Genotype-Phenotype Correlations in Charcot-Marie-Tooth Disease Type 2 Caused by Mitofusin 2 Mutations

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Background: Mutations in the gene encoding mitofusin 2 (MFN2) cause Charcot-Marie-Tooth disease type 2 (CMT2), with heterogeneity concerning severity and associated clinical features.

Objective: To describe MFN2 mutations and associated phenotypes in patients with hereditary motor and sensory neuropathy (HMSN).

Design: Direct sequencing of the MFN2 gene and clinical investigations of patients with MFN2 mutations.

Setting: Molecular genetics laboratory of a university hospital and the Limoges National Referral Center for Rare Peripheral Neuropathies.

Patients: One hundred fifty index patients with HMSN and a median motor nerve conduction velocity of 25 m/s or greater and without mutations in the genes encoding connexin 32 and myelin protein zero.

Main Outcome Measures: Results of genetic analyses and phenotypic observations.

Results: Twenty different missense mutations were identified in 20 index patients. Mutation frequency was 19 of 107 (17.8%) in patients with CMT2 and 1 of 43 (2.3%) in patients with a median motor nerve conduction velocity less than 38 m/s. Four patients had proven de novo mutations, 8 families had autosomal dominant inheritance, and 3 had autosomal recessive inheritance. The remaining 5 patients were sporadic cases with heterozygous mutations. Phenotypes varied from mild forms to early-onset severe forms. Additional features were encountered in 8 patients (32%). Six patients underwent sural nerve biopsy: electronic microscopy showed prominent mitochondrial abnormalities on longitudinal sections.

Conclusions: MFN2 mutations are a frequent cause of CMT2, with variable severity and either dominant or recessive inheritance. MFN2 gene testing must be a first-line analysis in axonal HMSN irrespective of the mode of inheritance or the severity of the peripheral neuropathy.

Arch Neurol. 2009;66(12):1511-1516
mutations diagnosed in the molecular genetics resource of the Limoges National Referral Center for Rare Peripheral Neuropathies.

**METHODS**

Between February 1, 2006, and October 31, 2008, 107 index patients with CMT2 and 43 patients with a median MNCV of 25 to 38 m/s (in the range of “intermediate” CMT) were screened for MFN2 mutations. None of the patients carried mutations in the genes encoding connexin 32 (GJB1) or myelin protein zero (MPZ). Written informed consent for genetic analyses had been obtained for all patients. DNA was extracted from blood leukocytes using standard techniques, and mutational analysis of MFN2 was performed by direct sequencing of all 19 exons and exon-intron boundaries, including the first 2 noncoding exons (primer sequences available on request). Both DNA strands were sequenced using BigDye Terminator Cycle Sequencing Kit v.1.1 (Applied Biosystems, Foster City, California). The products of sequencing reactions were separated using a genetic analyzer (model ABI3130xl; Applied Biosystems). The mutation search was then performed using Sequence Navigator version 1.0.1 (Applied Biosystems).

Comparison of mitofusin 2 (MFN2) sequences between species was performed using the National Center for Biotechnology Information HomoloGene Web server (http://www.ncbi.nlm.nih.gov/sites/entrez?db=homologene). Prediction of the impact of a mutation based on the changes in amino acid sequences was performed using PolyPhen (http://genetics.bwh.harvard.edu/pph) and PMut (http://mmib2.pcb.ub.es:8080/PMut/).

When a mutation had been found in an index case, it was subsequently searched for in all available family members. Clinical and paraclinical features of patients with MFN2 mutations were obtained from a detailed revision of laboratory database and patient files, the data being recorded on a dedicated standardized form. The CMT neuropathy score was used for clinical neurologic assessment.10

**RESULTS**

One hundred fifty apparently unrelated families were screened for MFN2 mutations. We found 20 different missense mutations in 25 patients from 20 different families (Table 1 and Figure 1). Patients 6 to 8 (p.[G108R]+[R707W]) belonged to the same family (siblings), as did patients 17 and 18 (p.R364P, mother and daughter), patients 21 and 22 (p.W740C, mother and daughter), and patients 23 and 24 (p.L745P, siblings). All other patients belonged to different families. Ten mutations in this series had not been previously reported (Table 1): 4 of them (p.H277Y, p.R364P, p.R364Q, and p.W740C) affected an amino acid residue that had already been found to be mutated in other series.3,5,6,9 All of the reported mutations affected amino acid residues conserved in many species (Table 2). In silico analysis of the 10 newly identified mutations using PolyPhen and PMut showed that all of the mutations were considered to be pathologic by at least 1 of the software programs and 6 of 10 by both (9 of 10 for PolyPhen and 7 of 10 for PMut).

