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The Postural Tachycardia Syndrome: A Concise Guide to Diagnosis and Management

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Introduction

During the last 20 years, there has been a tremendous growth in our knowledge of disorders that affect the autonomic nervous system. While at first these investigations centered on neurocardiogenic syncope, a subgroup of patients was identified who suffered from a similar, yet distinct, disorder manifested by postural tachycardia and exercise intolerance. This disorder is now referred to as the postural tachycardia syndrome (POTS) and encompasses a heterogenous group of disorders that share similar clinical characteristics.[1] The aim of this brief report is to outline the clinical picture, subtypes, diagnosis, and management of POTS.

Definitions

The hallmark of these disorders is orthostatic intolerance, defined as the provocation of symptoms on standing, which are relieved when becoming supine. Patients often relate complaints of palpitations, exercise intolerance, fatigue, lightheadedness, tremor, headache, nausea, near syncope, and syncope.[2] Patients may be severely limited as activities such as housework, bathing, and even meals may exacerbate symptoms. Recent studies have shown that many patients with POTS may suffer the same degree of functional impairment as patients with chronic obstructive pulmonary disease or congestive heart failure, yet these patients are often misdiagnosed as having chronic anxiety or panic disorder.[3] A grading system for the severity of orthostatic intolerance (similar to that for heart failure) has been developed (Table 1).

At present POTS is defined as the presence of orthostatic intolerance symptoms associated with a heart rate increase of 30 beats/minute (or a rate that exceeds 120 beats/minute) within the first 10 minutes of standing or upright tilt, which is seen in the absence of other chronic debilitating disorders, prolonged bed rest, or medications that impair vascular or autonomic tone.[3] It should be noted that many patients with orthostatic intolerance will not have orthostatic hypotension (a fall of >20/10 mmHg); rather there may be only a small drop in blood pressure, and no change or even a small increase in blood pressure upon assuming an upright posture. It has been pointed out that this focus on heart rate may overlook other autonomic symptoms such as disturbances in bowel function, sweating, and thermoregulatory function.

Classification

As was alluded to before, POTS is a group of different disorders associated with similar clinical manifestations. POTS is classified as being either primary or secondary. The primary forms are idiopathic and not associated with other diseases. The secondary forms occur in association with a known disease or disorder. Proper recognition of subtypes is essential in management[4] (Fig. 1).

The most common primary form of POTS is called the "partial dysautonomic" (PD) form.[1-3] These patients seem to suffer from a mild type of peripheral autonomic neuropathy characterized by an inability of the peripheral vasculature to constrict in the face of orthostatic stress. This causes a much greater than normal degree of blood pooling in the dependent areas of the body when upright, which in turn causes a compensatory increase in heart rate and contractility that attempt to maintain cerebral perfusion at constant levels. While this increase in heart rate and contractility may initially be fully compensatory, the degree of peripheral venous pooling may continue to increase over time and exceed this compensatory effect. These individuals then become increasingly dependent on their skeletal muscle pump to maintain adequate blood pressure until increased venous pooling exceeds its compensatory effects as well. There is a 5:1 female-to-male ratio. Many patients will report the abrupt onset of symptoms after a febrile illness (presumed viral), as well as after pregnancy, immunizations, sepsis, surgery, or trauma. It is currently felt that this form of POTS has an immune-mediated pathogenesis. Studies have demonstrated serum autoantibodies to alpha$_3$ acetylcholine receptors of the peripheral autonomic ganglia in patients with postviral autonomic neuropathy.

A second type of partial dysautonomic POTS (which we term "developmental") seems to afflict adolescents.[5] Onset is usually around 14 years, often following a period of very rapid growth. Symptoms progressively worsen and frequently reach their peak around age 16. Symptoms of orthostatic intolerance (and often severe headaches) may be of such intensity that the patient may be functionally disabled. Symptoms will then slowly start to fade over the ensuing years such that by young adulthood (19–24 years old) roughly 80%

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TABLE 1
The Grading of Orthostatic Intolerance*

