Muscle cramp in Machado–Joseph disease
Altered motor axonal excitability properties and mexiletine treatment

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Summary
Machado–Joseph disease is one of the most common hereditary spinocerebellar degenerative disorders with a wide range of clinical manifestations. Pathology studies have shown mild to moderate loss of anterior horn cells and, in terms of spinal pathology, Machado–Joseph disease is regarded as a type of lower motoneuron disease. Muscle cramps are often associated with lower motoneuron disorders, but features of cramps in Machado–Joseph disease patients have never been studied. We investigated the incidence and nature of muscle cramps in Machado–Joseph disease patients, the excitability properties of motor axons [strength–duration time constant (\(\tau_{SD}\)), threshold electrotonus, refractoriness and supernormality] using threshold tracking and the effects of mexiletine hydrochloride on those cramps. Of 20 consecutive patients, 16 (80%) had frequent, severe muscle cramps in the legs, trunk or arms that disturbed their daily activities. The frequency of pathological muscle cramps was similar to that for patients with amyotrophic lateral sclerosis (68%) and higher than those for patients with spinal muscular atrophy (33%) or peripheral axonal neuropathy (24%). Threshold-tracking studies showed that \(\tau_{SD}\), which in part reflects Na\(^+\) conductance at the resting membrane potential, was significantly greater in the Machado–Joseph disease patients than in normal subjects; severe muscle cramps were associated with a longer \(\tau_{SD}\). Threshold electrotonus, refractoriness and supernormality were not significantly different between Machado–Joseph disease patients and normal subjects. Eight Machado–Joseph disease patients with severe cramps, who received mexiletine treatment, experienced nearly complete relief with a partial normalization of \(\tau_{SD}\) (\(P = 0.08\)). Muscle cramps are a very frequent and disabling factor in Machado–Joseph disease. Pathological muscle cramps responded well to mexiletine treatment, and this is consistent with the hypothesis that they are caused by an increase in persistent Na\(^+\) conductance, possibly associated with axonal regeneration or collateral sprouting.

Keywords: Machado–Joseph disease; muscle cramps; strength–duration time constant; Na\(^+\) conductance; axonal excitability

Abbreviations: ALS = amyotrophic lateral sclerosis; CMAP = compound muscle action potential; \(I_{rh}\) = rheobase current; PN = peripheral neuropathy; SMA = spinal muscular atrophy; \(\tau_{SD}\) = strength–duration time constant

Introduction
Machado–Joseph disease is one of the most common autosomal dominant spinocerebellar degenerative disorders (Takano et al., 1998), with a wide range of clinical manifestations such as ophthalmoplegia, ataxia, pyramidal and extrapyramidal signs, and peripheral neuropathy (PN) (Rosenberg, 1992; Dürr et al., 1996). It is characterized by unstable expansion of (CAG)n trinucleotide repeat sequences in the Machado–Joseph disease1 gene on chromosome 14q32.1 (Kawaguchi et al., 1994). Pathology studies have shown mild to moderate loss of anterior horn cells in the spinal cord and loss of primary sensory neurons in the dorsal ganglia, resulting in peripheral axonal degeneration (Kinosita et al., 1995; Colding-Jorgensen et al., 1996; Dürr et al., 1996; Abele et al., 1997; van Shaik et al., 1997;
In terms of spinal pathology, Machado–Joseph disease is regarded as a type of chronic lower motoneuron disease.

Muscle cramps are often associated with such disorders involving lower motoneuron, such as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and peripheral neuropathies (McGee, 1990; Layzer, 1994). In disorders with motor axon involvement, loss of motoneurons is usually accompanied by collateral reinnervation of denervated muscles by the remaining motoneurons and the electrical irritability of unmyelinated nerve twigs may be enhanced by collateral sprouting (Janko et al., 1989).