Eight families displayed an autosomal-dominant pattern of inheritance (Table 1). Eleven patients had apparently sporadic disease; in 4 of them (patients 4, 5, 9, and 25), the absence of the mutation in both parents confirmed a de novo origin. Two other patients (patients 11 and 12) carried compound heterozygous mutations of the MFN2 gene (previously reported as cases 1/CMT742 and 2/CMT231 by Nicholson et al13). In both cases, parents carried the relevant single heterozygous mutation and had normal electrophysiologic examinations without objective clinical signs of neuropathy, confirming a recessive pattern of transmission. Another family with 3 affected children displayed a typical recessive inheritance pattern: patients 6, 7, and 8 were siblings with a moderate form of CMT2. Their parents had no signs or symptoms of peripheral neuropathy and had normal electroneuromyographic findings. Each parent carried a single heterozygous mutation.

Age at onset of symptoms was before 10 years in 21 patients (84%). Eight patients (32%) experienced their first symptoms before age 5 years. Regarding disease severity status, 3 groups of patients were delineated: 3 patients (12%) had a CMT neuropathy score of 0 to 12, corresponding to a mild form of the disease; 12 (48%) had a score of 13 to 24 (moderate severity); and 10 (40%) were severely affected, with a score greater than 24. The mean ages of the severity groups were 39.3, 34.4, and 19.5 years, respectively. Seven of the 8 patients who experienced their first symptoms before age 5 years had severe neuropathy. Of the 4 patients with an age at onset older than 10 years, 2 had a moderate form of disease and 2 had a mild form.

All of the patients had distal motor and sensory neuropathy that affected the 4 limbs, consistent with the diagnosis of CMT. However, some patients had other features: 3 of 25 patients (12%) had pyramidal signs, 3 (12%) had asymmetrical neuropathy, 3 (12%) had important vasomotor troubles, 2 (8%) had abnormal respiratory function (1 had clinical respiratory failure and 1 had reduced vital capacity: 66% of theoretical value), 2 (8%) had hearing loss, 1 (4%) had optic atrophy, and 1 (4%) had a distal intention tremor.

Median MNCVs were available for 21 patients. In patient 1, the absence of compound motor action potential did not allow MNCV measurement; in patient 8, electroneuromyography had not been performed (2 siblings with an identical phenotype, one of whom was the index case, had median MNCVs of 50 and 55 m/s); and in patients 18 and 24, median MNCV had not been recorded. All other patients had median MNCVs greater than 38 m/s except patient 12, whose MNCV was 34.8 m/s. Four patients underwent brain magnetic resonance imaging: patient 22 had normal findings, patient 21 showed diffuse brain atrophy at age 46 years, patient 19 had several subcortical white matter hyperintense signals on T2-weighted images but had a personal history of chronic hypertension, and patient 5 showed a tumor localized in the left temporal-insular region that was diagnosed as an epidermoid cyst.

Six patients underwent a sural nerve biopsy (patients 3, 4, 9-12). Histopathologic findings in patients 3, 4, 11, and 12 have already been reported.14,15 Patient 9 was affected by severe early-onset neuropathy, whereas patient 10 had a moderate form of CMT2. In both patients, electron microscopy of the nerve biopsy showed...
ultrastructural abnormalities similar to those observed in previously reported early-onset cases,\textsuperscript{15} with a marked decrease in the density of myelinated fibers and abnormally aggregated on longitudinal sections of the sural nerve (Figure 2).

In the present series, MFN2 mutations were found in 19 of 107 index patients with CMT2 (17.8%). Only 1 of 43 patients (2.3%) with median MNCVs of 25 to 38 m/s (34.8