Grade 0
Normal orthostatic tolerance
Grade I
Orthostatic symptoms are infrequent or occur only under conditions of increased orthostatic stress
Subject is able to stand >15 minutes on most occasions
Subject typically has unrestricted activities of daily living
Grade II
Orthostatic symptoms are frequent, developing at least once a week
Orthostatic symptoms commonly develop with orthostatic stress
Subject is able to stand >5 minutes on most occasions
Some limitation in activities of daily living is typical
Grade III
Orthostatic symptoms develop on most occasions and are regularly unmasked by orthostatic stresses
Subject is able to stand for >1 minute on most occasions
Patient is seriously incapacitated, being bed- or wheelchair-bound because of orthostatic intolerance
Syncope/presyncope is common if patient attempts to stand

*Symptoms may vary with time and state of hydration and circumstances. Orthostatic stresses include prolonged standing, a meal, exertion, and head stress.

are asymptomatic. The etiology is unclear but appears to reflect a transient period of autonomic imbalance that occurs in rapidly growing adolescents.

The second (and less common) form of primary POTS is referred to as the "hyperadrenergic" form. These patients tend to report a gradual and progressive onset of symptoms as opposed to an abrupt onset. Hyperadrenergic POTS patients report significant tremor, anxiety, and cold sweaty extremities when upright. Many will report a significant increase in urinary output after being upright for even a short period of time, and over half suffer from true migraine headaches. The hallmark of this form of POTS is that in addition to orthostatic tachycardia they will often display orthostatic hypertension, as well as exaggerated response to isoproterenol infusions. As opposed to the PD POTS patients, the hyperadrenergic patients have significantly elevated serum catecholamine levels with serum norepinephrine levels >600 ng/mL. There is often a family history of this disorder. Currently, hyperadrenergic POTS is felt to be a genetic disorder, in which a single point mutation produces a dysfunction of the reuptake transporter protein that clears norepinephrine from the intrasynaptic cleft. This in turn leads to excessive degree of norepinephrine serum spillover in response to a variety of sympathetic stimuli thereby producing a "hyperadrenergic" state that appears similar to a pheochromocytoma.

The term secondary POTS is used to describe various conditions that produce peripheral autonomic deinnervation but with sparing of cardiac innervation. The most common form of secondary POTS is chronic diabetes mellitus; however, it also occurs in conjunction with amyloidosis, sarcoidosis, alcoholism, Lupus, Sjogren's Syndrome, heavy metal intoxication, and following chemotherapy (especially from the vinca alkaloids).

A recently recognized and important cause of secondary POTS is due to the connective tissue disorder known as the joint hypermobility syndrome (JHS). An inherited condition, it is characterized by joint hypermobility, connective tissue fragility, and soft "velvety" skin with variable amounts of hyperextensibility. The condition is also associated with easy bruising, premature varicose veins, diffuse muscle and joint pain, and orthostatic acrocyanosis. Orthostatic intolerance develops in these patients due to the presence of abnormally elastic connective tissue in the vasculature, which results in an increase in vessel distensibility in response to the augmented hydrostatic pressure that occurs during orthostatic stress. This leads to excessive peripheral venous pooling with a resultant compensatory tachycardia. Recent studies have suggested that up to 70% of patients with hypermobility syndrome may suffer from some form of orthostatic intolerance. Adolescents with the developmental form of POTS frequently have been noted to have features of JHS. Studies are currently under way to better elucidate this potential relationship.

POTS may also be the presenting form of more severe autonomic nervous system disorders such as pure autonomic failure or multiple system atrophy. POTS may also present as a paraneoplastic syndrome seen in association with adenocarcinomas of the lung, breast, ovary, and pancreas. Current investigations have shown that these tumors produce

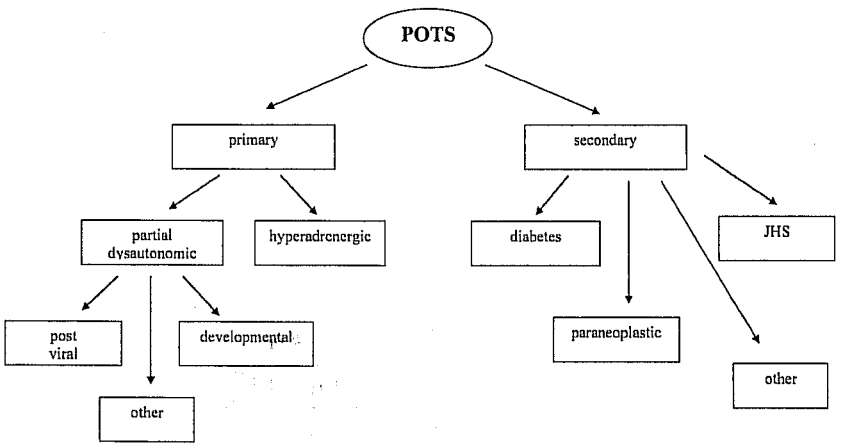

Figure 1. *Subtypes of postural tachycardia syndrome. POTS = postural tachycardia syndrome; JHS = joint hypermobility syndrome.*

autoantibodies against acetylcholine receptors in the autonomic ganglia similar to those seen in the postviral syndromes.

