Muscle Excitability Abnormalities in Machado-Joseph Disease

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Objectives: To estimate the frequency of and to characterize muscle excitability abnormalities in Machado-Joseph disease (MJD).

Design: Machado-Joseph disease is a common autosomal dominant cerebellar ataxia caused by an unstable CAG trinucleotide repeat expansion. Muscle cramps and fasciculations are frequent and sometimes disabling manifestations. However, their frequency and pathophysiological mechanisms remain largely unknown. Symptomatic patients with MJD (hereinafter MJD patients) with molecular confirmation were assessed prospectively. A standard questionnaire addressing clinical features of muscle cramps and fasciculations was used. The Cramps Disability Scale was used to quantify cramps-related disability. Patients underwent neurophysiological testing with routine techniques. F waves of the right median nerves were obtained, and persistence indexes were calculated. Four muscles (deltoid, first dorsal interossei, tibialis anterior, and vastus lateralis) were examined by needle electromyography. A semiquantitative scale (from 0 [no activity] to 4 [continuous activity]) was used to determine the frequency of rest fasciculations in each muscle.

Results: Fifty MJD patients (29 men) were included in the study. Their mean age at examination was 46.3 years, their mean age at onset of the disease was 35 years, and the mean duration of disease was 11.2 years. Abnormal CAGn varied from 59 to 75 repeats. Forty-one patients presented with muscle cramps; in 10, this was their first symptom. The frequency of cramps varied between 1 and 90 episodes a week. For 15 patients, cramps were the chief complaint, frequently disturbing sleep or work (Cramps Disability Scale score, 2 or 3). Lower limbs were affected in 37 individuals, but unusual regions, such as the face and abdominal muscles, were also involved. Fasciculations were found in 25 individuals; in 8 patients, they included facial muscles. However, fasciculations were not a significant complaint for any of these patients. The clinical and neurophysiological profile of MJD patients with and without cramps was not significantly different. However, MJD patients with fasciculations had more severe damage to their peripheral nerves.

Conclusions: Muscle excitability abnormalities were found in 41 MJD patients (82%), and they were the presenting complaint in 10 (20%). They are related to altered excitability of peripheral motor axons, but mechanisms underlying cramps and fasciculations are possibly distinct in MJD patients.

Arch Neurol. 2008;65(4):525-529

MACHADO-JOSEPH DISEASE (MJD) is the most common autosomal dominant cerebellar ataxia worldwide and is caused by an unstable CAG trinucleotide repeat expansion in the coding region of the MJD1 gene (OMIM 60704). It is characterized by remarkable phenotypic heterogeneity with a wide range of cerebellar, ocular, pyramidal, and extrapyramidal manifestations. On clinical grounds, 3 classic types of MJD are recognized: type 1, with marked pyramidal and dystonic signs and early onset; type 2, characterized by pure or predominant cerebellar ataxia; and type 3, with late-onset, more frequent, peripheral neuropathy (PN) and a more benign course. Peripherial neuropathy is, thus, frequent in MJD and may be an important source of disability. In some patients, motor axons are specifically damaged in a pattern resembling motor neuron disease. Muscle excitability abnormalities (namely, muscle cramps and fasciculations) are typical findings in patients with motor neuron disease, such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy. This is attributed to the collateral reinnervation that develops in these conditions to compen-
sate for axonal loss. Although such manifestations have long been recognized in MJD, systematic analysis of these features is still lacking and the few reports devoted to this issue relied on small series of patients or case reports.

We, therefore, aimed to identify the frequency, severity, clinical profile, and causative factors of muscle cramps and fasciculations in a large cohort of patients with MJD (hereinafter MJD patients) through clinical and neurophysiological evaluations.

