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Research Article

Electrodiagnostic Evaluation of Autonomic Dysfunction in Patients with Multiple Sclerosis

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Abstract

Background: Autonomic dysfunction frequently affects multiple organs and systems in people with multiple sclerosis (PwMS), and can have a significant negative impact on the quality of life. This study aimed to assess the effect of MS on autonomic nervous system (ANS) functions by electrodiagnostic measures and investigate the relationship of these measures with different demographic and clinical factors such as age, sex, disease duration, type of treatment, the Expanded Disability Severity Scale (EDSS) score, and the Composite Autonomic Symptom Score-31 (COMPASS-31) score.

Methods: forty patients with a definite diagnosis of relapsing-remitting MS and 35 age- and sex-matched controls. The EDSS to assess disease severity and the COMPASS-31 questionnaire to test for the degree of clinical autonomic disability, Ewing's cardiovascular autonomic tests, and sympathetic skin response (SSR) as electrophysiologic tests for autonomic dysfunction were done.

Results: The heart rate response to normal breathing (HRNB), deep breathing (HRDB), and systolic blood pressure (BP) drop after standing were significantly different in the PwMS relative to the controls. Moreover, PwMS exhibited abnormalities in SSR amplitude and latency. Disease duration was negatively correlated with HRNB, HRDB, and heart rate during the Valsalva maneuver (HTVals). As well as EDSS with HRNB and HRDB and COMPASS-31 with HRDB.

Conclusion: In MS, cardiac autonomic dysfunction affects both the parasympathetic and sympathetic NS. Alongside the sympathetic sudomotor system is also impacted. The length and severity of the disease were correlated with parasympathetic abnormalities.

Keywords: Multiple sclerosis, EDSS, Cardiovascular Autonomic Dysfunction, Sympathetic Skin Response, COMPASS-31

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease with the involvement of scattered regions of the central nervous system (CNS) that can also affect the autonomic nervous system (ANS) [1]. The ANS can be compromised in up to 90% of the people with MS (PwMS) [2]. The involvement of the ANS impacts the quality of life of PwMS [3]. Even though the involvement may be subclinical and usually overlooked due to insufficient clinical follow-up as its not part of routine clinical assessment of regular visit to MS clinics in order to optimize treatment interventions [2]. The association between MS-related CNS damage and autonomic dysfunction has been the subject of an expanding body of research [4-5].

Autonomic dysfunction frequently affects multiple organs and systems, involving the bladder, bowels, and heart, as well as sexual and sudomotor functions, and can have a significant negative impact on the quality of life [6-7]. There is still disagreement over which aspect of the ANS, sympathetic and/or parasympathetic, is mostly impaired at different stages of MS, despite extensive research on autonomic dysfunction in MS, including evaluation of heart rate variability (HRV) [5]. Studies show that sympathetic autonomic control is inadequate in MS, while others detail parasympathetic control's inadequacy [8–10]. Uncertainty exists regarding whether these

changes are a result of the structural damage to the CNS that MS causes or if they are an epiphenomenon of disrupted autonomic feedback cycles [5].

The objectives of our study are to assess the effect of MS on ANS functions using electrodiagnostic measures and to investigate the relationship between different autonomic measures and different demographic and clinical factors.

Materials and Methods

Participants

This is a two-center case-control study carried out at the Neurophysiology Unit, Baghdad Teaching Hospital, and Al-Imamain Al-Kadhimyian Medical City for the periods from October 2022 to November 2023. The studied subjects within the two groups were informed about the techniques and aims of the study and consent for participation was ensured from the patients as well as the controls.