Evaluation and Management

The most critical aspect of evaluation is the history. Elicit information about the onset of symptoms. Were they sudden or gradual? Were there any events associated with onset? What makes symptoms worse or better? Are other family members affected? Does the patient have gastrointestinal, sudomotor, or thermoregulatory problems? Are migraines also a problem?

A careful physical exam is also critical. Blood pressure and heart rate need to be taken in the supine, sitting, immediate standing, and at 2-, 5-, and 10-minute intervals. Ideally, the lower extremities should be watched for the development of a mottled bluish discoloration (acral cyanosis) that suggests peripheral venous pooling. Because the results obtained during standing are quite variable, we usually perform tilt table testing on most patients, as this setting is more controlled with fewer variables and with more reproducible results (in our experience better than that seen with neurocardiogenic syncope). Other tests of autonomic nervous system function may be useful in select POTS patients as a way of measuring the degree of systemic autonomic involvement. Sudomotor function can be determined by thermoregulatory sweat testing or by assessment of skin conductance, skin resistance, or sympathetic skin potentials. Serum catecholamine levels, both in the supine and upright positions, should be obtained in patients suspected of having the hyperadrenergic form of POTS. Bowel motility studies are useful in ascertaining the degree of gastrointestinal involvement present. More detailed descriptions of autonomic testing can be found elsewhere.[1]

Treatment is based upon subtype but must be individualized to the needs of each patient. Any drug the patient is taking that could contribute to the condition should be stopped if possible (Table 2). Any underlying condition that may be causing POTS should be identified and treated (i.e., sarcoidosis). All patients should be encouraged to begin a program of reconditioning working toward a goal of performing at least 20–30 minutes of aerobic activity three times a week. In addition, we encourage resistance training of the lower extremities to augment the effectiveness of the skeletal muscle pumps. Fluid intake of 2 L a day of water and 3–5 grams of salt per day are encouraged in all but the patients with the hyperadrenergic form of POTS. Compression hose can be helpful but must provide 30 mmHg pressure and be waist high to be effective.

Pharmacotherapy is initiated with the goal of getting patients well enough to pursue reconditioning. No drug is currently approved by the US FDA for the treatment of POTS; therefore, any use of pharmacotherapy is done "off label." Knowing the subtype is important in choosing appropriate pharmacotherapy (Table 3).

In the partial dysautonomic POTS, patient therapy is directed at augmenting fluid volume and increasing vascular resistance. We often begin with fludrocortisone, a mineral corticoid that promotes sodium and fluid retention, and also sensitizes peripheral alpha adrenergic receptors. The drug appears to be most helpful in younger patients. Usually, 0.1–0.2 mg daily is employed (never exceed 0.4 mg orally each day as adrenal suppression may occur). Next, we add a vasoconstrictor such as midodrine, starting at 5 mg orally three times a day. Dosages can be titrated up to 15–20 mg orally four times a day, if necessary. Since patients are most symptomatic early in the morning, we often advise patients to take their midodrine dose approximately 15 minutes prior to getting out of bed. We also advise patients that they can take an extra 5 mg dose as needed if severe breakthrough symptoms occur. The most common problems encountered with midodrine are nausea, "goose bumps," and scalp itching. If midodrine is not tolerated methylphenidate can be an effective alternative, especially because it comes in several long-acting preparations. Some investigators have also advocated the use of yohimbine.

If patients continue to be symptomatic, we add either a serotonin reuptake inhibitor (SSRI) or a norepinephrine reuptake inhibitor. While the SSRIs are very useful in the prevention of neurocardiogenic syncope, the norepinephrine reuptake inhibitors are somewhat more helpful in POTS patients. We usually employ bupropion in the XL form starting at 150 mg orally each day and titrating to 300 mg XL daily, if necessary.