Although amyotrophy and fasciculations have been described in Machado–Joseph disease (Rosenberg, 1992; Kinoshita et al., 1995; Colding-Jorgensen et al., 1996; Dürr et al., 1996; van Shaik et al., 1997), muscle cramps have not been systematically studied. Evidence of spinal motoneuronal involvement in Machado–Joseph disease led us to make a prospective study of muscle cramp and axonal excitability in Machado–Joseph disease patients.

The threshold tracking technique developed in the 1990s measures non-invasively various indices of axonal excitability (strength–duration properties, threshold electrotonus, refractoriness and superexcitability) in human subjects (Bostock et al., 1998; Kiernan and Bostock, 2000; Kiernan et al., 2000). These indices, which depend on Na+ and K+ conductances, membrane potential and passive membrane properties, provide indirect insight into Na+ and K+ channel functions. Recent threshold tracking studies in patients with ALS provided evidence of K+ channel dysfunction (Bostock et al., 1995) and an increase in persistent Na+ conductance (Mogyoros et al., 1998), which may induce spontaneous motor unit activity.

We performed clinical and electrophysiological studies to investigate whether Machado–Joseph disease patients suffer frequent muscle cramps and whether the disease is associated with specific changes in motor axonal excitability. Furthermore, since the excitability studies suggested that a specific ionic conductance was involved, we examined whether blocking it may provide a new therapeutic option.

**Subjects and methods**

**Patients**

Twenty consecutive patients with Machado–Joseph disease (10 male and 10 female) were studied. Genetic testing confirmed an expanded CAG repeat on chromosome 14q32.1 in all patients. The mean age was 55 years (range 26 to 73 years). Five patients had amyotrophy, dominant in the distal lower limb muscles. Fasciculations were present in six patients, and dystonia in the limbs in five patients.

Clinical and electrophysiological findings of Machado–Joseph disease patients were compared with those of ALS (n = 22, 10 male and 12 female; mean age 61 years), SMA (n = 6, four male and two female; mean age 60 years) or PN (n = 37, 20 male and 17 female; mean age 54 years). The diagnosis of ALS was based on the El Escorial criteria (Brooks, 1994). SMA included bulbo-spinal muscular atrophy and Kugelberg–Wielander disease, whereas PNs included chronic axonal neuropathy caused by neurotoxic drugs, diabetes mellitus, systemic vasculitis or vitamin B1 deficiency. For the threshold tracking studies, normal data were obtained from 32 age-matched healthy subjects (21 male and 11 female; aged 35–77 years; mean age 51 years).

All the patients and normal subjects gave their informed consent to the experimental procedures, which have been approved by the Ethics Committee of Chiba University School of Medicine.

**Clinical assessment of muscle cramps**

Patients were asked about the frequency, site, duration and precipitating factors of their muscle cramps. A ‘cramp disability score’ was used to evaluate the extent of disability in performing daily activities: 0, no cramp; 1 (mild), a complaint but no disability; 2 (moderate), a chief complaint, sometimes disturbing work or sleep; 3 (severe), a chief complaint, disturbing work or sleep daily. We regarded muscle cramps as pathological when they occurred more than twice per month, or involved muscles of the upper extremities or trunk.

**Conventional electrodiagnostic studies**

Nerve conduction studies of the median nerve were performed using conventional procedures. Compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis muscle and compound sensory nerve action potentials from the index finger after anti-dromic stimulation. Amplitudes of the initial negative peaks of CMAP and compound sensory nerve action potential were measured. EMG was performed on the first dorsal interosseous and tibialis anterior muscles.