Forty people with MS (PwMS) of relapsing-remitting type enrolled from the MS clinic in Medical City, comprised of 28 females and 12 males aged 15–55 years, and were referred for electrophysiological examination. The PwMS were carefully followed up, and they were receiving immunomodulatory therapy (interferon or natalizumab). Those PwMS who were on corticosteroid treatment within eight weeks of enrollment and had a history of diabetes mellitus, comorbid cardiac disease (e.g., arrhythmia, heart block, or pacemaker), neuropathy, Parkinson's disease, renal failure, and liver failure were all excluded from the study. Another 35 healthy individuals aged 17–58 years, comprised of 15 males and 20 females, served as the control group.

Clinical Examination

A detailed history and neurological examination were done by a senior neurologist. The presenting symptoms varied from visual impairment to brainstem involvement, pyramidal signs and symptoms, sensory symptoms, or a combination of all of these. The Expanded Disability Status Scale (EDSS) [11] was utilized to assess the level of disability (the greater the score, the worse the patient's disability). The 20-step scale scores (with 0.5 unit increments) range from 0 (normal) to 10 (death from MS), PwMS whose EDSS score is between 0 and >3.5 are considered mild cases; and PwMS whose score is between 4 and 9.5 are considered moderate or severe cases. [12].

The Composite Autonomic Symptom Score-31 (COMPASS-31) scale evaluates neurodegenerative system symptoms using 31 patient-reported questions. Assessment is done through six weighted domains: orthostatic intolerance (10 points); secretomotor (7 points); vasomotor (6 points); bladder (9 points); gastrointestinal (28 points); and pupillomotor (15 points). A higher score corresponds to worse autonomic dysfunction [13]. Using Keypoint (Medtronic, Denmark) and Micromed (Italy) electromyography machines were used throughout the study.

Nerve conduction studies

The nerve conduction study of the sural and radial nerves has been done according to the method of Preston and Shapero [14]. The sural to radial amplitude ratio is calculated to exclude peripheral neuropathy; a ratio of less than 0.21 was considered abnormal [14].

Autonomic function tests

Study participants were instructed to abstain from coffee, tea, tobacco, food, alcohol, cola, energy drinks, and drugs that affect ANS at least for 4 h on the scheduled test day and to avoid activities that would affect BP (like running and jumping) for 2 h before the tests. Additionally, the subjects were instructed to dress comfortably, take a shower the night before the test without using any lotions, powders, or creams below the neck, drink plenty of water, and maintain proper hydration. [15].

To assess ANS functions, the HRV, BP changes, and sympathetic skin response (SSR) were measured. These are carried out in a silent, semi-darkened environment where patients' skin temperatures are kept at least 35ºC and the room temperature is kept between 22 and 24ºC.

Using an electrocardiogram, recording of the HRV was done by placing the reference electrode at the left anterior axillary line above the fifth or sixth rib and putting the active recording electrode in the left anterior chest area in the intercostal area between the fourth and fifth ribs. The midline of the sternum served as the ground electrode's location.

The QRS complexes were displayed on the monitor after adjusting the sensitivity and sweep speed. The time intervals between subsequent QRS complexes are measured and serve as the foundation for HRV analysis [16]. The sensitivity of the device was set to 200 μV, the bandpass was 1–20 Hz, and the sweep speed was 0.5 seconds. The following four separate recordings were done: The test battery included recordings of HR responses to normal breathing (HTNB), HR responses to deep breathing (HRDB), HR responses to the Valsalva maneuver (HRVals), and HR responses to standing (HRS).

Additionally, blood pressure (BP) variations were measured after 3 minutes of standing.

The HRDB was expressed as a deep breathing difference, which is the difference between the maximum HR (shortest RR interval during inspiration) and the minimum HR (longest RR interval during expiration) measured by (beat per minute) in subject breathing at six cycles per minute [17]. Participants were instructed to avoid sudden inhalations or exhalations, to hold their breath, or to hyperventilate.

To assess the HRVals, the subject was in a supine position and the head was slightly elevated to about 30°. Then, the subject was asked to strain for 15 seconds against 40 mmHg by blowing into a mouthpiece attached to a sphygmomanometer, and the Valsalva ratio was calculated. The ratio represents the longest RR interval (30–45 seconds following the release of strain) to the shortest RR interval during strain (which is the minimal HR that occurs at 15–20 s after releasing the strain) [17].

