Postural orthostatic tachycardia predicts early conversion to multiple sclerosis after clinically isolated syndrome

Short title: POTS in MS

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Abstract

Background/aims: Interactions between the autonomic nervous system (ANS) and the immune system functions in multiple sclerosis have been suggested. We aimed to evaluate the ANS dysfunction, more specifically postural orthostatic tachycardia (POTS), as a possible predictor of conversion to multiple sclerosis (MS) in patients with clinically isolated syndrome (CIS).

Methods: In this observational, prospective, longitudinal study 84 patients were enrolled (56 females, mean age 32.9±8.9). Disease activity during a six-month period was monitored (relapses and/or MRI disease activity indicated by new T2 or T1 enhancing lesions), and following predictors analyzed: age, EDSS, MRI midbrain, pontine or medulla oblongata lesions and POTS on the head up tilt test.

Results: POTS was identified in 8 (9.5%) patients. Of 84 patients, 62 (73.8%) completed the six-month follow-up, and 28 (45.2%) patients converted to MS. Results of the multivariate regression analysis revealed age (10-year increase) and POTS as a significant predictors of early conversion to MS (OR 2.34, 95%CI 1.15 ± 4.78, p=0.019 and OR 12.40, 95%CI 1.13 ± 136.62, p=0.040). The logistic model was statistically significant, $\chi^2(6) = 13.885$, p=0.031.

Conclusion: POTS may be an indicator of a more active disease course in CIS patients and possibly be used as a prognostic factor.

Key words: clinically isolated syndrome, multiple sclerosis, postural orthostatic tachycardia syndrome, autonomic nervous system

Introduction

We have recently shown that postural orthostatic tachycardia syndrome (POTS) is more prevalent in multiple sclerosis (MS) patients in comparison to patients with symptoms of orthostatic intolerance and no neurological illness [1]. Furthermore, it has been suggested that autonomic nervous system (ANS) dysfunction may contribute to MS inflammatory and neurodegenerative processes [2].

The aim of the present study was to evaluate the possible role of ANS dysfunction presenting as POTS as a predictor of conversion to MS in patients with clinically isolated syndrome (CIS).

Methods

Patients

This was an observational, prospective, longitudinal study which included consecutive patients diagnosed with CIS from October 2014 until March 2016. The flowchart of the study is presented in Figure 1. Diagnosis of CIS was made in patients with acute or subacute development of neurological symptoms and/or signs lasting longer than 48 hours in the absence of fever or infection and with at least one demyelinating lesion larger than 3mm showing on brain and/or spinal cord MRI. MRI criteria for dissemination in time and space were reviewed as well and patients fulfilling the McDonald criteria at screening were excluded from the analysis [3]. The following parameters were collected during the baseline visit: age, expanded disability status scale (EDSS), presence of midbrain, pontine and medulla oblongata lesions on the baseline MRI.

Autonomic nervous system testing

ANS testing were performed in the Referral Center for Autonomic Nervous System Disorders, the only ANS center in Croatia by neurologists trained in ANS disorders. ANS testst included deep breathing test, heart rate and blood pressure response to Valsalva maneuver and 70° head-up tilt table test. The diagnosis of POTS was made if there was a sustained heart rate increment of ≥30 beats/minute during 10 min of head-up tilt, in 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 cause orthostatic intolerance [4]. If POTS was present, norepinephrine levels and

Quantitative Sudomotor Axon Reflex Test (QSART) were performed in order to investigate peripheral autonomic dysfunction as a possible cause of POTS.

Follow-up

The patients were then followed for six months. Conversion to MS was defined as presence of one or both of the following parameters [3]:

1. the patient developed second clinical attack
2. one or more new T2 and/or gadolinium enhancing lesions on a follow-up MRI

All baseline and follow-up MRIs were performed on a 1.5T MRI scanner. Analyzed MRI sequences included T2, FLAIR and T1 pre and postcontrast sequences. A neurologist with at least 5 years of experience with MS reviewed all MRIs.

