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Postural orthostatic tachycardia syndrome associated with multiple sclerosis

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Abstract

Background The aim of this study was to determine if there is a difference in the frequency of postural orthostatic tachycardia syndrome (POTS) in patients with multiple sclerosis (MS) compared to patients with symptoms of orthostatic intolerance and with no evidence of MS or other neurological illness.

Methods We analyzed data gathered from 293 patients who underwent the head-up tilt table test protocol. Group 1 included prospectively analyzed 112 with MS and group 2 included retrospectively analyzed 181 patients who were evaluated because of symptoms of orthostatic intolerance, and with no evidence of MS or other neurological illness. If POTS was identified the head-up tilt table test was repeated and supine as well as standing serum epinephrine and norepinephrine were determined.

Results POTS was identified in 39 patients: 21(19%) in the MS group comparing to 18 (10%) in the non MS group (p=0.035). There was no difference between groups in the occurrence of POTS associated syncope (p=0.52). There was no difference between groups in the epinephrine or norepinephrine in supine and standing positions. While both standing epinephrine and norepinephrine levels were significantly higher compared to levels in the supine position in the non MS group, only standing norepinephrine levels were significantly higher in the MS group.

Conclusions The results of this study suggest that POTS is associated with MS.

Key words: postural orthostatic tachycardia syndrome, multiple sclerosis, norepinephrine.

Introduction

Postural orthostatic tachycardia syndrome (POTS) is an autonomic disorder characterized by an exaggerated increase in heart rate which occurs during standing, without orthostatic hypotension in a patient with a history of specific symptoms. The diagnosis is made with a head-up tilt table test (HUTT), the result of which is characterized with a heart rate (HR) increment ≥30 bpm without orthostatic hypotension. Two major types of POTS are recognized on the basis of standing plasma norepinephrine levels (Low et al. 2009). Neuropathic POTS is a form of restricted autonomic neuropathy and is usually associated with standing plasma norepinephrine levels < 3.5 nmol/l. Hyperadrenergic POTS on the other hand is characterized by an excessive increase of plasma norepinephrine with an increase in blood pressure (BP) on standing.

Most cases of POTS are idiopathic, and secondary form of POTS occurs in association with a variety of other medical illnesses, such as diabetes mellitus, amyloidosis, sarcoidosis, alcoholism, lupus, Sjogren syndrome, chemotherapy, paraneoplastic syndrome, multisystem atrophy, or heavy metal poisoning (Thieben et al. 2007).

Although orthostatic dizziness has been commonly seen in multiple sclerosis (MS) patients (Vita et al. 1993), there have been no studies demonstrating the occurrence of POTS in patients with MS. One study described clinical characteristics of 9 patients with MS and POTS, emphasizing that MS patients may manifest autonomic dysfunction by developing POTS (Kanjwal et al. 2010).

The aim of the present study was to determine if there is a difference in a frequency of POTS in patients diagnosed with multiple sclerosis compared to patients with symptoms of orthostatic intolerance with no evidence of MS or other neurological illness.

Patients and methods

We analyzed data gathered from 293 consecutive patients who underwent the pain provoked (PP)-HUTT protocol from January 2011 till May 2012. The PP-HUTT was performed as previously described (Adamec et al. 2012). Patients were divided into two groups. Group 1 included 112 consecutive patients diagnosed with MS according to the revised McDonald criteria who were prospectively tested with PP-HUTT for evaluation of autonomic dysfunction regardless of symptoms of orthostatic intolerance (Polman et al. 2011). The control group, group 2 included retrospectively analyzed 181 patients who were evaluated because of symptoms of orthostatic intolerance, and with no evidence of MS or other neurological illness. Dehydration was evaluated clinically (skin turgor, dryness of mucus membranes, thirst, urine output and color).

Before testing, all patients signed informed consent approved by Ethical committee of the University Hospital Center Zagreb.

All patients who fulfilled criteria for POTS were included in further analysis. A diagnosis of POTS was based on the following criteria: sustained heart rate increment of ≥30 beats/minute within 10 min of head-up tilt, absence of orthostatic hypotension (defined as a fall in blood pressure > 20/10 mm Hg) and absence of conditions such as, overt dehydration, substantial weight loss, or systemic illnesses, which could provoke orthostatic intolerance (Freeman et al. 2011). Subjects with systemic illnesses which might affect autonomic function (diabetes, cardiac arrhythmias, adrenal disease) were excluded.

If POTS was identified on the first PP-HUTT, the patient (if willing) underwent a second PP-HUTT which was repeated within the next 14 days. During the repeated test two blood samples were obtained for determination of serum epinephrine and norepinephrine. Blood samples were collected from an indwelling catheter in a peripheral arm vein for measurement

of epinephrine and norepinephrine at rest and at the end of the standing phase. Blood was collected directly in chilled tubes containing EGTA and reduced glutathione for determination of cateholamines in plasma (Kabevette® N, Kabe Labortechnik GmbH). Plasma levels of cateholamines were measured on high pressure liquid chromatography (HPLC Prominence; Shimadzu GmbH) with an electrochemical detector CLC 100 (Chromsystems GmbH, Germany) using a commercially available HPLC kit and a reverse phase analytical column for HPLC analysis of catecholamines in plasma (Chromsystems GmbH, Germany).

