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Cerebral autoregulation is preserved in multiple sclerosis patients

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory disease that may also be associated with vascular dysfunction. One master component of vascular regulation is cerebral autoregulation (CA). We aimed to investigate the integrity of CA in MS patients and study its relationship with autonomic dysfunction (AD), magnetic-resonance-imaging (MRI) lesion load and hemodynamic parameters. We enrolled 20 relapsing-remitting MS and 20 healthy subjects. CA was assessed by transfer function analysis parameters (coherence, gain and phase), as obtained in the very low, low and high-frequency domains (VLF, LF, HF, respectively). We evaluated the autonomic parameters heart rate variability and spontaneous baroreflex sensitivity (BRS). There were no significant differences in CA parameters between MS and controls ($p > 0.05$). Lesion load was not correlated with any CA parameter. LF gain was positively correlated with BRS in both groups (MS: $p = 0.017$; controls: $p = 0.025$). Brainstem lesion load in MS was associated with higher systolic blood pressure (SBP; $p = 0.009$). Our findings suggest that CA is preserved in our MS cohort. On the other hand, AD in MS patients with brainstem lesions could contribute to the increase of supine SBP. Whether this systemic deregulation could contribute to disease burden remains to be investigated.

1. Introduction

Multiple sclerosis (MS) is an autoimmune, demyelinating disease of the central nervous system, where chronic inflammation and axonal injury lead to deficits in motor, sensory, cerebellar and cognitive functions [1].

Cardiovascular (CV) autonomic deregulation is also present in these patients, affecting both the sympathetic and parasympathetic nervous systems, which innervate cerebral vessels [2–4]. Additionally, a higher incidence of cerebrovascular events is present in MS patients in comparison to sex- and age-matched controls, suggesting that vascular dysfunction plays a role throughout the disease course [5,6]. Smoking is a major CV risk factor, as well as an environmental factor for MS development; however, widespread cerebral hypoperfusion seems to be the key factor in predisposing MS patients to ischemic brain lesions [7]. Nevertheless, most of the etiological mechanisms underlying these events remain unclear.

Indeed, an adequate blood perfusion is crucial to ensure brain metabolic demand. This mechanism is maintained by three major components: cerebral autoregulation (CA), cerebrovascular reactivity (VR) and neurovascular coupling [8]. VR was proven to be impaired in MS patients in several studies, even though there are some contradictory results [9,10]. Regarding CA, only one study was conducted, and it showed no significant differences in the autoregulatory mean velocity index between MS patients and controls; however, an autoregulation impairment was described after modeling variation in the cerebral blood flow velocity (CBFV) associated with a 1-mm Hg increase in the mean arterial blood pressure [11].

Thus, it is still unclear whether the CA mechanism remains intact in MS or if it has any relation to vascular and autonomic impairment, and, if CA deregulation plays a role in MS lesion burden. It is worth investigating CA role in MS because we know that it is both impaired by dysautonomia [12,13] and involved in cerebrovascular pathology [14].

Our main objective was to investigate the status of CA in patients with MS. Also, we aimed to study its relationship with the magnitude of autonomic dysfunction (AD) by applying a battery of cardiovascular tests (Ewing battery) and methods to quantify the autonomic system integrity (heart rate variability – HRV – and spontaneous baroreflex

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sensitivity – BRS). MRI brain lesion load and its correlation with CA and hemodynamic parameters were evaluated as well. We hypothesized that an impaired CA in MS patients might play a role in the disease burden.

2. Materials and methods

This matched case-control study was performed in São João Hospital Center in Porto, Portugal. The local institutional ethic committee approved the study and every participant gave written and signed consent.

2.1. Population studied

From our MS outpatient clinic, we randomly selected 20 MS patients to participate (12 females). Inclusion criteria were a definite diagnosis of MS, according to the 2010 McDonald criteria, and age above 18 years old. Only relapsing-remitting MS patients were engaged and those who experienced a relapse or had been submitted to corticosteroids treatment within the previous eight weeks were excluded. The control group was selected from the hospital and university staff and consisted of 20 age- and sex-matched healthy subjects. Exclusion criteria were the presence of comorbidities that could affect autonomic function, as known cardiovascular diseases (e.g., myocardial infarction, heart failure, atrial fibrillation) and dysautonomias (e.g., Parkinsonism, multiple system atrophy, diabetes, polyneuropathy). All patients were evaluated by an MS specialist within one month before enrollment, and the following data was recorded: age, gender, neurological examination, Expanded Disability Status Scale (EDSS) score, and duration of disease.

2.2. Experimental design: monitoring and autonomic test protocol

Before evaluation, patients and controls were instructed to pause vasoactive drugs in the previous 24 h and abstain from drinking coffee and alcohol or smoke in the previous 12 h. Measurements were performed in a quiet room with a temperature around 22 °C. CBFV was recorded bilaterally from M1 segment of the middle cerebral arteries (MCA), at a depth of 50–55 mm, with 2 MHz monitoring probes held with a headband. (Doppler BoxX, DWL, Singen, Germany). Blood pressure (BP) was continuously monitored in the patient's non-dominant hand using the non-invasive finger cuff Finapres (model 2300; Ohmeda, Englewood, CO, USA). Heart rate and R-R intervals (RRi) were assessed from a 3-lead ECG. End-tidal carbon dioxide was recorded with a capnograph (Respsen Nonin, Amsterdam, Netherlands) by nasal cannula. All data were synchronized and digitally recorded at 400 Hz with with Powerlab (AD Instruments, Oxford, UK) for offline analysis.

