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Blair P. Grubb, MD

Case Presentation: A 34-year-old woman had been well until 9 months previously when, after a febrile illness, she developed palpitations, fatigue, exercise intolerance, dyspnea on exertion, and frequent episodes of lightheadedness and near syncope. ECG, echocardiogram, and endocrine evaluation were all normal. On physical examination, she displayed a postural increase of 35 bpm on standing, along with a 15-point fall in diastolic blood pressure.

Introduction

The last 2 decades have witnessed a dramatic and substantial increase in our understanding of illnesses that result from disturbances in the autonomic nervous system. Initially, these investigations were focused on neurocardiogenic syncope. However, it soon became evident that a subgroup of patients suffered from a similar yet distinct type of autonomic disturbance manifested by postural tachycardia, with orthostatic and exercise intolerance as well as fatigue. This disorder has come to be known as the postural tachycardia syndrome (POTS) and appears to be a heterogeneous group of disorders that display similar clinical characteristics.[1]

Definitions

The principal feature of POTS is orthostatic intolerance, defined as the provocation of symptoms on standing that are relieved by recumbence.[1,2] Patients usually complain of palpitations, fatigue, lightheadedness, exercise intolerance, nausea, diminished concentration, tremulousness, syncope, and near syncope.[3] POTS is a subset of orthostatic intolerance that is associated with the presence of excessive tachycardia on standing. Symptoms may be of such severity that normal activities of life, such as bathing, housework, and even eating can be significantly limited. POTS patients have been reported to suffer from a degree of functional impairment similar to that seen in conditions such as chronic obstructive pulmonary disease and congestive heart failure, yet these patients are all-too-frequently misdiagnosed as having severe anxiety or panic disorder.[4,5]

POTS is currently defined as the presence of symptoms of orthostatic intolerance associated with a heart rate increase of 30 bpm (or rate that exceeds 120 bpm) that occurs within the first 10 minutes of standing or upright tilt, not associated with other chronic debilitating conditions such as prolonged bed rest or the use of medications known to diminish vascular or autonomic tone.[4] Most authors feel that a patient should have been symptomatic for >3 months. Although it is difficult to determine the true prevalence of POTS, current estimates suggest that at least 500 000 patients are affected by the disorder in the United States alone. Of this total, 25% are disabled and unable to work.[6] It should be noted that many patients with orthostatic intolerance due to POTS will not demonstrate orthostatic hypotension (defined as fall of >20/10 mm Hg on standing). Instead, they may display no change, a small decline, or even a modest increase in blood pressure.[2] Some investigators have noted that focusing on heart rate overlooks a number of other autonomic symptoms that may be present, such as disturbances in sweating, thermoregulation and bowel and bladder function. It should also be remembered that other orthostatic intolerance syndromes exist in addition to POTS, in which symptoms occur in the absence of dramatic heart rate increases.[6,7]

Classification and Clinical Features

As was mentioned previously, POTS is a heterogeneous group of disorders with similar clinical manifestations. Although a variety of different classification systems have been proposed, the one presented here seems to be both clinically useful and consistent with current medical evidence. POTS can be thought of as being either primary or secondary. The primary forms

From the Division of Cardiology, Department of Medicine, University of Toledo, Toledo Ohio.
Correspondence to Blair P. Grubb, MD, Cardiology, Mail Stop 1118, Health Science Campus, University of Toledo, 3000 Arlington Ave, Toledo, Ohio 43614. E-mail blair.grubb@utoledo.edu
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are not associated with other disease states, whereas the secondary forms occur in association with a known disease or disorder.