**Multiple excitability measurements based on threshold tracking**

Multiple excitability measurements were performed using a recently reported protocol designed to measure rapidly a number of different nerve excitability parameters (in ~10 min), which uses a computerized program (QTRAC version 4.3 with multiple excitability protocol TRONDHM; copyright, Institute of Neurology, London, UK) as described elsewhere (Kiernan and Bostock, 2000; Kiernan et al., 2000; Kuwabara et al., 2000). Briefly, CMAP was recorded from the abductor pollicis brevis with stimulation at the wrist. The protocol began with the measurement of stimulus–response curves for test stimuli of 0.2 ms and 1.0 ms duration. From
these curves, the strength–duration time constant ($\tau_{SD}$) and rheobase current ($I_{rh}$) were calculated using the formulae:

$$\tau_{SD} = 0.2 \left( I_{0.2} \times I_{1.0} \right) / \left( I_{1.0} \times 0.2 I_{0.2} \right)$$

$$I_{rh} = 1.25 \left( I_{1.0} \times 0.2 I_{0.2} \right)$$

where $I_{0.2}$ and $I_{1.0}$ are the respective threshold currents for test stimuli of 0.2 and 1.0 ms duration. The currents required to produce CMAPs of 10–90% of the maximal CMAP were measured from the stimulus–response curves, and used to calculate the $\tau_{SD}$ for CMAPs of different sizes. $\tau_{SD}$ is defined as ratio between the minimum charge threshold and the $I_{rh}$, and is equatable to chronaxie, while $I_{rh}$ is defined as the threshold current for a stimulus of infinitely long duration (Bostock et al., 1998).

In the remainder of the protocol, the current required to produce a CMAP that was 40% of the maximum was tracked using the computer program. To assess the recovery cycle of axonal excitability, test stimuli were delivered at various times after the supramaximal conditioning stimulus. Conditioning test intervals were decreased systematically from 200 to 2 ms. In the threshold electrotonus studies, membrane potential was altered by the use of subthreshold DC polarizing currents that were 40% of the unconditioned threshold. Depolarizing and hyperpolarizing currents, each lasting 100 ms, were used and their effects on the threshold for the test CMAP were measured.

**Treatment with mexiletine hydrochloride**

After their clinical and electrophysiological evaluations, the Machado–Joseph disease patients who suffered disabling muscle cramps (a disability score of 2 or 3) received oral mexiletine hydrochloride, which is an analogue of lidocaine. The initial dose was 150 mg daily for one month, increasing to 300 mg daily for the next month. Follow-up clinical and electrophysiological evaluations were made 2 months after the start of treatment.

**Statistical analysis**

Differences in medians were compared by the Mann–Whitney U test. The paired $t$-test was used to compare changes in clinical and electrophysiological parameters before and after treatment. Spearman’s rank correlation coefficient was used to test relation between the cramp disability score and excitability property indices.

**Results**

**The incidence and features of muscle cramps**

Pathological muscle cramps, defined as cramps occurring more than twice per month or involving muscles of the hands, arms or trunk, occurred in 16 (80%) of the 20 Machado–Joseph disease patients, 15 (68%) of the 22 ALS patients, two (33%) of the six SMA patients and nine (24%) of the 37 PN patients. The frequencies of cramps for each patient group are shown in Fig. 1A. The mean frequency per month was 13 times for Machado–Joseph disease patients, 10 times for ALS patients, twice for SMA patients and three times for PN patients. Figure 1B shows the clinical severity of the muscle cramps on the ‘cramp disability score’. Machado–Joseph disease patients were graded as having severe ($n = 5; 25\%$), moderate ($n = 5; 25\%$) or mild ($n = 7; 33\%$) muscle cramps. Of the 20 Machado–Joseph disease patients, 80% suffered pathological muscle cramping and 50% suffered cramping that disturbed their daily activities. In most Machado–Joseph disease patients, muscle cramps occurred spontaneously (during sleep or rest), during work or while walking—indicative that Machado–Joseph disease patients, as well as ALS patients, suffer severe muscle cramps more frequently than patients with SMA or PN.

No significant differences were found for age, age at onset, sex, disease duration, presence of amyotrophy or fasciculations, or the number of CAG repeats between Machado–Joseph disease patients with pathological muscle cramps and those without them (Table 1).

