Dysautonomia: Getting a handle on POTS

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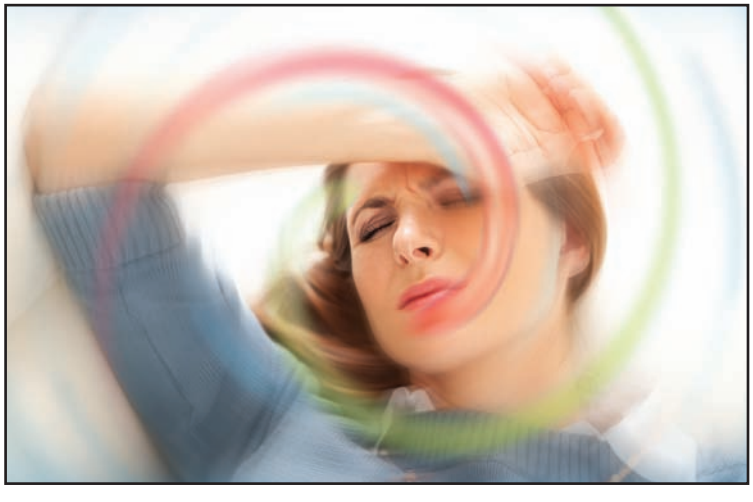
Orthostatic intolerance is a disorder that causes symptoms in patients when they stand up, which are relieved when they lay back down. A form of dysautonomia (autonomic nervous system [ANS] dysfunction), postural orthostatic tachycardia syndrome (POTS) is a disorder of chronic orthostatic intolerance. In dysautonomia, there's a problem that involves the sympathetic or parasympathetic components of the ANS. In POTS, there's an overreaction of the ANS, causing excessive tachycardia upon standing.

Patients with POTS experience a collection of symptoms that can have a significant impact on their daily lives. POTS affects women at a 5:1 ratio to men and the average age of diagnosis is between 20 and 40, usually due to misdiagnosis in the teenage years. Studies suggest that POTS effects one in 100 teens, but only about half of patients with POTS have an adult onset of the disorder.

Diagnosing and treating POTS can be frustrating. Patients are frequently misdiagnosed and may be given misleading information. Currently, there are only five academic centers that offer POTS fellowships for providers. This lack of education causes only a small number of physicians to be well versed in POTS management. It's been estimated that patients will wait more than 4 years and see more than seven providers before receiving the correct diagnosis, with 76% of them being misdiagnosed during this time. Timely and accurate diagnosis is the key to providing the appropriate education for patients with POTS to help them understand and cope with this disorder.



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How does it happen?

The ANS is responsible for the regulation of body functions that are automatic, such as heartbeat, breathing, digestion, BP, and temperature control. These functions are automatically controlled and fluctuate depending on a patient's circumstances. If there's a change in position, our ANS maintains our BP and heart rate by constricting the blood vessels in our lower body to compensate for the change. Our heart rate increases when we stand up, with the heart beating harder and faster due to the release of norepinephrine (the primary neurotransmitter in the sympathetic nervous system [SNS]). This increase in norepinephrine compensates for gravity that typically displaces blood downward. The brain will sense that it needs more blood flow due to the change in body position and signal the release of norepinephrine, increasing the heart rate and telling the blood vessels to tighten in the legs to push the blood back to the brain to prevent us from passing out (see

The orthostatic reflex). It's estimated that about one-third of our total blood volume is in our abdomen, buttocks, and lower extremities when standing.

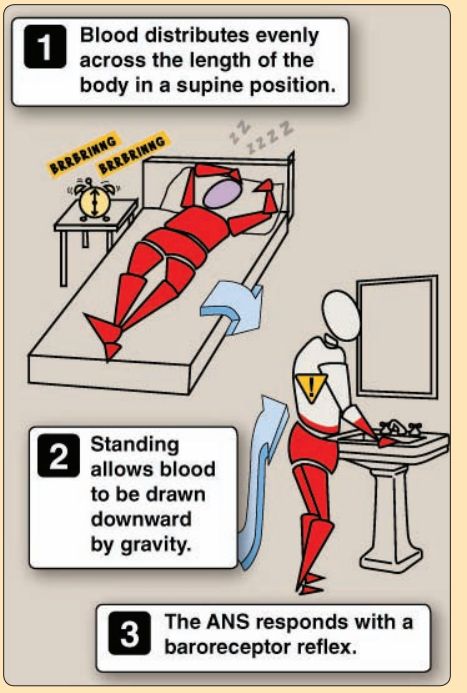
In POTS, this regulation of the ANS is abnormal. The blood will pool in the lower extremities, causing orthostatic intolerance. These patients have an exaggerated orthostatic tachycardic response, but they have an absence of orthostatic hypotension, which we normally think of in the case of hypovolemia. Patients with POTS will maintain or even increase their BP when standing. However, their heart rate increases too much, causing multiple symptoms that occur upon standing but improve when lying back down.

