The G93C Mutation in Superoxide Dismutase 1

clinicopathologic phenotype and prognosis

Luc Régal, MD; Ludo Vanopdenbosch, MD; Petra Tilkin, RN; Ludo Van Den Bosch, PhD; Vincent Thijs, MD, PhD; Rafael Sciot, MD, PhD; Wim Robberecht, MD, PhD

Background: Twenty percent of familial amyotrophic lateral sclerosis (ALS) is caused by mutations in the superoxide dismutase 1 gene (SOD1). Few data exist on their clinicopathologic phenotypes.

Objectives: To determine the clinical and pathologic phenotype associated with the G93C mutation in SOD1 and to compare survival in familial ALS related to this mutation with survival in other ALS subgroups.

Design: Retrospective study.

Setting: Tertiary referral center for neuromuscular disorders.

Patients: Twenty patients with the G93C mutation for whom clinical data were available and 1 patient with pathologic data.

Main Outcome Measures: Characteristics and survival compared with other ALS subgroups, adjusting for known prognostic factors.

Results: The G93C mutation was associated with a purely lower motor neuron phenotype without bulbar involvement. Presence of the mutation independently predicted longer survival compared with other ALS subgroups. Pathologic examination showed degeneration of the anterior horn, spinocerebellar tracts, and posterior funiculi, with minimal involvement of corticospinal tracts and no degeneration of brainstem motor nuclei. Survival motor neuron gene copy number had no significant influence on age at onset or survival in patients with the G93C mutation.

Conclusions: These findings add to the knowledge of SOD1-related familial ALS and demonstrate further clinicopathologic variability between different SOD1 mutations. Finally, they demonstrate the independent prognostic value of the G93C mutation.

Arch Neurol. 2006;63:262-267

Method:

Patients

Clinical records of patients with ALS examined in our institution were reviewed, and patients with definite or probable ALS were included. A diagnosis of FALS was made when a first-degree relative was affected. Our ALS database (January 1, 1993, to December 31, 2002) contained 20 patients with FALS from 4 families with SOD1(G93C), 10 patients with SOD1(L38V) FALS, 5 patients with SOD1(D90A) FALS, 18 patients with FALS without SOD1 mutations, and 359 patients with SALS. Onset was defined as onset of weakness, dysarthria, or dysphagia, because onset of fasciculations or cramps was found to be unreliable. Diagnostic delay was defined as the interval between onset and diagnosis. Survival was defined as the interval between onset and death or initiation of artificial ventilation. We determined percentage of pre-
dicted forced vital capacity (FVC) soon after diagnosis. No patients received artificial ventilation.

**NEUROPATHOLOGIC EXAMINATION**

The brain and spinal cord of a 57-year-old man with SOD1(G93C) and a 67-month survival were examined by routine techniques. Briefly, representative tissue blocks from formalin-fixed brain and spinal cord were processed with paraffin, and 5-µm-thick sections (through motor and other neocortices, basal ganglia, hippocampus, brainstem, and cervical, thoracic, and lumbar spinal cord) were stained with hematoxylin-eosin and with the Klüver-Barrera stain. Indirect immunoperoxidase stains were performed with the use of polyclonal ant ubiquitin antibodies (DAKO, Glostrup, Denmark) and polyclonal antineurofilament antibodies (Sigma Chemical Co, St Louis, Mo).

**GENETIC ANALYSIS**

The SOD1 genotyping of patients with FALS with screening of all 5 exons was performed as described previously, after informed consent was obtained. The copy number of the survival motor neuron 1 (SMN1) and SMN2 genes in 15 of the patients with SOD1(G93C) was determined by means of the multiplex ligation-dependent probe amplification technology, with a diagnostic kit for spinal muscular atrophy (Salsa P021; MRC Holland BV, Amsterdam, the Netherlands).

