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Autonomic dysfunction in people with neuromyelitis optica spectrum disorders

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Abstract

Aims: To determine the difference in autonomic symptom burden measured with the Composite Autonomic System Score-31 (COMPASS-31) and presence of objective dysautonomia in people with neuromyelitis optica spectrum disorders (pwNMOSD) compared to people with multiple sclerosis (pwMS).

Design/Methods: Twenty pwNMOSD and 20 pwMS, matched for age, sex and disease duration were enrolled. All patients completed the COMPASS-31. The quantification of cardiovascular autonomic dysfunction (CAD) was made using the two indices of the Composite Autonomic Scoring Scale (CASS): adrenergic index (AI) and cardiovagal index (CI).

Results: In all pwNMOSD, COMPASS-31 was >0. Sympathetic dysfunction was present in 8 (40%), parasympathetic dysfunction in 10 (50%) and orthostatic hypotension in 6 (30%) pwNMOSD. This group of patients had higher frequency and level on the pupilomotor domain of the COMAPSS-31 compared to pwMS (p=0.048 and p=0.006, respectively). A binary logistic regression model showed that drop in dBP during tilt-table test and normal function of autonomic nervous system, defined as AI=0 and CI = 0, were independent predictors of pwNMOSD (p=0.042 and p=0.029, respectively). If CAD was present, it was significantly worse in pwNMOSD compared to pwMS (p=0.003)

Conclusion: Significant proportion of pwNMOSD experience dysautonomia, which seems to be different from dysautonomia observed in pwMS.

Key words: Neuromyelitis optica spectrum disorders, autonomic dysfunction, multiple sclerosis

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory syndrome of the central nervous system (CNS), distinct from multiple sclerosis (MS), that is associated with serum aquaporin-4 immunoglobulin G antibodies (NMO-IgG) (1). According to the new NMOSD diagnostic criteria (2), there are six core clinical characteristics of NMO, including transverse myelitis, optic neuritis, area postrema syndrome, brainstem syndrome, diencephalic syndrome or symptomatic narcolepsy and symptomatic cerebral syndrome.
In recent years it has been shown that people with MS (pwMS) have a substantial involvement of the autonomic nervous system (ANS), and that this is mainly the consequence of brainstem and spinal cord involvement (3,4). Having in mind above mentioned, it is surprising that only few case reports exist describing autonomic dysfunction in patients with NMOSD (pwNMOSD), a disease that primarily involves areas of the CNS responsible for autonomic dysfunction (5,6).
Therefore, the aim of this study was to determine the extent of autonomic symptom burden in pwNMOSD measured with the Composite Autonomic System Score-31 (COMPASS-31) and presence of objective dysautonomia in pwNMOSD. Furthermore, we compared observed results with a historical cohort of pwMS.

Methods

This was a prospective study performed from January to December 2017 that included consecutive pwNMOSD according to the Wingerchuk 2015 criteria (2). pwNMOSD were recruited consecutively during their regular follow-up visits at the Outpatient Clinics of the

Departments of Neurology at Clinical Center of Serbia, Belgrade, Serbia and University Hospital Center Zagreb, Zagreb, Croatia.

Exclusion criteria included significant cardiac or pulmonary disease and medication with known influence on the autonomic nervous system (anticholinergics, antihypertensives, beta blockers, diuretics, antiarrhythmics, sympathomimetics, parasympathomimetics).

All participants signed informed consent approved by the ethical committees of the Faculty of Medicine University of Belgrade and University Hospital Center Zagreb.

Autonomic nervous system testing

All patients completed validated Serbian and Croatian versions of the Composite Autonomic System Score-31 (COMPASS-31) (7).

The following ANS tests were performed according to the previously described methodology (4): heart rate (Valsalva ratio (VR)) and blood pressure responses to the Valsalva maneuver, heart rate response to deep breathing (respiratory sinus arrhythmia (RSA)) and the tilt table test. The quantification of autonomic dysfunction was made using the two indices of the Composite Autonomic Scoring Scale (CASS): adrenergic index (AI) and cardiovagal index (CI) (8).Finally, cardiovascular autonomic dysfunction (CAD) was calculated by summing values of AI and CI (minimum values 0 indicating no CAD, and 1-7 indicating presence of CAD). One patient with NMOSD and four patients with MS were not able to carry Valsalva maneuver test properly, so AI index could not have been calculated.

