Autonomic Dysfunction in Machado-Joseph Disease

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Objective: Machado-Joseph disease is an autosomal dominant spinocerebellar ataxia with expanded trinucleotide repeats. Although autonomic nervous system degeneration was documented in postmortem reports, the autonomic dysfunction in patients with Machado-Joseph disease, either in clinical analysis or electrophysiological investigations, has not yet been studied in detail.

Methods: Fifteen patients with genetically confirmed Machado-Joseph disease and 34 healthy subjects were studied. The study design included a detailed questionnaire, R-R interval variation on deep breathing or Valsalva maneuver, and sympathetic skin response evoked by electrical stimulation of the median nerve or magnetic stimulation of the neck.

Results: Sixty-seven percent of patients had at least 3 symptoms involving different aspects of autonomic functions. Voiding problems and thermoregulatory disturbance were the most common symptoms. Ten (71%) of 14 patients had abnormal R-R interval variation with a significant reduction of the mean ratio. Prolonged latency or absence of sympathetic skin response to electrical stimulation was identified in 73% of patients and to magnetic stimulation, in 53%. R-R interval variation and sympathetic skin response showed good correlation with the functional stage. Electrical stimulation revealed the highest sensitivity, specificity, and positive predictive value compared with other tests.

Conclusion: The present investigation documents that autonomic dysfunction is not uncommon in patients with Machado-Joseph disease and might be related to the clinical progression.

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MACHADO-JOSEPH DISEASE (MJD) belongs to a group of genetic diseases with expanded trinucleotide repeats and is a neurodegenerative disease affecting multiple systems with heterogeneous phenotypic manifestations.1-4 Although the number of trinucleotide repeats inversely correlates with the age at onset,5-7 the relationship between genotype and clinical manifestations, particularly autonomic functions, is unclear.

In patients with neurodegenerative diseases, such as olivopontocerebellar degeneration or multiple system atrophy, various degrees of autonomic dysfunction are frequently observed and sometimes account for the dominant manifestations.8,9 Following this logic, autonomic dysfunction also should be evident in patients with MJD. Clinical analysis and neuropathological reports in the literature indicate that autonomic nervous system involvement might be important and overlooked in MJD.3,8,10-12

We examined autonomic function in 15 patients with MJD, using a detailed questionnaire and 2 electrophysiological tests. R-R interval variation (RRIV) and sympathetic skin response (SSR) have been reported to be reliable, objective, and quantitative methods in assessing the parasympathetic and sympathetic autonomic functions.13-15 In our investigation, we addressed the following issues: (1) Is autonomic dysfunction common in patients with MJD? (2) Does the frequency and severity of autonomic involvement in patients correlate with clinical features such as disease severity, disease duration, age at onset, and number of CAG repeats? and (3) Are SSR and RRIV sensitive methods for early detection of autonomic dysfunction in patients with MJD?

METHODS

SUBJECTS

Fifteen patients with MJD from 8 unrelated families (A-H) were included in this study. Di-
agnosis of MJD was confirmed by screening the expanded trinucleotide repeats on the MJD1 gene using standard methods. Table 1 summarizes the clinical features of the 15 patients. Functional stage was scored by the modified scale designed by Hirayama et al. (Figure 1). Clinical assessment of various autonomic symptoms was conducted using a detailed questionnaire modified from Low (Figure 2).

For electrophysiological studies of autonomic function, 34 healthy subjects were recruited as controls (15 men and 19 women; mean ± SD age: 39.7 ± 14.3 years [range, 20-73 years]). Patients and controls had no clinical evidence of neuropathies or carpal tunnel syndrome by nerve conduction studies, and none were taking sedative or cardiovascular drugs that might affect autonomic function. All subjects provided informed consent.