**STATISTICAL ANALYSIS**

Age at onset and diagnostic delay in patients with FALS (SOD1 related [G93C, L38V, D90A] and non–SOD1 related) and SALS were compared by analysis of variance. Pairwise comparisons were performed by unpaired, 2-tailed t tests. Kaplan-Meier curves of survival in SOD1(G93C)–related FALS, SOD1(L38V)–related FALS, non–SOD1-related FALS, and SALS were generated and compared by the log-rank test. Because only 5 patients with SOD1(D90A) were available, their data were not included. A Cox proportional hazards regression was performed with SOD1(G93C), age at onset, diagnostic delay, bulbar vs spinal onset, and percentage of predicted FVC as covariates. Hazard ratios were calculated for presence of SOD1(G93C), per year of greater age at onset, per month of increased diagnostic delay, for spinal onset, and per 10% increase in percentage of predicted FVC.

Age at onset and survival were compared in patients with SOD1(G93C) with 1 vs 2 copies of the SMN1 or SMN2 gene with an unpaired, 2-tailed t test.

The Bonferroni method was used to correct for multiple comparisons. A 2-sided significance level of .05 was used. Values are represented as mean ± SD, unless indicated otherwise. All statistical analyses were performed with SPSS 10.0 (SPSS Inc, Chicago, Ill).

**COMPARATIVE DATA**

We reviewed the English-language literature to compare data for patients with SOD1 mutations for which at least 1 detailed illustrated neuropathologic description and detailed clinical information on at least 10 patients with FALS were available. Care was taken not to include the same patients repeatedly. Whenever possible, the same criteria for age at onset, survival, and upper motor neuron involvement as in our study population were used.

**RESULTS**

**CLINICAL CHARACTERISTICS OF SOD1(G93C)**

All 20 patients with SOD1(G93C) FALS had slowly progressive weakness and atrophy, starting distally in the
lower extremities. Symptoms gradually spread proximally and to the upper extremities. Throughout the course, distal involvement predominated and bulbar function was preserved. Death resulted from respiratory failure in all 11 patients who had died. Deep tendon reflexes were initially present but gradually disappeared. There were no brisk reflexes, spasticity, Babinski signs, jaw jerk, or other upper motor neuron signs. Several patients (not the patient who underwent autopsy) had mild sensory symptoms, and in 1 patient with advanced disease, mild distal loss of pinpoint sensation was found.

**NEUROPATHOLOGIC FINDINGS**

Brain and spinal cord of a 57-year-old man with SOD1 (G93C) were obtained at autopsy, after a 67-month-long disease course.

The motor cortex appeared normal. No loss of brainstem motor neurons was observed, but in most brainstem motor nuclei, lipofuscin-loaded motor neurons were prominent. Lipofuscin was most prominent in hypoglossal motor neurons, which also showed hyaline inclusions. Loss of myelinated fibers was pronounced in the posterior column and spinothalamic tracts, but only mild in the lateral corticospinal tracts (Figure 1A). Severe loss of anterior horn cells was present, and many of the remaining neurons were atrophic and showed hyaline inclusions similar to the previously described Lewy body–like hyaline inclusions9 (Figure 1B) or ubiquitin-positive inclusions (Figure 1C). Most remaining neurons contained lipofuscin. The Clarke column was also degenerated. Neurofilament stains were unremarkable. Bunina bodies were absent.

**DEMOGRAPHIC CHARACTERISTICS**

Age at onset in SOD1 (G93C)–related FALS was 45.9 ± 10.6 years, significantly younger than in SALS (58.4 ± 12.0 years; P <.001). The onset was earlier in SOD1 (L38V)–related FALS than non–SOD1–related FALS (P = .004) and SALS (P <.01) (Table 1). Bulbar onset was noted in 105 (30.2%) of 348 patients with SALS but in none of the patients with SOD1–related FALS (P = .001).

Median disease durations were estimated by Kaplan-Meier curves (Table 1, Figure 2). Log-rank analysis showed a statistically significant difference among the groups (P <.001). Pairwise analysis showed that median disease duration in patients with SOD1 (G93C) (153.0 months) was significantly longer than that of patients with SALS (30.0 months), SOD1 (L38V) (24.0 months), and non–SOD1 FALS (43.0 months). There was no difference in survival between patients with SALS, non–SOD1 FALS, and SOD1 (L38V).