Descriptive statistical analysis was performed concerning the age and gender. Differences in the distribution of qualitative variables were confirmed by the χ2test, while the differences in quantitative variables, in respect of distribution, were analyzed by the parametric t-test or non-parametric Mann-Whitney test. P values less than 0.05 were considered statistically significant. SPSS stat 19 software was used to support our statistical analysis.

Results

There was no difference between groups in demographic data (Table 1). Syncope was significantly more frequent in the group 2 comparing to group 1 (23 versus 67 patients respectively, p=0.004), while there was no difference in the frequency of orthostatic hypotension between groups (17 versus 25 in group 1 and group 2 respectively, p=0.735).

POTS was identified in 39 patients: 21(19%) in group 1 comparing to 18 (10%) in group 2, and this difference was statistically significant (p=0.035) (Figure 1).

While all patients with POTS in group 2 had symptoms of orthostatic intolerance, only 4 (19%) patients with POTS in group 1 had symptoms of orthostatic intolerance. Differences between systolic and diastolic blood pressure (BP) and heart rate (HR) in the supine and

standing positions are presented in Table 2. There was no difference in systolic BP, diastolic BP, supine or standing HR; nor in the orthostatic increase in systolic BP, diastolic BP and HR between groups (Table 3.) As well, there was no difference between groups in the occurrence of POTS associated syncope (7 in group 1 and 6 in group 2, p=0.52).

Out of the 39 patients with POTS, 26 (67%) participated in the second part of the study, 16 in group 1 and 10 in group 2. There was no difference between groups regarding epinephrine levels in supine and standing positions nor there was a difference in epinephrine (standing – supine) (0.15 ± 0.12 vs 0.14 ± 0.07, p=0.80; 0.46 ± 0.86 vs 0.88 ± 1.02, p=0.27; 0.31 ± 0.78 vs 0.74 ± 1.06, p=0.25; respectively). There was no difference between groups regarding norepinephrine levels in supine and standing positions (1.23 ± 0.53 vs 0.97 ± 0.91, p=0.43; 2.94 ± 1.58 vs 3.60 ± 1.14, p=0.26; respectively), however there was a tendency to reach significantly greater difference between standing and supine norepinephrine levels in the group 2 (1.71 ± 1.33 vs 2.63 ± 0.93, p=0.07).

Differences in epinephrine and norepinephrine levels in the supine and standing positions for each group are presented in the Table 4. While both epinephrine and norepinephrine were significantly higher in the standing position in group 2, only norepinephrine was significantly higher in the standing position in the group 1 (MS patients). Norepinephrine values greater than 3.5 nmol/l were present in 6 patients in group 1 and 7 patients in group 2.

Discussion

The results of this study have shown that POTS is more frequent in MS patients in comparison to patients with symptoms of orthostatic intolerance with no neurological illnesses.

These results suggest a potential causal relationship between MS and POTS. These two diseases share several similarities. Typical age group for both conditions is between 20 and 50 years, and women tend to be more frequently affected (5:1 and 3.5:1 for POTS and MS, respectively) (Grubb 2008, Ebers 2008) Also, many symptoms are shared, namely orthostatic intolerance, fatigue and anxiety (Ritberg et al. 2011, Hoad et al. 2008). Several studies have correlated autonomic dysfunction in MS patients with fatigue, the authors of one study found that autonomic responses correlated with fatigue resembling a hypoadrenergic orthostatic response, possibly due to a sympathetic vasomotor lesion with intact vagal heart control (Flachenecker et al. 2003).

Autonomic dysfunction in MS is explained by lesions in regions responsible for autonomic regulation, such as nuclei in the periventricular region of fourth ventricle in the brainstem as well as medullar lesions (Vita et al. 1993, Stenager and Asbeth 1992). The total MRI brain MS lesion load is another pathologic substrate related to autonomic dysfunction incidence as demonstrated by Saari et al (Saari et al. 2004). On the other hand, autonomic dysfunction has been related to MRI findings of cervical spinal cord atrophy rather than the presence of hyperintensive lesions in that region postulating that it results not solely from demyelination but from axonal loss as well (de Seze et al. 2001). POTS has been reported occurring in MS patients and their connection is explained by the presence of demyelinating brainstem and hemispheral lesions which disrupt the physiological heart rate variability modulation (Kanjwal et al. 2010).

