SCA3 Presenting as an Isolated Axonal Polyneuropathy

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Objectives: To highlight an unexpected clinical presentation and to review the associated polyneuropathy phenotypes of SCA3.

Design: Clinical follow-up.

Setting: Neurological referral center.

Patient: Middle-aged man with no family history for SCA3.

Results: Presentation with an isolated axonal, distal, symmetric, sensorimotor polyneuropathy for 6 years before developing a cerebellar syndrome prompting genetic testing for SCA3.

Conclusion: SCA3 can present with an isolated axonal, distal, symmetric, sensorimotor polyneuropathy.

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SCA3 (or Machado-Joseph disease) is an autosomal dominant cerebellar ataxia (ADCA I) due to CAG repeat expansions in ataxin3. Patients with SCA type 3 have the latest onset and slowest progression with cerebellar ataxia and polyneuropathy, with or without progressive external ophthalmoplegia or pyramidal signs. We describe a patient with a unique presentation of an axonal distal sensorimotor polyneuropathy for 6 years before developing a cerebellar syndrome leading to the diagnosis of SCA3. We also review SCA3-associated polyneuropathy phenotypes.

REPORT OF A CASE

A 52-year-old man had leg weakness for 6 months and no family history for SCA3. His mother had diabetes mellitus and died at 86 years. His father’s age of death and details were unknown. The facial and cranial nerves were normal. He had distal lower limb weakness. Arm reflexes were sluggish, the knee jerks were brisk, ankle jerks were absent, and plantar responses were mute. Results of the sensory examination were unremarkable. Results of the following tests were either negative or normal: complete blood cell count, erythrocyte sedimentation rate, liver and thyroid function, VDRL, human T-lymphotropic virus 1, serum protein electrophoresis, rheumatoid factor, antinuclear antibody, Kveim, chest radiograph, and levels of glucose, urea, electrolytes, vitamin B12, folate, extractable nuclear antigen, antineutrophil cytoplasmic antibody, and cerebrospinal fluid. Electrophysiology showed absent (medians, ulnars, and surals) or small (radial, 4.6 µV) sensory nerve action potentials, absent soleus H-reflexes, normal motor conduction velocities and F-wave latencies (medians, ulnars, and common peroneal nerves), no conduction block, small lower limb compound muscle action potentials, and distal denervation in the upper and lower limbs consistent with an axonal sensorimotor polyneuropathy.

Six months later he reported cramps in his hands and legs. He had fasciculations in the biceps, triceps, thighs, and calves. There was now distal weakness in the upper and lower limbs. Reflexes were brisk with absent ankle jerks, an extensor right plantar, and no sensory signs. A year later, he reported worsening weakness of the upper and lower limbs. Reflexes were now diminished with flexor plantar responses. Sensory examination results remained normal. A sural nerve biopsy specimen confirmed a moderately severe axonal neuropathy affecting myelinated and unmyelinated axons, with some regeneration and secondary demyelination and remyelination. There was no vasculitis, abnormal infiltrates, or Schwann cell hyperplasia.

Two years later he walked with a cane. There was more distal weakness of the upper and lower limbs. All reflexes were ab-
sent except for the knee jerks. The right plantar was again extensor; the left plantar was equivocal. There was impaired pin-prick sensation in the left foot. A second autoimmune screen, including the levels of antigliadin, antiendomysial, antineuronal antibodies, and vitamin E were normal. Magnetic resonance imaging of the lumbosacral spine disclosed no abnormality. Three years later he reported poor balance resulting in falls. He had an ataxic gait out of proportion to the polyneuropathy and used a walker. There were broken smooth-pursuit eye movements, no nystagmus, and a mild intention tremor of the limbs. Computed tomography of the brain showed atrophy of the cerebellar hemispheres with preservation of the pons and olives. Magnetic resonance imaging showed no cervical cord pathology. Genetic analysis revealed an expanded CAG trinucleotide repeat (62) in ataxin3. A year later, nerve conduction study results showed a more severe polyneuropathy with absent sensory nerve action potentials in the upper and lower limbs, unrecordable lower limbs, and smaller upper limbs, compound muscle action potentials, and more severe distal denervation in the limbs.