Outcomes

The primary outcomes were to determine the extent of autonomic symptom burden measured with COMPASS-31 and presence of objective dysautonomia measured with AI and CI in pwNMOSD.

The secondary outcomes were to compare autonomic symptom burden measured with COMPASS-31 and presence of objective dysautonomia measured with AI and CI in pwNMOSD and people with multiple sclerosis (pwMS).

In order to achieve this, we used historical controls (pwMS) from our databases matched for age, sex and disease duration. The diagnosis of MS was based on the 2010 revisions of the McDonald criteria (9). All pwMS completed COMPASS-31, had calculated AI and CI, and did not meet any of the exclusion criteria.

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 (sex, frequency of orthostatic hypotension, frequency of pathological response on COMPASS-31 and CASS), while the differences in quantitative variables were determined with the use of a parametric t-test (age, disease duration, RSA, Valsalva index, HR, dBP and sBP) or a non-parametric Mann–Whitney test (EDSS, CASS, COMPASS-31). Correlation analysis was performed with Spearman's correlation. Univariable binary logistic regression model analysis was performed to see which variables are possible predictors for the likelihood that patients had NMO. Variables with $p<0.2$ were included in multiple logistic regression model. P values less than 0.05 were considered as significant.

Data availability statement

Any data not published within the article in an anonymized way will be shared by request from any qualified investigator.

Results

Twenty pwNMOSD were enrolled and demographic data are presented in Table 1. NMO IgG antibody was present in 14 (70%) patients. Clinical characteristics of the pwNMOSD are as follows: optic neuritis (ON) was one of the relapses in 14 (70%), transverse myelitis (TM) in 12 (60%), and area postrema and/or brainstem syndrome (AP-BS) in 9 (45%) patients.

Primary outcomes

In all pwNMOSD, COMPASS-31 was >0 (orthostatic intolerance domain was >0 in 10 (50%), vasomotor domain in 9 (45%), secretomotor in 10 (50%), gastrointestinal domain in 18 (90%), bladder domain in 12 (60%) and pupillomotor domain in 20 (100%) patients). Qualitative values of COMPASS-31 are presented in Table 1.

AI >0, indicating sympathetic dysfunction was present in 8 (40%) and CI>0, indicating parasympathetic dysfunction was present in 10 (50%) pwNMOSD. Orthostatic hypotension on tilt-table test was present in 6 (30%) of pwNMOSD. Qualitative values of AI and CI are presented in Table 1. Six (30%) pwNMOSD had CAD>3.

Table 2 presents descriptive data regarding clinical characteristics and the results of the ANS testing for pwNMOSD. When we divided patients in two groups, one group with the exclusive presentations with ON and other group with TM and/or AP-BS during their clinical

course, we did not find statistically significant difference in CAD values between these two groups, although majority of patients with exclusive ON presentation have non-pathological autonomic response (CAD=0) and mild (CAD=1-3) autonomic dysfunction. Also, 5 out of 6 patients with the exclusive presentations in the form of ON did not have OH. However, there was no statistically significant difference between these two groups regarding the presence of OH.

Secondary outcomes

In order to compare autonomic symptom burden and dysautonomia in pwNMOSD and pwMS, 20 pwMS were enrolled, matched for age, sex and disease duration. Demographic characteristics of pwMS are presented in Table 1. In 19 (95%) pwMS COMPASS-31 was >0 (orthostatic intolerance domain was >0 in 6 (30%), vasomotor domain in 3 (15%), secretomotor in 9 (45%), gastrointestinal domain in 18 (90%), bladder domain in 12 (60%) and pupilomotor domain in 13 (65%) patients). The frequency of presence of autonomic symptom burden was higher in pwNMOSD for the vasomotor and pupilomotor domains of the COMPASS-31 compared to pwMS ($p=0.048$ and $p=0.006$, respectively). Differences in qualitative values of COMPASS-31 between groups are presented in table 1. For both groups of participants, there was no statistically significant correlation between the disease duration and baseline variables (all $p>0.05$). Also, there was no statistically significant correlation between the EDSS and CAD values for both groups (all $p>0.05$).

