Chronic Pain in Machado-Joseph Disease

A Frequent and Disabling Symptom

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Background: Machado-Joseph disease (MJD) is one of the most common forms of neurodegenerative ataxia characterized by remarkable phenotypic heterogeneity. Although patients frequently report pain, systematic evaluation of this clinical feature is lacking.

Objectives: To compare the frequency of chronic pain among patients with genetically confirmed MJD, an age- and sex-matched healthy control group, and a disease control group of patients with amyotrophic lateral sclerosis (ALS).

Methods: We included 70 patients with MJD, 20 patients with ALS, and 70 control subjects from 2 clinical centers. All individuals underwent assessment with a standardized pain questionnaire. In addition, we used a visual analog scale to quantify pain intensity.

Results: Thirty-three patients with MJD (47%), 3 patients with ALS (15%), and 6 controls (9%) reported chronic pain. Lower back pain preceded ataxia in 6 patients with MJD. Twenty-nine patients with MJD had daily pain, which was continuous in 23. The mean visual analog scale score was 6.1 in patients with MJD. Pain was musculoskeletal in 26 patients with MJD, dystonic in 2, neuropathic in 2, and mixed in 3. Typically, pain was lumbar (n=17) or in the lower limbs (n=15). We did not find significant differences regarding duration of disease, sex, or severity of ataxia among patients with MJD with and without chronic pain. Expanded (CAG)n tandem repeats were longer in patients with MJD who experienced chronic pain (67.3 vs 65.2; \( P = .04 \)).

Conclusions: In our series, pain was significantly more frequent in patients with MJD than in controls. Chronic pain was a frequent and often disabling complaint among patients with MJD. The lower back was the most frequently reported location of pain in patients with MJD.

MACHADO-JOSEPH DISEASE (MJD) is the most frequently occurring autosomal dominant spinocerebellar ataxia worldwide.1,2 It is characterized by an adult-onset progressive cerebellar syndrome with remarkable phenotypic heterogeneity, and features such as dystonia, pyramidal abnormalities, rapid eye movement sleep behavior disorder, supranuclear ophthalmoplegia, and peripheral neuropathy are frequently found.3 In addition, sensory complaints and particularly painful sensations have been reported previously. In some families, diffuse joint pain was the presenting symptom, even preceding ataxia.3,4

Despite these findings, systematic evaluation of pain in patients with MJD is still neglected in the literature. Recognition of pain as an important feature of neurodegenerative diseases such as Parkinson disease (PD) and multiple system atrophy has been emphasized lately.5-7 In these diseases, pain was one of the most distressing manifestations found in nearly half of the patients.5-7 Damage to the basal ganglia and cerebellum probably underlies pain in PD and multiple system atrophy. In addition, severe painful spasms demanding aggressive therapy have been identified in inherited conditions such as Friedreich ataxia.8

In this study, we aimed to compare the prevalence of chronic pain in a large cohort of patients with genetically confirmed MJD, an age- and sex-matched healthy control group (controls), and a disease control group of patients with amyotrophic lateral sclerosis (ALS).

METHODS

STUDY DESIGN

Patients with MJD were recruited from the neurogenetics clinics at Campinas State University in Brazil and Brown University Medical School in the United States. The patients un-
derwent a detailed neurological evaluation with emphasis on painful complaints. Only individuals with genetically confirmed disease or symptomatic first-degree relatives of individuals with genetically confirmed disease were included in the study. Chronic pain was defined as pain lasting longer than 3 months with episodes on at least 50% of the days. A standardized questionnaire that addressed pain features such as age at onset, duration and frequency of episodes, anatomic distribution, and response to medication was administered to all patients with MJD. Pain was classified according to Goetz et al as musculoskeletal, dystonic, neuropathic, mixed, or unclassified. A visual analog scale was used to quantify pain intensity. The International Cooperative Ataxia Rating Scale (ICARS) and Epworth Sleepiness Scale were used to determine the severity of ataxia and daytime sleepiness in patients with MJD. Depressive symptoms were assessed with the Geriatric Depression Scale validated for the Portuguese language, and patients with MJD who were taking antidepressants were identified. The length of expanded (CAG)_n tandem repeats was recorded where available. Medical conditions known to predispose to or cause chronic pain were identified.

Families with autosomal dominant cerebellar ataxia but no molecular confirmation of MJD were excluded. Muscle cramps were not considered in this analysis.

A group of age- and sex-matched individuals with no neurological abnormalities was used for comparison. Most individuals in the control group were spouses or caretakers of patients with MJD. In addition, we included a disease control group of 20 patients with ALS in whom severe motor disability was not accompanied by extrapyramidal or sensory abnormalities.

### Statistical Analysis

We used analysis of variance to compare pain among patients with MJD, patients with ALS, and controls. We tested the differences between MJD patients with and without pain regarding quantitative and categorical data with a 2-sample t test and \( \chi^2 \) test, respectively. Statistical analysis was performed on SYSTAT statistical software, version 10.2 (Systat Software Inc, Richmond, California).