The HRS was obtained after the subject had been resting for at least 20 minutes. It is expressed as the ratio of the longest RR interval (slowest HR) at 30 s to the shortest RR interval (fastest HR) at 15 s, following an abrupt change in position from supine for 3 min to standing. The 30/15 ratio should be at least 1.04 [18].

Fluctuations of BP are assessed using a mercury sphygmomanometer (MDF 800 desk mercury sphygmomanometer, USA) depending on somewhat later responses to standing (first 4 min), and they are expressed as the difference between the baseline supine and the minimal BP after standing up. Systolic BP decline of more than 20 mmHg and of more than 10 mmHg for diastolic BP is considered abnormal [19].

The SSR was measured by placing the active electrode in the palm or sole and the reference electrode on the dorsum of the hand or foot of the same limb. As well as the ground electrode at the palm or the sole. An electrical stimulus with a current of 12–20 mA and a pulse width of 0.1 ms was applied to the midline nerve trace at the level of the contralateral wrist (or below the medial malleolus of the foot). To prevent potential habituation, the stimuli are presented erratically and abruptly at different times. Both the SSR amplitude (the peak-to-peak distance of the resulting wave in mV) and the SSR latency (the time necessary to achieve the beginning of the first deflexion of the wave in seconds) are recorded. [20]. The sweep speed was 500 milliseconds/division, the low-frequency filter was 0.5 Hz the high-frequency filter was 2000 Hz, and the amplifier sensitivity was 200–1000 μV/div.

Ethical Approval

The study was approved by the Iraqi Board for Medical Specialization (Order No. 240 on 22 January 2023). The studied subjects within the two groups were informed about the techniques and aims of the study, and consent for participation was ensured by the patients as well as the controls.

Statistical Analysis

Statistical analyses were performed using SPSS software version 25.0 (SPSS, Chicago). A normalcy test was performed on continuous data (Shapiro-Wilk test). A Student t-test was used to assess data having a normal distribution, which were shown as mean and standard deviation. Non-normally distributed data were reported as median and range, and the Mann-Whitney U test or the Kruskal-Wallis test were used to evaluate them (for two-group comparisons or three-group comparisons, respectively).

Categorical variables were presented as numbers and percentages and analyzed with the chi-square test. To explore the possible correlation of non-normally distributed data from the autonomic function test with each of the disease duration, EDSS scores, and COMPASS-31 scores by using Spearman's correlation test. A p-value less than 0.05 was considered to indicate a statistically significant difference.

Results

Demographic Data

No age or sex difference was shown between the two studied groups. The disease duration varies from 10 to 276 months. The COMPASS-31 scores were 40.85±7.29 (26-57). The median EDSS score for the patients was. Mild MS cases score 0 to >3.5, and moderate or severe cases score 4 to 9.5. Only 5 patients (12.5%) have a positive family history of MS. Forty percent of patients were on interferon-beta treatment, 57.5% were on immunomodulatory drugs, and only 1 patient was on no treatment (Table 1).

Autonomic Function Tests

Among the parasympathetic autonomic functions, the HRNB and HRDB were significantly lower in the PwMS relative to the controls ($p < 0.001$ and 0.017, respectively), as indicated in Table 2. The systolic PB drop from the supine to the standing position was significantly different between PwMS and controls ($p = 0.018$). Moreover, the palmar SSR latency was significantly prolonged ($p<0.001$), and the planter SSR amplitude was

significantly lower (p = 0.004) in PwMS as compared to the controls (Table 3).