### Table 1. Clinical Features of 15 Patients With Machado-Joseph Disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Age, y, mean ± SD (range)</td>
<td>40.2 ± 13.2 (20-75)</td>
</tr>
<tr>
<td>Age at onset, y, mean ± SD (range)</td>
<td>29.9 ± 10.3 (11-46)</td>
</tr>
<tr>
<td>Duration of disease, y, mean ± SD (range)</td>
<td>10.3 ± 6.9 (2-31)</td>
</tr>
<tr>
<td>No. of DAG repeats, mean ± SD (range)</td>
<td>76.3 ± 3.9 (68-82)</td>
</tr>
<tr>
<td>Nyctagmus</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Gait ataxia</td>
<td>14 (93.3)</td>
</tr>
<tr>
<td>Limb ataxia</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>Slow saccade</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Facial fasciculation</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Lid retraction</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Amyotrophy</td>
<td>2 (13.3)</td>
</tr>
</tbody>
</table>

R-R INTERVAL VARIATION

The subjects were relaxed, sitting comfortably, and had empty bladders. The study protocol was followed using a well-established, standard procedure. The responses were amplified using an electromyographic machine (Viking IV; Nicolet, Madison, Wis) with the bandpass between 1 and 30 Hz and with 2 minutes of analysis time. The subject was instructed to breathe deeply at a rate of 6 respiratory cycles per minute. The expiratory-inspiratory ratio on deep breathing was calculated by dividing the maximal R-R interval during expiration by the minimal R-R interval during inspiration. Heart rate variation on Valsalva maneuver was assessed by instructing subjects to take a full breath in and then blow into the mouthpiece connected to a manometer to the mark when 40 mm Hg had been attained for 15 seconds. The Valsalva ratio was determined by dividing the maximal R-R interval by the minimal R-R interval. The test excluded subjects with arrhythmia.

### SYMPATHETIC SKIN RESPONSES

This investigation used 2 methods for activating the sympathetic nervous system: electrical stimulation of the contralateral median nerve at the wrist and magnetic stimulation applied on the neck. The SSR recordings were performed according to well-established, standard procedure with the patient sitting comfortably in the room maintained at 22◦C. Responses were amplified with a bandpass between 0.2 and 3000 Hz, using an analysis time of 10 seconds. At least 5 responses were obtained and stored for analysis. Hand and finger skin temperatures were maintained at 32◦C to 34◦C. Electrical stimulation of the median nerve was delivered with
constant current square pulses of 5 to 15 mA in intensity for 0.2 millisecond and was administered at random intervals of longer than 1 minute to avoid habituation. Magnetic stimulation, which was generated by Magstim model 200 circular coil stimulator (Magstim, Whitland, Dyfed, Wales), was applied over the seventh cervical spinous process for 1 millisecond and was given at intervals that normally exceeded 1 minute. The optimal responses determined by the waveform with the largest amplitude were analyzed. Absence of waveform or prolonged latency were considered abnormal results.

### Statistical Analysis

Statistical analyses were performed using SPSS 10.0 for Windows (SPSS Inc, Chicago, Ill). All data were expressed as mean ± SD. The Mann-Whitney U test was used to compare electrophysiological data values between patients and control subjects. Sensitivity, specificity, and positive predictive value of each electrophysiological test were determined by the {\( \chi^2 \)} method. The relationship between various parameters was assessed using Pearson correlation or Spearman rank correlation acco...
ing to the type of data. A $P$ value lower than .05 was considered significant.

## RESULTS

### AUTONOMIC FUNCTION EVALUATION

Table 2 lists the most representative autonomic symptoms in the 15 patients with MJD. The most prevalent problems were cold intolerance and nocturia. Seven patients experienced orthostatic dizziness, but none of them ever had syncope. Orthostatic hypotension was noted in patient D-1 (age at onset, 46 years; disease duration, 6 years; CAG length, 72) and patient F-1 (age at onset, 42 years; disease duration, 5 years; CAG length, 78).

The same questionnaire was also given to 47 healthy controls and 21 patients with early-stage Parkinson disease. The frequencies of each autonomic symptom are listed in Table 2. The majority of symptoms occurred in fewer than 5% of healthy subjects except cold intolerance, dry mouth, and dry eye.

### R-R INTERVAL VARIATION

The RRIV results were abnormal in more than half of 14 patients without arrhythmia, based on age-specific normal values (Table 2). Figure 3 illustrates the traces of RRIV obtained from a healthy subject and a patient with MJD. Figure 4 shows scatterplots to demonstrate the significance. The sensitivity, specificity, and positive predictive value of RRIV under deep breathing were 42.9%, 93.8%, and 85.7%, respectively. Those for Valsalva maneuver were 64.3%, 66.7%, and 64.3%.