METHODS

SUBJECT SELECTION

A group of symptomatic patients prospectively followed up in our neurogenetics outpatient clinic with molecular confirmation of MJD were included in the study. Clinical (sex, height, age at disease onset, duration of disease, and clinical subtype) and genetic (length of expanded CAG repeat) data were recorded. The severity of ataxia was quantified with the International Cooperative Ataxia Rating Scale. A standardized questionnaire specifically addressing the presence and features of muscle cramps was used. The age at onset of cramps, the frequency and duration of the episodes, anatomical sites involved, and relief factors were identified. The Cramps Disability Scale (CDS) score was used to quantify its severity. We looked for spontaneous fasciculations on upper limb, lower limb, thoracic, abdominal, and facial muscles during the neurological examination.

Families with autosomal dominant cerebellar ataxia but no molecular confirmation of MJD were excluded. Individuals with medical conditions or those taking drugs known to predispose to muscle cramps were not included in the final analysis. A group of age- and sex-matched individuals with no neurological abnormalities and a group of patients with ALS were used for comparison. Most individuals in the healthy control group were spouses or unrelated caregivers of MJD patients. Patients with ALS met the El Escorial World Federation of Neurology criteria for defined disease.

This study was approved by our institution’s ethics committee, and written informed consent was obtained from all participants.

NEUROPHYSIOLOGICAL STUDIES

Patients with MJD underwent nerve conduction studies and needle electromyography (EMG) using an electromyograph (Neuropack 2 Electromyographer; Nihon Kohden, Tokyo, Japan). The protocol of the nerve conduction studies included sensory (median, ulnar, radial, and sural) and motor (median, ulnar, common peroneal, and tibial) nerves on both sides. According to nerve conduction study findings, patients were classified into 4 groups: 1, healthy; 2, exclusively sensory PN; 3, sensory motor PN; and 4, exclusively motor PN.

The H-reflex of the right tibial nerve was searched for according to routine techniques. H-reflex latency is expressed in milliseconds, and amplitude is expressed as the ratio of the amplitude of the maximum H-reflex to that of the maximum compound muscle action potential of the soleus muscle. We used 20 consecutive supramaximal stimuli to study F responses of the right ulnar nerve through routine stimulation (wrist) and recording techniques (abductor digiti minimi). We analyzed F-wave minimal latency and persistence.

Four muscles on the right side (deltoid, first dorsal interosseous, tibialis anterior, and vastus lateralis) were examined by monopolar needle EMG. Rest activity was analyzed for 5 minutes at 4 different points in each muscle. The morphological features of motor unit action potentials and interference pattern on voluntary muscle activation were recorded.

A semiquantitative scale was used to determine the frequency of fasciculations in each muscle (0 indicates no activity; 1, fasciculations < 25% of the period; 2, fasciculations between 25% and 49% of the period; 3, fasciculations between 50% and 75% of the period; and 4, fasciculations > 75% of the period), and a total fasciculation score represented the sum of individual scores (range, 0-16).

STATISTICAL ANALYSIS

We compared the prevalence and characteristics of muscle cramps among MJD patients, patients with ALS, and healthy controls using analysis of variance and χ². We then compared the clinical, genetic, and neurophysiological profile of MJD patients with and without muscle excitability abnormalities through Mann-Whitney and χ² tests. Statistical significance was considered at an α of 5%. Statistical analysis was performed using computer software (SYSTAT 10.2, Systat Software, Inc, San Jose, California).

RESULTS

Fifty MJD patients, 20 patients with ALS, and 50 age- and sex-matched controls were included in the study. Among MJD patients, the mean age at onset and the duration of disease were 35.0 and 11.2 years, respectively. The mean length of expanded CAGn was 66 (range, 59-75). According to nerve conduction studies, there were 20 patients in group 1, 12 in group 2, 13 in group 3, and 5 in group 4.

The main clinical data are shown in Table 1. Cramps began with a mean delay of 9.2 years after the onset of MJD. However, in a group of 10 patients, they preceded or began concomitantly with ataxia. The CDS scores in those patients were slightly higher than in the remaining MJD patients (1.45 vs 1.38; P = .08). In contrast to the whole group with MJD, in these patients, upper limbs were the major site of painful episodes (n = 5), followed by abdominal muscles (n = 3) and lower limbs (n = 3).

