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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.

1. 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.

2. 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

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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, and urine output and color).

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

All patients who fulfilled the 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/min 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, or 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 $\chi 2$ test, 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.

3. Results

There was no difference between groups in demographic data (Table 1). Syncope was significantly more frequent in group 2 comparing to group 1 (23 vs 67 patients respectively, $p=0.004$), while there was no difference in the frequency of orthostatic hypotension between groups (17 vs 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 ($p=0.035$) (Fig. 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 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.

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

4. 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) (Ebers, 2008; Grubb, 2008). Also, many symptoms are shared, namely orthostatic intolerance, fatigue and anxiety (Hoad et al., 2008; Rietberg et al., 2011). 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 (Stenager and Asbeth, 1992; Vita et al., 1993). The total MRI brain MS lesion load is another pathologic substrate related to autonomic dysfunction incidence as demonstrated by 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, and 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