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Clinical presentation and management of patients with hyperadrenergic postural orthostatic tachycardia syndrome. A single center experience

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Abstract

Background: *We present our single center experience of 27 patients of hyperadrenergic postural orthostatic tachycardia syndrome (POTS).*

Methods: *In a retrospective analysis, we reviewed the charts of 300 POTS patients being followed at our autonomic center from 2003 to 2010, and found 27 patients eligible for inclusion in this study. POTS was defined as symptoms of orthostatic intolerance (of greater than six months' duration) accompanied by a heart rate increase of at least 30 bpm (or a rate that exceeds 120 bpm) that occurs in the first 10 min of upright posture or head up tilt test (HUTT) occurring in the absence of other chronic debilitating disorders. Patients were diagnosed as having the hyperadrenergic form based on an increase in their systolic blood pressure of ≥ 10 mm Hg during the HUTT (2) with concomitant tachycardia or their serum catecholamine levels (serum norepinephnrine level ≥ 600 pg/mL) upon standing.*

Results: *Twenty seven patients, aged 39 ± 11 years, 24, (89%) of them female and 22 (82%) Caucasian were included in this study. Most of these patients were refractory to most of the first and second line treatments, and all were on multiple combinations of medications.*

Conclusions: *Hyperadrenergic POTS should be identified and differentiated from neuropathic POTS. These patients are usually difficult to treat and there are no standardized treatment protocols known at this time for patients with hyperadrenergic POTS.* (Cardiol J 2011; 18, 5: 527–531)

Key words: postural tachycardia syndrome, hyperadrenergic, orthostatic intolerance

Introduction

Postural orthostatic tachycardia syndrome (POTS) is characterized by symptoms of orthostatic intolerance upon assuming an upright posture and relief of these symptoms by recumbency [1, 2]. The current definition of POTS is the presence of symptoms of orthostatic intolerance (> 6 months duration) associated with a heart rate (HR) increase of 30 bpm (or rate that exceeds 120 bpm) that occurs within the first 10 min of standing or upright tilt, not associated with other chronic debilitating conditions

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such as prolonged bed rest or the use of medications known to diminish vascular or autonomic tone [1, 2].

In recent years there has been a substantial improvement of our understanding of POTS. Although the exact etiology remains elusive, we know that the syndrome of postural tachycardia is not a single clinical entity, but rather a heterogeneous group of various related clinical syndromes having a final common presentation of orthostatic intolerance.

The commonest form of POTS, called the neuropathic or partial dysautonomic form, results from neuropathy preferentially involving the lower extremities with resultant venous pooling [3–6]. Another group of patients suffer from centrally driven abnormal sympathetic activation. This form of postural tachycardia syndrome is called hyperadrenergic POTS, and comprises about 10% of all POTS patients. Patients suffering from hyperadrenergic POTS have been observed to have an orthostatic plasma norepinephrine level ≥ 600 pg/mL and a rise of systolic blood pressure (SBP) of ≥ 10 mm Hg upon standing [1, 2, 6–8]. We present our single center experience of 27 hyperadrenergic POTS patients.

Methods

This was a retrospective study approved by our local Institutional Review Board. We reviewed charts of 300 POTS patients seen at our autonomic center between 2003 and 2010 and found 27 patients eligible for inclusion in this study.

Criterion for diagnosis of POTS

Postural orthostatic tachycardia was defined as symptoms of orthostatic intolerance (of greater than six months' duration) accompanied by a HR increase of at least 30 bpm (or a rate that exceeds 120 bpm) observed during the first 10 min of upright posture or head up tilt test (HUTT) occurring in the absence of other chronic debilitating disorders [1, 2]. Symptoms include fatigue, orthostatic palpitations, exercise intolerance, light-headedness, diminished concentration, headache, near-syncope and syncope. In a retrospective chart review, we collected data including demographic information, presenting symptoms, laboratory data, tilt-table response, and treatment outcomes.

Criterion for diagnosis of hyperadrenergic postural tachycardia syndrome

Patients were diagnosed as having the hyperadrenergic form based on an increase in their SBP of ≥ 10 mm Hg during the HUTT [2] with concomitant tachycardia or their serum catecholamine levels (serum norepinephnrine level ≥ 600 pg/mL) upon standing [1, 2]. Each patient had been evaluated for the presence of a pheochromocytoma by a computed tomography scan of the abdomen, as well as metaiodobenzylguanidine scanning. In no patient was a pheochromocytoma detected.