## Results

Seventy patients with MJD, 20 patients with ALS, and 70 age- and sex-matched controls were included in the study. The mean ages were 37.5, 48.8, and 37.2 years, respectively. The proportions of women were similar: 32 of 70 patients with MJD, 6 of 20 patients with ALS, and 34 of 70 controls. In 52 patients with MJD, genetic and clinical data, including ICARS and Epworth Sleepiness Scale scores, were available for final analysis. In these patients, the mean ICARS score was 38.6 (range, 4-91), the mean Epworth Sleepiness Scale score was 8.4 (range, 0-18), and the mean length of expanded (CAG)_n tandem repeats was 66.3 (range, 59-75 tandem repeats).

Eleven patients with MJD fulfilled major depression criteria and 3 were taking antidepressants on a regular basis. Among the patients with MJD, 10 men were farmers and 15 women were housekeepers.

We found chronic pain in 33 patients with MJD (47%), 3 patients with ALS (15%), and 6 controls (9%) (\( P < .001 \)). The frequencies of chronic rheumatic and orthopedic conditions causative of pain were similar in patients with MJD and controls. Among the patients with MJD, the mean age at pain onset was 38.9 years (Table 1). Pain preceded ataxia in 5 patients and began concomitantly with it in another 6. Twenty-nine patients with MJD had daily episodes of pain, which was continuous during the day in 23. The mean visual analog scale score was 6.1 (range, 2-10). Pain was classified as musculoskeletal in 26 patients, dystonic in 2, neuropathic in 2, and mixed in 3. In most patients it was typically lumbar (17 patients) or in the lower limbs (15 patients). Nine patients had more than 1 painful anatomic site. Nonsteroidal anti-inflammatory drugs or opiates were prescribed for pain relief in 21 patients with MJD, but only 12 of those reported improvement.

We did not find significant differences between patients with MJD with or without pain in relation to age at disease onset or to the proportion of women (Table 2). In both groups, the ICARS and Epworth Sleepiness Scale scores were similar, as were the proportion of patients with dystonia, peripheral neuropathy, and pyramidal signs. The frequency of associated major depression was similar in both groups (4 of 22 vs 7 of 30; \( P = .05 \)), but all 3 of the patients regularly taking antidepressants had chronic pain. Similarly, the proportion of nonambula-

### Table 1. Pain Features Among Patients With MJD, Patients With ALS, and Control Subjects

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Patients With MJD (n=70)</th>
<th>Patients With ALS (n=20)</th>
<th>Controls (n=70)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>37.5 (12.4)</td>
<td>48.8 (9.3)</td>
<td>37.2 (13.5)</td>
<td>.16</td>
</tr>
<tr>
<td>Pain features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) with pain</td>
<td>33 (47)</td>
<td>3 (15)</td>
<td>6 (9)</td>
<td>.001</td>
</tr>
<tr>
<td>Age at pain onset, mean (SD), y</td>
<td>38.9 (11.7)</td>
<td>47.3 (7.7)</td>
<td>53.2 (4.6)</td>
<td>.06</td>
</tr>
<tr>
<td>VAS score, mean (SD)</td>
<td>6.1 (2.2)</td>
<td>3.3 (2.0)</td>
<td>4.5 (2.0)</td>
<td>.10</td>
</tr>
<tr>
<td>Topographic distribution, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar region</td>
<td>17</td>
<td>0</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Head/neck</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Perineal region</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ALS, amyotrophic lateral sclerosis; MJD, Machado-Joseph disease; NA, not applicable; VAS, visual analog scale.
MJD1 allele would help to elucidate this point.5,13-15 In particular, dysfunction of striatal15 and thalamo-diencephalic 13 dopaminergic circuits has been implicated in making this process a chronic vicious cycle. Since the first report of MJD in Azorean families, lower back pain has been recognized as a feature of MJD possibly caused by abnormal gait and posture,3 but this has not been a widely recognized symptom. However, our findings of similar ICARS scores in patients with and without pain as well as the occurrence of severe pain in individuals with mild ataxia argue against such a simple mechanism. Besides, the low frequency of chronic pain among patients with ALS points to different pain mechanisms in these conditions.

Pain was felt in a stocking-glove distribution, had associated allostynia, and was worse at night in 2 patients. It was associated with severe and predominantly sensory peripheral neuropathy in these cases. In 2 additional patients, discomfort occurred with dystonic spasms and improved with botulinum toxin injections. Despite this, most of the patients had musculoskeletal or joint pain as classified by Goetz et al.3 This is also similar to previous descriptions of patients with PD.

Longer expanded alleles at the MJD1 locus such as those found in our patients with MJD who experienced frequent pain are known to be associated with more frequent extrapyramidal manifestations due to basal ganglia damage,16 a finding consistent with the dopaminergic pain hypothesis. Also in support of this idea, 2 patients with pain, mild ataxia, and pronounced parkinsonian features started levodopa therapy, but instead of motor improvement they had subjective pain relief. Spinal cord ascending pathways for pain sense are frequently involved in MJD,19 which may explain this response. Pain in PD is not usually responsive to levodopa, suggesting differences between MJD pain and PD pain.

Our results should be considered tentative, limited by the small size of our control population. However, we have found that chronic pain is a frequent and dis-
abbling symptom in patients with MJD that has been underrecognized. Although multifactorial in nature, pain may be related to the primary neurodegenerative process caused by the expanded polyglutamine tract, as well as by the secondary problems of dystonia, neuropathy, and abnormal postures. Further studies are soon needed to identify the best therapeutic strategies for pain in MJD.

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