Table 1. Demographic data of the study population

Parameter	Patients (n=40)	Controls (n=35)	p-value
Age, years	35.4±9.80	39.71±11.21	0.402
Sex			
Males	12(30%)	15(42.86%)	0.180
Females	28(70%)	20(57.54%)	
Disease duration, months	74.8±56.66		
Range	10-276		
EDSS score			
Mild MS	35(87.5%)		
Moderate/severe MS	5(12.5%)		
COMPASS-31	40.85±7.29		
Range	26-57		
Family History of MS	35(87.5%)		
No	5(12.5%)		
Yes			
Past Medical History	35(87.5%)		
No	3(7.5%)		
Hypertension	2(5%)		
Thyroid Disease			
Smoking			
Yes	6(15%)		
No	31(77.5%)		
Passive	3(7.5%)		
Treatment Type			
Interferon Beta	16(40%)		
	23(57.5%)		
Immunomodulatory	1(2.5%)		
No			

EDDS = Expanded Disability Status Scale; COMPASS-31 = Composite Autonomic Symptom Score-31) scale; MS = multiple sclerosis

Table 2. Parasympathetic Autonomic Functions of the study population

Parameter	Patients (n=40)	Controls (n=35)	p-value
HRNB (beat/min)			
Mean±SD	17.07±6.25	23.17±6.33	0.001
Median	14.88	23.0	
Range	6-50	6.3-34	
HRDB (beat/min)			
Mean±SD	25.44±11.7	28.6±7.46	0.017
Median	23	27	
Range	9-53	18-54	
HRVM			
Mean±SD	1.62±0.66	1.67±0.36	0.088
Median	1.44	1.6	
Range	0.98-3.63	1.04-2.9	
HRS			
Mean±SD	1.39±0.68	1.48±0.53	0.060
Median	1.11	1.21	
Range	0.5-3.26	1-3.1	

HRNB = heart rate response to normal breathing; HRDB = heart rate response to deep breathing; HRVM = heart rate response to Valsalva maneuver; HRS = heart rate response to standing

Table 3. Sympathetic Autonomic Functions of the study population

Parameter	Patients (n=40)	Controls (n=35)	p-value
SBP drop, mmHg			0.018
Mean±SD	-7.65±16.19	0.57±6.84	
Median	-10.0	0.00	
Range	-53-20	-10-10	
DBP drop, mmHg			0.197
Mean±SD	-8.95±16.1	-3.57±6.25	
Median	-10.0	0.00	
Range	-50-20	-20-5	
Palmar SSR Latency, sec			0.001
Mean±SD	1.60±0.52	1.30±0.19	
Median	1.51	1.3	
Range	0.85-3.9	0.5-1.56	
Palmar SSR amplitude, mV			0.667
Mean±SD	3.67±2.55	3.73±1.96	
Median	3.1	3.6	
Range	0.28-9.96	1-7.7	
Planter SSR latency, sec			0.207
Mean±SD	2.2±0.6	2.02±0.52	
Median	2.1	2.0	
Range	0.9-3.57	1-4.1	
Planter SSR amplitude, mV			0.004
Mean±SD	1.65±1.04	2.74±1.66	
Median	1.4	2.69	
Range	0.18-4.4	0.39-6.5	

SBP = systolic blood pressure; DBP = diastolic blood pressure; SSR = sympathetic skin response

Based on the number of abnormal autonomic function tests, PwMSs were stratified into 10 (25%) showed no abnormality in the sympathetic and parasympathetic autonomic function tests; 12 (30%) presented with one abnormal autonomic function test; 11 (27.5%) with two; 5 (12.5%) with three; and only two (5%) with an abnormality in four autonomic function tests (Table 4).