HUTT protocol

The protocol used for tilt table testing has been described elsewhere [1, 7, 9–12], but basically consisted of a 70-degree baseline upright tilt for a period of 30 min, during which time HR and blood pressure were monitored continually. If no symptoms occurred, the patient was lowered to the supine position and an intravenous infusion of isoproterenol started, with a dose sufficient to raise the HR to 20–25% above the resting value. Upright tilt was then repeated for 15 min. Patients were included in the study if they had a POTS pattern on HUTT (rise in HR without any change in blood pressure).

Treatment protocols

The treatment protocols employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere [1, 7, 9––12]. Briefly, a sequence of therapies was employed that included physical counter maneuvers and aerobic and resistance training, as well as increased dietary fluids and sodium. If these were ineffective, pharmacotherapy was initiated in a sequence generally consisting of beta-blockers, central sympatholytics, fludrocortisone, midodrine, and selective serotonin reuptake inhibitors, either alone or in combination. As this was a retrospective chart review, a formal questionnaire to assess the response to treatment or an assessment of response to treatment by HUTT testing was not employed. Information about the subjective symptoms and sense of well-being from each patient was collected from the patient's charts, physician communications and direct patient inquiry. A treatment was considered successful if it provided symptomatic relief.

Statistical analysis

Statistical analysis was done using SPSS15. The data is observational and is presented as mean ± ± SD and percentages.

Results

Table 1 summarizes the clinical features, comorbid conditions, precipitating events and symp-

Table 1. Clinical features of patients with hyperadrenergic postural orthostatic tachycardia.

Age (years)	39 ± 11
Sex (female)	24 (88.9%)
Race (Caucasian)	22 (81.5%)
Co-morbidity:	
Hypertension	9 (33.3%)
Diabetes mellitus	2 (7.4%)
Coronary artery disease	2 (7.4%)
Migraine	8 (29.6%)
Joint hypermobility syndrome	5 (18.5%)
Mitochondrial cytopathy	1 (3.7%)
Precipitating event:	
Trauma	1 (3.7%)
Pregnancy	3 (12.5%)
Viral infection	3 (11.1%)
Symptoms:	
Fatigue	14 (51.9%)
Orthostatic palpitation	13 (48.2%)
Orthostatic hypertension	5 (18.5%)
Dizziness/pre-syncope	16 (59.3%)
Syncope	11 (40.7%)
Anxiety	18 (67%)
Tremulousness	18 (67%)
Excessive sweating	14 (52%)
Nausea	9 (33%)
Diarrhea	10 (35%)
Bloating	9 (33%)

toms of patients suffering from hyperadrenergic POTS. Twenty seven patients aged 39 ± 11, 24 (89%) of them female and 22 (82%) of them Caucasian were included in this study.

Precipitating events

The precipitating events in patients suffering from hyperadrenergic POTS were pregnancy (12.5%), viral infection (11.1%) and trauma (1%).

Comorbidity

Hypertension (33.3%), migraine (29.6%) and joint hypermobility syndrome (18.5%) were common co-morbidities in this group of patients.

Symptoms of POTS

Dizziness and pre-syncope (60%) were the common symptoms, followed by fatigue (51%) and orthostatic palpitations (48%). Orthostatic hypertension was seen in 19% of patients. Table 1 summarizes other symptoms encountered in our patient population.

Table 2. Medication use and response to different medications used in patients with hyperadrenergic postural orthostatic tachycardia.

Medication	Used in patients	Response to medication
Adderall	4/27 (14.8%)	4/4 (100%)
Florinef	4/27 (14.8%)	1/4 (25%)
Clonidine	12/27 (44.4%)	10/12 (83.3%)
Beta-blockers	24/27 (88.9%)	13/20 (65.0%)
Midodrine	9/27 (33.3%)	4/7 (57.1%)
SSRI	9/27 (33.3%)	3/7 (42.9%)
SSRI/NERI	17/27 (62.9%)	7/13 (53.9%)
Modafinil	5/27 (18.5%)	3/5 (60.0%)
Epogen	2/27 (7.4%)	1/2 (50.0%)
Mestinon	11/27 (40.7%)	2/8 (25.0%)

SSRI — selective serotonin reuptake inhibitors; NERI — norepinephrine reuptake inhibitors

Tilt table test

All patients demonstrated a typical hyperadrenergic POTS response to the tilt table test. The mean rise in HR on a tilt test was 35 ± 3 bpm and the mean time to peak HR was 8 ± 3 min. The mean increase in SBP was 13 ± 3 mm Hg.

Norephinephrine levels

The standing norepinephrine levels were calculated in each patient. The mean norepinephrine levels in these patients were 828 ± 200 pg/mL (normal range: 520 pg/mL).