The most frequent form of primary POTS is the "partial dysautonomic" (or PD) form. These patients appear to suffer from a mild form of peripheral autonomic neuropathy characterized by the inability of the peripheral vasculature (especially the nervous system) to maintain adequate vascular resistance in the face of gravitational stress.[5] This leads to a much greater than normal degree of blood pooling in the dependent areas of the body (legs, lower arms, and the mesenteric vasculature) while upright. The sequestration of blood away from the central vasculature elicits a compensatory increase in heart rate and myocardial contractility in an attempt to maintain cerebral perfusion at constant levels. Whereas the increase in heart rate and inotropy may initially be compensatory, the extent of peripheral venous pooling can continue to increase over time and exceed this compensatory effect. The patient then becomes increasingly dependent on the skeletal muscle pump to augment venous return and maintain adequate blood pressure.[4] However, the degree of venous pooling may continue to increase and overcome this compensatory effect as well. A roughly 5:1 female to male ratio exists in this form of POTS. Many of these patients report that their symptoms begin after an acute febrile illness (presumed to be viral), as well as after pregnancy, surgery, sepsis, or trauma.[7] It is presently felt that in many patients this form of POTS is an autoimmune disorder.[8]

A second (and less frequent) form of POTS is termed the "hyperadrenergic" form.[9] These patients often describe a more gradual and progressive emergence of symptoms over time rather then an abrupt onset. Patients with hyperadrenergic POTS often complain of significant tremor, anxiety, and cold sweaty extremities while upright. Over half of these patients experience migraine headaches as well as a significant increase in urinary output after being upright for only a short period of time. A characteristic of this form of POTS is that patients will often display orthostatic hypertension in addition to orthostatic tachycardia. Many will also have an exaggerated response to intravenous isoproterenol, as well as significantly elevated serum norepinephrine levels (>600 ng/mL) on standing. The disorder often has a strong family history. A study by Shannon et al found that some patients have a single point mutation that produces a poorly functioning reuptake transporter protein that recycles norepinephrine within the intrasynaptic cleft.[10] This process leads to an excessive degree of norepinephrine serum spillover in response to a number of sympathetic stimuli, producing a "hyperadrenergic" state (similar to that seen in pheochromocytoma).

The term secondary POTS is used to describe a variety of conditions that produce a state of peripheral autonomic deinnervation or vascular unresponsiveness with relative sparing of cardiac innervation.[4] A frequent cause of secondary POTS is chronic diabetes mellitus. However, it also may be seen in association with amyloidosis, sarcoidosis, alcoholism, lupus, Sjögren syndrome, chemotherapy, and heavy metal poisoning.

In some patients, POTS may be the presenting picture of a more severe autonomic nervous system disorder such as pure autonomic failure or multiple system atrophy.[7,11] POTS can also be a form of paraneoplastic syndrome that can be seen with adenocarcinomas of the lung, breast, ovary, and pancreas. It has been reported that these tumors produce autoantibodies to the acetylcholine receptors of the autonomic ganglia similar to those identified in the postviral syndromes.[12]

An alternative system of classification has been proposed by Steward on the basis of laboratory measurements of peripheral blood flow and peripheral arterial resistance. Details of this system of classification are described elsewhere.[13]

Evaluation and Management

The first and most important step is to obtain a detailed history of the illness. When did the symptoms begin? Was the onset sudden or gradual? What events were associated with the onset of symptoms (such as infection, surgery, or traumas)? What conditions improve or worsen symptoms? Is there a family history of similar problems? Are migraines an issue?

A thorough physical examination is equally important. Both heart rate and blood pressure should be measured supine, sitting, immediately on standing, and after intervals of 2, 5, and 10 minutes. Examination of the extremities during this period may reveal a mottled bluish discoloration (acral cyanosis) that suggests peripheral vascular pooling. Because the exact heart rate and blood pressure responses can vary with upright posture, we often perform tilt-table testing on patients because it constitutes a more controlled setting with fewer variables. In some patients, it may be useful to assess other aspects of autonomic nervous system function through additional investigations such as thermoregulatory sweat testing, as well as assessment of skin resistance, conductance, and sympathetic skin potentials. Serum samples for determination of norepinephrine, epinephrine, and dopamine levels should be obtained in the supine and upright positions in patients suspected of having the hyperadrenergic form of POTS.

