Unexpected Intermediate Nerve Conduction Velocity Findings in Charcot-Marie-Tooth Syndromes Classified as Demyelinated or Axonal in a Pediatric Population

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Abstract

Introduction Among the hereditary motor and sensory neuropathies (HMSN), demyelinating forms are the best characterized, with a clear predominance of CMT1A. The axonal and intermediate forms are less described. The aim of this study is to report the genetic diagnosis of Charcot-Marie-Tooth (CMT) according to the nerve conduction velocity (NCV) findings in a pediatric population.

Methods We retrospectively described a population of HMSN children with a confirmed genetic diagnosis of demyelinated, intermediate, or axonal forms. We compared the results of the genetic analyses with those of motor NCV in median nerve according to whether they were below 25 m/s (demyelinating group); between 25 and 45 m/s (intermediate group), or above 45 m/s (axonal group).

Results Among the 143 children with an HMSN, 107 had a genetic diagnosis of which 61 had an electromyogram. On NCV findings: seven (11%) pertain to the axonal group, 20 (32%) to the intermediate group, and 34 (55%) to the demyelinating group. When NCV was above 45 m/s, CMT2A was the predominant genetic diagnosis (70%) when NCV were below 25 m/s, CMT1A was the predominant genetic diagnosis (71%).
Intermediate NCV findings group was the more heterogeneous with seven genetic CMT subgroups (60% CMT1A, CMT1B, CMT1X, CMT2A, CMT2N, CMT4G).

**Conclusion** Taking NCV values between 25 and 45 m/s to define an intermediate group of CMT in children leads to the inclusion of non-typically "intermediate", especially CMT1A. We emphasize the broad spectrum of NCV in CMT1A that justified the systematic search of PMP22 duplication/deletion screening before next generation sequencing panel.

Hereditary motor and sensory neuropathies (HMSN) represent the most frequently inherited neuromuscular diseases with a prevalence of 1/2500 in the general population. HMSN is a heterogeneous group of disorders associated with greater than 80 disease causing genes or loci to date.

Initially, Charcot-Marie Tooth (CMT) syndromes (or HMSN) were classified according to the mode of transmission (autosomal or X-linked; dominant or recessive) and motor nerve conduction velocity (NCV) findings in median nerve. The median motor NCV is below 38 m/s for the demyelinating form (CMT1) and above 38 m/s for the axonal form (CMT2). Axonal CMTs (or CMT2) were associated with mutations in gene causing axonal dysfunction and demyelinated CMTs (or CMT1) were associated with mutation in gene causing demyelination. However, experience with the rising number of CMT genes showed that there are some patients with clinicoelectrophysiological features that do not fit into either CMT1 or CMT2. This group of CMT was thus classified as "intermediate CMTs" and these were originally characterized by the absence of clinically observed nerve hypertrophy; a median MNVC between 25 and 45 m/s, a prolonged distal motor latency, a preserved mean compound muscle action potential (CMAP) amplitude and a nerve biopsy showing axonal changes, clusters of regenerating myelinated fibers, loss of larger fibers noted from unimodal diameter histograms, and onion bulbs with fewer lamellae than in CMT1.

While demyelinating CMTs are currently well characterized with a clear predominance of CMT1A, intermediate and axonal CMT are less known in the pediatric population. Axonal CMTs represent approximately 30% of all CMTs. Only 40% can be resolved genetically, compared to 90% in the demyelinating CMT. Mutations in the MFN2 gene are the most frequently detected causes of CMT2A (20 to 30%) followed by mutations in the GARS (CMT2D), GDAP1 (CMT2H/K), and NEFL (CMT2E) genes (10%). The other mutations reported are sporadic.

The intermediate CMTs represent approximately 6% of CMTs. Several authors have previously reported a predominance of mutations in the X-linked CMT genes with an overrepresentation of CMT1X mutations (GJB1 mutations).

Intermediate CMTs have been classified according to the mode of transmission, by distinguishing X-linked intermediate CMT (mutation in GJB1 or DRP2), autosomal dominant intermediate CMT (DNM2, YARS, MPZ, INF2, GNB4, NEFL, MNF2, AARS, and DCTN2), or autosomal recessive intermediate CMT (GDAP1, KARS, PLEKHG3, and COX6M).