There was a trend toward significant differences between MJD patients with and without cramps regarding age (46.9 vs 43.2 years; P = .39), duration of disease (11.9 vs 8.0 years; P = .06), and expanded CAGn (66.1 vs 68.0; P = .10). Although the proportion of MJD clinical subtypes was not different among individuals with and without cramps (P = .81), 8 of the 11 patients with type 1 in the entire group had muscle cramps. The frequency of PN was not different between MJD patients with and without cramps (26 of 41 vs 4 of 9; P = .45). We analyzed whether cramps in those with MJD might be related to altered muscle excitability by studying F responses and the H-reflex of tibial nerves. Ulnar nerve F-wave persistence and minimal latency were not significantly different (P = .3 and .32, respectively) between MJD patients with and without cramps. In addition, we found higher amplitudes (ratio of the amplitude of the maximum H-reflex to that of the maximum compound muscle action potential of the soleus muscle, 0.29 vs 0.17; P = .39) and shorter latencies (22.1 vs 23.8 milliseconds; P = .82) of H responses among
MJD patients with cramps; however, these differences did not reach statistical significance.

Carbamazepine treatment, 200 mg twice a day, was introduced in 15 patients who had CDS scores higher than 1 following initial evaluation. After 6 months, all 15 patients had significant improvement (CDS score, 0). One patient complained of dizziness, but medication was otherwise well tolerated.

Fasciculation was not reported as a spontaneous complaint by any patient. It was clinically evident on neurological examination in 15 patients, 8 of whom had facial involvement. Needle EMG identified fasciculations in 25 individuals. In contrast, all patients with ALS had fasciculations on needle EMG, and all but 1 had fasciculations on clinical examination. No healthy control had clinical fasciculations. The mean total fasciculation score was 2.5 (range, 1-10). Data on MJD patients with and without fasciculations are summarized in Table 2. Most MJD patients with fasciculations were of clinical subtype 3. There was a higher frequency of PN among MJD patients with fasciculations. The H-reflex was not obtained in 60% and 32% of MJD patients with and without fasciculations, respectively (n=15 and 8, respectively). Excluding those patients with abolished H-reflexes, we also found prolonged latencies (32.8 vs 29.9 milliseconds; P=.008) and reduced amplitudes (ratio of the

Table 1. Demographic and Clinical Data in Patients With MJD, Patients With ALS, and Healthy Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With MJD (n=50)</th>
<th>Patients With ALS (n=20)</th>
<th>Controls (n=50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male to female ratio</td>
<td>29:21</td>
<td>14:6</td>
<td>26:24</td>
<td>.39</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>46.3 (10-73)</td>
<td>48.8 (36-70)</td>
<td>47.5 (29-71)</td>
<td>.74</td>
</tr>
<tr>
<td>Cramp features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of cramps, No. (%)</td>
<td>41 (82)</td>
<td>11 (55)</td>
<td>2 (4)</td>
<td>.02</td>
</tr>
<tr>
<td>Frequency of cramps, episodes/mo</td>
<td>17</td>
<td>37</td>
<td>3</td>
<td>.52</td>
</tr>
<tr>
<td>CDS score, mean (range)</td>
<td>1.39 (1-2)</td>
<td>1.45 (1-3)</td>
<td>1.0 (1)</td>
<td>.48</td>
</tr>
<tr>
<td>Topographic distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limbs</td>
<td>37</td>
<td>10</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>13</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Head/neck</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALS, amyotrophic lateral sclerosis; CDS, Cramps Disability Scale; MJD, Machado-Joseph disease; NA, not available.

aData are given as number of individuals in each group unless otherwise indicated.

bThis difference was significant.