The two types of POTS (neuropathic and hyperadrenergic) differ in several aspects. Hyperadrenergic POTS is associated with upright plasma norepinephrine > 3.54 nmol/l (600 pg/mL). This subgroup has greater supine HR and diastolic BP, standing HR, systolic and diastolic BP, as well as greater orthostatic increase in systolic and diastolic BP (Garland et al. 2007). While we found significant increase in all three parameters (systolic and diastolic BP,

HR) in all patients with POTS upon standing, we found no differences in these parameters between groups.

We found no difference between groups in the occurrence of POTS associated vasovagal syncope. There are conflicting opinions on whether postural tachycardia syndrome predisposes to syncope. In our cohort, 33% of patients had syncope on PP-HUTT, which is comparable with other studies (Ojha et al. 2010). We observed only one case of cardioinhibitory syncope (in the non MS group). It has been suggested that this subgroup of patients with POTS and cardioinhibitory syncope is infrequent and that these patients are highly symptomatic and report frequent clinical symptoms which are suggestive of orthostatic intolerance (Kanjwal et al. 2011).

Measurement of serum norepinephrine levels in supine and standing positions adds valuable additional information to the diagnosis and management of POTS. It has been shown that POTS patients with norepinephrine values greater than 3.5 nmol/l have increased values of HR and BP, supine and upright plasma dihydroxyphenylglycol levels and upright plasma dihydroxyphenylacetic acid levels as well as greater increase in L-3,4-dihydroxyphenyalanine, dopamine and dihydroxyphenylacetic acid upon standing (Garland et al. 2007). In our cohort we observed no difference in systolic or diastolic BP, HR, epinephrine and norepinephrine levels in supine or standing positions between groups.

The shortcomings of this study are the limitations inherent in retrospective, observational studies, there were no healthy controls and not all patients with POTS had epinephrine and norepinephrine levels determined. However the control group consisted of patients with symptoms of orthostatic intolerance, where one would expect a higher prevalence of POTS. Because of this, the higher frequency of POTS in the MS group is even more significant.

Venous blood epinephrine and norepinephrine levels were measured, as it has been the case in most published studies.

In conclusion, the results of this study suggest that POTS is associated with MS. Further prospective studies are needed to clarify this association.

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Tables

Table 1. Demographic characteristics of the groups (293 patients; group 1, 112 and group 2 181 patients).

Variable	**Group 1**	**Group 2**	**P value**
Age (years)	35.68±8.82	37.27±12.40	0.24
Gender (female/male)	81/31	133/48	0.89

Table 2. Differences between systolic and diastolic blood pressure (BP) and heart rate (HR) in the supine and standing positions (39 patients with POTS; group 1, 21 and group 2 18 patients).

Variable	**HUTT phase**	**Mean±standard deviation**	**P value**
Average Systolic BP	Supine	108.10±16.26	0,009
	Standing	117.13±13.39	
Average Diastolic BP	Supine	67.14±11.96	0,001
	Standing	75.16±8.67	
Average Heart Rate	Supine	74.89±15.21	<0,001
	Standing	108.60±16.62	

Table 3. Differences in systolic and diastolic blood pressure (BP) and heart rate (HR) between groups (39 patients with POTS; group 1, 21 and group 2 18 patients).

Variable	Group	Mean±standard deviation	P value
Systolic BP supine	1	104.55±21.37	0,21
	2	111.15±9.66	
Dyastolic BP supine	1	65.19±15.14	0,35
	2	68.81±8.41	
Heart rate supine	1	75.83±16.44	0,72
	2	74.07±14.44	
Systolic BP standing	1	117.46±15.76	0,90
	2	116.85±11.36	
Dyastolic BP standing	1	73.98±10.66	0,43
	2	76.18±6.64	
Heart rate standing	1	108.50±17.24	0,97
	2	108.69±16.50	
Systolic BP difference (standing – supine)	1	12.91±20.36	0,15
	2	5.70±8.33	
Dyastolic BP difference (standing	1	8.78±8.14	0,54

– supine)	2	7.37±5.95	
Heart rate difference (standing – supine)	1	32.67±9.12	0,53
	2	34.62±10.08	

Epinephrine normal values <0.46; norepinephrine normal values <2.49

Table 4. Differences in epinephrine and norepinephrine in the supine and standing positions for each group (26 patients with POTS; group 1, 16 and group 2 10 patients).

Group 1		
	Mean ± standard deviation (nmol/l)	P value
Epinephrine Su	0.15125±0.119693	0.18
Epinephrine St	0.46038±0.862409	
Norepinephrine Su	1.23063±0.526732	0.001
Norepinephrine St	2.93688±1.576222	
Group 2		
Epinephrine Su	0.14060±0.071056	0.049
Epinephrine St	0.87810±1.021648	
Norepinephrine Su	0.97350±0.914720	<0.001
Norepinephrine St	3.60080±1.136774	

Su Supine, St Standing

Figures

Figure 1. Frequency of postural orthostatic tachycardia syndrome between groups.