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Autonomic dysfunction in clinically isolated syndrome suggestive of multiple sclerosis

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Abstract

Objectives: The aim of this study was to determine the extent of autonomic dysfunction in patients with clinically isolated syndrome (CIS) by using a standardized battery of autonomic tests in the form of the composite autonomic scoring scale (CASS).
Methods: This was a prospective, cross sectional study which included 24 consecutive patients who were diagnosed with CIS and 17 healthy controls. In all participants, heart rate and blood pressure responses to the Valsalva maneuver, heart rate response to deep breathing and blood pressure response to passive tilt were performed. In 16 patients, Quantitative Sudomotor Axon Reflex Test (QSART) and catecholamine measurement was performed.
Results: The proportion of CIS patients with pathological adrenergic index was statistically significantly higher compared to healthy controls (12 vs 2, p=0.018), while there was no difference in cardiovagal index between groups. Five patients had a sudomotor index of 1 (in 4 there was hypohydrosis < 50% and in 1 persistent foot hyperhydrosis). When combining adrenergic, cardiovagal and sudomotor index into CASS, 8 patients (50%) had evidence of autonomic dysfunction, 7 mild and one moderate.
Conclusion: Sympathetic nervous system is frequently affected in CIS patients.
Significance: CASS is able to detect autonomic nervous system dysfunction in CIS patients.

Key words: autonomic dysfunction, composite autonomic scoring scale, clinically isolated syndrome

Highlights

- Composite autonomic scoring scale detected sympathetic nervous system dysfunction in half of the clinically isolated syndrome (CIS) patients.
- The parasympathetic nervous system seems to be preserved in the early stages of multiple sclerosis.
- Quantitative Sudomotor Axon Reflex Test detects sudomotor dysfunction in half of the CIS patients.

1. Introduction

Autonomic nervous system (ANS) is frequently affected in patients with multiple sclerosis (MS), and affection of cardiovascular, thermoregulatory, genito-urinary and gastrointestinal parts of the ANS has been described with varying percentages in MS patients (Adamec and Habek, 2013).
Alterations to the cardiovascular system are particularly worrisome because they may result in orthostatic intolerance and cardiac arrhythmia (Jurić et al., 2012). Moreover, in MS patients who fall, dysregulation of the ANS could be another explanation beside cerebellar or pyramidal involvement. (Merkelbach et al. 2006) It is interesting however, that asymptomatic changes in the orthostatic reaction seem to outweigh symptomatic abnormalities. (Merkelbach et al. 2006)
As the cardiovascular reflex mechanisms tested in autonomic laboratories are mainly controlled by baroreflexes, which are controlled by the nuclei in the brainstem, it is thought that involvement of the brainstem by a demyelinating process is responsible for ANS dysfunction in MS. There are limited numbers of studies investigating the correlation between MRI disease burden and ANS dysfunction. It has been shown that midbrain MS lesions account for most of the cardiovascular abnormalities in MS patients, but hemispheric MS lesions also seemed to be involved. (Saari et al., 2004) Others have shown that ANS dysfunction in MS was correlated with spinal cord cross-sectional area reduction but not with spinal cord hyperintensities, indicating that ANS dysfunction is more closely related to axonal loss, rather than demyelinating lesions. (de Seze et al., 2001) Furthermore, several studies have shown that ANS dysfunction correlates with the disease duration and disability measured with expanded disability status scale (EDSS), further suggesting that axonal loss may be responsible for ANS dysfunction in MS. (Gunal et al., 2002; Kale et al., 2009; de Seze et al., 2001)
Another aspect of cardiovascular dysfunction in MS is exercise capacity. Exercise and physical rehabilitation in MS is very important because they lead to enhancement of physical fitness and muscle strength, and improvement in quality of life. Several studies have investigated heart rate and blood pressure responses to incremental dynamic exercise protocols in people with MS. These studies revealed that some MS patients failed to increase heart rate and/or systolic blood pressure sufficiently, as compared with the control group. (Hansen et al. 2013; Hale et al., 2009)
Different prevalence of cardiovascular autonomic dysfunction can be explained with different tests used to investigate both, sympathetic (adrenergic and cholinergic) and parasympathetic functions, and different populations of patients enrolled in these studies. The correlation between single autonomic tests is weak suggesting that different tests measure different aspects and/or different anatomical areas within the ANS. (Merkelbach et al. 2006) The most commonly used tests for parasympathetic nervous system are Valsalva ratio, heart rate response to deep breathing, the 30/15 ratio and for sympathetic nervous system blood pressure response to Valsava ratio (however with different interpretation of the Valsalva curve), isometric hand grip, blood pressure response to passive tilt-up test. (Gunal et al., 2002; Hale et al., 2009; McDougall and McLeod., 2003; Acevedo et al., 2000; Kodounis et al., 2005)
Nevertheless, the common denominator from these studies is that the