Table 4. Number and percentage of patients according to the abnormal autonomic function tests

Autonomic Function Tests*	Number (%)
No abnormality	10 (25)
One abnormal test	12 (30)
Two abnormal tests	11(27.5)
Three abnormal tests	5 (12.5)
Four abnormal tests	2(5)

* include cardiovascular and SSR tests

According to the severity of autonomic dysfunction, 10 (25%) PwMS showed no abnormality in the sympathetic and parasympathetic autonomic function tests, 20

(50%) showed early autonomic dysfunction, 7 (17.5%) showed definite dysfunction, and only 3 (7.5%) showed severe autonomic dysfunction. Furthermore, none of the PwMS presented with parasympathetic autonomic dysfunction solely. Fifteen (75%) out of those with early autonomic dysfunction have sympathetic involvement, and five (25%) have both sympathetic and parasympathetic involvement. Three (42.86%) of those with definitive autonomic dysfunction have sympathetic involvement, and four (57.14%) have both sympathetic and parasympathetic involvement. Finally, out of those with severe dysfunction, one (33.33%) shows sympathetic dysfunction, and two (66.67%) have both sympathetic and parasympathetic autonomic dysfunction (Table 5).

Correlation Analysis

With Spearman's correlation, the disease duration was correlated negatively with HRNB (r = -0.415; p = 0.008), HRDB (r = -0.404; p <0.01), and HRVals (r = -0.473; p = 0.002), as shown in Figure 1. Similarly, the EDDS was correlated negatively with HRNB (r = -0.349; p = 0.027) and HRDB (r = -0.383; p = 0.015), whereas it was correlated positively with planter SSR amplitude (r = 0.420; p = 0.019; and r = 0.361) (Figure 2).

Moreover, Figure 3 indicates a negative correlation between the COMPASS-31 score and HRDB (r = -0.316; p = 0.047). Within the PwMS group, there was no association between all autonomic function tests and sex, family history of MS, or treatment type.

Table 5. Number and percentage of patients according to the type and severity of autonomic dysfunction

Autonomic dysfunction Involvement	Autonomic Dysfunction Total number	Sympathetic	Parasympathetic	Combined
No	10(25%)	0(0%)	0(0%)	0(0%)
Early	20(50%)	15(75%)	0(0%)	5(25%)
Definitive	7(17.5%)	3(42.86%)	0(0%)	4(57.14%)
Severe	3(7.5%)	1(33.33%)	0(0%)	2(66.67%)

Discussion

Parasympathetic system affection was addressed by the finding of significantly lower values of HRNB and HRDB in PwMS relative to the control group. This finding is in harmony with many studies conducted on 25 Italian patients [21], 34 Spanish patients [22], 26 German patients [23], 55 Iraqi patients [24], and 20 Egyptian patients [25]. The longer duration of MS has been connected to progressive deterioration of parasympathetic regulation, which is in agreement with many studies [24–26]. Also, abnormalities seem to be linked to the, as measured by the EDSS.