Following potential predictors were analyzed: age, EDSS, presence of midbrain, pontine and medulla oblongata lesions on the baseline MRI and presence of POTS.

Ethical committees of the University Hospital Center Zagreb and University of Zagreb, School of Medicine approved the study. All participants signed informed consent.

Statistical analysis

Statistical analysis was performed using the IBM SPSS software, version 20. The Kolmogorov-Smirnov test was applied to test whether the data have a normal distribution. Differences in the distribution of qualitative variables were determined with the $\chi 2$ test, while the differences in quantitative variables, with respect to the distribution, were determined with the use of parametric t-test and non-parametric Mann-Whitney test. Multivariate logistic regression was used in order to determine which variables are significant predictors for specific model. P values less than 0.05 were considered as significant.

Results

Eighty-four CIS patients (56 females, mean age 32.9±8.9) were enrolled. Baseline patients' characteristics are presented in Table 1. POTS was identified in 8 (9.5%) patients. Clinical symptoms, norepinephrine values and QSART results of POTS patients are presented in Table 2. There was no difference in age, EDSS, presence of midbrain, pontine and medulla oblongata lesions on the baseline MRI between patients with and without POTS (all $p>0.05$).

Of the 84 patients, 62 (73.8%) completed the six-month follow-up and 28 (45.2%) patients converted to MS (Figure 1). There was no difference between patients who completed the six-month follow-up and those who did not, regarding age, EDSS, presence of midbrain, pontine and medulla oblongata lesions on the baseline MRI, total number of T2 lesion on the baseline MRI and presence of POTS (2 POTS patients did not completed six-month follow-up) (all $p>0.05$).

Results of the multivariate regression analysis revealed age (10-year increase) and POTS as significant predictors of early conversion to MS (Table 3). The logistic model was statistically significant, $\chi^2(6) = 13.885$, $p=0.031$. The presented model explained 26.8% (Nagelkerke R^2) of the variance in conversion to MS. It correctly classified 71.0% of cases.

Discussion

This study has identified two risk factors for early conversion to MS within the first 6 months after CIS.

The first one is age, with 10-year increase being associated with early conversion to MS. This finding is in contrast with previous studies showing the opposite, that younger age was associated with an increase in risk of a second clinical attack or conversion to MS [5,6]. However, these studies only used second clinical attack, and not MRI parameters of disease activity, as evidence of conversion to MS, which together with a small sample size may explain this discrepancy.

The second risk factor is the presence of POTS, which is becoming recognized as one of the more frequent forms of orthostatic intolerance [7]. It has recently been shown that POTS is more frequent in MS patients in comparison to patients with symptoms of orthostatic intolerance and no neurological illness [1]. This observation is interesting from several aspects. MS and POTS share a similar age of onset, gender preponderance and several symptoms such as fatigue and dizziness. Furthermore, some studies suggest an autoimmune basis in some percentage of POTS patients [8]. Autonomic dysfunction is present in a substantial proportion of MS patients even at the beginning of the disease and studies suggest that the sympathetic and parasympathetic nervous systems occur with a different pattern in MS [9]. Initial sympathetic activation seems to be driven by MS clinical activity/relapses with a subsequent progressive sympathetic dysfunction. In contrast, parasympathetic dysfunction correlates with progression of clinical disability, resulting more likely from structural CNS

damage in MS [10]. One of the suggested causes of POTS is centrally driven abnormal sympathetic activity and this could explain POTS in MS patients. This type of POTS is considered to be associated with values of standing NE higher than 3.5 nmol/L [11]. In our cohort two patients had standing NE values >3.5nmol/L, and none had evidence of neuropathy when inspected by QSART further indicating central cause of POTS in our cohort of CIS patients. However, QSART was available in only 5 out of 8 POTS patients and one had mild sudomotor dysfunction without any other evidence of small fiber neuropathy. Moreover, a close relationship between autoimmune and autonomic system has been suggested, in the way that pathologic interactions between them may fail to trigger anti-inflammatory mechanisms, which are essential to prevent repeated inflammatory attacks, a key pathogenic feature of MS [12]. Furthermore, the finding that POTS occurs more frequently during relapse compared to remission in patients with relapsing remitting MS may indicate a connection between ANS dysfunction and disease activity [13]. Bearing this in mind, results in this study suggest that POTS in MS is associated with disease activity. Therefore, given the presented evidence one should consider that POTS in MS may be a reflection of disrupted autonomico-immunological interaction playing a role in the underlying mechanisms of the disease.