sympathetic nervous system is affected in the acute stages of MS (relapses), while the affectibility of parasympathetic nervous system progresses with the disease duration and EDSS. (Nasseri et al., 1999; Flachenecker et al., 2001)
Testing the thermoregulatory autonomic function is another problem, because most of the tests used cannot quantitatively identify differences in sweating or determine whether diminished sweating is due to a decreased number of active sweat glands, altered innervation of the glands, and/or reduced output from activated glands. (Low, 1993) One of the most commonly employed tests for the testing of sudomotor function is a sympathetic skin response (SSR). One study indicated that that SSR is a useful tool for assessment of autonomic function and can be complementary to EDSS and other electrophysiological studies in patients with MS and CIS. (Aghamollaii et al., 2011) Despite this, SSR is not commonly used in clinical practice because current procedures are not sufficiently reliable for diagnostic purposes and it shows imperfect correlations both with clinical features and other measurements of autonomic, in particular, sudomotor dysfunction. (Vetrugno et al., 2003) On the other hand, good evidence exists that Quantitative Sudomotor Axon Reflex Test (QSART) detects a diminished peripheral sweating response as a consequence of impairments in autonomic control of sudomotor function in MS patients (Davis et al., 2010).
To overcome these shortcomings in ANS research a standardized battery of autonomic tests, preferably in the form of a grading scale, which enables diagnosis, grading, and follow-up of autonomic dysfunction, is needed. One such scale is the Composite Autonomic Scoring Scale (CASS), which covers all these prerequisites in disorders of peripheral and central nervous system with ANS involvement (Davis et al., 2005).
Taking all of this into account, and the fact that the ANS has never been systematically investigated in patients with an initial demyelinating event suggestive of MS (clinically isolated syndrome - CIS), the aim of this study was to determine the extent of autonomic dysfunction in patients with CIS by using a standardized battery of autonomic tests in the form of CASS.

2. Methods

2.1. Design

This was a prospective, cross sectional study which included consecutive patients who were diagnosed with a first clinical symptom of multiple sclerosis (CIS) from the 1st of August 2014 until 1st of February 2015 at the Department of Neurology, University Hospital Center Zagreb - a tertiary medical center and a referral center for multiple sclerosis. Diagnosis of CIS was made with the following criteria: 1) acute or subacute development of neurological symptoms and/or signs lasting longer than 48 hours in the absence of fever or infection, 2) brain and spinal cord MRI showing at least 2 demyelinating lesions larger than 3 mm or 1 lesion larger than 3 mm that corresponded to the symptom and/or sign, 3) CSF analysis was performed in all patients for cells, protein level and presence of oligoclonal IgG bands (OCB). Age and gender matched controls participated in the cardiovascular autonomic system testing.

A subset of CIS patients participated in the Quantitative Sudomotor Axon Reflex Test (QSART) and catecholamine measurement portion of the study.
Ethical committees of the University Hospital Center Zagreb and University of Zagreb, School of Medicine approved the study. All participants signed informed consent.