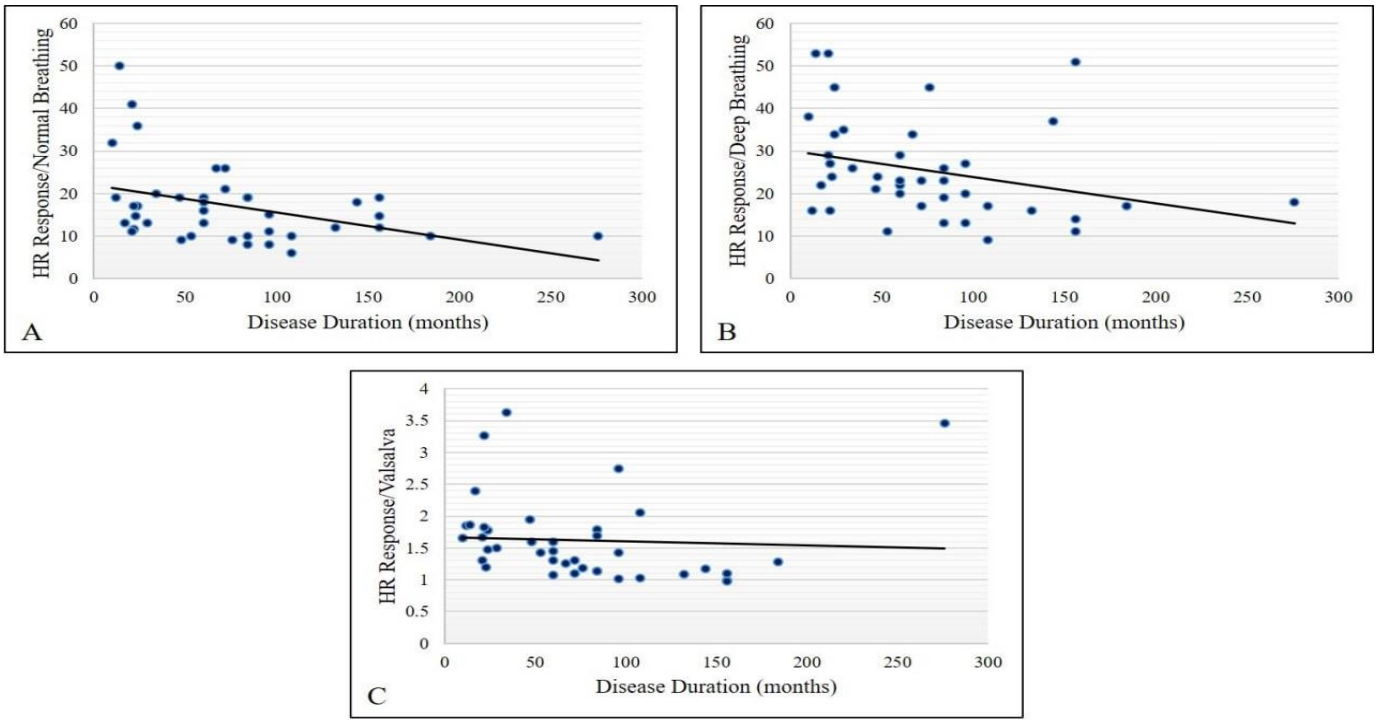

Figure 1. Scatter plot and regression line disease duration and HRNB and disease duration (A), HRDB (B), and HRVals (C).