Treatment varies somewhat according to the subtype of POTS but must be individualized to meet the needs of each patient. Any drug that the patient is taking that could be contributing to the patient's symptoms should be discontinued if possible (see Table 1). Any condition that could be causing POTS should be identified (eg, amyloidosis or cancer) and adequately treated. All patients should be encouraged to begin a gradual program of physical reconditioning, working toward a goal of performing 20 to 30 minutes of aerobic activity 3 times a week. In addition, we also encourage the patient to engage in gentle resistance training of the lower extremities and abdomen in order to strengthen the

Table 1. Drugs That Can Cause or Worsen Orthostatic Intolerance

α receptor blockers
Angiotensin-converting enzyme inhibitors
ß-blockers
Bromocriptine
Calcium channel blockers
Diuretics
Ethanol
Ganglionic blocking agents
Hydralazine
Monoamine oxidase inhibitors
Nitrates
Opiates
Phenothiazines
Sildenafil citrate
Tricyclic antidepressants

skeletal muscle pump. A fluid intake of ≈2 L per day, as well as 3 to 5 g of salt per day should be encouraged (except in the hyperadrenergic form). Elastic compression stockings are sometimes helpful; the most effective ones are waist high and provide at least 30 mm Hg of ankle counter pressure. Whereas conservative measures may be adequate in some patients with POTS, others will be so severely affected that some sort of pharmacotherapy will be needed. Medications are used with the goal of stabilizing the condition enough that they can pursue reconditioning. No drug is presently approved by the US Food and Drug Administration for the treatment of POTS, and the treatments listed here are all "off label" (Table 2). It is important to try and identify the broad subtype when choosing a therapy for POTS.

In patients suffering from the partial dysautonomic form of POTS, initial therapy is directed at augmenting fluid volume and increasing peripheral vascular resistance. To augment volume, we employ the mineral corticoid fludrocortisone acetate starting at 0.1 to 0.2 mg per day. An alternative agent is desmopressin acetate (DDAVP) 0.1 mg to 0.2 mg orally at bedtime. If needed, we then add a vasoconstrictor such as midodrine 5 mg orally 3 to 4 times daily. The dose may be slowly shifted up to 10 to 15 mg QID if necessary. As many patients are most symptomatic in the morning, we often advise that they take their first dose of midodrine 15 to 20 minutes before getting out of bed. If midodrine is effective but not tolerated, methylphenidate can be an effective alternative.

In patients who are not responsive to or intolerant of the above-mentioned therapies, we often add either a serotonin reuptake inhibitor (SSRI) or a norepinephrine reuptake inhibitor. Whereas the SSRIs are more helpful in neurocardiogenic syncope, the norepinephrine reuptake inhibitors appear to be somewhat more useful in POTS. If an SSRI is used, those with a combined serotonin norepinephrine effect (duloxetine and venlafaxine) appear to work best.

A promising new therapy is pyridostigmine (Mestinon), an acetylcholinesterase inhibitor that is thought to facilitate ganglionic neural transmission in both the sympathetic and parasympathetic nerves.[14] 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). We usually start with a dose of 30 mg orally BID and titrate to 60 to 90 mg orally 3 times a day if necessary.

In patients who are severely affected by POTS and in whom no other therapy is effective or tolerated, we use the drug erythropoietin (EPO). Although initially introduced to treat anemia, EPO has been found to process potent vasoconstrictive effects with demonstrated utility in treating orthostatic

Table 2. Therapeutic Options in POTS

Treatment	Application	Effective in	Problems
Reconditioning	Aerobic exercise 20 min 3 times/wk	PD, H	If too vigorous, may worsen symptoms
Hydration	2 L qd	PD	Edema
Salt	2–4 g/d	PD	Edema
Bupropion (Wellbutrin XL)	150–300 mg qd	PD, H	Tremor, agitation, insomnia
Clonidine HCl (Catapres)	0.1–0.3 mg bid; 0.1–0.3 mg patch/wk	H	Dry mouth, blurred vision
Desmopressin acetate (DDAVP)	0.1–0.2 mg qhs	PD	Hyponatremia, headache
Duloxetine HCl (Cymbalta)	20–30 mg qd	PD, H	Nausea, sleep disturbance
Erythropoietin (Epogen, Procrit)	10 000–20 000 U SC/wk	PD	Pain at injection site, expensive
Escitalopram oxalate (Lexapro)	10 mg qd	PD, H	Tremor, agitation, sexual problems
Fludrocortisone acetate	0.1–0.2 mg qd	PD	Hypokalemia, hypomagnesemia, edema
Labetalol HCl (Trandate, Normodyne)	100–200 md bid	H	Fatigue
Methylphenidate (Ritalin, Methylin, Concerta, etc.)	5–10 mg tid	PD	Anorexia, insomnia, dependency
Midodrine (ProAmatine)	5–10 mg tid	PD	Nausea, itching scalp, supine hypertension
Octreotide acetate (Sandostatin)	50–200 μg SC tid	PD	Nausea, diarrhea, gallstones
Pyridostigmine bromide (Mestinon)	30–60 mg qd	PD	Nausea, diarrhea
Venlafaxine HCl	75 mg qd or bid	PD, H	Nausea, anorexia, tremor