AI >0, indicating sympathetic dysfunction was present in 7 (35%) and CI>0 indicating parasympathetic dysfunction was present in 6 (30%) pwMS. Orthostatic hypotension on tilt-table test was present in 3 (15%) of pwMS. There was no statistically significant difference in

any of the studied parameters between groups (all p>0.05). Differences in qualitative values of AI and CI between groups are presented in table 1. None of the pwMS had CAD>3. Differences in heart rate (HR), systolic blood pressure (sBP) and diastolic blood pressure (dBP) between groups are presented in table 1. pwNMOSD had significantly greater drop in dBP during tilt-table test compared to pwMS, p=0.044 (Figure 1).

Finally, an univariable logistic regression analysis was used to asses which variables are possible predictors for differentiation between pwNMOSD from pwMS (Table 3). Variables with p<0.2 were included in a multiple logistic regression model (Table 4). Due to small number of participants, only the most significant variables were included in further analysis, and model was based on drop in dBP during tilt-table test and normal function of autonomic nervous system, defined as CAD =0. Also, disease duration was included in the model, because this variable is known to influence the results of the autonomic nervous system tests. In the multiple regression model (Chi square = 9.853, p=0.02), CAD=0 increases the likelihood of having NMOSD (Exp (B) =9.487, p=0.029). Although normal CAD was more frequently detected in pwNMOSD, if it was present, value was significantly worse in pwNMOSD compared to pwMS (Figure 2).

Discussion

This study has revealed several characteristics of dysautonomia in pwNMOSD: 1) pwNMOSD have significant autonomic symptom burden and objectively documented CAD; and 2) compared to pwMS, the frequency of presence of CAD is lower, however, if CAD is present in pwNMOSD, it is more likely to have value >3 (defined as simultaneous presence of orthostatic hypotension and parasympathetic dysfunction).

It is interesting to note that the only difference regarding autonomic symptoms between pwNMOSD and pwMS was in frequency and severity of pupillomotor abnormalities. There are several possible explanations for this. The first one is the observation that pwMS have a reduction of parasympathetic tone and a relative increase in sympathetic dilatator tone to the pupils(10). As a consequence, pwMS may exhibit some of the pupillomotor symptoms examined by the COMPASS-31. Unfortunately, similar investigations in pwNMOSD are lacking, however one can hypothesize that pwNMOSD may have more severe involvement of the pupillomotor system based on the findings of the present study. Another possible explanation is related to the characteristics of optic neuritis in these two conditions. Sensitivity to light and photopsia are known manifestations of optic neuritis, and it is well established that differences exist in optic neuritis between pwNMOSD and pwMS (11).First of all, pupil response components can be affected differently in optic neuritis (12). Furthermore, recent studies have shown that the final visual acuity is significantly worse in pwNMOSD compared to pwMS (11,13). Further emphasizing the importance of this difference is a study that showed vision-related quality of life to be reduced in pwNMOSD compared to pwMS patients, and this difference is driven by more severe optic neuritis in pwNMOSD (14). As COMPASS-31 evaluates autonomic symptom burden and is one of the patient related measures of autonomic dysfunction, including problems with the vision, our finding supports the influence of visual symptoms on pwNMOSD.

On the other hand, although cardiovascular autonomic dysfunction is an important consequence of MS (4,15), it has never been systematically investigated in pwNMOSD. There are several case reports describing orthostatic hypotension or postural orthostatic tachycardia syndrome in pwNMOSD (5,6). In the present study we have found significant proportion of pwNMOSD having CAD. This can be explained by preferential involvement of

the nuclei in the periventricular region of fourth ventricle in the brainstem and the spinal cord, regions responsible for autonomic regulation (16). One of the devastating consequences of spinal cord involvement at Th6 or above, which has recently been described in pwNMOSD, is a so called autonomic dysreflexia, a condition characterized with a low baseline systemic arterial blood pressure and orthostatic hypotension that can be interposed by sudden-onset hypertensive episodes (17).