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>MNCV, Median, m/s</th>
<th>Age at Onset, y</th>
<th>Phenotype Particularities</th>
<th>Inheritance</th>
<th>Mutations</th>
<th>Previous Report</th>
</tr>
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<tbody>
<tr>
<td>1/F/33</td>
<td>No CMAP</td>
<td>&lt;10</td>
<td>Severe</td>
<td>D</td>
<td>p.R94W</td>
<td>Severe CMT2, optic atrophy\textsuperscript{6}; severe CMT2\textsuperscript{12}</td>
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<tr>
<td>2/M/6</td>
<td>54</td>
<td>&lt;10</td>
<td>Severe</td>
<td>S</td>
<td>p.R94W</td>
<td>Severe CMT2, optic atrophy\textsuperscript{6}; severe CMT2\textsuperscript{12}</td>
</tr>
<tr>
<td>3/F/2</td>
<td>63</td>
<td>&lt;5</td>
<td>Severe, respiratory failure, optic atrophy</td>
<td>S</td>
<td>p.R104W</td>
<td>Severe CMT2, optic atrophy\textsuperscript{11}; CMT2, pyramidal signs, hearing loss, cognitive impairment\textsuperscript{12}</td>
</tr>
<tr>
<td>4/F/4</td>
<td>52</td>
<td>&lt;5</td>
<td>Severe</td>
<td>DN</td>
<td>p.R104W</td>
<td>Severe CMT2, optic atrophy\textsuperscript{11}; CMT2, pyramidal signs, hearing loss, cognitive impairment\textsuperscript{12}</td>
</tr>
<tr>
<td>5/F/18</td>
<td>&gt;38</td>
<td>&lt;10</td>
<td>Severe, reduced vital capacity</td>
<td>DN</td>
<td>p.R104W</td>
<td>Severe CMT2, optic atrophy\textsuperscript{11}; CMT2, pyramidal signs, hearing loss, cognitive impairment\textsuperscript{12}</td>
</tr>
<tr>
<td>6/M/19</td>
<td>55</td>
<td>&lt;10</td>
<td>Moderate</td>
<td>R</td>
<td>[G108R] + [R707W] (homozygous): severe CMT2, early onset, hearing loss, kyphosis, lipodystrophy\textsuperscript{11}</td>
<td></td>
</tr>
<tr>
<td>7/F/24</td>
<td>50</td>
<td>&lt;10</td>
<td>Moderate</td>
<td>R</td>
<td>[G108R] + [R707W] (homozygous): severe CMT2, early onset, hearing loss, kyphosis, lipodystrophy\textsuperscript{11}</td>
<td></td>
</tr>
<tr>
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<td>ND</td>
<td>&lt;10</td>
<td>Moderate</td>
<td>R</td>
<td>[G108R] + [R707W] (homozygous): moderate CMT2, early onset, hearing loss, kyphosis, lipodystrophy\textsuperscript{11}</td>
<td></td>
</tr>
<tr>
<td>9/F/5</td>
<td>48.5</td>
<td>&lt;5</td>
<td>Severe, asymmetrical</td>
<td>DN</td>
<td>p.H128R</td>
<td>No</td>
</tr>
<tr>
<td>10/F/67</td>
<td>47.7</td>
<td>&lt;10</td>
<td>Moderate</td>
<td>S</td>
<td>p.S156I</td>
<td>No</td>
</tr>
<tr>
<td>11/F/32</td>
<td>41</td>
<td>&lt;5</td>
<td>Severe, hearing loss, scoliosis</td>
<td>R</td>
<td>[A164V] + [T362M] Case previously reported by Nicholson et al\textsuperscript{13}</td>
<td></td>
</tr>
<tr>
<td>12/M/34</td>
<td>34.8</td>
<td>&lt;5</td>
<td>Severe, hearing loss</td>
<td>R</td>
<td>[D214N] + [C398R] Case previously reported by Nicholson et al\textsuperscript{13}</td>
<td></td>
</tr>
<tr>
<td>13/F/18</td>
<td>&gt;38</td>
<td>&lt;10</td>
<td>Moderate</td>
<td>D</td>
<td>T236M</td>
<td>CMT2\textsuperscript{12}</td>
</tr>
<tr>
<td>14/M/5</td>
<td>48.3</td>
<td>&lt;5</td>
<td>Moderate</td>
<td>S</td>
<td>V244M</td>
<td>CMT2\textsuperscript{12}</td>
</tr>
<tr>
<td>15/M/63</td>
<td>45.8</td>
<td>&lt;10</td>
<td>Moderate</td>
<td>D</td>
<td>G276R</td>
<td>Mild CMT2 ± optic atrophy\textsuperscript{9}</td>
</tr>
<tr>
<td>16/M/73</td>
<td>52.3</td>
<td>&gt;10</td>
<td>Moderate, pyramidal signs, vasomotor troubles</td>
<td>D</td>
<td>H277Y</td>
<td>No</td>
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<tr>
<td>17/F/49</td>
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<td>&lt;5</td>
<td>Severe</td>
<td>D</td>
<td>R364P</td>
<td>No</td>
</tr>
<tr>
<td>18/F/12</td>
<td>ND</td>
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<td>Severe</td>
<td>D</td>
<td>R364P</td>
<td>No</td>
</tr>
<tr>
<td>19/F/64</td>
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<td>&gt;10</td>
<td>Moderate</td>
<td>S</td>
<td>R364Q</td>
<td>No</td>
</tr>
<tr>
<td>20/F/26</td>
<td>41</td>
<td>&lt;10</td>
<td>Moderate, asymmetrical</td>
<td>D</td>
<td>F665S</td>
<td>No</td>
</tr>
<tr>
<td>21/F/46</td>
<td>54.7</td>
<td>&lt;10</td>
<td>Mild, pyramidal signs</td>
<td>D</td>
<td>W740C</td>
<td>No</td>
</tr>
<tr>
<td>22/F/16</td>
<td>56.9</td>
<td>&lt;10</td>
<td>Moderate, asymmetrical, pyramidal signs, vasomotor troubles, tremor</td>
<td>D</td>
<td>W740C</td>
<td>No</td>
</tr>
<tr>
<td>23/M/38</td>
<td>48.2</td>
<td>&gt;10</td>
<td>Mild, vasomotor troubles</td>
<td>D</td>
<td>L745P</td>
<td>No</td>
</tr>
<tr>
<td>24/F/34</td>
<td>ND</td>
<td>&gt;10</td>
<td>Mild</td>
<td>D</td>
<td>L745P</td>
<td>No</td>
</tr>
<tr>
<td>25/F/13</td>
<td>&gt;38</td>
<td>&lt;10</td>
<td>Moderate</td>
<td>DN</td>
<td>M747T</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: CMT2, Charcot-Marie-Tooth disease type 2; D, dominant; DN, de novo; MFN2, mitofusin 2; MNCV, motor nerve conduction velocity; ND, not determined; R, recessive; S, sporadic case with at least 1 parent unavailable for genetic testing.
patients with optic atrophy or hearing loss had severe mutations, were found in 3 patients (12%). All of the have not been previously reported in patients with onset severe axonal neuropathy to “classic” CMT2. As pre-
disease severity and age at onset, phenotypes vary from early-
descriptions of patients with
of the present patients seems grossly similar to previous
HR2, heptad repeat 2 domain; and TM, transmembrane domain.