### SYMPATHETIC SKIN RESPONSES

The results of electrical stimulation were abnormal in 11 (73.3%) of 15 patients and of magnetic stimulation, in 8 (53.3%) (Table 2). Figure 5 displays the representative traces of normal SSR results, prolonged latency, and absence of waveform. Four patients displayed absence of waveform for both electrical stimulation and magnetic stimulation. Mean±SD latencies of electrical stimulation were considerably prolonged in 11 patients with MJD (right hand, $1628.2 ± 157.3$ milliseconds compared with $1404 ± 87.5$ milliseconds; $P < .001$; left hand, $1634.6 ± 219.2$ milliseconds compared with $1408.5 ± 104.1$ milliseconds; $P < .001$) (Figure 6). Similar prolonged latencies were noted in magnetic stimulation (right hand, $1626.4 ± 240.7$ milliseconds compared with $1407 ± 141.7$ milliseconds; $P = .005$; left hand, $1560 ± 224.6$ milliseconds compared with $1393 ± 147.8$ milliseconds; $P = .015$).
Mean amplitudes of electrical stimulation or magnetic stimulation did not differ between the control and patient groups (Figure 6). There were no differences in SSR measurements between either side. For electrical stimulation, the sensitivity, specificity, and positive predictive value were 73.3%, 97.1%, and 91.7%, respectively. Those for magnetic stimulation were 53.3%, 86.7%, and 66.7%.

**RELATIONS BETWEEN CLINICAL AND ELECTROPHYSIOLOGICAL STUDIES**

Similar inverse correlation was observed between number of trinucleotide repeats and age at onset in our patients. However, no correlations were observed among autonomic symptoms, electrophysiological tests, and clinical factors such as disease severity, disease duration, age at onset, and number of CAG repeats.

The results of deep breathing correlated with functional stage ($P = .04$), orthostatic dizziness ($P = .03$), and pyramidal signs ($P = .03$). The results of Valsalva maneuver correlated well with nocturia ($P = .04$) and diarrhea ($P = .03$). The results of electrical stimulation correlated with functional stage ($P = .002$) but were inversely correlated with parkinsonian signs ($P = .008$) and dry mouth ($P = .04$). The results of magnetic stimulation also correlated closely with functional stage ($P = .001$) and gait ataxia ($P = .008$).

This study investigated autonomic functions in patients with genetically confirmed MJD from 8 unrelated families. Four major findings were obtained. First, autonomic symptoms were common in patients with MJD. Second, abnormal reduction of RRIV, suggesting parasympathetic cardiovagal dysfunction, was present in 10 (71%) of 14 patients. Third, 11 (73%) of 15 patients had absence or prolonged latency of SSR, evoked either by electrical stimulation or magnetic stimulation, suggesting sympathetic sudomotor dysfunction. Fourth, both RRIV and SSR correlated closely with functional stage, but correlations among the different clinical features varied.

Ten patients (66%) had at least 3 diverse symptoms involving different aspects of autonomic functions (Table 2). In the literature, the rate of autonomic dysfunction in MJD varied from 5% to 55%. Although it is unclear why the incidence of autonomic perturbation is higher in the present series, most reports on this issue did not show detailed clinical manifestations. Autonomic dysfunction in MJD may sometimes be overlooked owing to marked motor disturbances. Accordingly, increased awareness of these symptoms is important in treating patients with MJD.
Intriguingly, the rate of autonomic dysfunction in MJD appeared higher in Asian individuals than in white individuals.13,14 The most frequent manifestation was urinary disturbance. Sequeiros and Coutinho1 reported difficulty in sphincter control in 5.8% of 143 Portuguese patients. The nationwide epidemiological survey in Japan reported voiding dysfunction in 31.3% of 66 patients.8 Clinical analysis of autonomic functions in Chinese patients is not still available. Soong et al17 reported autonomic dysfunction in 6 of 25 patients but did not describe their symptoms. In our series, 53% of patients also had urinary disturbance of nocturia and/or urine incontinence. Although this phenomenon was in concordance with the Japanese groups, the racial difference of distinct autonomic manifestation in MJD might need further elucidation.