Of all the currently available SSRIs, we have noted that those with combined serotonin and norepinephrine reuptake inhibition (such as venlafaxine and duloxetine) are often the most effective. Tolerance for these agents is usually good (approximately 80%) with the most common side effects being gastrointestinal upset, tremor, and sleep disturbance. Less common side effects include agitation and sexual dysfunction. We will on occasion combine an SSRI with bupropion to achieve the same type of combination effect. A very promising new therapy is pyridostigmine, an acetylcholinesterase inhibitor that facilitates neural transmission at the ganglionic level of both sympathetic and parasympathetic nerves. The drug is particularly useful in postviral POTS patients as well as patients with POTS secondary to a primary autoimmune disorder (such as Sjogren's syndrome or Lupus). The starting dose is 30 mg orally twice a day, titrating to 60 mg orally twice daily, if necessary.

In severely affected patients, where other forms of therapy have either been poorly tolerated or ineffectual, we employ the drug erythropoietin. Originally developed for the treatment of anemia, it is also a potent vasoconstrictor that is quite useful in the treatment of orthostatic disorders.

Due to the fact that erythropoietin (EPO) has to be administered by subcutaneous injection and because of its

TABLE 2

Pharmacologic Agents That May Cause or Worsen Orthostatic Intolerance

Angiotensin-converting enzyme inhibitors
Alpha receptor blockers
Calcium channel blockers
Beta blockers
Phenothiazines
Tricyclic antidepressants
Bromocriptine
Ethanol
Opiates
Diuretics
Hydralazine
Ganglionic-blocking agents
Nitrates
Sildenafil citrate
MAO inhibitors

MAO, monoamine oxidase.

TABLE 3
Therapeutic Options in POTS

Treatment	Application	Form Effective in	Problems
Reconditioning	Aerobic exercise 20 min 3 times/week	PD, H	If too vigorously done may worsen symptoms
Hydration	2 liters po/day	PD	Edema
Salt	2–4 grams/day	PD	Edema
Fludrocortisone	0.1–0.2 mg po q day	PD	Hypokalemia, hypomagnesemia, edema
Midodrine	5–10 mg po tid	PD	Nausea, scalp itching, supine hypertension
Methylphenidate	5–10 mg po tid	PD	Anorexia, insomnia, dependency
Bupropion	150–300 mg XL/q day	PD, H	Tremor, agitation, insomnia
SSRI-Escitaloprim	10 mg po/day	PD, H	Tremor, agitation, sexual problems
Pyridostigmine	30–60 mg po bid	PD	Nausea, diarrhea
Erythropoietin	10,000–20,000 i.v. sq q week	PD	Pain at injection site, expensive
Octreotide	50–200 micrograms sq tid	PD	Nausea, diarrhea, gallstones
Clonidine	0.1–0.3 mg po bid 0.1–0.3 mg patch q week	H	Dry mouth, blurred vision
Labetalol	100–200 mg po bid	H	Fatigue

PD = partial dysautonomic; H = hyperadrenergic; POTS = postural tachycardia syndrome.

considerable expense, we normally reserve its use to patients who have proven refractory to or intolerant of other forms of therapy. Prior to starting EPO, a complete serum blood count (CBC) as well as a serum iron, total iron binding capacity, and ferritin level should be obtained. EPO can be employed as long as the hematocrit (HCT) is less than 50. The usual starting dose is 10,000 units injected subcutaneously once weekly. It usually takes 4–6 weeks to see the full effect of a particular dose amount. While the red cell augmentation effect and the hemodynamic effect are independent, they tend to rise in parallel. Patients appear to achieve the best hemodynamic effect when the HCT is in the low to mid-40 range. Once EPO therapy is initiated, a CBC should be checked monthly to assure that the HCT does not exceed 50. If the HCT on EPO therapy goes over this amount, we usually have the patient skip doses until it drops below 50, and then restart EPO at a lower dose (in a manner not dissimilar to the way warfarin is managed with respect to the international normalized ratio [INR]). The most common complaint of patients on EPO therapy is pain at the injection site. This can be minimized by allowing the EPO (which is kept refrigerated) to warm prior to injection. One way to do this is to roll the vial between the hands until it becomes warm. An additional way to minimize injection discomfort is to place an ice cube on the injection site 3–5 minutes before use; alternatively, a lidocaine patch or cream can be applied 15–30 minutes before use. Many patients will require supplemental oral iron for EPO to have its best effect. If no clinical improvement is seen from the starting EPO dose after 4–6 weeks, the weekly dose can be increased to 20,000 units. We have rarely had to exceed this dose in POTS patients. A rare complication of EPO therapy is that the patient can develop a "serum sickness" like reaction to EPO, characterized by fever, chills, nausea, and a general sense of malaise. We have only seen this occur in a handful of patients over the last 12 years; it resolves promptly after the agent is discontinued.