We also found significant differences in CAD between pwNMOSD and pwMS. While pwMS have more frequently mild CAD, pwNMOSD more frequently have no CAD, compared to pwMS.However, when it is present in pwNMOSD, it is more severe compared to pwMS and characterized with orthostatic hypotension and parasympathetic dysfunction. This can be explained by more extensive involvement of the regions responsible for autonomic regulation in pwNMOSD. Previous studies have shown a distinct pattern of autonomic dysfunction in different phases of MS. In the early phase there is a predominant sympathetic dysfunction with sparing of the parasympathetic system and parasympathetic dysfunction increases with disease duration significantly correlating with an increase in clinical disability (4,15,18). Contrary to this, pwNMOSD do not exhibit such pattern of dysautonomia.

Finally, disability in NMOSD is totally dependent on the CNS locations of lesions leading to the development of clinical attacks (19). Therefore, one can speculate that the pattern and frequency of autonomic dysfunction must be different according to the involved site. While our data show that patients with ON as an exclusive presentation of NMOSD have neither OH, nor autonomic dysfunction (or very mild if present), due to small sample size, we were unable to show that difference in the frequency of OH in this group of patients is statistically significant in comparison with patients with TM and/or AP-BS. Future studies with larger cohort of patients are needed to address this question.

This study has several limitations. There is possible recruitment bias because all patients were enrolled from tertiary medical centers. However, NMOSD is relatively rare condition and in our region most patients are treated in a single center. Another limitation is the fact that we used historical pwMS as controls, however we used this approach in order to stratify patients according to age, sex and disease duration in order to exclude the impact these factors have on autonomic test results.

In conclusion, significant proportion of pwNMOSD experience dysautonomia, which seems to be different from dysautonomia observed in pwMS. Comprehensive assessment of autonomic function in NMO patients and further research in this field is warranted.

References

1. Sellner J, Boggild M, Clanet M, Hintzen RQ, Illes Z, Montalban X, Du Pasquier RA, Polman CH, Sorensen PS, Hemmer B. EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol 2010;17:1019-32.
2. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, de Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lana-Peixoto M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Wellik KE, Weinshenker BG; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89.
3. de Seze J, Stojkovic T, Gauvrit JY, Devos D, Ayachi M, Cassim F, Saint Michel T, Pruvo JP, Guieu JD, Vermersch P. Autonomic dysfunction in multiple sclerosis: cervical spinal cord atrophy correlates. J Neurol 2001;248:297-303.