2.2.Cardiovascular autonomic system testing

All tests were performed in a quiet and dimly lit room. Patients were instructed not to drink coffee, smoking or intake of nicotine containing substitutes the morning before the testing. Blood pressure and heart rate values were recorded using Task Force Monitor (TFM) (CNSystems Medizintechnik AG, Austria). After the patient was supine on the testing table, pressure cuff and ECG electrodes were adjusted at appropriate sites. A peripheral vein catheter was installed in the antecubital or radial vein of the right arm, and 15 minutes of settling period was given before recording.
The following tests were performed as described previously (Freeman, 2006; Novak, 2011): heart rate and blood pressure responses to Valsalva maneuver, as a measure of parasympathetic and sympathetic function, respectively; heart rate response to deep breathing as a measure of parsymapthetic function and blood pressure response to passive tilt in the duration of 10 minutes, as a measure of sympathetic function.
The Valsalva maneuver was performed in the supine position by blowing for 15 s through a mouthpiece connected to a mercury manometer. The height of the mercury column was maintained at 40 mm. There was a small air leak in the system to prevent closing of the glottis. The test was repeated until a reproducible response was obtained and the pressure curves on visual inspection allowed measurements of the pressure changes. The Valsalva ratio (VR) was calculated as the ratio of the shortest RR interval during or after phase II of the maneuver to the longest RR interval in phase IV of the maneuver. Measurement of the blood pressure response to Valsalva maneuver relied on single beats before and during the test, and the following parameters were calculated: maximal drop of the mean blood pressure during phase II compared to the level before the start of the test, the peak of the mean blood pressure at the end of late phase II (recovery), overshoot in the phase IV, maximal pulse pressure drop during phase II and pressure recovery time. Direct readings of the calculated mean made by the TFM were used for mean blood pressure levels.
The heart rate variability with deep breathing was performed in the supine position over 9 respiratory cycles; the best six responses were chosen and the respective respiratory sinus arrhythmia (RSA) amplitudes were averaged. RSA amplitude was defined as the difference between the end of expiration and end of inspiration in heart rate.
After these tests, a 10-minute 70° tilted phase followed. Responses to passive tilt were defined either as orthostatic hypotension (OH) or postural orthostatic tachycardia (POTS). OH was defined as a sustained reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of 10 mm Hg within 3 min of head-up tilt to 70° on a tilt table, and POTS was defined as the presence of symptoms of orthostatic intolerance associated with the increment of heart rate (HR) ≥30 bpm for adults, and ≥40 bpm for patients younger than 19 years on

passive tilt and in the absence of orthostatic hypotension. (Freeman et al., 2011) All results were interpreted according to the cardiovagal index (parasympathetic function) and adrenergic index (sympathetic function) of the CASS. (Low, 1993)

2.3. Quantitative Sudomotor Axon Reflex Test (QSART)

Patients were rested in supine position 15 minutes before the test. Recordings were performed in an acclimatized room kept on a stable controlled temperature.
QSART was performed with the Q-Sweat (WR Medical Electronics Co Maplewood, MN, USA). Recording sites were: 1) the medial forearm (75 % distance from the ulnar epicondile to the pisiform bone); 2) the proximal leg (5 cm distal to the fibular head laterally); 3) the distal leg (5 cm proximal to the medial malleolus medially); 4) proximal foot over the extensor digitorum brevis muscle. Multicompartment chambers (sampling area 0.7871 cm^2, volume 0.1229 cm^3) were used for evoked responses. Chambers were first assembled according to the manufacturer recommendation. Recording sites were cleaned with the alcohol and chambers were placed water-tight. Chambers were then filled with 10% acetylcholine (Acetylcholine iodide A7000, Sigma, UK) w/v in sterile water. Sweat production below the sweat compartment of the chamber was continuously measured by circulating air connected to a high precision hygrometer. Gel Trode return electrodes were placed about 5 cm next to the chamber. The stimulation was not started until the baseline sweat was flat, around 50 nanoliters/minute and all channels gave similar baseline sweat output (difference < 15 %). After the baseline values were obtained, iontophoresis of acetylcholine into the skin was performed by passing a 2 mA of constant current across the skin for 5 min. Previously published age and gender dependent reference values for sweat volume of each recording site were used. (Novak, 2011) Data were presented relative to the lower limit for the age group for hypohidrosis or upper limit for the age group for hyperhidrosis. Sudomotor volume results were interpreted according to the sudomotor index of the CASS. (Low, 1993)

2.4. Plasma catecholamine levels

Blood samples were collected directly from a peripheral vein catheter in chilled tubes containing EGTA and reduced glutathione for determination of plasma catecholamine levels in the 10th minute of the supine phase and in the 10th minute of the tilted phase (Kabevette® N, Kabe Labortechnik GmbH). Plasma levels of catecholamine 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).

