Neurocardiogenic Syncope Coexisting with Postural Orthostatic Tachycardia Syndrome in Patients Suffering from Orthostatic Intolerance: A Combined form of Autonomic Dysfunction

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Introduction: *There is anecdotal evidence that one or more forms of orthostatic intolerance (OI) subgroups may coexist in the same patients. However, there is a paucity of published data on the clinical features and management of patients who suffer from coexisting features of postural tachycardia syndrome (POTS) and neurocardiogenic syncope (NCS). We herein present our experience of 18 patients who we found displayed evidence of coexisting NCS and POTS.*

Methods: *We reviewed charts of 300 POTS patients seen at the University of Toledo Syncope and Autonomic Disorders Center from 2003 to 2010 and found 18 patients eligible for inclusion in this study. Patients were included in this study if they reported clinical symptoms consistent with both POTS and NCS and then demonstrated a typical POTS pattern (a rise in heart rate without change in blood pressure [BP]) on head up tilt table (HUTT) within the first 10 minutes of upright posture followed by a neurocardiogenic pattern (a sudden fall in heart rate and/or fall in blood pressure) reproducing symptoms that were similar to the patients spontaneous episodes.*

Results: *We found 18 patients, mean age (30 ± 12), with 15 (84%) women and three (16%) men, who met the inclusion criterion for this study. Each of these 18 patients demonstrated a typical POTS pattern within the first 10 minutes on initial physical exam and on a HUTT. Continued tilting beyond 10 minutes resulted in a sudden decline in heart rate (which in some patients manifested as an asystole that lasted anywhere between 10 and 32 seconds [mean of 18 seconds]) and/or a fall in BP in each of these patients demonstrating a pattern consistent with neurocardiogenic subtype of OI. The mean time to the NCS pattern of a fall in BP and heart was 15 minutes with a range of 13–20 minutes. This group of patients was highly symptomatic and reported frequent clinical symptoms that were suggestive of OI. Recurrent presyncope, syncope, orthostatic palpitations, exercise intolerance, and fatigue were the principal symptoms reported.*

Conclusion: *NCS may coexist with POTS in a subgroup of patients suffering from OI. (PACE 2010; 1–6)*

orthostatic intolerance, postural tachycardia syndrome, neurocardiogenic syncope

Introduction

Orthostatic intolerance (OI) syndromes refer to a heterogeneous group of disorders of hemodynamic regulation that are characterized by excessive pooling of blood in the dependent areas of the body during upright posture, thereby resulting in insufficient cerebral perfusion during upright posture causing a variety of symptoms that are relieved by recumbency. Symptoms may include syncope, near syncope, fatigue, palpitations, exercise intolerance, lightheadedness, diminished concentration, and headache.[1–4] Based on clinical presentation and head up tilt table response (HUTT), OI can be broadly divided into subgroups that include neurocardiogenic syncope (NCS), postural tachycardia syndrome (POTS), and dysautonomic (autonomic failure) syndromes.

There is anecdotal evidence that one or more forms of these subgroups may coexist in the same patients. However, there is paucity of published data on the clinical features and management of patients who suffer from coexisting features of POTS and NCS. We herein present our experience of 18 patients who we found displayed evidence of coexisting NCS and POTS.

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Methods

This was a retrospective study approved by our Institutional Review Board (IRB) at the University of Toledo. We reviewed charts of 300 POTS patients seen at our autonomic center at the University of Toledo from 2003 to 2010 and found 18 patients eligible for inclusion in this study.

Criterion for Diagnosis of OI

As mentioned earlier, OI consists of a heterogeneous group of disorders of hemodynamic regulation characterized by excessive pooling of blood in the dependent areas of the body during upright posture resulting in insufficient cerebral perfusion causing symptoms during upright posture relieved by recumbency.

POTS

POTS was defined as ongoing symptoms of OI (of greater than 6 months duration) accompanied by a heart rate increase of at least 30 beats/min (or a rate that exceeds 120 beats/min) observed during the first 10 minutes of upright posture or HUTT occurring in the absence of other chronic debilitating disorders.[1,2] Symptoms may include fatigue, orthostatic palpitations, exercise intolerance, lightheadedness, 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.