Another potential therapy is the somatostatin analog octreotide, which has potent vasoconstrictive effects. It is administered by subcutaneous injection starting at 50 μg subcutaneously 2–3 times a day; dosages may be titrated up to 100–200 μg three times a day. A long-acting injectable form (lasting weeks) has also been developed. While some PD POTS patients may benefit from small doses of beta blockers (i.e., metoprolol 25 mg orally once or twice daily), the majority tend to feel worse on these agents.

The hyperadrenergic form of POTS is best treated by agents that block the release of norepinephrine or block its effects. Clonidine is often useful in these patients, starting at 0.1 mg a day and titrating upward. The patch form of the agent is particularly useful as it provides a steady level of the drug for up to a week at a time. Labetalol is often effective, due to its alpha and beta blocking effects. Dosages of 100–400 mg orally twice a day may be employed. Methyldopa is also helpful in select patients. Both the SSRIs and the norepinephrine reuptake inhibitors have been helpful in controlling patients' symptoms.

It is important to differentiate between patients with POTS and those suffering from inappropriate sinus tachycardia (IST). There are similarities between the hyperadrenergic form of POTS and IST. Clinical presentations are similar and IST appears to be more common in women. Both conditions display an exaggerated response to isoproterenol infusion and some investigators have suggested that they may represent different aspects of the same disease process. POTS patients, however, display a greater degree of postural change in heart rate and the supine (resting) heart rate rarely exceeds 100 beats/minute (as opposed to IST where the resting heart rate is often more than 100 beats/minute). In addition, IST patients tend not to display the same degree of postural change in serum norepinephrine levels as those seen in hyperadrenergic POTS patients. The differentiation between POTS and IST is important as radiofrequency catheter ablation of the sinus node can make PD POTS patients markedly worse, and rarely seems to benefit patients with hyperadrenergic POTS.

In the secondary forms of POTS, therapy is first directed at correcting the underlying disorder to as great an extent possible. Patients with diabetes mellitus or JHS-related POTS are treated as peripheral dysautonomic POTS. Patients with POTS secondary to sarcoidosis or amyloidosis may also benefit from steroid therapy. Paraneoplastic POTS patients often respond well to pyridostigmine, and symptoms often resolve with treatment of the malignancy.

It should be remembered that patients suffering from POTS may experience an inability to pursue normal employment or educational opportunities and often suffer significant

psychosocial disruption. Patients frequently require the services of psychologists, social workers, and lawyers to address these aspects of their illness. The attitude of the treating physician is crucial. Hope is a powerful medicine that should be encouraged by all.

Prognosis

There is only limited data available at present on the prognosis of POTS patients. We are still in the process of following patients and analyzing their outcomes. Nonetheless some general trends have been noted. In patients suffering from postviral onset POTS, roughly one-half will make a good practical recovery over a 2–5 year period. Here, we define recovery as the relative absence of orthostatic symptoms with the ability to perform the normal activities of daily living with little or no restriction. However there are some patients that will not enjoy this degree of recovery and occasionally patients experience a progressive decline in functional status over time. In general, the younger the patient the better the prognosis. In adolescents with the "developmental" form of POTS, approximately 75% will experience a significant recovery by the time they are in their early to mid-twenties. The vast majority of patients (~90%) will respond to a combination of physical therapy and pharmacotherapy. Patients with the hyperadrenergic form of POTS usually require treatment indefinitely. The prognosis of patients with the secondary POTS syndromes is usually determined by the prognosis of the underlying causative disorder.

Summary

The postural tachycardia syndrome is a heterogenous group of disorders that disturb normal autonomic control. Successful treatment is often dependent on identifying the subtype and pursuing a comprehensive treatment program.

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