Autonomic nervous system abnormalities may predict cardiovascular changes after initiation of siponimod in the treatment of secondary progressive multiple sclerosis

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Background and aims: Siponimod is a sphingosine-1-phosphate (S1P) receptor1,5 modulator showing superiority over placebo in terms of preventing disability progression in people with secondary progressive multiple sclerosis (SPMS). The aim of this study was to identify whether autonomic nervous system (ANS) dysfunction identified prior to treatment initiation can predict siponimod related decrease in heart rate (HR) after treatment initiation.

Design/Methods:

Patients

This study enrolled consecutive persons with the diagnosis of SPMS from November 2019 to July 2020 in the University Hospital Center Zagreb, Department of Neurology, who were eligible for treatment with siponimod based on local regulations. The diagnosis of SPMS was based on the Lublin et al. criteria. The following parameters were collected for each patient: age, sex, Expanded Disability Status Scale (EDSS), disease duration, MRI activity in the previous year defined as a new or enlarging T2 and/or gadolinium enhancing T1 lesion, relapse in the previous year, previous treatments and cytochrome P450 (CYP)2C9 genotyping.

ANS testing

ANS testing was performed under standardized conditions: between 9:00AM and 01:00PM in a Laboratory for the ANS testing; the participants were connected to the Task Force Monitor (TFM) (CNSystemsMedizintechnik AG, Austria); and 5 minutes of settling period was given before recording was initiated. The protocol afterwards consisted of 10-min supine resting position, Valsalva maneuver, deep breathing test, 10 min tilt-up table test, 5-min supine resting period, ingestion of siponimod, followed by a 180-min supine resting period recordings. During the whole examination, patients were asked to report any symptoms.

Results of the ANS testing were interpreted in the form of cardiovagal and adrenergic indices, reflecting parasympathetic and sympathetic nervous system function, respectively. (Low, 1993) Cardiovagal index was calculated based on the results of the HR response to Valsalva maneuver and deep breathing test. Adrenergic index was calculated based on the results of BP response to the Valsalva maneuver and tilt-up table test. Data extracted from the TFM were used for heart rate variability (HRV) analysis. The following HRV parameters were used for analysis: high-frequency (HF) (0.15–0.4 Hz) and low frequency (LF) (0.04–0.15 Hz) power of RR intervals expressed in absolute units, HF expressed in normalized units (HFnu), low to high frequency ratio (LF/HF) and standard deviation of NN intervals (SDNN).

For the purpose of further analysis, values for HR and BP (systolic (sBP) and diastolic (dBP)) were interpreted as an average value for the 10 minutes in the supine position prior to treatment initiation and average values for the 30-min intervals in the period of 3 hours after treatment initiation.

Results: Baseline characteristics of the cohort are presented in Table 1. After treatment initiation, there was a statistically significant drop in HR (71.1±9.2 sup, 66.3±8.1 3rd-6th, p<0.001) and elevation of sBP (113.0±12.4 sup, 117.1±10.8 3rd-6th, p=0.04). Values of the dBP followed similar trend as for sBP, however not reaching statistically significance (72.8±9.6 sup, 74.9±8.4 3rd-6th, p=0.13). There were no extreme fluctuations of HR and BP in individual patients. None of the patients reported any symptoms during the testing.

There was a statistically significant correlation between SDNN before treatment initiation and ΔHR (rp=0.474, p=0.014). Results of the univariable and multivariable linear regression analyses are presented in Table 2. Disease duration and SDNNsup were identified as predictors for ΔHR, where higher SDNN and longer disease duration were predictive of smaller ΔHR.