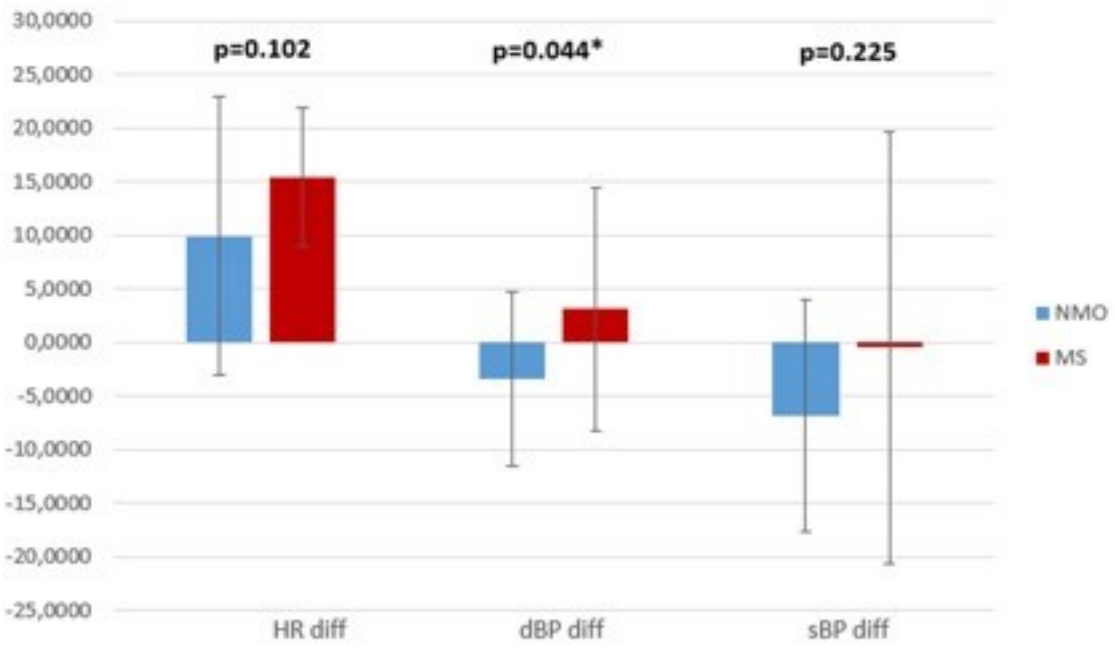
4. Habek M, Crnošija L, Lovrić M, Junaković A, Krbot Skorić M, Adamec I. Sympathetic cardiovascular and sudomotor functions are frequently affected in early multiple sclerosis. Clin Auton Res 2016;26:385-393.
5. Barun B, Adamec I, Lovrić M, Habek M. Postural orthostatic tachycardia syndrome: additional phenotypic feature of neuromyelitis optica spectrum disorder. Neurol Sci 2014;35:1623-5.
6. Berry R, Panegyres PK. Peduncular Hallucinosis and Autonomic Dysfunction in Anti-Aquaporin-4 Antibody Syndrome. Cogn Behav Neurol 2017;30:116-124.
7. Drulović J, Gavrilović A, Crnošija L, Kisić-Tepavčević D, KrbotSkorić M, Ivanović J, Adamec I, Dujmović I, Junaković A, Marić G, Martinović V, Pekmezović T, Habek M. Validation and cross-cultural adaptation of the COMPASS-31 in Croatian and Serbian patients with multiple sclerosis. Croat Med J 2017;58:342-348.
8. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 1993;68:748–752.
9. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
10. Pozzessere G, Rossi P, Valle E, Froio CP, Petrucci AF, Morocutti C. Autonomic involvement in multiple sclerosis: a pupillometric study. Clin Auton Res 1997;7:315-9.
11. Akaishi T, Nakashima I, Takeshita T, Kaneko K, Mugikura S, Sato DK, Takahashi T, Nakazawa T, Aoki M, Fujihara K. Different etiologies and prognoses of optic neuritis in demyelinating diseases. J Neuroimmunol 2016;299:152-157.
12. Barbur JL, Moro S, Harlow JA, Lam BL, Liu M. Comparison of pupil responses to luminance and colour in severe optic neuritis. ClinNeurophysiol2004;115:2650-8.

13. Masuda H, Mori M, Uzawa A, Muto M, Uchida T, Ohtani R, Akiba R, Yokouchi H, Yamamoto S, Kuwabara S. Recovery from optic neuritis attack in neuromyelitisoptica spectrum disorder and multiple sclerosis. J Neurol Sci 2016;367:375-9.
14. Schmidt F, Zimmermann H, Mikolajczak J, Oertel FC, Pache F, Weinhold M, Schinzel J, Bellmann-Strobl J, Ruprecht K, Paul F, Brandt AU. Severe structural and functional visual system damage leads to profound loss of vision-related quality of life in patients with neuromyelitis optica spectrum disorders. Mult Scler Relat Disord 2017;11:45-50.
15. Adamec I, Crnošija L, Junaković A, KrbotSkorić M, Habek M. Progressive multiple sclerosis patients have a higher burden of autonomic dysfunction compared to relapsing remitting phenotype. ClinNeurophysiol 2018;129:1588-1594
16. Habek M. Evaluation of brainstem involvement in multiple sclerosis. Expert Rev Neurother2013;13:299–311.
17. Furlan JC. Autonomic dysreflexia following acute myelitis due to neuromyelitisoptica. Mult Scler Relat Disord 2018;23:1-3.
18. Flachenecker P, Reiners K, Krauser M, Wolf A, Toyka KV. Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. MultScler2001;7:327–334.
19. Abboud H, Petrak A, Mealy M, Sasidharan S, Siddique L, Levy M. Treatment of acute relapses in neuromyelitisoptica: Steroids alone versus steroids plus plasma exchange. Mult Scler 2016;22:185-92.

