Journal of the Neurological Sciences 367 (2016) 133–137

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Autonomic dysfunction in multiple sclerosis is better detected by heart rate variability and is not correlated with central autonomic network damage

Gonçalo Videira [a,*], Pedro Castro [a], Bítia Vieira [a], João Pedro Filipe [b], Rosa Santos [a], Elsa Azevedo [a], Maria José Sá [a,c], Pedro Abreu [a]

[a] Dept. Neurology, Centro Hospitalar de São João, Faculty of Medicine of University of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[b] Dept. Neuroradiology, Centro Hospitalar de São João, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[c] Faculty of Health Sciences, University Fernando Pessoa, Praça 9 de Abril 349, 4249-004 Porto, Portugal

ARTICLE INFO

Article history:
Received 17 April 2016
Received in revised form 19 May 2016
Accepted 24 May 2016
Available online 25 May 2016

Keywords:
Autonomic nervous system
Central autonomic network
Heart rate variability
Magnetic resonance imaging
Multiple sclerosis

ABSTRACT

Background: MS-associated autonomic dysfunction (AD) in multiple sclerosis (MS) is poorly understood and the best method for its detection unestablished. We compared classical Ewing battery and newer methods as heart rate variability (HRV) and spontaneous baroreflex sensibility (BRS) to detect AD in MS and related them to central autonomic network (CAN) lesions.
Methods: We enrolled 20 relapsing-remitting MS patients, median age of 36 (interquartile range 32–46) years, disease duration of 5.5 (2.2–6.8) years, Expanded Disability Status Scale (EDSS) score of 1.0 (1.0–1.5) and 20 age- and gender-matched healthy controls. We assessed Ewing battery and spontaneous HRV and BRS. CAN involvement was evaluated by magnetic resonance imaging.
Results: HRV showed both parasympathetic and sympathetic significant impairment in MS ($p < 0.05$). From Ewing battery only isometric test was significantly decreased in MS ($p = 0.006$). Disease duration and severity, lesion burden and CAN involvement were not correlated with laboratorial parameters.
Conclusions: Our MS cohort had both sympathetic and parasympathetic dysfunction independently from disease duration, neurological deficits and lesion burden or CAN involvement. HRV analysis maybe more useful than classical Ewing battery to screen AD.

1. Introduction

Along the course of multiple sclerosis (MS) the autonomic nervous system (ANS) seems to be increasingly affected [1]. Indeed, it is estimated that as much as 18 to 42% of patients present autonomic dysfunction (AD) symptoms, yet, these quality of life disturbing symptoms are frequently overlooked by the clinicians [2–6]. Some reasons may contribute: firstly, the occurrence of MS symptoms with greater clinical impact, such as motor, sensory or visual changes, may somewhat hide AD; secondly, the best method to detect AD in MS remains unestablished, despite the recognized usefulness of some laboratory tests [2,3,7–10] and of standardized questionnaires [1,11] to diagnose AD in MS patients; and finally, the pathophysiology of AD in MS is poorly understood [11]. ANS control centres within central nervous system, called the central autonomic network (CAN), have not yet been properly studied, although some specific spinal and brain locations have been proposed [12].

The main objective of our study is to compare the performance of the classical standardized Ewing battery of cardiovascular tests [13] with newer methods based on heart rate variability (HRV) and spontaneous baroreflex function (BRS) to detect AD in MS patients. Additionally, we aim to test the hypothesis that the presence of AD in MS may be related to CAN involvement which would contribute to better understating of AD pathophysiology.

2. Materials and methods

2.1. Studied population

In this matched case-control study, 20 relapsing-remitting MS patients from Centro Hospitalar São João were randomly proposed to

* Corresponding author at: Dept. Neurology, Centro Hospitalar de São João, Faculty of Medicine of University of Porto, Portugal.
E-mail addresses: pgoncalomv@gmail.com (G. Videira), pedromacc@gmail.com (P. Castro), vieira.bitia@gmail.com (B. Vieira), mail.jpfilipe@gmail.com (J.P. Filipe), rosampsantos2@gmail.com (R. Santos), eazevedo@med.up.pt (E. Azevedo), mjsa@med.up.pt (M.J. Sá), pmabreu@netcado.pt (P. Abreu).

http://dx.doi.org/10.1016/j.jns.2016.05.049
0022-510X/

participate. Inclusion criteria for involvement were definitive diagnosis of MS (according to the 2010 McDonald criteria) and age above 18 years old. Those with active disease or treatment with corticosteroids within 8 weeks of enrolment were excluded. Control group consisted of 20 age- and sex-matched healthy subjects, recruited from the hospital and university staff. Exclusion study criteria was the presence of any disorder that could interfere with the autonomic function. The *Ethics Committee of Centro Hospitalar São João* approved this work and all the participants gave written informed consent.

2.2. Clinical assessment

A MS specialist evaluated the patients less than 1 month before enrolment. Age, gender, detailed neurological examination, time of disease, annualized relapse rate [14] and Expanded Disability Status Scale (EDSS) [15] score were recorded. Every relapse and respective location (optic nerve, brain hemispheres, brainstem or spinal cord) were registered, based on clinical and imaging findings [16].

2.3. Autonomic tests

Participants were asked to stop alcohol, coffee, smoking and any medication that could alter autonomic function 24 h before testing. Evaluations were carried out in a quiet room with a constant temperature around 22 °C. Blood pressure was continuously monitored in the non-dominant hand with a Finometer device (FMS, Amsterdam, Netherlands) with its pressure height correction unit placed at heart level. Heart rate (HR) and R-R intervals (RRi) were assessed from a 3-lead ECG. All data were digitally recorded at 400 Hz in commercial analogue-digital converter for offline analysis with dedicated software based on MATLAB (Natick, USA).