It is useful and interesting to identify factors that can modify the variable expression in clinical symptoms and demographic data in a multisystem degenerative disease. Durr et al,18 as well as Hirayama et al,8 reported that the disease duration seemed to be a factor that could partially explain the heterogeneity of ataxia, dysarthria, dysphagia, fasciculation, pyramidal syndrome, ophthalmoplegia, and possibly the autonomic dysfunction. However, these 2 reports did not include comprehensive clinical investigation or correlative statistical analysis. Table 3 reassesses the relationship between clinical factors and autonomic dysfunction by reanalysing the individual data from another 4 studies.5-7,10 Including ours, these 5 studies showed no differences in the repeat length, age at onset, age at examination, and disease duration between the presence and absence of autonomic dysfunction. A larger sample size is required to search for possible factors influencing the nature and progression of autonomic dysfunction.

Table 3. Relationship Between Clinical Factors and Autonomic Dysfunction Calculated From Individual Reports *

<table>
<thead>
<tr>
<th>Source</th>
<th>Autonomic Dysfunction</th>
<th>Presence or Absence</th>
<th>Sample Size</th>
<th>No. of CAG Repeats</th>
<th>Age at Examination, y</th>
<th>Age at Onset, y</th>
<th>Duration of Disease, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schols et al</td>
<td>Incontinence</td>
<td>+</td>
<td>55</td>
<td>67 ± 3.5</td>
<td>50.6 ± 12.3</td>
<td>37.3 ± 9.3</td>
<td>13.4 ± 6.2</td>
</tr>
<tr>
<td>Watanabe et al</td>
<td>Urinary disturbance</td>
<td>+</td>
<td>66</td>
<td>71.5 ± 2.7</td>
<td>50.6 ± 12.3</td>
<td>37.3 ± 9.3</td>
<td>13.4 ± 6.2</td>
</tr>
<tr>
<td>Soong et al</td>
<td>Orthostatic hypotension</td>
<td>+</td>
<td>65</td>
<td>73.1 ± 3.5</td>
<td>41.9 ± 14.1</td>
<td>33 ± 12.9</td>
<td>8.9 ± 3.4</td>
</tr>
<tr>
<td>Kazuta et al</td>
<td>ANS dysfunction</td>
<td>+</td>
<td>60</td>
<td>72.2 ± 2.9</td>
<td>40 ± 13.9</td>
<td>33 ± 12.2</td>
<td>8.9 ± 3.4</td>
</tr>
<tr>
<td>Kazuta et al</td>
<td>Orthostatic hypotension</td>
<td>−</td>
<td>19</td>
<td>73.9 ± 5.2</td>
<td>41.7 ± 13.9</td>
<td>33.6 ± 12.2</td>
<td>8.1 ± 3.6</td>
</tr>
</tbody>
</table>

Abbreviations: ANS, autonomic nervous system; NA, not available; +, present; −, absent.

*Comparisons of number of CAG repeats, age at examination, age at onset, and duration of disease were made between patients with and without autonomic dysfunction; all P > .05. Values are expressed as mean ± SD unless otherwise indicated.

of our patients had abnormal SSR results. In contrast to the RRIV, the findings of this investigation were consistent with previous works.10,17,20 We found that the abnormal frequency was higher in electrical stimulation (73%) than magnetic stimulation (53%). The evoked SSR after magnetic stimulation is presumed mainly from direct activation of postganglionic sympathetic neurons with little influence from sensory afferent fibers.12 The present findings suggest that the afferent pathway and central modulation of sudomotor function might be more frequently affected than the efferent pathway and that electrical stimulation was more sensitive than magnetic stimulation in detecting sudomotor dysfunction in patients with MJD.

In this series, correlation between electrophysiological tests and autonomic symptoms was variable and weak. Although such findings were also reported by other groups,21 a serial follow-up study with a larger sample size is warranted to identify the effect of these autonomic tests in predicting clinical outcome. In this series, however, we found good correlation of such tests and clinical progression and documented the validity of RRIV and SSR in patients with MJD. Electrical stimulation revealed the highest sensitivity, specificity, and positive predictive value. The RRIV of deep breathing showed a higher predictive value than the Valsalva maneuver for detecting parasympathetic dysfunction in MJD.

In conclusion, our investigation found that autonomic dysfunctions were not uncommon in patients with MJD, using either clinical or electrophysiological studies. The high rate of abnormalities in RRIV and SSR indicated that both the parasympathetic and sympathetic nervous systems were affected in MJD and were correlated with the progression of disease.
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