Figure 1. Localization of mitofusin 2 (MFN2) mutations. Previously reported
mutations are from http://www.molgen.ua.ac.be/cmtmutations. Red
denotes dominant mutations identified in severe cases; blue, recessive
mutations are from http://www.molgen.ua.ac.be/cmtmutations. Red
mutations indicate dominant mutations identified in severe cases; blue, recessive
mutations are from http://www.molgen.ua.ac.be/cmtmutations. Red

Six patients in the present series underwent sural nerve biopsy, in all cases before MFN2 was identified as a ma-
ajor gene for CMT2. In all of them, prominent mitochondrial abnormalities were found in myelinated and un-
myelinated axons. Peripheral nerve biopsy is an invasive investigation and should not be performed before MFN2 screening in patients with typical CMT2. However, in patients with atypical features who have undergone sural nerve biopsy, careful examination of longitudinal sections using electron microscopy should be systematic to identify abnormal mitochondria suggestive of a defect in mitochondrial dynamics. From our experience, we rec-
ommend screening of patients with such abnormalities for MFN2 mutations.

In line with previous study findings, the mutations identified in the present series are localized in or in close
vicinity of the GTPase or heptad repeat (HR) domains of MFN2. In 6 of the 7 severe cases with dominant MFN2 mutations (patients 1-5 and 9), the mutation was located immediately upstream of or in the GTPase do-
main, and all of them involved highly conserved amino acids (Figure 1 and Table 2). Two severe cases har-
bored the p.R94W mutation, which has been previously reported to be a hot spot for MFN2 mutations. The p.R104W mutation (which had been found in 3 families before this study) was present in 3 unrelated pa-
tients in this series. This residue, therefore, seems to be
a new hot spot for MFN2 mutations. Both p.R94W and p.R104W mutations result from a C→T transition in a CpG dinucleotide (the CGG codon translated to argi-
ne being replaced by a TGG codon translated to trypt-
ophan). CpG dinucleotides are known to be more prone
to point mutations (approximately 10-fold over other di-
nucleotides) because they frequently contain a methyl-
cytosine that can be deaminated to thymine.

The only dominant mutation responsible for a severe
neuropathy and not localized in close vicinity of the
GTPase domain was p.R94W (patients 1 and 2). This
mutation replaces the conserved arginine by a proline resi-
due, which may severely affect protein stability. An-
other mutation replacing arginine 346 by a tryptophan residue (which is also predicted to be damaging for the secondary structure of MFN2) had previously been found in several patients with severe forms of CMT2. In the present series, we also identified another mutation at position 364 that results in substitution of glutamine for arginine. This mutation is likely to have less drastic con-
sequences on MFN2 structure and function and was, in-
deed, found in a patient with a milder phenotype (pa-
tient 19).