2.5. Outcomes

Primary outcome was to the determine prevalence of cardiovascular autonomic system pathology using autonomic tests in CIS patients compared to healthy controls. This was assessed by: 1) the proportion of patients with pathological adrenergic index of the CASS score in CIS patients compared to healthy controls; 2) the proportion of patients with pathological cardiovagal index of the CASS score in CIS patients compared to healthy controls.
Secondary outcomes were: 1) to determine the prevalence of sudomotor abnormalities in CIS patients assessed by sudomotor index of the CASS; 2) to determine the prevalence and the degree of autonomic dysfunction according to CASS; 3) to determine is there a difference in catecholamine levels in patients with and without autonomic dysfunction.

2.6. 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 were determined with the use of parametric t-test. P values less than 0.05 were considered as significant.

3. Results

3.1. Patients

During the study period 24 patients and 17 healthy controls were enrolled. There was no statistical difference in age (25,9 vs 24,06; p=0,213) and gender (17 females in group 1 and 7 in group 2; p=0,058). In the CIS group there were 7 cases of optic neuritis, 6 of incomplete transverse myelitis, 8 brainstem/cerebellar, 2 cases of hemispheral and 1 multifocal type of CIS. Median EDSS was 1.0 (range, 0-2.0). Seven out of 24 patients (29,2%) complained of symptoms of orthostatic intolerance, but only 4 of them had positive adrenergic index (Pearson Chi-Square = 0.202, p=0.653).

3.2. Primary outcomes

The median time from the index relapse to the autonomic investigation was 54.5 days (6-273 days). There was no difference in proportion of patients with pathological blood pressure response to Valsalva maneuver or to passive tilt between groups. The proportion of CIS patients with pathological adrenergic index was statistically significantly higher compared to healthy controls. On the other hand, there was no difference in cardiovagal index between groups. There was no difference in the proportion of pathological Valsalva ratio or respiratory sinus arrhythmia between groups. Values for all these data are presented in Table 1. On the other hand, the mean Valsalva ratio was significantly higher in the CIS group compared to healthy controls (Table 2).

Adrenergic index positively correlated with the EDSS (Pearson's Chi square, p=0.041), meaning that patients with normal adrenergic index had lower EDSS. In the CIS group there were 5 cases of POTS, while we did not identify any cases of POTS in the healthy control group, although this did not reach statistical significance. On the other hand, CIS patients had significantly higher chance for pathological HUTT response compared to healthy controls (Table 1).

3.3. Secondary outcomes

3.3.1. QSART
Altogether 16 patients participated in the QSART substudy. Out of them, 8 had a pathological response on at least one tested site (Figure 1). Hypohydrosis was present in 4 patients and persistent foot sweating in one patient. Sweat production in the forearm was reduced of 2 patients (6% and 30% (patients 2 and 5 in the Table 3, respectively)) and in the foot of 2 patients (35% and 42% (patients 1 and 10 in the Table 3, respectively)). Sweat production was increased in the forearm of 1 patient (5%, patient 14 in the Table 3), distal leg in 2 patients (17% and 10% (patients 11 and 16 in the Table 3, respectively)), and in the foot of 1 patient (7%, patient 15 in the Table 3). Five patients had sudomotor index of 1 (four had hypohydrosis < 50% minimal referent value and one had persistent foot hyperhidrosis) (Table 3).

3.3.2. CASS
When combining adrenergic, cardiovagal and sudomotor indicies into CASS, 8 patients (50%) had evidence of autonomic dysfunction, 7 mild and one moderate. It should be noted that none of the patients had parasympathetic dysfunction (Table 3).

3.3.3. Plasma catecholamine levels
Plasma catecholamine levels were determined in 15 patients; in one the blood withdrawal was not successful due to obstruction of the peripheral vein catheter. There was no difference in epinephrine and norepinephrine levels in the supine and standing positions between patients with or without sympathetic nervous system dysfunction (Table 4).

4. Discussion

Results of this study have shown autonomic dysfunction to be present in the earliest stages of MS. This autonomic dysfunction can primarily manifest as an effect on the sympathetic nervous system while the parasympathetic nervous system seems to be preserved in the early stages of the disease. This finding is in line with previous studies, which showed sympathetic nervous system dysfunction during relapses compared to patients with stable disease. (Flachenecker et al., 2011; Adamec et al., 2013) The finding that the mean Valsalva ratio was significantly higher in the CIS group compared to healthy controls indicates sympathetic vasomotor dysfunction in the CIS group, which further supports predominantly sympathetic nervous system dysfunction in active phases of MS. (Sandroni et al., 1991)