**Nerve conduction studies and EMG**

Routine electrodiagnostic study results showed axonal loss of motor and sensory nerve fibres. The mean (SD) of the median CMAP amplitude value was 8.1 (2.5) mV for the Machado–Joseph disease patients, and 10.9 (3.1) mV for the normal
subjects. The mean (SD) median compound sensory nerve action potential amplitude value was 13.3 (8.2) mV for the Machado–Joseph disease patients and 34.0 (13.1) mV for the normal subjects. EMG showed that all but one Machado–Joseph disease patient had increased duration and polyphasia of the motor unit potentials, indicative of chronic denervation with reinnervation.

Axonal excitability measurement

Figure 2 and Table 2 show the results of multiple excitability measurements of the right median nerves of 20 Machado–Joseph disease patients and 32 age-matched normal subjects. Threshold current and $I_{th}$ for CMAP of 50% of the maximum were similar for Machado–Joseph disease patients and normal subjects. The $\tau_{SD}$ was significantly longer for Machado–Joseph disease patients. For 50% CMAP, the mean±SEM of $\tau_{SD}$ was 0.48±0.02 for the Machado–Joseph disease patients and 0.39±0.01 for normal subjects ($P = 0.001$). Fig. 3A compares the $\tau_{SD}$ values for 50% CMAP of patients with Machado–Joseph disease, ALS, SMA or PN, and those of normal subjects. The Machado–Joseph disease group had the longest $\tau_{SD}$ and the SMA and PN groups had significantly longer $\tau_{SD}$ values than the normal subjects. The $\tau_{SD}$ value for the ALS patients was longer than that for the normal subjects, but the difference was not significant. Fig. 3B shows that $\tau_{SD}$ correlates with the clinical severity of muscle cramps in Machado–Joseph disease patients ($P = 0.034$). Due to the fact that $\tau_{SD}$ depends, in part, on a threshold conductance, probably generated by persistent Na+ channels (Bostock and Rothwell, 1997), these results raise the possibility that frequent muscle cramping in Machado–Joseph disease patients is caused by an increase in persistent Na+ conductance.

In threshold electrotonus, threshold changes produced by subthreshold depolarizing and hyperpolarizing currents were similar for the Machado–Joseph disease patients and normal subjects, but the patients tended to have a smaller threshold change at the end of 100 ms hyperpolarizing currents [Fig. 2B; $TE_{h}$ (90–100 ms) in Table 2]. Threshold electrotonus is especially sensitive to voltage-dependent K+ conductances; therefore, these findings suggest there is no significant change in K+ channel function in motor axons of Machado–Joseph disease patients. In contrast, ALS patients had greater threshold changes for depolarizing conditioning currents; the threshold changes 10–30 ms after the start of depolarizing conditioning stimulus [$TE_{d}$ (10–30 ms) in Table 2] and the threshold changes 90–100 ms after depolarizing conditioning stimulus [$TE_{d}$ (90–100 ms) in Table 2] were significantly greater than those of normal controls.

Patterns of the excitability recovery cycle were similar for the Machado–Joseph disease patients and normal subjects (Fig. 2C, Table 2). Threshold changes in the refractory, supernormal and late subnormal periods did not differ significantly for the patients with Machado–Joseph disease, SMA, PN or the normal subjects. In contrast, ALS patients had larger threshold change in the supernormal period and the