Medications and response to the medications

Most of these patients were on a combination of medications. The algorithm we used has been described in the 'Methods' section under 'Treatment protocol'. Most of these patients were receiving a combination of various first and second line medications. These patients were refractory to various combinations of medications. Table 2 summarizes various medications we commonly used in these patients.

Discussion

Our understanding of the disorder now called POTS has substantially increased over the past two decades. The early descriptions of the disorder focused on a group of patients who had been previously healthy until a sudden febrile illness (presumably viral) brought on an abrupt onset of symptoms [3].

Later investigations revealed that POTS is better understood as a physiological state most commonly due to an inability of the peripheral vasculature to maintain adequate resistance in the face of orthostatic stress, allowing for excessive pooling of blood in the more dependent areas of the body [1, 13, 14]. The resultant functional decline in circulatory volume elicits a compensatory increase in HR and myocardial contractility. While compensatory in mild cases, this mechanism is unable to fully compensate in more severe cases, resulting in a reduction in effective circulation and varying degrees of cerebral hypoperfusion. Later investigations revealed that POTS is not a single condition, but rather a heterogeneous group of disorders resulting in a similar physiological state [8, 13–15].

Clinical findings of hyperadrenergic POTS in our series

Precipitating events. The less common form of primary POTS, the hyperadrenergic form, tends to have a gradual and progressive onset of symptoms as opposed to an abrupt onset [2, 16]. In our study, one patient had onset years after traumatic brain injury, three had symptoms following pregnancy, and another three had an onset of symptoms following a viral illness.

Symptoms of POTS. 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. In our series, 55–65% of patients reported symptoms of hyperadrenergic state in the form of anxiety, tremulousness and excessive sweating. Orthostatic palpitations and pre-syncope/dizziness were reported in 50–60% of the patients. Fatigue was one of the commonest symptoms reported in our patient series and syncope was also reported in 40%. Some patients with POTS may experience syncope in the absence of significant decline in blood pressure. A sudden increase in cerebrovascular resistance resulting in decline in cerebral oxygenation that occurs in the presence of orthostatic stress has also been reported in these patients [17–20]. The higher incidence of syncope and fatigue may be because of the selection bias in this study as many of these patients had been referred from various centers for a second opinion regarding diagnosis and management and were often difficult to treat with refractory symptoms.

Gastrointestinal symptoms were reported in almost 30% of the patients in this study. There have been reports of gastrointestinal symptoms in patients suffering from POTS. Patients with hyperadrenergic forms tend to have diarrhea rather than constipation [2, 7]. In our series, almost 30% of patients had gastrointestinal symptoms in form of nausea, bloating and diarrhea.

In our study, most patients demonstrated symptoms of adrenergic overactivity in the form of palpitations, tremulousness and almost one third of our patients were hypertensive, receiving more than two medications to control their blood pressure. Almost 20% of our patients demonstrated orthostatic rise in their blood pressure of more than 20 mm Hg. In some ways the symptoms patients experience are suggestive of pheochromocytoma, although no patient had evidence of this.

The patients suffering from hyperadrenergic variant of POTS appear to have an increased centrally mediated drive of norepinephrine or a defect in norepinephrine reuptake, resulting in increased availability of norepinephrine at the synaptic junctions. Beta-blockers and centrally acting sympatholytics like clonidine, by counteracting the excess norepinephrine either by decreasing the centrally mediated release or by receptor blockage, may result in a substantial decline in norepinephrine mediated effects [1, 2, 8, 15, 16].

Future perspective

There has been a substantial increase in the efforts to understand the pathophysiology and etiology of POTS. Recent research has shown that this syndrome may have multiple etiologies, and we now know that POTS can have multiple variants resulting from these multiple etiologies including partial dysautonomia [3] centrally mediated hyperadrenergic stimulation [8], norepinephrine transporter dysfunction [16], autoimmune anti body against cholinesterase receptors [21], POTS associated with deconditioning [22] and hypovolumia [23]. A recently published study reported that POTS may be a manifestation of autonomic cardiac neuropathy [24]. POTS has been reported after traumata [25] and infections [26] as well.

The clinical profile of our patients was similar to the patients reported in other studies. Also our observations that beta-blockers and centrally acting sympatholytics work better in patients presumed to have hyperadrenergic variant of POTS were consistent with those in other series [2, 7].

Conclusions

Patients of hyperadrenergic POTS should be identified and differentiated from those with neu-

ropathic POTS. These patients are usually difficult to treat and there are no standardized treatment protocols known at this time for patients with hyperadrenergic POTS. A randomized control trail in future may help evaluate the role of optimal therapy in these patients.

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