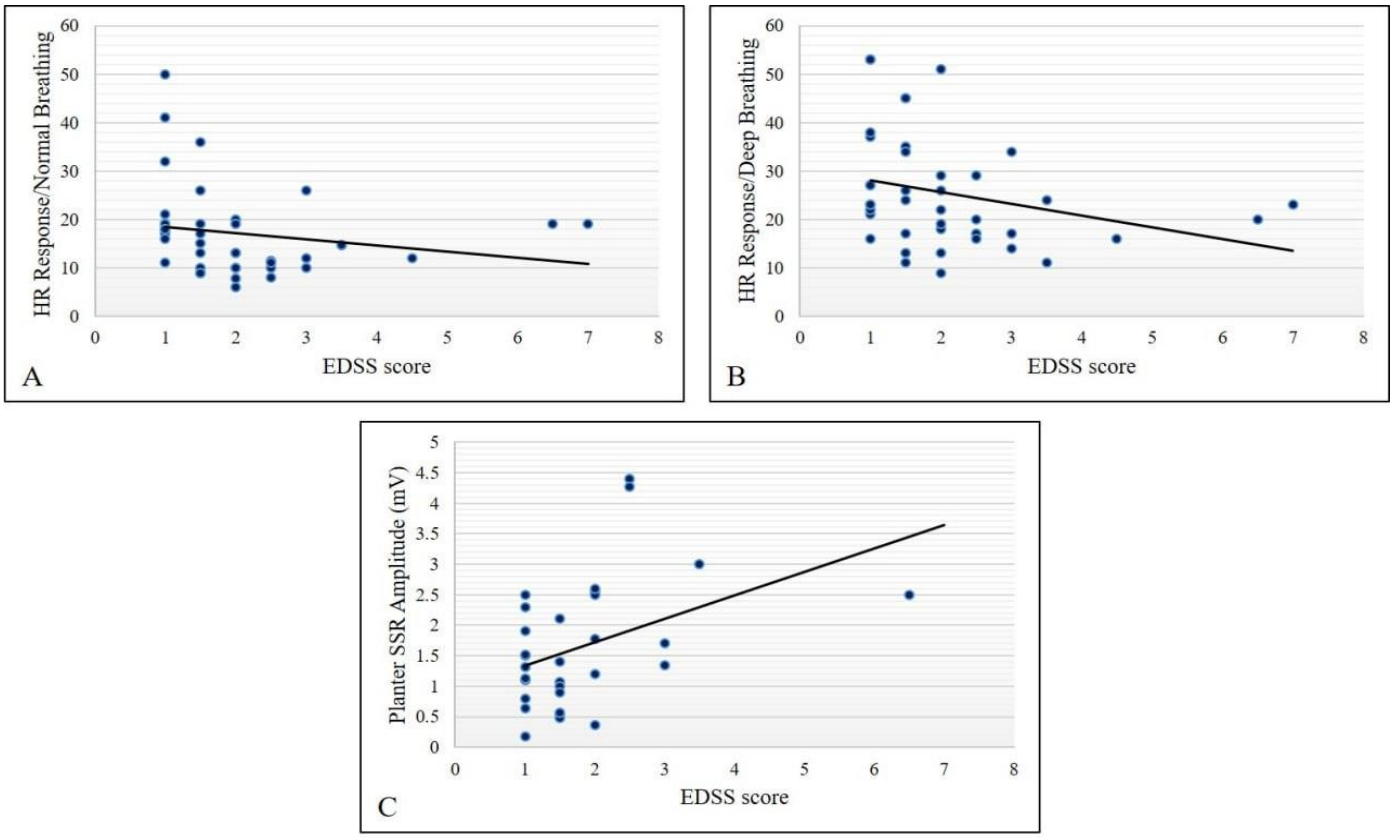

Figure 2. Scatter plot and regression line between EDSS and HRNB (A), HRDB (B), and planter SSR amplitude (C).

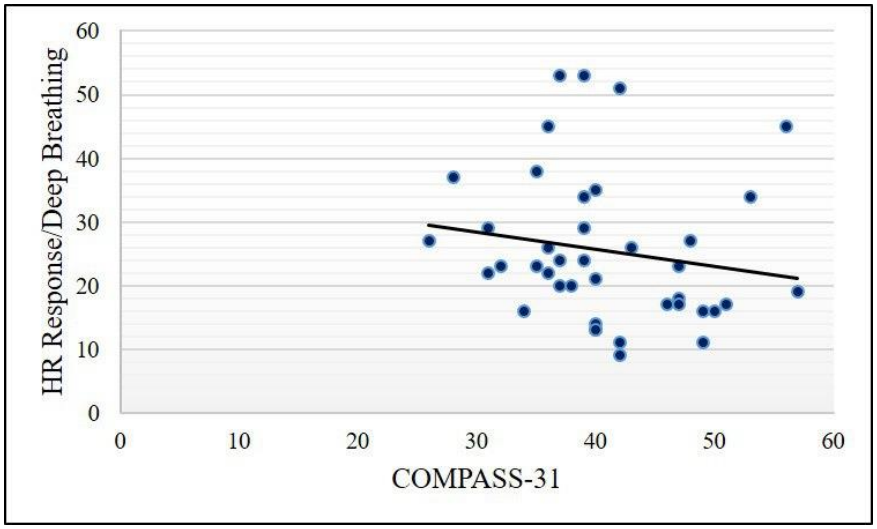

Figure 3. Scatter plot and regression line between COMPASS-31 and HRDB

Our study showed a correlation between HRNB and HRDB with the EDSS score, indicating parasympathetic autonomic dysfunction with an increased EDSS score. These findings were also observed by Adamec and his associates [27]. On the contrary, other studies revealed no association [23–25].