**Table. Peripheral Neuropathy in SCA3 CAG Repeat Length, Clinical and Electrophysiological Data**

<table>
<thead>
<tr>
<th>No. of Patients/ Sex</th>
<th>Age at Presentation</th>
<th>CAG Repeat Length</th>
<th>Follow-up, y</th>
<th>EMG &amp; Nerve Conduction</th>
<th>PN Phenotype</th>
<th>Ataxia/ Pyramidal/ Extrapyramidal</th>
<th>PEO</th>
<th>Other</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/M</td>
<td>53, 50, 57 (At time of report)</td>
<td>53a</td>
<td>13b</td>
<td>2 Denervation, 2 absent/red SNAPs, 2 red CMAPs</td>
<td>3 SM/Y/Y</td>
<td>33/66/66</td>
<td>3 RLS, 3 fascics</td>
<td>van Alfen et al11</td>
<td></td>
</tr>
<tr>
<td>Mean of 18 (10 PN)c</td>
<td>41.7 (27-56)</td>
<td>7.9 ± 4.8</td>
<td>10 red SNAPs, 2 red MNCVs</td>
<td>10 SM/Y/Y</td>
<td>100/28/</td>
<td>78</td>
<td>Abele et al11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of 14 (8 PN)c</td>
<td>18-54</td>
<td>69-90</td>
<td>6 (1-21)</td>
<td>Not done</td>
<td>6b/Y/Y</td>
<td>82/59/18</td>
<td>45</td>
<td>Chakravarty et al12</td>
<td></td>
</tr>
<tr>
<td>Mean of 22 (6 PN)b,c</td>
<td>34 (9-60)</td>
<td>62-80</td>
<td>6 (1-21)</td>
<td>1-11</td>
<td>3 SM, 1 S/Y/Y</td>
<td>75/25/11</td>
<td>3 Cramps, 3 fascics</td>
<td>Giunti et al11</td>
<td></td>
</tr>
<tr>
<td>Mean of 58 (31/M, 27/F)</td>
<td>37.8 ± 11.3</td>
<td>63-82</td>
<td>9.1 ± 5.9</td>
<td>Red SNAPs and CMAPs, normal or red NCVs</td>
<td>58 SM/Y/Y</td>
<td>. . ./ . . ./ . . .</td>
<td>Klockgether et al13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of 13 (7 PN)</td>
<td>42.5 (24-60)</td>
<td>68-77</td>
<td>2-26</td>
<td>6 SM, 1S</td>
<td>5 SM, 1 S, 1 NSym, 1 NSym, 1 NSym</td>
<td>. . ./ . . ./ . . .</td>
<td>Kubis et al13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M</td>
<td>40</td>
<td>66, 66, 69</td>
<td>2, 9, 14</td>
<td>2 Abnormal, 1 normal</td>
<td>. . ./Y/Y</td>
<td>100/100/66</td>
<td>33</td>
<td>Lau et al13</td>
<td></td>
</tr>
<tr>
<td>2/M</td>
<td>42, 50</td>
<td>72, 75, 78, 78</td>
<td>6, 19, 22</td>
<td>2 Absent SNAPs, red CMAPs</td>
<td>2 SM, 1 S/Y/Y</td>
<td>100/100/66</td>
<td>100</td>
<td>Lin and Soong13</td>
<td></td>
</tr>
<tr>
<td>Mean of 21 (5 PN)c</td>
<td>30.1 (21-60)</td>
<td>67 (61-72)</td>
<td>9.1 (1-21)</td>
<td>4 SM, 3 normal neuropathy, 1 normal</td>
<td>5 SM/Y/Y</td>
<td>95/76/38</td>
<td>62</td>
<td>Takiyama et al15</td>
<td></td>
</tr>
<tr>
<td>Mean of 8 (3/M, 5/F)</td>
<td>47 (38-56)</td>
<td>67 (61-72)</td>
<td>9.1 (1-21)</td>
<td>4 SM, 3 normal neuropathy, 1 normal</td>
<td>4 SM, 3 S/Y/Y</td>
<td>. . ./ . . ./ . . .</td>
<td>van de Warenburg et al15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/M</td>
<td>50, 62</td>
<td>54, 62a</td>
<td>10-24</td>
<td>1 Absent/red SNAPs, CMAPs</td>
<td>SM, S/Y, 1/1, 1/1Y</td>
<td>100/100/66</td>
<td>1 Fasical</td>
<td>van Schaik et al13</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>52</td>
<td>62</td>
<td>13</td>
<td>Absent SNAPs, small CMAPs, normal MCVs and F-waves, chronic denervation</td>
<td>SM/Y/Y</td>
<td>100/100/66</td>
<td>Present case</td>
<td>van Schaik et al13</td>
<td></td>
</tr>
<tr>
<td>116/173 PN/total cases</td>
<td>9 S, 99 SM</td>
<td>1 NSym</td>
<td>18 . . ./</td>
<td>Present case</td>
<td>9 S, 99 SM</td>
<td>1 NSym</td>
<td>18 . . ./</td>
<td>Present case</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CMAP, compound muscle action potential; ellipses, unknown; EMG, electromyography; fascics, fasciculations; MNCV, motor nerve conduction velocity; N, no; NCV, nerve conduction velocities; red, reduced; PEO, progressive external ophthalmoplegia; PN, polyneuropathy; RLS, restless leg syndrome; S, sensory; SM, sensorimotor; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; Y, yes.