However, when interpreting ANS dysfunction in MS, one has to bear in mind that the definition of cardiovascular autonomic dysfunction in MS patients is controversial. Some authors are arguing that cardiovascular dysautonomia in MS should be diagnosed using a definition of at least one abnormal cardiac autonomic test, while others require at least two abnormal studies. Recently performed meta-analysis showed that the proportion of patients with autonomic dysfunction was two-fold higher when using the definition of only one abnormal autonomic test (42.1%) compared to that using at least two abnormal results (18.8%). (Racosta et al., 2015). However, interpretation of autonomic dysfunction in the form of CASS overcomes this problem. Direct disturbances of the sympathetic cardiac function in MS were visualized with I-123 MIBG myocardial scintigraphy, further supporting importance of ANS in MS (Lorberboym et al., 2008). Unlike sympathetic dysfunction, two studies have shown parasympathetic dysfunction progress during the course of the disease and that it is related to progression of disability measured with EDSS. (Flachenecker et al., 2001; Nasseri et al., 1999) It seems that parasympathetic dysfunction is driven by the disease pathology itself, although in the present study sympathetic cardiac dysfunction correlated with the EDSS, as well.
Another finding of our study is that most of the patients with sympathetic dysfunction do not have symptoms of orthostatic intolerance. This is in line with the studies showing that patients with structural disorders of the autonomic nervous system, in spite of their extensive pathologic changes, tend to harbor proportionally fewer symptoms; for example, the majority of patients do not realize when their systolic blood pressure drops by nearly 90 mmHg (Arbogast et al., 2009). Another finding supporting this discrepancy is the poor correlation between the autonomic questionnaires with the outcome of autonomic tests (Labuz-Roszak and Pierzchala, 2007).
Cardiac autonomic dysfunction in MS has several implications. The first one is the possibility of increased risk of cardiac arrhythmias in MS patients with severe cardiac autonomic dysfunction. It has been shown that MS is associated with prolonged P wave duration and increased P wave duration and dispersion, compared to healthy controls (Kocer et al., 2005). More importantly, prolonged P-wave duration and increased P wave duration and dispersion have been reported to carry an increased risk for atrial fibrillation (Dilaveris et al., 1998). This can have important clinical implication, especially regarding treatment of MS patients. Various cardiac arrhythmias have been reported during corticosteroid therapy for MS relapses, and sinus bradycardia and atrial fibrillation were detected more commonly in patients with history of urinary dysfunction, thus patients with ANS dysfunction (Vasheghani-Farahani et al., 2011). In addition, the chronic use of many drugs commonly used by MS patients could further downregulate sympathetic nervous system by interfering with norepinephrine synthesis/release and/or interfering with the function of the adrenergic receptors in both the brain and in the periphery (Sternberg, 2012). It has even been suggested that sympathetic nervous system dysfunction in combination with norepinephrine levels would have the potential to identify MS patients who have a reduced response to immunomodulatory therapies. (Sternberg, 2012). On the other hand, new oral MS therapy, like fingolimod, is known to have cardiac side-effects, and one case report suggested that some