Neurocardiogenic syncope

NCS was defined as episodic syncope (transient loss of consciousness) with spontaneous recovery. Criterion for diagnosis of NCS included a HUTT response consistent with NCS (a sudden decrease in heart rate and/or decrease in blood pressure) that reproduced a patient's spontaneous symptoms of recurrent transient loss of consciousness with spontaneous recovery.

Protocol for HUTT

The protocol used for tilt table testing has been described elsewhere,[1–8] but basically consisted of a 70-degree baseline upright tilt for a period of 30 minutes, during which time heart rate 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 heart rate to 20%–25% above the resting value. Upright tilt was then repeated for a period of 15 minutes.

Criterion for Diagnosis of Combined OI

Patients where included in this study if they reported clinical symptoms consistent with both POTS and NCS and then demonstrated a typical POTS pattern (a rise in heart rate without change in blood pressure) on assuming upright posture or HUTT within the first 10 minutes followed by a neurocardiogenic pattern on continued HUTT (a sudden fall in heart rate and/or fall in blood pressure) reproducing symptoms that were similar to the patients spontaneous episodes.

Treatment Protocol

The treatment protocols employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere.[1–8] 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 β-blockers, central sympatholytics, fludrocortisone, midodrine, and selective serotonin reuptake inhibitors, either alone or in combination.

If patients failed to respond to these medications, second- and third-line medications such as octreotide, erythropoietin, and pyridostigmine were employed.

As this was a retrospective chart review, a formal questionnaire to assess the response to treatment or assessment of response to treatment by HUTT testing was not employed. The information about the subjective symptoms and sense of well being from each patient was collected from the patient charts, physician communications, and direct patient inquiry. A treatment was considered successful if the patient reported that it provided symptomatic relief.

Statistics

This is an observational study. The statistical analysis was done by using SPSS 17 version (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean $\pm$ standard deviation and categorical data as percentages. A *t*-test was used for comparisons of means, and a statistical significance was reached at a P value of <0.05.

Results

A total of 300 charts of patients followed at the University of Toledo Syncope and Autonomic Disorders center were screened. These patients had been seen over a period of 7 years. We found 18 patients, mean age (30 ± 12), with 15 (84%) women and three (16%) men, who met the inclusion criterion for this study. Table I summarizes

Table I.

Baseline Clinical Characteristics of the Study Patients (N = 18)

Age (years)	30 ± 12
Sex (females)	15 (84%)
Symptoms of orthostatic intolerance	
Orthostatic palpitations	17 (95%)
Dizziness	16 (89%)
Inability to concentrate	16 (89%)
Syncope	18 (100%)
Presyncope	18 (100%)
Fatigue	17 (95%)
Chest pain	11 (61%)
Medications	
β-blockers	9 (50%)
Selective serotonin reuptake inhibitors (SSRI)	8 (45)
Norepinephrine reuptake inhibitors/SSRI	11 (61%)
Midodrine	9 (50%)
Modafinil	3 (16%)
Fludrocortisone	4 (22%)
Pyridostigmine	17 (94%)
Octreotide	1 (6%)
Erythropoietin	4 (22%)
Comorbid conditions	
Hypermobility	4 (22%)
Hypertension	4 (22)
Diabetes Mellitus	1 (6%)
Migraine	9 (50%)
Precipitating factor	
None	10 (83.3%)
Infectious mononucleosis	2 (16.6%)

the clinical features, comorbid conditions, and medications used in these patients.

This group of patients was highly symptomatic with frequent clinical symptoms that were suggestive of OI. Recurrent presyncope, syncope, orthostatic palpitations, exercise intolerance, and fatigue were the dominant symptoms reported. Each of these patients carried a diagnosis of POTS initially, but due to the nature of their symptoms each patient was further evaluated by a HUTT.