Autonomic testing was explained to the volunteers. Maximum contraction strength with the dominant hand was measured using a dynamometer. Patients lied supine for 30 min before evaluation. Assessment of CA, baroreflex function and short-term heart rate variability (HRV) was based on data from a 10-min period of resting in the supine position with uncrossed legs.

Afterward, the autonomic tests protocol was performed as described elsewhere [3], based on the Ewing battery. In brief, 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, we calculated: expiratory–to–inspiratory amplitude ratio of HR (E:I ratio) during synchronized deep breathing at 6 cycles/min; the Valsalva ratio, i.e., averaged HR ratio between II and IV phases of three Valsalva maneuvers; the quotient of RRi around 30th beat by that at the 15th after standing; the difference between the systolic BP (SBP) at rest and after standing during 5 min to assess orthostatic hypotension; and diastolic BP (DBP) response to handgrip isometric work at 30% of his maximum strength for 5 min. A final total score (ETS) was obtained by adding 0 if the tests were normal, 1 if borderline and 2 if abnormal [3].

2.3. Cerebral autoregulation, spontaneous baroreflex sensitivity and heart rate variability measurements

Data was visually inspect for artifact removal. Extra-beats were removed by linear interpolation. Beats were marked on R-waves of ECG. For each heartbeat, systolic, mean and diastolic values of arterial BP (SBP, MBP, and DBP, respectively) and CBFV were calculated and visually corrected if needed.

CA parameters coherence, gain and phase were calculated using transfer function analysis, as recommended [15]: time-series of spontaneous oscillations in mean CBFV and MBP were interpolated at 10 Hz with a third-order polynomial spline; then an averaged periodogram was calculated by Welch method with Hanning window of window length of 102 s; 50% superposition; and triangular three-point window spectral smoothing filter. Coherence was calculated between input auto-spectra of ABP over cross-spectra of CBFV/ABP and transfer functions of phase and gain were determined by dividing the cross-spectrum by the input auto-spectrum. Values were reported in three frequency bands: very low (VLF: 0.02–0.07 Hz), low (LF 0.07–0.20 Hz) and high (HF: 0.20–0.50 Hz).

The BRS was evaluated in both the time and frequency domains. In the time domain, using the cross-correlation method xBRS, in which the regression slope between SBP and RRi was computed [16]. In resume, xBRS computes the correlation between beat-to-beat systolic blood pressure and normal RRi interval, resampled at 1 Hz, in a sliding 10 s window, with delays of 0–5 s for interval. The delay with the greatest positive correlation is selected and, when significant at $p < 0.01$, slope and delay are recorded as one xBRS value. The mean value of xBRS is finally calculated. In the frequency domain, the baroreceptor gain (BRG) was calculated based on the cross-correlation gain between the power spectral densities of SBP and RRi. Spectral analysis from time-series of SBP and RRi were achieved with the same parameters as in described in to access CA. TFA parameter gain was calculated by dividing the cross-spectrum by the input auto-spectrum. BRG was obtained in the band of low frequencies (LF: 0.04–0.15 Hz). xBRS determination of BRS maybe more reliable in patients with low BRS due to autonomic impairment since it is facilitated by the absence of thresholds for pressure and interval variation. Since MS patients might have disautonomia we decided to include to different methods that could strengthen and confirm significant correlations.

The frequency domain was used to assess HRV. The fast Fourier transformation was applied to the RRi tachogram, and a spectrum of the HRV signal was obtained. Again, this spectral analysis followed the same parameters described to achieve averaged periodogram described in CA. The following parameters were calculated: total power spectrum of RRi and its low (LF: 0.04–0.15 Hz) and high (HF: 0.15–0.04 Hz) frequency ranges.

2.4. MRI

The brain MRI had been obtained within one year before enrollment. The spinal MRI was the last imaging to be performed, and none of the subjects experienced a relapse after imaging. We assessed the presence of T2-weighted lesions in the following central autonomic network (CAN) structures: insula, anterior cingulate cortex, hypothalamus, amygdala, periaqueductal gray matter, parabrachial nucleus, nucleus of the solitary tract, ventrolateral reticular formation of the medulla and medullary raphe. By adding 1 point for each affected structure, we calculated a CAN score for each patient. The number of T2-weighted lesions in supratentorial areas, brainstem, cerebellum, and spinal cord was calculated, as well as the total number. MRI protocols were performed in 1.5T (Siemens MAGNETOM SymphonyTim syngo) and 3T (Siemens MAGNETOM TrioTim syngo) scanners. These imaging protocols included, 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 images (3770–4000 ms/11–22 ms [TR/TE]), T2-weighted images (3770–4000 ms/88–106 ms [TR/TE]) and axial and sagittal fluid-attenuated inversion-recovery (FLAIR) images (8000-9000 ms/