Next generation sequencing (NGS) panels have dramatically shortened the time required to obtain a molecular diagnostic result, but it does not allow to make a systematic diagnosis. In this complex classification some genes involved may have different modes of inheritance and give various electroneuromyographic (ENMG) forms. While NGS panels improved the diagnostic rate of HMSNs, a number of patients with axonal or intermediate electroneuromyographic findings still could not be diagnosed using this method. Moreover, the new variants identified with NGS, are sometimes difficult to interpret and justify the implementation of a rigorous clinical and ENMG evaluation in parallel.

The electrophysiological NCV limits of intermediate CMT are not clearly defined, with authors suggesting different classifications with NCV between 25 and 45 m/s, between 30 and 40 m/s or between 35 and 45 m/s. Limited electroneuromyographic data are available in pediatric onset CMT in the literature. The aim of the current study is to report the genetic diagnosis of CMT in a pediatric-onset population according to the electrophysiological findings classified as demyelinated, intermediate, or axonal in NVC values.

**Methods**

The current study retrospectively selected children under 18 years followed for an HMSN between 1986 and 2018 with a confirmed genetic diagnosis from two sites of AOC (Atlantique-Occitanie-Caraibes) Reference Centers for Neuromuscular Diseases (Toulouse and Montpellier). Patients with pediatric onset HMSN were selected using the CEMARA, then BAMARA French databases for rare diseases and their data were reported from their medical records.

The clinical data was extracted from a neurological examination performed by a pediatric neurologist which included signs of peripheral neuropathy and research of other neurological signs such as pyramidal syndrome that can orient on CMT genes. The clinical examination included an evaluation of the patient’s walk and orthopaedic complications such as foot deformations or scoliosis. Age at the first sign and age at the first consultation were collected, as well as disease progression was noted when patients had follow-up consultations. The French translation of CMTPeds, that allows to score the functional evolution of children with...
Table 1 Molecular diagnosis in genotyped pediatric patient

<table>
<thead>
<tr>
<th>Genetic diagnosis</th>
<th>N = 107</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1A (dup PMP22)</td>
<td>69</td>
<td>64%</td>
</tr>
<tr>
<td>CMT2A (MFN2)</td>
<td>12</td>
<td>11%</td>
</tr>
<tr>
<td>CMT1B (MPZ)</td>
<td>9</td>
<td>8%</td>
</tr>
<tr>
<td>CMTX1 (GJB1)</td>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td>CMT2B (DNM2)</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>CMT2N (AARS)</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>CMT2Z (MORC2)</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>CMT4D (NDRG1)</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>CMT4G (HK1)</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>CMT4F (PRX)</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>

Note: HMSN type CMT1A is the most common form of CMT in both children and adults, followed by CMT2A, CMT1B, and CMTX1. The other forms are rarer.

HMSN, is available since 2017 and so was not used in this study. Moreover, data collected from the computerized records and patients’ papers did not allow CMTPeds scores to be established afterward.10,11

The electroneuromyographic assessments were carried out by different examiners before genetics diagnosis. We focused on collecting data related to the median nerve specifically the NCV, which was reported in patient records. We classified patients depending on electrophysiological NCV values in a demyelinating group (NCV< 25 m/s), an intermediate group (NCV between 25 and 45 m/s), an axonal group (NCV> 45 m/s), or in a group with unexcitability of nerve fibers. As in Berciano’s review, we have chosen to keep the NCV values originally described in the definition of intermediate CMTs from 25 to 45 m/s. The values of CMAP were not reported because too many data were missing.

The genetic analyses were performed in the molecular genetics’ laboratories of the Limoges and Lyon Hospitals. As the studies take place over many years, the techniques of molecular analysis have evolved. Both of these laboratories first search for deletions/duplications in the PMP22 gene using fluorescence in situ hybridization and then Multiplex ligation-dependent probe amplification. Genetic research was initially carried out by SANGER analysis of one gene at a time, guided by clinical, electrophysiological, and even histological data when a biopsy was performed. At the end of this study, the analyses were carried out thanks to CMT gene panels and then confirmed by SANGER method. Genetic analyses were performed from blood samples after obtaining informed written consent from the child’s parents.

Results

Genetics Characteristics of the HMSN Population

Among our population of 143 children with HMSN, 107 had a molecular diagnosis. CMT1A, CMT2A, CMT1B, and CMT1X, were the main subgroups representing 88% of genotyped HMSN. A family history was found in 70% of CMT1A patients, 55% of CMT1B patients, 33% of CMT1X patients, and 36% of CMT2A patients.