In a multivariate analysis, the hazard ratios (and corresponding 95% confidence intervals) for age at onset, diagnostic delay, spinal site of onset, and percentage of predicted FVC were 1.03 (1.02–1.05; P <.001), 0.94 (0.91–0.96; P <.001), 0.64 (0.44–0.93; P = .02), and 0.84 (0.78–0.91; P <.001), respectively, all statistically significant. In addition, the presence of the G93C mutation was found to represent an independent, statistically significant, positive prognostic factor for survival (hazard ratio, 0.2; 95% confidence interval, 0.05–0.81; P = .02).

**SMN GENE ANALYSIS**

Two patients had 1 SMN1 gene copy but 3 SMN2 copies, and 9 patients had 1 SMN2 gene copy. There was no
Table 2. Clinicopathologic Comparison With Other SOD1 Mutations

<table>
<thead>
<tr>
<th>SOD1 Mutation*</th>
<th>A4V</th>
<th>H46R</th>
<th>I113T†</th>
<th>G93C</th>
<th>D101N*</th>
<th>A4T</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients‡</td>
<td>167</td>
<td>62</td>
<td>29</td>
<td>20</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>With clinical neurologic details</td>
<td>19</td>
<td>56</td>
<td>10</td>
<td>20</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>With pathologic details</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>47 ± 14</td>
<td>45 ± 10</td>
<td>57 ± 13</td>
<td>46 ± 11</td>
<td>41 ± 10</td>
<td>44 ± 11</td>
</tr>
<tr>
<td>Range</td>
<td>21-78</td>
<td>25-68</td>
<td>26-84</td>
<td>33-71</td>
<td>26-57</td>
<td>21-60</td>
</tr>
<tr>
<td>Survival, y</td>
<td>1.2 ± 0.9</td>
<td>17 ± 7.5</td>
<td>4.2 ± 4.2</td>
<td>13 ± 4</td>
<td>2.4 ± 0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Range</td>
<td>0.5-4.0</td>
<td>6-47</td>
<td>0.6-21</td>
<td>5-20</td>
<td>1.1-4.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Clinical information

<table>
<thead>
<tr>
<th>Onset site</th>
<th>Spinal/bulbar</th>
<th>Lower limb</th>
<th>Upper limb/ Lower limb</th>
<th>Lower limb</th>
<th>Lower limb/ Lower limb</th>
<th>Lower limb/ Lower limb</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMN signs</td>
<td>- (Sens) (EO)§</td>
<td>-/Sens</td>
<td>- (Sens)</td>
<td>- (Sens)</td>
<td>- (Sens)</td>
<td></td>
</tr>
<tr>
<td>Atypical signs</td>
<td>- (Sens) (EO)§</td>
<td>-/Sens</td>
<td>- (Sens)</td>
<td>- (Sens)</td>
<td>- (Sens)</td>
<td></td>
</tr>
<tr>
<td>Pathologic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor cortex</td>
<td>+/+/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>CST degeneration</td>
<td>+/+/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>Motor cortex</td>
<td>-/+</td>
<td>+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>CST degeneration</td>
<td>+/+/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>Motor cortex</td>
<td>-/+</td>
<td>+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>CST degeneration</td>
<td>+/+/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>Other neurodegeneration</td>
<td>SN/dorsal vagal nucleus, gracile nucleus</td>
<td>±SN/dorsal vagal nucleus</td>
<td>±SN/dorsal vagal nucleus</td>
<td>±SN/dorsal vagal nucleus</td>
<td>±SN/dorsal vagal nucleus</td>
<td>±SN/dorsal vagal nucleus</td>
</tr>
<tr>
<td>LBHI</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>References</td>
<td>2, 3, 10-14</td>
<td>13, 15-18</td>
<td>2, 13, 14, 19-26</td>
<td>Current study</td>
<td>27-29</td>
<td>30-32</td>
</tr>
</tbody>
</table>

