sodium - 600mg once daily (10mg sodium)**
This is given to patients if they are unable to tolerate a higher intake of salt or the 24hr urinary sodium is low. The aim is to get the 24 hr urinary sodium to about 150- 170 mmol/24hrs

**Selective Serotonin Reuptake inhibitors (SSRI's)** Sertraline starting at 25mg od (other SSRIS may be used) or Serotonin Norepinephrine Reuptake Inhibitors (SNRI's) Venlafaxine and duloxetine
SSRI's are used because serotonin is the principal neurotransmitter used in autonomic control, in particular blood pressure. SSRI's are particularly useful in reflex syncope and have been useful in some patients with PoTS. There are reports that SSRI's are effective in treating the chest pain which is often associated with some patients with PoTS

Side effects: gastrointestinal upset, tremor, and sleep disturbance. Less common side effects include agitation and sexual dysfunction.
**Pyridostigmine** - Start dose of 30mg BD and titrate to 60-90mg tds if necessary

An acetylcholinesterase inhibitor that is thought to facilitate ganglionic neural transmission in both the sympathetic and parasympathetic nerves. The drug appears most effective in patients with postviral PoTS, as well as in those with PoTS secondary to an autoimmune disorder (such as lupus or Sjögren syndrome).

Side effects – Nausea, constipation, weakness