The remaining 2 severe cases (patients 11 and 12) were
apparently sporadic and harbored compound heterozy-
gous MFN2 mutations: in each case, one mutation was
located in the GTPase domain and the other near the HR1
domain. Another family with recessively inherited CMT2
presented with a less severe phenotype. In this family, 3
children (patients 6-8) were affected by axonal neuropa-
thy beginning in childhood and harbored compound heterozygous mutations, one located in the GTPase do-
main (p.G108R) and the other in the HR2 domain (p.R707W). Another patient with recessively inherited
CMT2 of moderate severity had been found to harbor a

m/s) carried an MFN2 mutation. The clinical presentation
of the present patients seems grossly similar to previous
descriptions of patients with MFN2 mutations: regarding
disease severity and age at onset, phenotypes vary from early-onset severe axonal neuropathy to “classic” CMT2. As
previously reported in patients with MFN2 mutations, some of the present patients presented with additional clinical
features, such as pyramidal signs, optic atrophy, and hearing loss. Pyramidal signs were observed in patients with
mild or moderate forms of CMT2 only, not in patients with
severe peripheral neuropathies. A possible explanation for
this observation is that in severe cases, the pyramidal signs
could be masked by an important peripheral motor and sen-
sory impairment. We observed that several patients had
asymmetrical neuropathy, as reported in a recent series of
patients with CMT2. Important vasomotor troubles, which
have not been previously reported in patients with MFN2
mutations, were found in 3 patients (12%). All of the
patients with optic atrophy or hearing loss had severe
neuropathies.

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homozygous p.R707W mutation. This HR2 mutation may, therefore, be associated with less severe forms of axonal CMT. In our family, both heterozygous parents had no signs or symptoms of peripheral neuropathy and normal electroneuromyographic findings. This is the first multiplex family reported to date, to our knowledge, with recessively inherited CMT2 due to MFN2 mutations.

It has been known for a long time that autosomal recessive disorders tend to occur earlier and have greater severity than autosomal dominant disorders. This has been illustrated by William Allan in 1939 for CMT, considered as a single clinical entity at that time. He observed that individuals with dominantly inherited CMT had a milder phenotype and a later onset than did those affected by a recessive form of CMT. In MFN2-related neuropathies, the situation seems less clear-cut: in the present series, 3 of 11 patients with dominantly inherited CMT2 had severe forms and 2 of 11 had onset before 5 years of age, whereas 3 siblings with recessively inherited CMT2 had a moderate phenotype. However, mild forms (patients 21, 23, and 24) were encountered in patients with dominant inheritance only, and 3 of 11 patients with dominant forms had an age at onset older than 10 years (vs 0 of 5 with recessive forms, 0 of 4 with de novo forms, and 1 of 5 with sporadic forms).

In conclusion, these observations demonstrate that MFN2 mutations can be responsible for peripheral neuropathies of various severities, with dominant or recessive inheritance. This highlights the importance of screening all patients with axonal forms of CMT for MFN2 mutations.

### Table 2. Amino Acid Conservation Among Species for Mutations Identified in This Series

<table>
<thead>
<tr>
<th>Index Patient No.</th>
<th>Nucleotide Change</th>
<th>Amino Acid Change</th>
<th>Exon</th>
<th>Cf</th>
<th>Rn</th>
<th>Mm</th>
<th>Gg</th>
<th>Dr</th>
<th>Dm</th>
<th>Ce</th>
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<tbody>
<tr>
<td>1, 2</td>
<td>c.280C&gt;T</td>
<td>p.R94W</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3-5</td>
<td>c.310C&gt;T</td>
<td>p.R104W</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>c.338A&gt;G</td>
<td>p.H128R</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>c.457G&gt;T</td>
<td>p.S156I</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
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<td>p.A164V</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>12</td>
<td>c.640G&gt;A</td>
<td>p.D214N</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>p.H277Y</td>
<td>9</td>
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<td>p.T362M</td>
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Abbreviations: Ce, Caenorhabditis elegans (Fzo protein); Cf, dog; Dr, Danio rerio fish; Dm, Drosophila melanogaster (Marf protein); Gg, chicken; Mm, mouse; Rn, rat; +, present; −, absent.
mutations, irrespective of the apparent mode of inheritance or disease severity.

Accepted for Publication: June 29, 2009.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by a post-doctoral scholarship from the Société Française de Neurologie (Dr Calvo).

Role of the Sponsor: The funding source had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

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