Abbreviations: BS, brainstem; CST, corticospinal tract; EO, external ophthalmoplegia; GP, globus pallidus; LBHI, Lewy body–like hyaline inclusions; LC, locus ceruleus; NA, not available; OI, oliva inferior; PC, posterior column; SCT-Cl, spinocerebellar tract and Clarke nucleus; Sens, sensory signs; SN, substantia nigra; SOD1, superoxide dismutase 1 gene; UMN, upper motor neuron; −, absent; +, mild; ++, moderate to severe.

*Clinical signs and neuropathological findings of anterior horn degeneration were moderate to severe in all of the mutations.
†Reduced penetrance and apparently sporadic cases.22-25
‡Number of patients included in weighted means of age at onset.
§Two reports§,16,18 did not specifically include the number of patients included in analysis of duration; therefore, these patients were not included in the corresponding weighted means.
||Signs shown in parentheses were rarely reported (typically only once). Scorings separated by virgules (/) occurred in comparable numbers, in order of frequency.
¶Prolonged artificial ventilation.
#Roman numerals indicate the corresponding somatic motor nuclei of the cranial nerves.
**Discordance between degeneration in Clarke nucleus and SCT.
††There were neurofibrillary tangles associated with the degeneration of SN, LC, and GP; in other cases, hyaline conglomerates and argyrophilic inclusions were observed.

statistically significant difference in age at onset or survival between patients with 1 or 2 SMN1 gene copies, nor between patients with 1 or 2 SMN2 gene copies, although onset was earlier in the population with 2 SMN2 copies than in that with 1 SMN2 copy (42.7 ± 3.4 vs 50.3 ± 3.4 years; P = .17)

We present clinical data on the largest group of patients with SOD1(G93C)–related FALS yet reported, and the first pathologic data of a patient with this mutation, to our knowledge.

In our population, SOD1(G93C) was associated with a purely lower motor neuron clinical phenotype and absence of bulbar involvement. Aside from variability in age at onset and survival, this phenotype was quite constant in comparison with some other SOD1 mutations, especially SOD1(I113T) (Table 2). The SMN gene copy number, previously proposed as a susceptibility or prognostic factor in SALS,31,32 did not explain this variability in our patients. This suggests that other modifiers exist.19

Predominant lower motor neuron involvement, as found in our patients with SOD1(G93C) FALS, is also a frequent finding in other SOD1 mutations, especially in SOD1(A4V) and SOD1(A4T) (Table 2). Although pathologic data on SOD1-related ALS are limited, findings similar to those in our patient, such as mild corticospinal tract involvement, prominent myelin loss in posterior columns and spinocerebellar tracts, and degeneration of Clarke column, seem to define the pathologic picture in SOD1(A4V).3, SOD1(A4T),30 and SOD1(E100G).35 However, in these reports, brainstem involvement was more pronounced than in our patient, who showed only hyaline inclusions in the hypoglossal nucleus, without neuronal loss. Absence of Bulina bodies has been a consistent finding in SOD1-related ALS, except for 1 patient with a de novo H80A mutation16 and a patient with an insertion at codon 127.37

The earlier onset of SOD1(G93C)–related FALS compared with SALS is a shared feature of most SOD1 mu-
tations and FALS in general. Among SOD1 mutations, SOD1(L38V) and SOD1(G37R) have been shown to present earlier than other mutations, reflected in a mean age at onset of 38 years in our patients with SOD1(L38V).

In our population, the comparison with patients with FALS carrying other mutations in SOD1 did not reach statistical significance, probably because of small numbers. Indications of a better prognosis associated with SOD1(G93C) (median survival, 153 months) were reported before, but these analyses were done only on patients with FALS and did not adjust for all the known prognostic variables. We demonstrated that SOD1(G93C)-related FALS has a significantly better prognosis than SALS, non–SOD1-related FALS, and SOD1(L38V)-related FALS, independent of age at onset, site of onset, percentage of predicted FVC, and diagnostic delay. The independent prognostic value of these latter factors was confirmed.