Table 1 Muscle cramping in patients with Machado–Joseph disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/Sex</th>
<th>Age at onset (years)</th>
<th>Frequency (per month)</th>
<th>Site</th>
<th>Disability scale</th>
<th>No. of CAG repeats</th>
<th>Fasciculation</th>
<th>Amyotrophy</th>
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<td></td>
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<tr>
<td>1</td>
<td>53M</td>
<td>45</td>
<td>30</td>
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<td>3</td>
<td>58</td>
<td>+</td>
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<tr>
<td>2</td>
<td>65F</td>
<td>51</td>
<td>15</td>
<td>Hands, trunk, legs</td>
<td>3</td>
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<td>66</td>
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<td>–</td>
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<td>62M</td>
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<td>Hands, legs</td>
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<td>42</td>
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<td>67</td>
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<td>44</td>
<td>90</td>
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<td>Legs</td>
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<td>68</td>
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<td>–</td>
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<td>No pathological muscle cramping</td>
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<td>48F</td>
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<td>1</td>
<td>Legs</td>
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<td>+</td>
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threshold change (supernormality) was significantly greater than that of normal subjects (Table 2, $P < 0.01$).

**Effects of mexiletine treatment**

Ten of the 20 Machado–Joseph disease patients suffered muscle cramps that disturbed their daily activities. They were treated with mexiletine chloride, an analogue of lidocaine. Treatment was discontinued for two patients because of nausea and diarrhoea. In eight patients treated for >2 months, the frequency of muscle cramps decreased markedly (Fig. 4A). Two months after treatment, the mean frequency per month had decreased from 24 to three times. All eight patients had nearly complete relief from muscle cramps. The $\tau_{SD}$ tended to decreased after treatment (Fig. 4B; $P = 0.08$). The $I_R$ was increased slightly, but the difference was not significant ($P = 0.11$). Other excitability indices, threshold electrotonus, refractoriness and supernormality did not differ significantly from before treatment.

**Discussion**

The present study has documented that, in Machado–Joseph disease patients, muscle cramps are very frequent and disturb patients’ daily activities. The motor axon $\tau_{SD}$ is significantly longer than in normal subjects and treatment with mexiletine hydrochloride provides marked relief from disabling muscle cramps. Muscle atrophy and fasciculation frequently occur in Machado–Joseph disease patients (DuÈrr et al., 1996), whereas muscle cramp has rarely been described (Colding-Jorgensen et al., 1996). We found that 80% of the Machado–Joseph disease patients studied had pathological muscle cramps and 50% experienced severe cramps that disturbed their daily activities. Moreover, Machado–Joseph disease and ALS are disorders most frequently associated with pathological muscle cramps, and changes in axonal excitability properties were somewhat different in the two disorders.

**Muscle cramps and changes in axonal excitability properties in Machado–Joseph disease**

As our findings confirmed, muscle cramps are often associated with disorders involving the lower motoneurons. The origin of those cramps is not clear, but distal axons, especially intramuscular nerve terminals, are suggested to generate ectopic burst activities (Denny-Brown, 1953; Lambert, 1969; Layzer, 1994). The ionic mechanisms of the hyperexcitability of diseased motor axons have yet to be clarified, but it has been shown that after axonal injury Na$^+$ channels are overexpressed on the axolemma when nerves are growing and sprouting (Devor et al., 1989), and that local remodeling of Na$^+$ channels is considered a cause of the hyperexcitability that produces ectopic firing (Devor et al., 1992; Matzner and Devor, 1994). There was EMG evidence of chronic denervation with reinnervation in our Machado–Joseph disease patients, as commonly seen in patients with motoneuron disease or PN.