Our study also found a decrease in HRV indices with an increase in COMPASS-31 score. Similar results were seen in a study involving type 2 diabetics [28] and fibromyalgia patients [29]. The systolic BP drop was significantly higher in the PwMS compared to the controls, denoting sympathetic autonomic dysfunction. In agreement with these findings, Guibilei et al. [30] reported that the sympathetic dysfunction in PwMS was postulated to be due to the substantial involvement of the sympathetic vasomotor system, which is accountable for the orthostatic intolerance. In contradiction, the sympathetic cardiovascular tone seemed to be increased in MS according to Monge-Argiles et al. [22]. This unexpected outcome was attributed to PwMS having more habits (and then relaxation) for clinical tests than the control group did [22].

The significant prolongation of palmar SSR latency and the attenuation of planter SSR amplitude denote sympathetic sudomotor affection. These findings were reported in PwMS by many studies [31–34]. It is worth stating that reduced activity of

the sympathetic NS could be directly evaluated by the sudomotor function with the help of SSR assessment [8, 35-36]. The damage to the central sudomotor pathways caused by demyelination has been suggested as the most important pathological pathway of sudomotor dysfunction in MS [37-38]. Sympathetic autonomic data were positively correlated with disease duration and severity indexed by EDSS in the current study. In general, various autonomic dysfunctions have been linked by several authors to the duration and activity of the disease [23, 31-32, 34, 39-40], while others did not reveal such dependency [6, 8]. According to Flachenecker et al., impairment in parasympathetic control may be the result of MS.; however, compromised sympathetic function may have a pathogenetic role in the development of MS [23].

Although the underlying etiology of cardiovascular dysfunction is unclear, it is believed to be related to lesions, particularly in the parietal lobe, insula, limbic regions, and midbrain. [41-42]. For instance, several observational studies found that lesions affecting spinal cord [31], brainstem [40], midbrain [43], and hippocampal [44] were linked with markers of cardiovascular dysfunction, including decreased HRV and elevated BP variability. It was hypothesized that variations in study subjects, sample sizes, and racial composition would produce different findings. As for ANS dysfunction severity: the diagnosis of cardiovascular dysfunction is supported by the presence of two or more abnormal tests [45].

In our study, 52.2% of the PwMS had two or more abnormal autonomic (cardiovascular and SSR) tests. This figure was within the range reported by others [24-25, 35, 46–48]. Considering PwMS had one positive test (borderline), 12 (30%) had only one abnormal test. This finding is almost compatible with those of several previous studies in which more than half of the patients had at least one abnormal test [45, 49-50]. However, higher percentages were reported by other authors [21, 31, 46]. These variations may be explained by various patient selection standards, approaches, clinical training programs, and in-study medications. Additionally, the prevalence of abnormal results in cardiovascular ANS varies due to the lack of standardized test performance or differentially used cut-off values. A large sample size and cohort study, as well as testing autonomic function by clinical questioners and electrophysiological measures is required to identify subclinical cardiovascular and sudomotor alterations in newly diagnosed MS patients as well as those who present with relapse, this will be the main areas of future research.

Conclusion

The PwMS, cardiac autonomic dysfunction affects both the parasympathetic and sympathetic NS. Alongside the cardiovascular system, the sympathetic sudomotor system is impacted. The length and severity of the disease were correlated with parasympathetic abnormalities. Patients with one abnormal test labeled as early autonomic involvement only affected the sympathetic division, whereas those with two or more abnormal tests labeled as definitive autonomic dysfunction involved both the sympathetic and parasympathetic divisions. No correlation was observed within the PwMS group between any autonomic function tests and age, sex, treatment type, or family history of MS.

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Authors' contributions

Conceptualization: M . M . , F . H ., Methodology: M.M., F.H. and A.H., Formal analysis and investigation: M.M. and F.H., Writing: F.H., M.M., Resource: A.H., Supervision: F.H. and A.H.

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