The reason for the better prognosis and particular phenotype of SOD1(G93C) remains elusive, as are the reasons why other mutations, like SOD1(A4V), have a worse prognosis. However, our data are useful to estimate prognosis in these rare families and may help to validate theories about the pathogenicity of SOD1 mutations. Indeed, the remarkable differences in clinical severity, age at onset, and type (lower-upper, spinal-bulbar) of motor neuron involvement between certain SOD1 mutations may be a reflection of their different biological properties. A hint to possible mechanisms in this diversity of phenotypes was provided in a recent report on the selective association of mutant SOD1 with mitochondria of affected tissues in transgenic mouse models of ALS. More research into differences in molecular mechanisms between SOD1 mutations with well-defined clinicopathologic phenotypes in humans is needed to solve these issues.

Accepted for Publication: October 5, 2005.

Correspondence: Wim Robberecht, MD, PhD, Department of Neurology, University Hospital KU Leuven, Herestraat 49, 3000 Leuven, Belgium (wim.robberecht@uz.kuleuven.ac.be).

Author Contributions: Study concept and design: Régal, Vanopdenbosch, Van Den Bosch, and Robberecht. Acquisition of data: Vanopdenbosch, Tilkin, Sciot, and Robberecht. Analysis and interpretation of data: Régal, Vanopdenbosch, Thijs, Sciot, and Robberecht. Drafting of the manuscript: Régal, Tilkin, and Robberecht. Critical revision of the manuscript for important intellectual content: Régal, Vanopdenbosch, Van Den Bosch, Thijs, Sciot, and Robberecht. Statistical analysis: Thijs and Robberecht. Obtained funding: Robberecht. Administrative, technical, and material support: Régal, Tilkin, Sciot, and Robberecht. Study supervision: Vanopdenbosch, Van Den Bosch, Sciot, and Robberecht.

Funding/Sponsorship: This study was supported by a grant from the Interuniversity Attraction Poles programs P5/19 and P5/35 of the Belgian Federal Science Policy Office, Belgium.

Previous Presentation: This study was presented in part at the 53rd Annual Meeting of the American Academy of Neurology; May 10, 2001; Philadelphia, Pa. A published abstract appears in Neurology. 2001;56(8, suppl 3):A445.

Acknowledgment: We thank Gert Matthijs, PhD, for the molecular analysis of the patients’ samples.

REFERENCES


**Correction**

Errors in Table. In the Original Contribution by Régal et al titled “The G93C Mutation in Superoxide Dismutase 1: Clinicopathologic Phenotype and Prognosis,” published in the February issue of the *ARCHIVES (2006;63:262-267),* several errors occurred on page 265 in Table 2. In that table, the asterisk next to the column heading “D101N” should have been a dagger to refer to “Reduced penetrance and apparently sporadic cases.” In addition, the table headings “Other neurodegeneration” and “LBHI” should have been indented to indicate that these are also pathologic findings, and the following definitions should have appeared at the end of the Abbreviations footnote: “(for UMN signs: −, absent; +, hyperreflexia; +++, Babinski sign or spasticity).” The corrected table is reprinted here with its footnotes.

