Age related axonal neuropathy in spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD)

Thomas Klockgether, Ludger Schöls, Michael Abele, Katrin Bürk, Helge Topka, Frank Andres, Georgios Amoiridis, Rainer Lüdtke, Olaf Riess, Franco Laccone, Johannes Dichgans

Abstract
To identify determinants of peripheral involvement in spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD) the influence of CAG repeat length, age of onset, disease duration and age on the results of nerve conduction studies was analysed in 58 patients with SCA3/MJD. Patients with SCA3/MJD showed marked reduction of compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes indicating axonal neuropathy of both motor and sensory fibres. In addition, there was moderate slowing of nerve conduction suggestive of mild peripheral demyelination. Multivariate regression showed that CMAP and SNAP amplitudes decreased with age, but were not affected by CAG repeat length, age of onset, or disease duration. The age related decline of CMAP and SNAP amplitudes in SCA3/MJD was greater than in normal subjects. The data suggest that the degree of peripheral damage in SCA3/MJD does not depend on CAG repeat length, age of onset, or disease duration, but is mainly related to the time period over which the SCA3/MJD mutation exerts its effect.

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table

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=91)</th>
<th>SCA3 (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>m-NCV (m/s)</td>
<td>46.7</td>
<td>3.0</td>
</tr>
<tr>
<td>DL (ms)</td>
<td>3.9</td>
<td>0.5</td>
</tr>
<tr>
<td>CMAP (mV)</td>
<td>23.0</td>
<td>6.9</td>
</tr>
<tr>
<td>s-NCV (m/s)</td>
<td>49.0</td>
<td>4.1</td>
</tr>
<tr>
<td>SNAP (µV)</td>
<td>17.8</td>
<td>7.5</td>
</tr>
</tbody>
</table>

SCA3/MJD=spinocerebellar ataxia type 3/Machado-Joseph disease; m-NCV=motor nerve conduction velocity (tibial nerve); DL=distal motor latency; CMAP=compound muscle action potential; s-NCV N=sensory nerve conduction velocity (sural nerve); SNAP=sensory nerve action potential.
Age related neuropathy in spinocerebellar ataxia type 3/Machado-Joseph disease

All patients underwent nerve conduction studies using standard neurographic procedures. Motor nerve conduction studies were performed on the tibial nerve of the left leg. Sensory nerve conduction velocities of the sural nerve of the left leg were measured antidiromically. Amplitudes of the evoked motor (abductor hallucis muscle) and sensory responses were measured with surface electrodes. Skin temperature was routinely controlled, and the limbs were warmed if necessary.

Electrodiagnostic variables used for regression analysis were motor nerve conduction velocity (m-NCV), distal motor latency (DL), amplitude of compound muscle action potential (CMAP), sensory nerve conduction velocity (s-NCV), and amplitude of the sensory nerve action potential (SNAP).

Results

The NCVs of patients with SCA3/MJD were normal or moderately reduced. Mean m-NCV was 45.1 (SD 4.4) m/s (controls: 46.7 (SD 3.0 m/s) and mean s-NCV 44.7 (SD 5.2) m/s (controls: 49.0 (SD) 4.1 m/s). Mean DL was slightly prolonged (4.4 (SD 1.1) vs 3.9 (SD 0.5) ms). CMAP and SNAP amplitudes were markedly reduced in SCA3/MJD. Mean CMAP amplitude was 16.4 (SD 7.6) mV (controls: 23.0 (SD 6.9) mV), and mean SNAP amplitude 6.7 (SD 4.7) µV (controls: 17.8 (SD 7.5) µV) (table).

Simple linear regressions with Bonferroni adjustment disclosed significant negative correlations of CMAP and SNAP amplitudes with age (p=0.0020, p=0.0017) and age of onset (p=0.0032, p=0.0018), as well as CMAP amplitudes with disease duration (p=0.0195). By contrast, CMAP and SNAP amplitudes were positively correlated with CAG repeat length (p=0.0392, p=0.0019). There were no significant correlations of m-NCV, DL, or s-NCV with CAG repeat length, age of onset, disease duration, and age. Therefore, the CMAP and SNAP data were further analysed using multivariate regression.

To select the appropriate statistical model, we used a stepwise regression procedure based on the Akaike information criterion. As a result of this procedure, we chose a statistical model for analysis of both CMAP and SNAP data in which included age as the only covariable. Addition of any other covariable did not yield a better fit. Regression analysis showed that age was negatively correlated with both CMAP (p<0.0001, r=-0.59) and SNAP amplitude (p<0.0001, r=-0.69) (figure). The annual decline of the CMAP amplitude was significantly faster in SCA3/MJD (0.36 mV/year) than in controls (0.17 mV/year, p=0.0146; t test within analysis of variance (ANOVA) with age-group interaction). Similarly, SNAP amplitude declined faster in patients (0.26 µV/year) than in controls (0.18 µV/year). However, this difference failed to reach significance. Whereas the CMAP and SNAP amplitudes decreased with age but were not additionally affected by CAG repeat length, age of onset, disease duration, and age, CMAP and SNAP amplitudes decreased with age but were not additionally affected by CAG repeat length, age of onset, and disease duration.

Discussion

The present nerve conduction data show that SCA3/MJD is associated with marked reduction of CMAP and SNAP amplitudes indicating axonal neuropathy of both motor and sensory fibres. In addition, there was moderate slowing of nerve conduction suggestive of mild peripheral demyelination. Whereas the degree of nerve conduction slowing was not significantly related to CAG repeat length, age of onset, disease duration, and age, CMAP and SNAP amplitudes decreased with age but were not additionally affected by CAG repeat length, age of onset, and disease duration.

The present results agree with those of earlier nerve conduction studies in SCA3/MJD showing marked attenuation of CMAP and SNAP amplitudes and mild reduction of NCVs.10,11 The neuropathological basis of these abnormalities is loss of myelinated and unmyelinated fibres with an increase in endoneurial collagen.10 Although not explicitly shown for SCA3/MJD, CMAP and SNAP amplitudes may be taken as an indirect measure of the number of peripheral motor and sensory axons.

Our analysis shows that age is the most important determinant of the severity of axonal loss in SCA3/MJD. Loss of peripheral axons is a normal phenomenon occurring with age.12 In patients with SCA3/MJD, however, the age related decline of CMAP and less so of SNAP amplitudes was faster than in normal subjects suggesting that the mutated SCA3/MJD gene product accelerates the normal age related loss of peripheral axons. In addition, our data sug-
gest that SNAP amplitudes are themselves smaller in patients than in normal subjects.


It was therefore of interest to study the influence of CAG repeat length on the loss of peripheral axons. Initial analysis with simple linear regression suggested a paradoxical association of small CAG repeat expansions with more severe axonal neuropathy. However, subsequent analysis using multivariate methods disclosed that this association is an artefact explained by the colinearity of CAG repeat length and age. We were unable to demonstrate an effect of CAG repeat length on CMAP and SNAP amplitudes.

Our data suggest that the mechanisms underlying the loss of peripheral axons in SCA3/MJD are different from those leading to degeneration of central neurons. Whereas the velocity and extent of the CNS degeneration seem to depend on CAG repeat length, the severity of peripheral damage is mainly related to the time period over which the SCA3/MJD mutation exerts its effect. There is no evidence that there is an additional effect of CAG repeat length on the loss of peripheral axons.

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