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Autonomic dysfunction in multiple sclerosis: cervical spinal cord atrophy correlates

Abstract Autonomic dysfunction has rarely been studied in patients suffering from multiple sclerosis (MS). Some hypotheses have concerned the pathophysiology, especially with regard to a possible spinal cord origin. However, there have been no previous studies on autonomic dysfunction in MS and spinal cord lesions. This study assessed the frequency of autonomic dysfunction (AD) in MS and the correlation to spinal cord magnetic resonance imaging (MRI) findings. We prospectively studied 75 MS patients (25 with relapsing-remitting forms, 25 with secondary progressive forms and 25 with primary progressive forms). We performed sympathetic skin response, R-R interval variability and orthostatic hypotension testing. Spinal cord MRI was performed to detect demyelinating lesions (sagittal and axial plane) or spinal cord atrophy. Clinical and laboratory evidence of AD was found in 84% and 56% of MS patients, respectively. The correlation of the latter with disability was evaluated using the Extended Disability Status Scale. AD was more frequent in primary progressive MS than in the other two forms. AD was correlated with spinal cord cross-sectional area reduction but not with spinal cord hyperintensities. This study confirms that the frequency of AD in MS, especially in primary progressive forms, has until now been underestimated. Furthermore, AD appears to be more closely related to axonal loss, as demonstrated by spinal cord atrophy, than to demyelinating lesions.

Key words Dysautonomia · Multiple sclerosis · Spinal cord atrophy · Magnetic resonance imaging · Autonomic nervous system

Introduction

Autonomic dysfunction (AD) has rarely been studied in multiple sclerosis (MS) [4, 7, 11, 17, 19, 23, 38]. However, bladder or bowel dysfunction is found to be frequent during the course of the disease and is related to autonomic nervous system impairment [20]. Orthostatic hypotension is reported in about 15% of MS patients, and cardiac adaptation disorders seem to be frequent as they have been reported in 30–80% of patients [11, 15, 16, 17, 23, 38]. Several studies have considered the potential of laboratory tests for AD as a diagnostic tool for MS, but these have been found to be of less diagnostic value than magnetic resonance imaging (MRI) or cerebrospinal fluid analysis [13, 23]. A few studies have considered AD in various forms of the disease [15, 17, 38], but only one has considered the primary progressive form [11]. Most of the previous studies have failed to find any correlation between AD and brain or brainstem lesions detected on MRI [4, 15, 17, 19, 36]. Only two studies have found a correlation between AD and brainstem lesions on MRI [1, 38]. Since AD is frequently associated with spinal cord injury [3, 28, 40], a potential role of spinal

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cord lesions in such dysfunction is possible. However, there have been no previous studies concerning AD and spinal cord MRI. Recent studies have shown that spinal cord atrophy is closely correlated with disability in MS [25, 27, 32, 33]. Although spinal cord atrophy is due not only to axonal loss, it appears to be the best marker of axonal loss at this level [29] and is correlated with a more extended atrophy in the brainstem or brain [12].

The aims of this study were to assess the frequency of AD in MS and to determine whether it is more frequently associated with a particular form of the disease. We also looked for a correlation between AD and spinal cord MRI findings (demyelinating lesions or spinal cord atrophy) with a view to improving our understanding of the physiopathological mechanisms.

**Methods**

**Patients**

We prospectively studied 75 patients with clinically and laboratory definite MS according to the criteria of Poser et al. [31]. We included only patients aged between 30 and 60 years and with an score on the Extended Disability Status Scale (EDSS) of 3 or more [22], the latter criterion being to reduce the EDSS variation between the different forms of the disease. Patients were evaluated according to the definition by Lublin et al. [26] of the clinical forms of the disease and were divided into three subgroups: 25 patients presented relapsing-remitting forms and 25 secondary progressive. Details of the patients’ characteristics are shown in Table 1. Exclusion criteria were drugs or diseases such as diabetes mellitus which could affect the autonomic nervous system.

Fifteen healthy subjects (nine women, six men) were used as a control group. Mean age was 40.7 years (range 30–60). All patients and controls were informed of the goal of the study and gave written informed consent.