### Table 2. Clinicopathologic Comparison With Other *SOD1* Mutations

<table>
<thead>
<tr>
<th><em>SOD1</em> Mutation*</th>
<th>A4V</th>
<th>H46R</th>
<th>I113T†</th>
<th>G93C</th>
<th>D101N†</th>
<th>A4T</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients‡</td>
<td>167</td>
<td>62</td>
<td>29</td>
<td>20</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>With clinical*</td>
<td>19</td>
<td>56</td>
<td>10</td>
<td>20</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>With pathologic details</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>Mean ± SD</td>
<td>47 ± 14</td>
<td>45 ± 10</td>
<td>57 ± 13</td>
<td>46 ± 11</td>
<td>41 ± 10</td>
</tr>
<tr>
<td>Range</td>
<td>21-78</td>
<td>25-68</td>
<td>26-84</td>
<td>33-71</td>
<td>26-57</td>
<td>21-60</td>
</tr>
<tr>
<td>Survival, y</td>
<td>Mean ± SD</td>
<td>1.2 ± 0.9</td>
<td>17 ± 75</td>
<td>4.2 ± 42</td>
<td>13 ± 4</td>
<td>2.4 ± 0.9</td>
</tr>
<tr>
<td>Range</td>
<td>0.5-4.0</td>
<td>6-47</td>
<td>0.6-21</td>
<td>5-20</td>
<td>1.1-4.0</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset site</td>
<td>Spinal/bulbar</td>
<td>Lower limb</td>
<td>Upper limb/ lower limb</td>
<td>Lower limb</td>
<td>Lower limb/ upper limb</td>
<td>Lower limb/upper limb</td>
</tr>
<tr>
<td>UMN signs</td>
<td>– ( )</td>
<td>–/+</td>
<td>–/−/+/+</td>
<td>–</td>
<td>−/+ (+)</td>
<td>− ( )</td>
</tr>
<tr>
<td>Atypical signs</td>
<td>– (Sens) (EO)¶</td>
<td>–/Sens</td>
<td>–</td>
<td>– (Sens)</td>
<td>–</td>
<td>– (Sens)</td>
</tr>
<tr>
<td>Pathologic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BS motor nucleus#</td>
<td>++ II/X</td>
<td>−/+ II</td>
<td>++ II/VII/X</td>
<td>−</td>
<td>−/+ II</td>
<td>−</td>
</tr>
<tr>
<td>Motor cortex</td>
<td>−/+</td>
<td>+</td>
<td>++/++</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>CST degeneration</td>
<td>+/++</td>
<td>−/+</td>
<td>++/++</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>PC degeneration</td>
<td>+/++</td>
<td>−/+</td>
<td>++/++</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>SCT-Cl degeneration</td>
<td>+/++</td>
<td>−/+</td>
<td>++/++</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Other neurodegeneration</td>
<td>−/SN/dorsal vagal nucleus, gracile nucleus</td>
<td>−</td>
<td>−/OI/SN, LC, GP</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>LBHI</td>
<td>+</td>
<td>−/+</td>
<td>−††</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>References</td>
<td>2, 3, 10-14</td>
<td>13, 15-18</td>
<td>2, 13, 14, 19-26</td>
<td>Current study</td>
<td>27-29</td>
<td>30-32</td>
</tr>
</tbody>
</table>

Abbreviations: BS, brainstem; CST, corticospinal tract; EO, external ophthalmoparesis; GP, globus pallidus; LBHI, Lewy body–like hyaline inclusions; LC, locus ceruleus; NA, not available; OI, oliva inferior; PC, posterior column; SCT-Cl, spino cerebellar tract and Clarke nucleus; Sens, sensory signs; SN, substantia nigra; SOD1, superoxide dismutase 1 gene; UMN, upper motor neuron; −, absent; +, hyperreflexia; +++, Babinski sign or spasticity.

*Clinical signs and neuropathological findings of anterior horn degeneration were moderate to severe in all of the mutations.
†Reduced penetrance and apparently sporadic cases.23,29
‡Number of patients included in weighted means of age at onset.
††Signs shown in parentheses were rarely reported (typically only once). Scorings separated by virgules (/) occurred in comparable numbers, in order of frequency.
¶Prolonged artificial ventilation.
§Roman numerals indicate the corresponding somatic motor nuclei of the cranial nerves.
**Discordance between degeneration in Clarke nucleus and SCT.
††There were neurofibrillary tangles associated with the degeneration of SN, LC, and GP; in other cases, hyaline conglomerates and argyrophilic inclusions were observed.

(Reprinted) Arch Neurol/Vol 63, July 2006 www.archneurol.com

©2006 American Medical Association. All rights reserved.