Figures

Figure 1. Changes in heart rate (HR), systolic blood pressure (sBP) and diastolic blood pressure (dBP) between tilted and supine positions during the tilt-table test.

Figure 2. Cardiovascular autonomic dysfunction (CAD) values between pwNMOSD and pwMS.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p=0.225
HR diff
dBP diff
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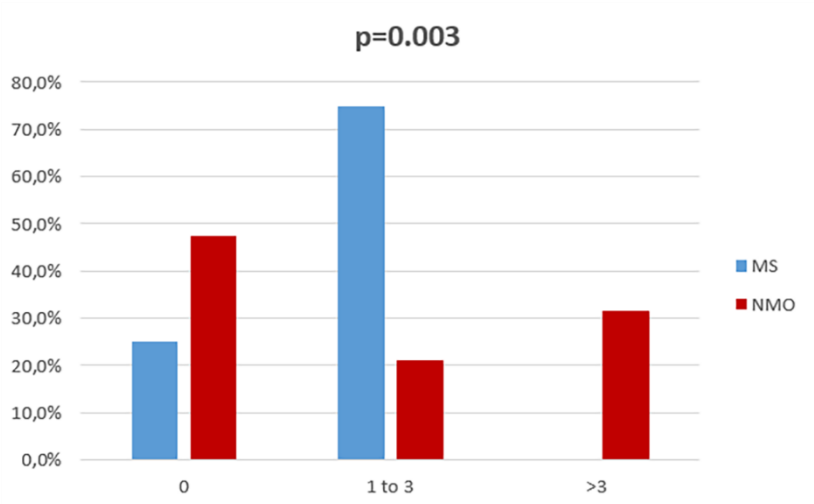
p=0.003
80,0%
70,0%
60,0%
50,0%
40,0%
30,0%
20,0%
10,0%
0,0%
0
1 to 3
>3
MS
NMO

Table 1. Demographic data and results of the autonomic nervous system testing of the studied cohort.

		NMOSD	MS	P value
General characteristics				
Age, years (mean, SD)		48.2 (10.8)	46.3 (10.3)	0.572
Female (N,%)		16 (80%)	16 (80)	1.000
Disease duration, years (mean, SD)		9.8 (8.0)	7.7 (6.6)	0.360
EDSS (median, range)		2.5 (0-7.5)	3.0 (1.0-8.0)	0.174
Heart rate and blood pressure values				
HR su (mean, SD)		76.9 (12.4)	75.3 (15.1)	0.719
sBP su (mean, SD)		118.5 (14.1)	114.7 (20.5)	0.508
dBP su (mean, SD)		79.2 (10.5)	75.6 (10.2)	0.285
HR st (mean, SD)		86.8 (11.9)	90.7 (16.3)	0.399
sBP st (mean, SD)		111.7 (13.8)	114.3 (16.6)	0.596
dBP st (mean, SD)		75.8 (10.2)	78.8 (12.9)	0.425
Objective dysautonomia				
RSA (mean, SD)		16.4 (8.8)	16.9 (10.8)	0.861
VR (mean, SD)		1.6 (0.3)	1.8 (0.5)	0.135
OH (N, %)		6 (30)	3 (15)	0.256
AI (median, range)		0 (0-3)	0 (0-3)	0.832
CI (median, range)		0.5 (0-1)	0 (0-3)	0.355
	0	9 (47.4)	4 (25)	0.003

CAD (N, %)	1-3	4 (21.1)	12 (75)	
	>3	6 (231.6)	0 (0)	
Autonomic symptom burden				
COMPASS-31 (median, range)		12.2 (2.5-50.8)	12.9 (0-43.9)	0.813
OI (median, range)		2 (0-28.0)	0 (0-20.0)	0.365
Vasomotor (median, range)		0 (0-3.3)	0 (0-3.6)	0.184
Secretomotor (median, range)		1.1 (0-4.3)	0 (0-8.6)	0.461
GI (median, range)		3.6 (0-10.7)	4.5 (0-11.6)	0.380
Bladder (median, range)		1.1 (0-10.0)	1.1 (0-7.8)	0.749
Pupillomotor (median, range)		1.3 (0.3-3.7)	0.7 (0-3.7)	0.044