Our electrophysiological findings show that changes in motor axonal excitability properties in Machado–Joseph disease are characterized by markedly increased $\tau_{SD}$ values, but there are no significant changes in threshold electrotonus, refractoriness and supernormality. Some studies have measured $\tau_{SD}$ in patients with ALS (Mogyoros et al., 1998), acquired neuromyotonia (Maddison et al., 1999; Kiernan et al., 2001), chronic inflammatory demyelinating polyneuropathy (Cappelen-Smith et al., 2001) or Guillain–Barré
syndrome (Kuwabara et al., 2002). The $\tau_{SD}$ of a nerve is a nodal property, which in normal subjects is longer for sensory axons than for motor ones (Mogyoros et al., 1996). This difference appears to be due to greater voltage-dependent Na$^+$ conductance at the resting membrane potential in sensory axons, probably non-inactivating Na$^+$ conductance due to persistent Na$^+$ channels (Baker and Bostock, 1997; Bostock and Rothwell, 1997; Mogyoros et al., 1998). The $\tau_{SD}$ also depends on membrane potential and passive membrane properties (Bostock, 1983; Bostock et al., 1998). There are a number of possible explanations for the increased $\tau_{SD}$ in motor axons of Machado–Joseph disease patients: an increase in persistent Na$^+$ conductance; membrane depolarization; and a larger membrane constant due to structural changes such as demyelination. Threshold electrotonus and supernormality are particularly sensitive to membrane potential (Kiernan and Bostock, 2000), and our results did not suggest altered membrane potential in Machado–Joseph disease. Our nerve conduction study results and previous Machado–Joseph disease pathology studies showed no evidence of demyelination (Kinoshita et al., 1995). We speculate that an increase in persistent Na$^+$ conductance is most likely to explain the longer $\tau_{SD}$; this is consistent with the partial decrease in $\tau_{SD}$ after mexiletine treatment. The increase in persistent Na$^+$ conductance might, in part, contribute to the generation of abnormal muscle cramps in Machado–Joseph disease.

The longer $\tau_{SD}$ would be associated with lower $I_{rh}$, but our findings failed to show this reciprocal relationship: despite the longer $\tau_{SD}$, $I_{rh}$ was not significantly lower for Machado–Joseph disease patients than for normal controls. This might be because of changes in the geometry of the nerve due to axonal loss and subsequent fibrosis within the nerve in Machado–Joseph disease (Kinoshita et al., 1995). Structural changes are more likely to affect $I_{rh}$ than $\tau_{SD}$ (Mogyoros et al., 1996) and this possibly explains the lack of normal inverse relationship between $\tau_{SD}$ and $I_{rh}$ in our Machado–Joseph disease patients.

As discussed, most muscle cramps and fasciculations probably arise from axonal terminals (Roth, 1982; Layzer, 1994), at which persistent and classical Na$^+$ channels are expressed predominantly in nerve regeneration. Since

![Table 2](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (n = 32)</th>
<th>Machado–Joseph disease (n = 20)</th>
<th>ALS (n = 22)</th>
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<td>Age (years)</td>
<td>51 (2)</td>
<td>55 (3)</td>
<td>61 (2)</td>
</tr>
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<td>5.5 (0.4)</td>
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<td>$I_{rh}$ (mA)</td>
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<td>3.7 (0.3)</td>
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<td>0.48 (0.02)**</td>
<td>0.43 (0.03)</td>
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<td>Threshold electrotonus</td>
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<tr>
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<td>69.1 (0.9)</td>
<td>70.9 (1.3)*</td>
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<tr>
<td>TEd (90–100 ms) (%)</td>
<td>46.1 (0.7)</td>
<td>48.0 (1.4)</td>
<td>54.0 (1.7)**</td>
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<td>TEd (90–100 ms) (%)</td>
<td>–122.8 (3.2)</td>
<td>–112.6 (4.1)</td>
<td>–128.0 (5.7)</td>
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<tr>
<td>Recovery cycle</td>
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<tr>
<td>Refractoriness (%)</td>
<td>67.6 (12.9)</td>
<td>56.7 (5.1)</td>
<td>88.9 (34.3)</td>
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<tr>
<td>Supernormality (%)</td>
<td>–24.7 (1.2)</td>
<td>–23.3 (2.0)</td>
<td>–33.5 (2.0)**</td>
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<td>Late subnormality (%)</td>
<td>15.0 (0.9)</td>
<td>15.0 (2.0)</td>
<td>13.3 (1.3)</td>
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</tbody>
</table>