HUTT Response

All the patients reported here had clinical features and a physical exam consistent with the diagnosis of POTS. In view of their refractory symptoms and frequent syncope, they were referred to our center for further evaluation. A detailed physical examination was performed in each of these patients. All of these patients demonstrated a typical POTS pattern with minimal change in blood pressure and an increase in heart rate in an office-based physical examination, confirming their diagnosis of postural orthostatic tachycardia (Table II). Each of these patients was further evaluated by a standard HUTT. The HUTT confirmed the diagnosis of POTS, but in addition, continuing the tilt beyond 10 minutes demonstrated a response consistent with NCS. Thus, a dual response was noted on a HUTT with initial POTS followed by neurocardiogenic decompensation pattern (see Table III and Fig. 1). Continued tilting beyond 10 minutes resulted in a sudden decline in heart rate (which in some patients manifested as an asystole that lasted anywhere between 10 and 32 seconds, mean of 18 seconds).

The mean time to the NCS pattern of a fall in blood and heart was 15 minutes with a range of 13–20 minutes. Thirteen patients demonstrated NCS without a provocative isoproterenol infusion and three patients demonstrated NCS response after isoproterenol infusion.

Table II.

Hemodynamic Parameters as Assessed in an Outpatient Office. Most of These Patients Demonstrated This Pattern of Increase in Heart Rate Without Significant Change in Blood Pressure (POTS Pattern) within 5 Minutes of Standing

	Sitting	Standing
Heart rate (beats per minute)	72.2 ± 10	121 ± 14
Systolic blood pressure (mmHg)	129 ± 16	122 ± 16

Table III.

Heart Rate and Blood Pressure Response in Patients with Combined Orthostatic Intolerance on a HUTT. Note a Dual Response with Initial Pattern Consistent with POTS (Increase in Heart and Minimal Change in Blood Pressure); Prolonged Tilting at 20 Minutes Demonstrated a Typical Neurocardiogenic Pattern with Fall in Heart Rate Associated with Fall in Blood Pressure

	0 minutes	10 minutes	20 minutes
Heart rate (beats per minute)	73 ± 10	123 ± 15	43 ± 15
Blood pressure (mmHg)	126 ± 15	118 ± 14	75 ± 12

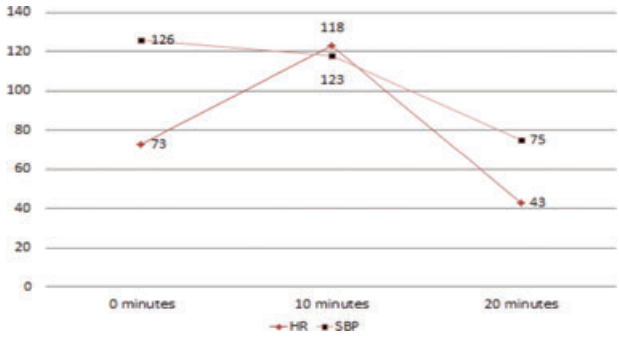

Figure 1. *Line diagram demonstrating a dual response with initial pattern consistent with POTS (increase in heart and minimal change in blood pressure); prolonged tilting at 20 minutes demonstrated a typical neurocardiogenic pattern with fall in heart rate associated with fall in blood pressure.*

Response to Medications

All of these patients failed first-line medications. Second-line medications including pyridostigmine was tried in 17 of 18 patients. Of these 17 patients, improvement in symptoms of OI was observed in five patients only. None of these patients had complete elimination of their syncope. However, a subjective improvement in the severity and frequency of symptoms of OI intolerance was reported by five (30%) of the patients treated with pyridostigmine. One patient is being treated with octreotide and another four with erythropoietin, as pyridostigmine failed to improve heart rate and blood pressure in these patients.

Pacemaker Implantation

Nine patients were further evaluated by implantable loop recorder (ILR). Five patients demonstrated prolonged periods of complete heart block and asystole on the tracings that were downloaded following episodes of abrupt onset of convulsive syncope.

Each of these five patients received dual-chamber closed loop cardiac pacemaker with near-complete elimination of their episodic loss of consciousness.