NMOSD – neuromyelitis optica spectrum disorder, MS – multiple sclerosis, SD – standard deviation, EDSS – Expanded disability status scale, su – supine, st – standing, HR – hear rate, sBP – systolic blood pressure, dBP – diastolic blood pressure, RSA – respiratory sinus arrhythmia, VR – Valslava ratio, OH – orthostatic hypotension, AI – adrenergic index, CI – cardiovagal index, CAD – cardiovascular autonomic dysfunction, COMAPSS-31 - Composite Autonomic System Score-31, OI – orthostatic intolerance, GI – gastrointestinal.

Table 2. Descriptive presentation of the clinical characteristics and the results of the ANS testing for pwNMOSD.

Patient ID	TM	ON	AP-BS	OH	AI	CI	CAD
1	-	+	-	+	3	1	4
2	+	-	-	+	3	1	4
3	-	+	-	-	1	1	2
4	+	+	-	-	0	1	1
5	+	+	-	-	1	0	1
6	-	+	-	-	0	0	0
7	+	+	-	-	0	1	1
8	-	+	-	-	0	0	0
9	-	+	-	-	0	0	0
10	-	+	-	-	0	0	0
11	+	+	-	-	0	0	0
12	+	-	+	-	0	0	0
13	-	+	+	+	3	1	4
14	+	-	+	-	NA	1	NA
15	+	-	+	+	3	1	4
16	+	+	+	-	0	0	0
17	+	+	+	-	0	0	0
18	+	-	+	+	3	1	4
19	-	-	+	-	0	0	0
20	+	+	+	+	3	1	4

TM - transverse myelitis, ON - optic neuritis, AP-BS - area postrema and/or brainstem syndrome, OH – orthostatic hypotension, AI – adrenergic index, CI – cardiovagal index, CAD – cardiovascular autonomic dysfunction, NA – not available

Table 3. Results of the univariable logistic regression analysis used to investigate which variables are possible predictors for differentiation between pwNMOSD from pwMS.

	Exp(B)	95% C.I. for EXP(B)		p value
Age, years	1,018	0,958	1,082	0.562
Sex	1,000	0,212	4,709	1.000
Disease duration, years	1,042	0,955	1,138	0.351
EDSS	0,762	0,555	1,048	0.094
HR su	1,009	0,963	1,056	0.711
sBP su	1,013	0,976	1,051	0.500
dBP su	1,035	0,972	1,102	0.279
HR st	0,980	0,937	1,026	0.392
sBP st	0,988	0,948	1,031	0.587
dBP st (mean, SD)	0,977	0,924	1,033	0.417
HR st-su	0,943	0,876	1,015	0.118
sBP st-su	0,972	0,927	1,019	0.241
dBP st-su	0,931	0,865	1,002	0.055
AI	1,165	0,682	1,989	0.577
CI	1,291	0,473	3,526	0.618
CAD = 0	2,700	0,636	11,467	0.178
COMPASS-31	1,009	0,961	1,059	0.717

Parameters of the univariable binary regression model, EDSS – Expanded disability status scale, HR – hear rate, sBP – systolic blood pressure, dBP – diastolic blood pressure, AI – adrenergic index, CI – cardiovagal index, CAD – cardiovascular autonomic dysfunction,

COMAPSS-31 - Composite Autonomic System Score-31, su – supine, st – standing, st-su – difference between standing and supine position.

Table 4. Results of the multiple logistic regression model.

	Exp(B)	95% C.I. for EXP(B)		p value
NMOSD				
Drop in dBP during tilt-table test	0.897	0.807	0.996	0.042
CAD =0	9.487	1.263	71.246	0.029
Disease duration	1.089	0.959	1.235	0.187

NMOSD – neuromyelitis optica spectrum disorder, dBP – diastolic blood pressure, CAD – cardiovascular autonomic dysfunction, C.I. – confidence interval