a Not pathologically expanded.
b Sex distribution unavailable.
c Data of those with neuropathy only not available separately.

Our patient presented with a progressive axonal, distal, symmetric, sensorimotor polyneuropathy. A cerebellar syndrome developed 6 years later. We have not found a similar presentation of SCA3 in the literature. Chronic idiopathic
axonal polyneuropathy, considered initially, is a diagnosis of exclusion; the earlier onset and progression of the severe polyneuropathy in our patient also argue against this diagnosis. The known association of polyneuropathy and SCA3, long follow-up, and low incidence of SCA3 make a chance association between these 2 unlikely. In retrospect, the right extensor plantar response recorded 1 year after presentation signaled a multiple system disorder. It was not confirmed 1 year later. After a further 2 years, it was extensor again. However, the patient returned for follow-up 3 years later, by then he also had ataxia.

Patients with SCA3 who develop a polyneuropathy may present with a late-onset ataxic syndrome. Patients with symptoms or signs of a polyneuropathy may have electrophysiological evidence of an axonal sensorimotor polyneuropathy, a motor or sensory neuropathy, or normal findings. Reduced sensory nerve action potentials were seen in 13 of 17 patients with SCA3; only 36% had absent or reduced reflexes and vibration sense. Myelinated and unmyelinated fibers are decreased in number and relatively hypomyelinated with a smaller mean axon size, consistent with distal axonopathy.

There is an inverse correlation between CAG trinucleotide repeat length and onset of disease in SCA3. The polyneuropathy appears late and correlates with shorter CAG trinucleotide repeat length. There is an inverse correlation between age and compound muscle action potentials or sensory nerve action potentials in SCA3, with decline at a more rapid rate than in normal aging. Conduction velocity slowing was not correlated with CAG repeat length. CAG repeat expansions in ataxin-3 have a bimodal distribution, with populations of normal (<41) and disease-causing expansions (>62).

A male with a progressive, severe, asymmetric proximal polyneuropathy from age 50 years with no central nervous system or cerebellar signs, a family history of SCA3, and a 54-repeat trinucleotide expansion is recorded. He had non–insulin dependent diabetes, and IgG-k monoclonal gammopathy. Two relatives with ataxia and peripheral neuropathy or pyramidal signs had SCA3 CAG trinucleotide repeat expansions within the pathogenic range. The proband’s intermediate-range 54 repeat may not be unequivocally related to his isolated polyneuropathy, particularly with its predominantly proximal and asymmetrical phenotype. There are no reports of such a phenotype in the 116 other cases of polyneuropathy and SCA3 (Table). CAG repeats within the intermediate range (53-54) have only been reported to be associated with disease in 4 members of 1 other pedigree.

SCA3 published polyneuropathies are sensorimotor in 85.3% (99 of 116 patients) and sensory in 7.8% (9 of 116 patients). All those with polyneuropathy and a pathologically expanded CAG repeat had distal symmetrical presentations (Table).

SCA3 should be considered a rare differential diagnosis of an axonal, distal, symmetric, sensorimotor polyneuropathy of unknown etiology in a middle-aged patient despite the absence of a positive family history. However, genetic investigation of such an unusual oc-
currence would be impractical unless it had clear therapeutic or genetic counseling implications.

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Author Contributions: Drs Graves and Guiloff had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Graves and Guiloff. Acquisition of data: Guiloff. Analysis and interpretation of data: Graves and Guiloff. Drafting of the manuscript: Graves and Guiloff. Critical revision of the manuscript for important intellectual content: Graves and Guiloff. Administrative, technical, and material support: Graves and Guiloff. Study supervision: Guiloff.

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REFERENCES