Discussion

The exact pathophysiology of postural tachycardia syndrome remains elusive. Our understanding of the disorder now called POTS has substantially increased in the last 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.[9] Later investigations revealed that POTS is better understood as a physiological state most commonly due to 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.[10,11] The resultant functional decline in circulatory volume elicited a compensatory increase in heart rate 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 similar physiological state.[9–13]

Recent research has shown that this syndrome may have multiple etiologies and we now know that POTS can have multiple variants such as partial dysautonomia,[9] centrally mediated hyperadrenergic stimulation,[12,13] norepinephrine transporter dysfunction,[14] and an autoimmune antibody against acetylycholinesterase receptors,[15] POTS associated with deconditioning,[15] and hypovolumia.[16] In a recently published study, it was reported that POTS may be a manifestation of autonomic cardiac neuropathy.[17]

More recently, interest has grown in the assessment of parasympathetic function in patients suffering from POTS. Raj reported a group of POTS patients in whom vagal function was preserved as assessed by normal sinus arrhythmia ratio on deep breathing.[18] Alshekhlee et al. describe a series of four POTS patients who had a surge of parasympathetic activity resulting in marked cardioinhibition and vasodepression.[19] They postulated that either a compensatory parasympathetic surge or a central aberration altering both sympathetic as well as parasympathetic output in a balanced fashion may account for increased parasympathetic activity in this group of patients.

We postulate that an initial compensatory increase in sympathetic outflow that increases the inotropy as well as chronotropy of the heart may fatigue or norepinephrine stores may become exhausted, resulting in a state of relative sympathetic withdrawal causing a state of bradycardia and hypotension in this group of patients. Assessing both sympathetic as well parasympathetic nervous system function at various stages of the HUTT may answer many of the questions, which our report could not address. Ojha et al. have reported that as many as 38% of patients suffering from POTS experience syncope during HUTT, and they suggest that the low-pressure baroreceptors that have been implicated as contributing to some forms of POTS may confer upon these patients an increased risk of syncope.[20] In a recent study from

Fu et al.,[21] it was observed that patients with POTS have a smaller heart in comparison to the controls. Also they observed that the autonomic function was intact in their group of patients. In this report, exercise training improved or even cured symptoms of POTS. With continued research in the area of OI, we hope to learn more about the pathophysiology of the POTS and its related syndromes.

There were some interesting observations from our study. Syncope (which, as mentioned previously, occurs in 10%–38% of historical controls of POTS patients in general) occurred in all patients in this group. This observation could be explained by a late-phase surge in parasympathetic tone or sympathetic withdrawal leading to both cardio inhibition as well as vasodepression. Almost all patients in this study had difficulty treating OI with each patient failing first- and second-line medications. Response to third-line medication, including Pyridostigmine, was also modest. Recently, Ivarbidine, a selective inhibitor of a cardiac pacemaker current inhibitor, has been reported to be effective in patients with inappropriate sinus tachycardia,[22] tachycardia with POTS,[23] and tachycardia associated with autonomic dysfunction.[24] In one report,[23] Ivarbidine was reported to improve symptoms of POTS in a patient who had failed multiple other medications. The patient described in the report had history of intermittent bradycardia and heart block for which he had received a pacemaker. Since these results were recently published, none of our patients had received Ivarbidine so far. But Ivarbidine therapy may be beneficial in patients suffering from POTS. In the future, we expect more studies will be published on the use of Ivarbidine in postural tachycardia that will define the role of this therapy in POTS patients a better way.

In our study, the patients who were found to have prolonged episodes of asystole or complete heart block on ILR subsequently benefited from dual-chamber pacemaker placement. Thus, POTS patients who present with unusually frequent and severe episodes of syncope should be considered for evaluation by an ILR to assess whether baradycardia and/or asystole occurs during clinical events.

Limitations

There were several important limitations in the current study. The study was retrospective and included small number of patients. None of the patients underwent additional autonomic function assessment besides HUTT. Response to therapy was subjective and not objectively assessed by a formal questionnaire or a response to a repeat HUTT.

Conclusion

NCS may coexist with POTS in a subgroup of patients suffering from OI. This group of patients with mixed-form OI may be difficult to treat and may have syncope as a dominant symptom. Also, POTS patients presenting with unusually frequent and severe episodes of syncope may benefit from further evaluation by ILR, as some of these patients, having NCS as well, may be candidates for cardiac pacing.

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