The literature suggests that dysautonomia is either disease-based or syndromic. Disease-based dysautonomia can affect the ANS either centrally, such as in Parkinson disease and multiple body system atrophy, or peripherally in the case of pure autonomic failure or in small fiber neuropathies (for example, with diabetes or other genetic, inflammatory, and immune system disorders). Syndromic dysautonomia includes POTS, reflex syncope, chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, gastroparesis, and interstitial cystitis.

Studies have shown that although POTS is considered a syndromic dysautonomia, about half of these patients also have small fiber neuropathy. There are different types of small fiber nerves, including sensory, sudomotor, and vasomotor. The small fiber vasomotor nerves help regulate blood vessel constriction. When these nerves are damaged, the blood vessels can't constrict. About half of patients with POTS have dysfunction of the sudomotor nerves, making this syndrome still not completely understood.

Some factors suggest that autoimmunity plays a role in POTS. The disorder occurs predominantly in female patients and those who have an increased rate of estrogen-dependent comorbidities. About half of patients with POTS have a post viral onset, and mast cell abnormalities are known to occur in the early phases of many autoimmune diseases. Mast cell activation syndrome is an immunologic condition in which mast cells inappropriately release chemical mediators in excessive amounts. Common triggers include foods containing high levels of histamines, temperature extremes, exercise, exertion, stress, and hormone changes. It's important to stick to foods that haven't been fermented; fresh, unprocessed foods have the lowest levels of histamines (see *Histamine-rich foods to avoid*).

The orthostatic reflex



Source: Preston RR, Wilson T. *Lippincott Illustrated Reviews: Physiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.

Primary or secondary

POTS has been classified as either primary or secondary. Primary subtypes include neuropathic POTS, hyperadrenergic POTS, and hypovolemic POTS.

Neuropathic POTS is associated with small fiber neuropathy. This peripheral denervation causes a less-than-normal norepinephrine release and less sympathetic activation in the lower extremities.

In hyperadrenergic POTS, there's excessive SNS activity and increased levels of norepinephrine. These patients may have a significant elevation in BP upon standing, suggesting that the baroreflex is impaired.

In hypovolemic POTS, the plasma and red blood cells (RBCs) are both low. The plasma volume is controlled by aldosterone and there may be a partial loss of sympathetic nerves in the kidneys, which may be the reason for low aldosterone.

All of these primary types have connections to the peripheral nervous system, including impaired volume control and irregular SNS activity.

Secondary POTS is related to another illness. Hypermobile Ehlers Danlos syndrome (hEDS) patients have been found to have more autonomic symptoms than other EDS types. In a few recent studies, it was found that 49% of hEDS patients were diagnosed with POTS and another 31% had orthostatic intolerance. Other diseases known to cause autonomic neuropathy and potentially secondary POTS include diabetes, Lyme disease, and autoimmune disorders such as lupus and Sjögren syndrome.

Signs and symptoms

POTS is often considered an "invisible illness." Some of the more obvious signs include swollen lower limbs after upright activity or a delay in capillary refill. Patients may have acrocyanotic legs after being in a dependent position caused by small blood vessel constriction, decreased blood flow to the skin, and possibly abnormalities in nitric oxide activity that lead to the legs having a dark reddish-blue color. They may have livedo reticularis—a mottled reticulated vascular pattern described as a lace-like purple discoloration of the skin—possibly due to blood vessel spasms or an abnormality of the circulation near the skin surface. Bier spots—a benign vascular abnormality characterized by white spots on the skin surrounded by pale halo erythema—may occur due to raised pressure caused by the small vein constriction.

Patients may experience cardiovascular symptoms, such as palpitations, shortness of breath, flushing, and lightheadedness or they may feel like they're going to pass out. They can have problems with gastrointestinal motility being either too fast, causing irritable bowel symptoms such as abdominal pain, cramping, and diarrhea, or too slow, with symptoms such as bloating, constipation, and even gastroparesis. They may be sensitive to heat or cold due to poor temperature regulation of the skin, resulting in increased or decreased sweating. Due to decreased cerebral perfusion, patients may have profound fatigue, brain fog, blurred vision, impaired memory, weakness, exercise intolerance, poor sleep quality, and migraines.

Gynecologic problems have also been noted in patients with POTS. Studies have shown that patients may experience endometriosis, uterine fibroids, ovarian cysts, and dysfunctional bleeding at a higher rate when compared with control patients.

As you can see, POTS presents with diverse symptoms that may limit a patient's ability to care for his or her family, work, or attend school.