Parameter	Siponimod cohort (N=26)
Clinical data	
Age, years (mean ± SD)	51.0±9.5
Sex, females (N, %)	16 (61.5)
EDSS (median, range)	6.0 (3.0-6.5)
Disease duration, years (mean ± SD)	17.9±8.8
Active MRI in the previous year (N=20), (N, %)	8 (40.0)
Relapses in the previous year (N, %)	11 (42.3)
Treatment naïve (N, %)	9 (34.6)
Previous DMT (N, %)*	17 (65.4)
Interferons	14
Fingolimod	5
Glatiramer acetate	2
Dimethyl fumarate	1
Natalizumab	2
CYP2C9 genotype (N, %)	
1/1	18 (69.2)
1/2	5 (19.2)
1/3	3 (11.5)
Autonomic nervous system testing	
Valsalva ratio (N=17) (mean ± SD)	1.81±0.44
Respiratory sinus arrhythmia (N=21) (mean ± SD)	13.10±4.80
Cardiovagal index (N=20) (median, range)	0 (0-1)
Orthostatic hypotension (N=23) (N, %)	4 (17.4)
Adrenergic index (N=23) (median, range)	0 (0-3)
HF, ms^2 (median, range)	174.01 (4.01-1913.30)
LF, ms^2 (mean ± SD)	312.28±343.51
HFnu(mean ± SD)	41.24±14.74
HF/LF (mean ± SD)	1.89±1.61
SDDN, ms (mean ± SD)	22.98±12.52

Table 1. Baseline characteristics of the cohort.

	Univariable linear regression			Multivariable linear regression		
	B	95% C.I. for B	p value	B	95% C.I. for B	p value
ΔHR						
Age	0.066	-0.134-0.266	0.502			
Sex	0.035	-3.815-3.885	0.985			
EDSS	1.190	-0.866-3.245	0.244			
Disease duration	0.261	0.072-0.449	0.009	0.283	0.128-0.438	0.001
Orthostatic hypotension	0.851	-4.328-6.030	0.737			
Cardiovagal index	-3.746	-8.547-1.056	0.119			
Adrenergic index	0.071	-1.617-1.759	0.931			
HF_{sup}	0.005	0.000-0.010	0.035			
LF_{sup}	0.005	0.000-0.010	0.065			
$HFnu_{sup}$	-0.006	-0.136-0.124	0.925			
LF/HF_{sup}	0.050	-1.136-1.236	0.931			
$SDNN_{sup}$	0.172	0.037-0.306	0.014	0.188	0.080-0.297	0.002
ΔsBP						
Age	0.091	-0.311-0.493	0.645			
Sex	-1.370	-9.155-6.415	0.719			
EDSS	-0.471	-5.462-4.520	0.847			
Disease duration	0.401	-0.024-0.826	0.063	0.301	-0.125-0.728	0.157
Orthostatic hypotension	2.385	-7.998-12.768	0.639			
Cardiovagal index	-6.567	-15.823-2.688	0.153			
Adrenergic index	0.189	-2.967-3.346	0.902			
HF_{sup}	0.002	-0.009-0.012	0.756			
LF_{sup}	0.005	-0.006-0.016	0.394			
$HFnu_{sup}$	-0.247	-0.484--0.011	0.041	-0.199	-0.441-0.042	0.101
LF/HF_{sup}	1.516	-0.771-3.803	0.183			
$SDNN_{sup}$	0.124	-0.176-0.425	0.401			
ΔdBP						
Age	0.100	-0.197-0.396	0.494			
Sex	-2.356	-8.055-3.342	0.401			
EDSS	-0.570	-4.265-3.124	0.752			
Disease duration	0.364	0.063-0.666	0.020	0.297	-0.008-0.602	0.055
Orthostatic hypotension	1.598	-6.106-9.302	0.672			
Cardiovagal index	-2.649	-10.565-5.266	0.490			
Adrenergic index	0.305	-2.389-3.000	0.815			
HF_{sup}	0.000	-0.008-0.007	0.960			
LF_{sup}	0.001	-0.007-0.010	0.733			
$HFnu_{sup}$	-0.182	-0.357--0.006	0.043	-0.134	-0.307-0.038	0.121
LF/HF_{sup}	1.280	-0.395-2.955	0.128			
$SDNN_{sup}$	0.024	-0.202-0.251	0.825			

Table 2. Results of the univariable and multivariable linear regression model. Due to the number of participants, only 2 variables with the lowest p value were included in the multivariable logistic regression model.

Conclusion: ANS abnormalities may be predictive of cardiovascular abnormalities associated with treatment initiation with siponimod. A larger study is needed to confirm these observations.