Note: The Food and Drug Administration has not approved any drug for treating POTS. H indicates hyperadrenergic; SC, subcutaneous.

disorders. Protocols for its use are given elsewhere.[5] The usual starting dose is 10 000 IU subcutaneously once weekly. Complete blood counts are monitored monthly to ensure that the hematocrit does not exceed 50%.

An additional therapy for refractory patients is the somatostatin analog octreotide, because of its potent vasoconstrictive effects. It is administered by subcutaneous injection beginning at 50 micrograms 2 to 3 times daily.

In the hyperadrenergic form of POTS, patients often respond best to agents that block norepinephrine or its effects.[9,10] One agent that is particularly helpful is clonidine HCl in either pill or patch form. We start the oral form at 0.1 mg PO 1 to 2 times a day and filtrate upward. The patch form of clonidine is quite useful because it provides a constant and continuous amount of the drug for up to 1 week at a time. The combined α and β blocking drugs labetalol and carvedilol are quite useful in some patients as pure β-blockers may exacerbate symptoms (because of unopposed α receptor stimulation). Methyldopa has been reported to be useful in some patients, as has phenobarbital. In addition, both the SSRIs and norepinephrine reuptake inhibitors are useful in select patients.

It is sometimes challenging to be able to differentiate between POTS and inappropriate sinus tachycardia (IST) because hyperadrenergic POTS and IST share several characteristics.[15] Clinical presentations are similar, IST is also more common in women, and both conditions display an exaggerated response to isoproterenol infusions, (suggesting to some investigators that the disorders are related). One distinguishing feature is that patients with POTS tend to display a more pronounced degree of postural change in heart rate than those with IST. In the supine position, the heart rate in POTS patients is rarely >100 bpm whereas in IST the resting heart rate is often >100 bpm. Patients with IST do not display the same degree of postural change in norepinephrine levels as those patients with hyperadrenergic POTS. It is important to differentiate between the 2 conditions because catheter ablation of the sinus node rarely leads to improvement in patients with hyperadrenergic POTS and often makes those with the PD form worse.

In the secondary forms of POTS, therapy should be directed at the treatment of the underlying disorder (if possible). Patients with POTS due to diabetes mellitus are treated the same as in the PD form. Individuals with paraneoplastic POTS respond well to pyridostigmine, and symptoms usually resolve after treatment of the malignancy.

Prognosis and Impact of POTS

At present, only limited data are available on the prognosis of patients with POTS. Investigations are presently underway analyzing the outcomes of patients (overall, as well as within different subgroups); however, some basic trends have been observed. Over one half of the patients with postviral onset POTS appear to make a reasonable recovery over a 2- to 5-year period, with recovery defined as the relative absence of orthostatic symptoms alone with the ability to perform the activities of daily living with minimal restriction. However, some patients do not recover, and a small subset will worsen over time. For the most part, the younger the patient, the better the prognosis. In general, close to 90% of patients will respond to a combination of physical therapy and pharmacotherapy. Patients with the hyperadrenergic form of POTS usually require therapy indefinitely. The prognosis of those patients with secondary POTS is usually determined by the prognosis of the underlying disorder.

Summary

The postural tachycardia syndrome is a heterogenous group of disorders with similar characteristics that occur as a result of disturbances of normal autonomic control. Successful treatment is often dependent on identification of the subtype together with pursuit of a comprehensive treatment program.

Disclosures

None.

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