Histamine-rich foods to avoid

- Smoked meats and those with high levels of preservatives, such as bacon, ham, and salami
- Pickled or canned foods, such as sauerkraut and kimchi
- Shellfish
- Eggplant
- Salted or canned fish, such as tuna or sardines
- Fermented grain in sourdough bread
- Nuts, such as peanuts, cashews, and walnuts
- Fermented soy products, such as miso and soy sauce
- Alcohol

Diagnosis

The diagnostic criteria for POTs are as follows:

- heart rate increase of greater than or equal to 30 beats/minute from supine to standing within 10 minutes (greater than or equal to 40 beats/minute for ages 12 to 19)
- the absence of orthostatic hypotension (defined as greater than or equal to a 20/10 mm Hg drop in BP within 3 minutes of standing)
- symptoms of orthostatic intolerance lasting 6 months or more
- symptoms exacerbated by standing and improved with recumbency
- absence of other overt causes of orthostatic symptoms or tachycardia.

Although several phenotypes of POTS have been found, it's important to keep in mind that these subtypes aren't distinct diagnoses but more characteristics of the syndrome. Many patients with POTS have several or all of these characteristics, and there's considerable subtype overlap. A simple test to categorize patients doesn't exist.

The tilt table test, which measures heart rate and BP during posture and position changes, is considered the gold standard of testing for POTS. Blood and urine tests can help rule out other causes that may mimic POTS. Blood volume studies to determine hemodynamic status and an autonomic breathing test to measure how the heart rate and BP respond during exercise may also assist in diagnosis. Lastly, a quantitative sudomotor axon reflex test is a thermoregulatory sweat test that can be used to determine if autonomic neuropathy exists.

Pharmacologic management

Currently, there are no FDA-approved treatments specifically for POTS. However, several medications can be used to decrease symptoms.

Blood volume expanders have been used with reasonable success in patients with POTS. Fludrocortisone is a mineralocorticoid that enhances renal sodium reabsorption in the distal tubules of the kidneys to expand blood volume. Desmopressin and erythropoietin are also used to increase blood volume. Desmopressin has been shown to reduce tachycardia but may cause hyponatremia. Erythropoietin is used to increase RBC mass and may also stimulate vasoconstriction in patients with POTS. Outside of the potential vascular complications, such as stroke and myocardial infarction, erythropoietin is costly and requires injection, which makes its use less attractive. Intermittent I.V. saline infusion is another option, but again involves cannulation and infusion, making it cumbersome for patients. It may be effective with acute symptoms to prevent hospitalization.

Vasoconstrictors such as midodrine may improve venous return and decrease reflex tachycardia. Octreotide is a somatostatin analog that works by causing vasoconstriction in mainly the splanchnic circulation. It may help maintain venous return in patients with POTS when standing, as well as prevent the compensatory increase in heart rate.

The beta-blocker propranolol is helpful in lower doses for symptom control by decreasing the heart rate and reducing acute symptoms. However, adverse reactions of beta-blockers include an increase in fatigue and dizziness. A less-is-more approach is better tolerated by patients with POTS.

The use of the extended-cycle birth control pill ethinyl estradiol and levonorgestrel has shown promise in teenagers with gynecologic comorbidities by limiting their periods and estrogen fluctuation to just four times a year.

Nonpharmacologic management

Several treatment measures exist to manage POTS without medication, such as increasing fluid intake to 2 to 3 L/day of nonsugary, caffeine-free drinks. Increasing salt intake to an average of 10 g/day is also helpful because many patients have low urinary sodium levels. Salt and fluid will increase circulatory volume and BP.

on the web

Dysautonomia International:
www.dysautonomiainternational.org/page.php?ID=30

Genetic and Rare Diseases Information Center:
https://rarediseases.info.nih.gov/diseases/9597/postural-orthostatic-tachycardia-syndrome

POTS UK:
www.potsuk.org

Vanderbilt Autonomic Dysfunction Center:
www.vumc.org/adc/38847

The use of medical compression devices, such as abdominal binders or those that cause compression in the calf and thighs, is helpful to decrease blood pooling in the lower extremities. Also, instruct patients to avoid sudden movements and prolonged periods of standing that cause lower extremity blood pooling and aggravate POTS symptoms.

Seated or supine exercises, such as rowing machines, recumbent cycling, and swimming, three times per week can help improve stroke volume and decrease tachycardia. Patients with POTS need frequent rest periods and should gradually increase their exercise intensity. Also, limiting activities that require the arms to be raised above the head may help reduce tachycardia.

Avoiding triggers is beneficial for symptom management. The use of cooling vests and avoiding heat and hot showers are suggested to limit vasodilation. Large meals may increase symptoms as blood flow is diverted to the gut, causing nausea and anxiety related to SNS activity. Smaller, more frequent low-carb, high-protein meals are suggested. Good sleep habits can make a significant difference in overall fatigue levels. Symptoms of orthostatic intolerance tend to be more severe in the morning, so getting a good night's rest may help.

A helping hand

You can have a significant impact by increasing your own knowledge about POTS. Help your patients with POTS by educating them about their illness. POTS can be scary, and most patients become hypervigilant when symptomatic. This increased stress and anxiety, along with their overall symptoms, can affect their quality of life. Remember that some patients have spent years trying to find the reason behind their symptoms. Early identification is key to the successful management of POTS. ■

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