All patients underwent a clinical study at least 1 month after a relapse. We used the EDSS to evaluate disability. A clinical examination and a questionnaire, including four measures (manifestations occurring after changing position, skin abnormalities, thermic dysfunction, and sphincter dysfunction), were carried out by the same neurologist (J.D.S.; see Appendix).

**Sympathetic skin response**

The relaxed subject lay on a couch in a quiet dimly lit room. Room temperature was maintained at 30°C or higher. Standard electromyographic disk electrodes were placed bilaterally on the palm (G1) and dorsum (G2) of the hands and on the sole (G1) and dorsum (G2) of the feet. Electromyography (DANTEC keypoint) was used with filter settings of 2–1000 Hz, sensitivity of 0.05–1 mV per division and sweep speed of 0.5 s per division. Single square electrical pulses of 0.1 ms duration and slightly above motor threshold intensity were applied to the right median nerve at the wrist. Stimuli were given at irregular intervals, but the delay between two stimuli was always greater than 30 s. The amplitude and latency of each response were not assessed as they varied greatly on consecutive stimulations. We also performed recording after noise stimulation to excluded sensory afferent defect. The response was considered absent if no consistent voltage change was seen using a sensitivity of 50 μV per division after at least six trials. The SSR was considered abnormal if the response was absent at one or more recording sites, as suggested by several authors [2, 5, 6].

**R-R interval variability**

Electrocardiographic R-R intervals were recorded on a computer to determine the RRIV. Three mainly parasympathetic tests were applied during the electrocardiographic recording [14, 39].

For deep breathing, the patient was seated quietly and instructed to breathe deeply and evenly at six breaths/min (5 s breathing in and 5 s breathing out). The maximum and minimum heart rate during each 10 s breathing cycle was measured. The mean difference between the two values during three successive breathing cycles gave the “maximum minus minimum” heart rate.

For the Valsalva manoeuvre, the subject was asked to sit quietly and then blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg and maintain the pressure for 15 s. The ratio of the longest to the shortest R-R interval during the manoeuvre was then measured. The response was expressed as the mean ratio of three successive Valsalva manoeuvres.

For standing up, the subject was asked to lie quietly on a couch and then stand up as quickly as possible. Heart-rate response was expressed as the ratio of the longest R-R interval around the 15th beat after standing up to the shortest R-R interval around the 15th. The values of the various RRIV tests were classified as normal, borderline or abnormal according to Ewing’s criteria [14]. In order to exclude false positives, borderline results were considered as normal.

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<table>
<thead>
<tr>
<th>Tab. 1 Clinical characteristics of multiple sclerosis patients and controls (EDSS Extended Disability Status Scale)</th>
<th>All MS (n=75)</th>
<th>Relapsing-remitting (n=25)</th>
<th>Secondary progressive (n=25)</th>
<th>Primary progressive (n=25)</th>
<th>Controls (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (women/men)</td>
<td>46/29</td>
<td>16/9</td>
<td>16/9</td>
<td>13/12</td>
<td>9/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean</td>
<td>43.7</td>
<td>43.1</td>
<td>43.8</td>
<td>47.4</td>
</tr>
<tr>
<td>95 % CI</td>
<td>41.8–45.6</td>
<td>39.7–47.5</td>
<td>41.1–46.5</td>
<td>44.5–50.3</td>
<td>38.9–42.5</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>Mean</td>
<td>12.1</td>
<td>12.5</td>
<td>13.8</td>
<td>9.4</td>
</tr>
<tr>
<td>95 % CI</td>
<td>10.6–13.6</td>
<td>10.9–14.1</td>
<td>11.5–16.1</td>
<td>6.9–11.9</td>
<td></td>
</tr>
<tr>
<td>EDSS</td>
<td>Mean</td>
<td>5.5</td>
<td>4.4*</td>
<td>6.2</td>
<td>5.7–6.7</td>
</tr>
<tr>
<td>95 % CI</td>
<td>5.2–5.8</td>
<td>4–4.8</td>
<td>5.4–6.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 vs. with progressive forms