types of arrhythmias associated with fingolimod might be related to ANS dysfunction (Gialafos et al., 2014).
The second implication is the influence of autonomic dysfunction on fatigue, which is one of the most common symptoms of MS. Several studies have shown that in patients suffering from fatigue, fatigue experience is associated with decreased blood pressure or with sympathetic and parasympathetic autonomic dysfunction. (Freeman and Komaroff, 1997; Flachenecker et al., 2003)
It has earlier been mentioned that norepinephrine levels together with sympathetic nervous system dysfunction may have the potential to identify MS patients who have a reduced response to therapy. While one study showed that resting plasma norepinephrine was significantly lower in MS patients compared to healthy controls (Keller et al., 2014), and another study showed that norepinephrine and epinephrine levels are significantly lower in active MS patients compared to stable MS patients (Flachenecker et al., 2001), in the present study we were not able to show differences in catecholamine levels in MS patients with positive CASS compared to MS patients with negative CASS.
Furthermore, we have shown that half of the CIS patients have varied pathologies on QSART. Thermoregulation has, to the best of our knowledge, only been studied once in CIS patients (only in patients with optic neuritis) with sympathetic skin response. This study has shown increased latencies, indicating sudomotor failure (Saari et al., 2010). QSART has rarely been studied in MS, mainly because it is considered that an absent response indicates a lesion of the postganglionic axon. However, with increased duration of the preganglionic lesion the response may become abnormal. This has been shown nicely in a study investigating cholinergic sweating responses with pilocarpine iontophoresis. Authors observed diminished peripheral sweating responses as a consequence of impairments in autonomic control of sudomotor function. (Davis et al., 2005) The importance of identifying thermoregulatory disturbance in MS is seen from several observations: 1) pathophysiological principle of temperature-induced conduction block in demyelinated axonal segments (Uhthoff's phenomenon), 2) fluctuations in body temperature can be problematic for MS patients when infections have been masked due to the absence of a typical fever response, resulting in serious medical conditions, 3) heat induced fatigue and 4) effects of heat sensitivity to exercise (Davis et al., 2010).
While CASS has been investigated in several central and peripheral nervous system disorders, this is the first study investigating CASS score in early MS (Lipp et al., 2009). CASS detected sympathetic nervous system dysfunction in half of the CIS patients, proving to be a good option for detection of autonomic dysfunction in MS, as well.
The limitations of this study are the relatively small number of patients enrolled and that we only enrolled healthy controls for the testing of the cardiovascular autonomic system. However, the number of patients is comparable to all other previous studies investigating autonomic dysfunction in MS, and for QSART and catecholamines well established normal values exist.
In conclusion, CASS is able to detect autonomic nervous system dysfunction in CIS patients, in whom the sympathetic nervous system is frequently affected.

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Tables

Table 1. Differences in the proportion of positive main sympathetic and parasympathetic indexes between CIS patients and healthy controls.

	CIS (n=24)	**Healthy controlos (n=17)**	**p value**
Valsalva ratio	1	1	1.000
RSA	0	0	
Valsalva BP	9	2	0.150
OH	2	0	0.502
POTS	5	0	0.065
HUTT (OH or POTS)	7	0	0.029*
Adrenergic index (CASS)	12	2	0.018*
Cardiovagal index (CASS)	1	0	1.000

RSA respiratory sinus arrhythmia; Valsalva BP blood pressure response to Valsalva maneuver, OH orthostatic hypotension; POTS postural orthostatic tachycardia syndrome; HUTT head up tilt table test; CASS Composite Autonomic Scoring Scale.

Table 2. Differences between parasympathetic indexes between CIS patients and healthy controls.

Cardiovagal function	**Group**	**Mean**	**SD**	**p value**
RSA	CIS	28.25	8.13	0.176
	HC	25.36	5.26	
VR	CIS	2.27	0.32	0.045*
	HC	2.07	0.29	

RSA respiratory sinus arrhythmia; VR Valsalva ratio; HC healthy control.

Table 3. Characteristics of the subset of patients included in the Quantitative Sudomotor Axon Reflex Test and catecholamine measurement part of the study.

Patient	Type of CIS	Adrenergic index	Cardiovagal Index	Sudomotor index	CASS
1	TM	0	0	1	1
2	TM	0	0	1	1
3	B	1	0	0	1
4	TM	0	0	0	0
5	ON	0	0	1	1
6	ON	0	0	0	0
7	ON	0	0	0	0
8	ON	1	0	0	1
9	TM	0	0	0	0
10	B	3	0	1	4
11	H	0	0	0	0
12	B	0	0	0	0
13	ON	0	0	0	0
14	TM	0	0	0	0
15	TM	0	0	1	1
16	B	1	0	0	1

ON optic neuritis; TM transverse myelitis; B brainstem, H hemispheric type of CIS.

Table 4. Differences in catecholamine measurements between the patients with and without evidence of sympathetic nervous system dysfunction.

Catecholamines	Adrenergic CASS	Mean (nmol/l)	St. deviation	p value
E_{Su}	0	0.19	0.18	0.646
	1	0.23	0.21	
E_{St}	0	0.29	0.21	0.935
	1	0.28	0.17	
N_{Su}	0	1.51	0.41	0.873
	1	1.43	1.26	
N_{St}	0	3.06	1.14	0.619
	1	3.45	1.66	

E_{Su} – supine epinephrine; E_{St} – standing epinephrine; N_{Su} – supine norepinephrine; N_{St} – standing norepinephrine

Figures

Figure 1. Shows proportion of patients with different responses on Quantitative Sudomotor Axon Reflex Test and Composite Autonomic Scoring Scale in 16 patients participating in the substudy.