Table 2. Demographic, Clinical, and Genetic Features of Patients With MJD With and Without Fasciculations

<table>
<thead>
<tr>
<th>Variable</th>
<th>With Fasciculations (n=25)</th>
<th>Without Fasciculations (n=25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male to female ratio</td>
<td>17.8</td>
<td>12.13</td>
<td>.15</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165</td>
<td>158</td>
<td>.83</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.3</td>
<td>41.2</td>
<td>.006</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>38.9</td>
<td>31.2</td>
<td>.02</td>
</tr>
<tr>
<td>ICARS score</td>
<td>35.0</td>
<td>39.4</td>
<td>.41</td>
</tr>
<tr>
<td>MJD clinical subtype, No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>10</td>
<td>.005</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No. of expanded CAG repeats (genetic data)</td>
<td>64.7</td>
<td>68.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neurophysiological data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with peripheral neuropathy, No. (%)</td>
<td>20 (80)</td>
<td>10 (40)</td>
<td>.004</td>
</tr>
<tr>
<td>Sural nerve SNAP amplitude, µV</td>
<td>11.2</td>
<td>14.1</td>
<td>.04</td>
</tr>
<tr>
<td>Sural nerve CV, m/s</td>
<td>44.8</td>
<td>45.4</td>
<td>.09</td>
</tr>
<tr>
<td>Absent H-reflex, No. (%)</td>
<td>15 (60)</td>
<td>8 (32)</td>
<td>.04</td>
</tr>
<tr>
<td>F-wave minimal latency, ms</td>
<td>26.8</td>
<td>22.0</td>
<td>.05</td>
</tr>
<tr>
<td>F-wave persistence, %</td>
<td>41.5</td>
<td>63.5</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: CV, conduction velocity; ICARS, International Cooperative Ataxia Rating Scale; MJD, Machado-Joseph disease; SNAP, sensory nerve action potential.

aData are given as mean value unless otherwise indicated.

bThis difference was significant.
amplitude of the maximum H-reflex to that of the maximum compound muscle action potential of the soleus muscle, 0.13 vs 0.40; \( P < .001 \) of H-reflex in MJD patients with fasciculations.

**COMMENT**

In this cohort, muscle cramps were found in 41 patients with MJD (82%) and in some of them they were a major source of disability, as shown by the high frequency of episodes (mean, 17 episodes per month) and CDS scores (1.39 vs 1.00 in healthy controls). This high point prevalence is particularly noteworthy as we compare it with that of age- and sex-matched controls (4%) and especially with that of patients with ALS (55%), who are prone to frequent muscle cramps.7 There was a previous study10 investigating muscle cramps in MJD that included 20 consecutive Japanese patients; the study found pathologic cramps in about 80% of them. The remarkably similar results found in these 2 different ethnic populations of MJD patients indicate that this estimate probably reflects the true frequency of cramps in the disease. In addition, a recent survey15 of clinical findings in a group of 127 patients with spinocerebellar ataxia (SCA) also found muscle cramps to be more frequent in MJD than in other forms of SCA.

Muscle cramps were mostly a late complaint but, in a significant proportion of patients (n = 10), they preceded or began concomitantly with ataxia. In addition, these early-onset cramps more frequently involved the upper limbs and were slightly more distressing compared with the most usual types of cramps found in those with MJD and in healthy controls. This clinical observation points to the possible value of cramps as a preclinical symptomatic marker of the disease among at-risk individuals. Similarly, patients with late-onset spinal muscular atrophy due to homozygous mutations of the SMN (OMIM 600354) gene may have cramps as the initial and isolated manifestation.16 This relevant clinical issue could be addressed in a study comparing muscle cramps among SCA3-positive and SCA3-negative at-risk individuals prospectively.