After autonomic tests have been explained [10] and maximum contraction strength in dominant hand (or non-paretic hand if dominant was affected) was measured with a dynamometer, the subject was positioned supine and rested for 30 min. Next, Ewing battery was applied as described previously [17]. Shortly, we calculated [10]: expiratory–to–inspiratory amplitude ratio of HR (E:I ratio) during synchronized deep breathing at 6 cycles/min; the Valsalva ratio (VR), i.e., averaged HR ratio between II and IV phases of three Valsalva manoeuvres [9]; the quotient of RRi around 30th beat by that at the 15th after standing; the difference between the systolic blood pressure (SBP) at rest and after standing during 5 min to assess orthostatic hypotension; and diastolic blood pressure (DBP) response to handgrip isometric work at 30% of his maximum strength for 5 min. Each test was scored as normal (zero), borderline (one) and abnormal (two) and the sum resulted in Ewing score [13].

2.4. Heart rate variability and spontaneous baroreflex sensitivity

The last 10 min of resting recording were used to analyse short-term HRV and BRS in both time and frequency domains [10]. HRV was assessed in time domain using standard deviation (SDNN), root mean squared difference (rMSSD) and proportion of successive intervals greater than 50 ms (pNN50%) of normal RRi (NN). On frequency domain, HRV was characterized by total power (TP) spectrum of RRi [18], at low frequency (LF; 0.04–0.15 Hz) for sympathetic ANS and at high frequency for parasympathetic (HF; 0.15–0.40 Hz), the LF/HF ratio, and normalized LF (LFnu) and HF (HFnu) [19]. For BRS in time domain, we used sequence method based on the identification of all spontaneous sequences of ≥3 consecutive beats of increase or decrease of SBP (≥1 mmHg), the baroreflex response of lengthening or shortening of RRi (≥3 ms) [20,21]. The slope of regression line between SBP/RRi is the BRS [21]. In frequency domain, BRS was achieved by spectral method using the cross-correlation gain between the power spectral densities of SBP on that of RRi at LF and HF bands [22]. Lower HRV [20] and BRS [22] correlates with worse AD.

2.5. MRI

Brain MRI was obtained within less than a year before enrolment. Spinal MRI analysed was the last performed. None of the subjects experienced relapse after imaging. Presence of T2-weighted lesions in the white matter adjacent to the following CAN structures was assessed: insula, anterior cingulate cortex, hypothalamus, amygdala, periaqueductal grey matter (PAG), parabrachial nucleus, nucleus of the solitary tract, ventrolateral reticular formation of the medulla and medullary raphe. A CAN score was calculated adding 1 point for each CAN structure affected (maximum of 9 points). The number of all T2-weighted lesions was then counted in supratentorial areas, brainstem, cerebellum, spinal cord and total number of lesions. The presence of lesions on T1-weighted images, enhancing or non-enhancing, was also assessed. MRI protocols included studies performed on 1.5 T (Siemens MAGNETOM SymphonyTim syngo) and 3 T (Siemens MAGNETOM TrioTim syngo) scanners with, at least, coronal and axial T1-weighted images (511–750 ms/8.6–8.7 ms [TR/TE]), spin-echo or fast spin-echo axial proton density (3770–4000 ms/11-22 ms [TR/TE]) and T2-weighted images (3770–4000 ms/88–106 ms [TR/TE]), and axial and sagittal fluid-attenuated inversion-recovery (FLAIR) images (8000–9000 ms/91–93 ms [TR/TE]), all with 5 mm section thickness. Contrast-enhanced T1-weighted images were obtained with 0.1 mmol/kg gadolinium using typical T1-weighted parameters as described above.

2.6. Statistical analyses

Shapiro-Wilk test was used to inspect normality of continuous variables. Student *t*-test or Mann-Whitney were used to compare the distribution across two groups. Pearson or Spearman rho coefficients were used to determine the correlation between two variables. Statistical significance was inferred at $p < 0.05$ level. All statistics were performed using IBM Statistical Package for Social Sciences (SPSS) Statistics v21™.

3. Results

MS patients (12 women) had median age of 36 [interquartile range (IQR) 32–46] years, disease duration of 5.5 (2.2–6.8) years, EDSS of 1.0 (1.0–1.5) and annualized relapse rate was 0.33 (0–0.48) relapses/year. Detailed clinical data is presented in Table 1.

3.1. Autonomic assessment: comparing MS and control groups

Hemodynamic data and autonomic tests results of MS and healthy controls are compared in Table 2. Baseline blood pressure and HR were similar ($p < 0.05$). Ewing battery showed no significant differences except for isometric handgrip subtest, which was weaker in MS ($p = 0.006$). This test was abnormal in 14 MS patients (70%) as well as in 5 controls (25%). E:I ratio tended to be lower in the MS ($p = 0.063$). BRS was similar between groups ($p < 0.05$). As for HRV, MS patients had lower SDNN ($p = 0.007$), rMSSD ($p = 0.028$), pNN50% ($p = 0.011$), power at LF ($p = 0.024$) and HF ($p = 0.021$) bands, but similar LF/HF ratio ($p = 0.689$).

3.2. MS group: relationship between clinical features and laboratory tests

There was no correlation between autonomic laboratorial results and age, gender, EDSS and annualized relapse rate ($p > 0.05$). A previous brainstem syndrome relapse was associated with a higher Ewing score ($p = 0.010$).

One patient didn't have MRI results available for analysis. The presence of any spinal, brainstem or CAN lesion was not associated with autonomic laboratorial results except for spinal involvement and a higher SDNN ($p = 0.042$) and a tendency for higher rMSSD ($p = 0.053$) and pNN50% ($p = 0.066$). There was no significant association between