Limitations of our study are a small cohort size and the fact that the MRI imaging protocols were not standardized. Furthermore, 26.2% patients did not complete the six-month follow-up mainly because MRI was not performed. However, we found no difference between all baseline characteristics between patients who did and those who did not completed the six-month follow-up. The main strength of our study is that autonomic dysfunction has never been considered in prospective MS studies up to now and represents a good basis for future research.

In conclusion, we found relatively high proportion of MS patients have POTS in the earliest stages of the disease. We also found that autonomic dysfunction presenting as POTS may be an indicator of a more active disease course and possibly be used as a prognostic factor. Considering the recent literature, which argues for a greater role of autonomic nervous system in MS, and the results presented here, further studies in this field are justified and desirable.

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Table 1. Baseline characteristics.

Baseline characteristic	N=84
Gender, N (%)	
Female	56 (66.7%)
Male	28 (33.3%)
Age, mean (SD)	32.9 (±8.9)
CIS type, N (%)	
Optic neuritis	25 (29.8%)
Transverse myelitis	25 (29.8%)
Brainstem/cerebellum	24 (28.6%)
Hemispheric	8 (9.5%)
Multifocal	2 (2.4%)
EDSS, median (range)	1 (0-3.5)
Midbrain MRI lesions, N (%)	
Present	9 (10.7%)
Absent	75 (89.3%)
Pontine MRI lesions, N (%)	
Present	29 (34.5%)
Absent	55 (65.5%)
Medulla oblongata MRI lesions, N (%)	
Present	11 (13.1%)
Absent	73 (86.9%)
POTS, N (%)	
Present	8 (9.5%)
Absent	76 (90.5%)

Table 2. Description of CIS patients who had POTS on head-up tilt table test.

No.	Type of CIS	Supine			Tilt-up			QSART	Reported symptoms of autonomic dysfunction					
		E	NE	D	E	NE	D		Orthostatic intolerance	Vasomotor	Secretomotor	GI	Bladder	Pupillomotor
1	H	0.15	1.39	0.38	0.11	2.99	0.20	normal	-	-	-	+	-	-
2	BS	NA	NA	NA	NA	NA	NA	normal	+	-	+	+	-	+
3	BS	0.082	0.26	0.20	0.29	1.45	0.50	normal	-	-	+	-	-	-
4	TM	0.082	1.15	0.20	0.25	2.34	0.20	foot hypohidrosis	+	-	-	+	-	+
5	BS	0.082	1.27	0.18	0.34	2.11	0.37	normal	-	-	-	+	-	-
6	TM	0.22	5.06	NA	0.4	10.01	NA	NA	+	+	+	+	-	+
7	TM	0.17	1.18	0.2	0.36	2.7	0.3	NA	-	-	-	+	-	+
8	M	0.16	3.32	0.64	0.24	3.81	0.2	NA	+	-	-	+	-	+

H – hemispheric, BS – brainstem, TM – transverse myelitis, M – multifocal; GI – gastrointestinal, E – epinephrine (normal values <0.46 nmol/l), NE – norepinephrine (normal values <2.49 nmol/l); D - dopamine

Table 3. Results of the multivariate regression analysis for predictors of early conversion to multiple sclerosis.

Predictors	OR	95%CI
Age (10-year increase)	2.34	1.15 ± 4.78*
EDSS	1.72	0.89 ± 3.31
Midbrain lesions	1.36	0.22 ± 8.55
Pontine lesion	0.64	0.16 ± 2.60
Medulla oblongata lesions	3.20	0.45 ± 22.62
POTS	12.40	1.13 ± 136.62*

Figures

Figure 1. Study flowchart.