The pathogenesis of muscle cramps is still not completely understood, but clinical and experimental data indicate that abnormal excitability of peripheral nerves is important.17 In motor neuron disease, death of motor neurons leads to degeneration of distal intramuscular terminals and subsequent collateral sprouting of nearby rami. In these regenerating motor axons, there is overexpression of ionic channels that leads to spontaneous ectopic activity and muscle cramps.18 A previous study19 with MJD patients using the threshold tracking technique found a correlation between cramps and increased axonal excitability. Late responses and, especially, H-reflexes are neurophysiological techniques that measure the degree of excitability of the motor neuron pool.19,20 There was a trend toward earlier onset and longer CAG repeats among MJD patients with cramps, which partly explains why they had more frequent pyramidal and extrapyramidal signs but not PN. These data suggest that cramps may occur earlier than PN in the disease course. In addition, we found shortened latencies and increased amplitudes for H-reflex potentials among patients with cramps, but differences were not statistically significant. Overall, these findings suggest that altered excitatory inputs from corticospinal fibers rather than peripheral nerve damage underlie abnormal excitability and muscle cramps in MJD patients.

In our patients, carbamazepine effectively relieved cramps in a 6-month follow-up. We needed low doses to obtain this effect, thus minimizing the risks for serious adverse reactions. Carbamazepine has been successfully used to treat patients with muscle excitability abnormalities, such as myotonic disorders21 and Isaacs syndrome22; the effects of the drug at voltage-gated sodium channels on axonal membranes probably account for this clinical response.21,22 This is a promising result that needs to be confirmed in better-designed controlled trials.

Fasciculations are typical manifestations in motor neuron disease and have been previously reported in some families with MJD.8,23 However, data on the prevalence and distribution are scarcely available. In our cohort, clinically visible fasciculations were identified in 15 of 50 MJD patients and in 19 of 20 patients with ALS. Using needle EMG, we found fasciculations in half of MJD patients. Despite this, spontaneous facial fasciculations were present in 8 MJD patients but in only 1 patient with ALS. The severe damage to pontine facial nuclei, which is frequent in MJD but not in ALS, probably accounts for this difference.24,25 Previous data indicate that fasciculations are a reliable clinical sign found in SCA1, SCA2, and SCA3 but not in other SCAs.15 The frequency of fasciculations was not significantly different among the 3 subtypes; however, the number of enrolled patients was few (SCA1, n = 13; SCA2, n = 19; and SCA3, n = 20). Facial fasciculation seemed to be less frequent in SCA1 than in SCA2 and SCA3, whereas limb fasciculations are relatively common in all 3 disorders.26 In addition, some patients with SCA2 present myokymic discharges rather than short-lived fasciculations typical of SCA3.27 These findings raise a question about the clinical value of fasciculations (especially facial) as a useful sign of MJD in the appropriate context.

Fasciculations are thought to arise from spontaneous discharges of a single motor unit caused by altered excitability in peripheral motor axons.17 This abnormal excitability is closely related to the severity of motor neuron damage in conditions such as spinal muscular atrophy and ALS. We hypothesized that fasciculations in MJD also had a similar pathogenesis. Patients with MJD with fasciculations were older, their disease began later, and they had smaller CAG repeat expansions than MJD patients without fasciculations. In addition, MJD patients with fasciculations had mostly clinical subtype 3 and had more frequent (20 of 25 patients [80%]) and severe PN. There were lower persistence indexes, altered latencies of F waves, and abnormal H-reflexes in MJD patients with fasciculations. These results suggest altered muscle excitability possibly secondary to degeneration of the motor neuron pool as an important factor in the origin of fasciculations. Experimental models of MJD have lately shown that ataxin-3 may interfere with potassium channel function, leading to a sig-
sificant reduction of the resting membrane potential of neurons. Such electrical abnormality, which seems to precede neuronal death, may help to explain why muscle excitability abnormalities are frequent and sometimes an early manifestation in MJD patients.

In conclusion, muscle excitability abnormalities are frequent and sometimes disabling manifestations of MJD. They are related to altered excitability of peripheral motor axons, but mechanisms underlying cramps and fasciculations are possibly distinct in MJD patients. However, large prospective studies are needed to clarify this issue and to define the best therapeutic approach.

Accepted for Publication: July 26, 2007.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by grant 04/13725-4 from the Fundação de Amparo à Pesquisa do Estado de São Paulo.

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