Threshold and $I_{rh}$ are for CMAP of 50% of the maximum. TEd (10–30 ms), TEd (90–100 ms) = threshold reduction between the specified latencies after depolarizing current; TEd (90–100 ms) = threshold reduction between the specified latencies after hyperpolarizing current. *P < 0.05; **P < 0.005

![Fig. 3](image) (A) $\tau_{SD}$ for patients with Machado–Joseph disease (MJD), ALS, SMA and PN. NC = normal control; *P < 0.05; **P < 0.005. (B) Relationship between the cramp disability scale score and $\tau_{SD}$ in Machado–Joseph disease patients (P = 0.034).
threshold tracking measures excitability properties at the point of stimulation (median nerve at the wrist in this study), our wrist findings may underestimate the distal increase in $\tau_{SD}$. Moreover, whereas 11 of our 20 patients with Machado-Joseph disease had cramps in the hands, muscle cramps occur preferentially in leg muscles, especially those of the calves. Again, our findings for the median nerves may underestimate the changes in excitability.

**Differences in axonal membrane properties in Machado-Joseph disease and ALS**

In this study, the Machado-Joseph disease and ALS patients had more frequent and severe muscle cramps than patients with SMA or PN. Why muscle cramps are especially prominent in Machado-Joseph disease and ALS is unclear, but we can speculate that changes in membrane properties may differ qualitatively or quantitatively in the various disorders that affect motor axons; our study confirmed abnormal threshold electrotonus, suggesting dysfunction of K+ channels (Bostock et al., 1995) and slightly greater $\tau_{SD}$ (Mogyoros et al., 1998) in ALS. The combination of multiple factors, including altered Na+ and K+ conductances, may contribute to the generation of muscle cramps in ALS. In contrast, changes in axonal excitability properties in Machado-Joseph disease were characterized by longer $\tau_{SD}$ but there was no significant change in threshold electrotonus and supernormality, which suggests that K+ channel function is not altered. Amyotrophy is frequent in Machado-Joseph disease patients (Duerr et al., 1996), but less so than in patients with ALS (or SMA), suggestive of a lesser degree of motoneuron loss, and the greater ability of motoneurons in Machado-Joseph disease to regenerate or sprout. Patients with genetically confirmed SMA have been reported who experienced frequent muscle cramps as an isolated neurological abnormality associated with EMG evidence of denervation and reinnervation (Bussaglia et al., 1997). Finally, recent reports have raised the possibility that polyglutamine aggregates cause aberrant transcriptional regulation (Shimohata et al., 2000; Steffan et al., 2000), and this may lead to enhanced expression of ion channels.

**Mexiletine treatment for muscle cramps in Machado-Joseph disease patients**

Our findings show that mexiletine given orally dramatically relieves disabling muscle cramping in Machado-Joseph disease patients. Mexiletine is not used conventionally for treatment of muscle cramps, but we tried this agent because the findings of our excitability study raised the possibility of more prominent persistent Na+ conductance in Machado-Joseph disease patients. The partial decrease in $\tau_{SD}$ in our patients after mexiletine treatment is consistent with its action of Na+ channel blockade. Mexiletine is an analogue of lidocaine and is a widely used, safe, class Ib anti-arrhythmic agent. It is suggested that the action of lidocaine on the heart is attributed to a selective action on persistent Na+ current (Ju et al., 1992). Lidocaine selectively blocks late Na+ current, which could be mediated by persistent Na+ channels, in rat large sensory neurons (Baker, 2000). The most frequent side effects of mexiletine are nausea or other abdominal symptoms, which occurred in two of our 10 Machado-Joseph disease patients who were receiving mexiletine. Its side effects are dose-dependent; thus, further investigation is needed to determine the optimal or minimal dose at which there is a suppressive effect on muscle cramping associated with Machado-Joseph disease. We believe that mexiletine treatment improves the quality of life of Machado-Joseph disease patients who suffer severe muscle cramping.

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