Electroneuromyographic Classification

ENMG data was available for analysis for 59 HMSN patients (55% of our cohort) and identified 28 patients with demyelinating NCV values, 20 with intermediate NCV values, seven with axonal NCV values, and four with non-excitable median nerve. The seven patients with axonal NCV values had a genotyped diagnosis of CMT2A (n = 5) and CMT2Z (n = 2). The 20 patients with intermediate NCV values, had a genotyped diagnosis of CMT1A (n = 12), CMT2A (n = 2), CMT4G (n = 2), CMT1X (n = 1), CMT1B (n = 1), CMT2B (n = 1) and CMT2N (n = 1). The CMT groups are reported according to the ENMG results in Fig. 1. The four patients with a non-excitable ENMG belonged to CMT2A (n = 2), CMT1A (n = 1), and CMT4F (n = 1) subgroups.

Patients who did not have an ENMG were distributed as follows: 37/69 CMT1A, 2/9 CMT1B, 3/4 CMT1X, 3/12 CMT2A, and 4/7 CMT4G. Usually when a relative had a diagnostic of HMSN, genetic analysis was performed first, and the ENMG was not systematically done. The characteristics of patients with genotype confirmed axonal and intermediate HSMNs are reported in Tables 2 and 3, respectively.

Clinical Characteristics by Subgroup

CMT1A

Among the 69 CMT1A, 33 had an ENMG: 20 with demyelinating finding, 12 with intermediate finding, and one with a non-excitable median nerve.

![Fig. 1](image-url) Distribution according to the electroneuromyographic classification of different CMT in our pediatric population. Demyelinating group defined on NCV under 25 m/s was mainly composed of CMT1A and CMT1B. Intermediate group defined on NCV between 25 and 45 m/s was mainly composed of CMT1A and various subgroups. Axonal group defined on NCV above 45 m/s was mainly composed of CMT2A.
The symptoms of patients with intermediate finding did not differ from the other CMT1A patients. Orthopaedic disorders such as flat feet were the most prevalent first signs of the disease. The diagnosis was generally reached at school age by testing the ability to walk on tip toes, by the observation of more frequent falls or orthopaedic signs in the sporadic form and earlier in life by observation of more subtle signs when there was a concomitant family history of HMSN. The functional impact was minor, in teenagers with initial pain and fatigue symptoms.

### Table 2: Electrophysiologic and genetics characteristics of patients with axonal electroneuromyographic finding (>45 m/s)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Fam vs. Spo</th>
<th>Age at onset (years)</th>
<th>Age at diag</th>
<th>NCVm/s</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>Familial</td>
<td>5</td>
<td>14</td>
<td>46.6</td>
<td>CMT2Z (MORC2): p.Arg252Trp</td>
</tr>
<tr>
<td>M</td>
<td>Familial</td>
<td>12</td>
<td>12</td>
<td>56</td>
<td>CMT2Z (MORC2): p.Arg252Trp</td>
</tr>
<tr>
<td>F</td>
<td>Familial</td>
<td>NA</td>
<td>NA</td>
<td>56.7</td>
<td>CMT2A (MFN2): p.Arg94Trp</td>
</tr>
<tr>
<td>F</td>
<td>Familial</td>
<td>4</td>
<td>5</td>
<td>60.5</td>
<td>CMT2A (MFN2): p.Lys390Arg</td>
</tr>
<tr>
<td>F</td>
<td>Sporadic</td>
<td>5.5</td>
<td>9</td>
<td>54.7</td>
<td>CMT2A (MFN2): p.Arg94Glyc</td>
</tr>
<tr>
<td>M</td>
<td>Sporadic</td>
<td>1.6</td>
<td>5</td>
<td>65.5</td>
<td>CMT2A (MFN2): p.Val244Met</td>
</tr>
<tr>
<td>M</td>
<td>Sporadic</td>
<td>1.7</td>
<td>5.5</td>
<td>48.3</td>
<td>CMT2A (MFN2): p.Arg104Trp</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; Fam, familial; M, male; NA, no data available; Spo, sporadic.
Note: CMT2A represents the majority of pediatric axonal forms. In our population a rare familial mutation of CMT2Z was found in two brothers of the same family. However, the two patients with a familial CMT2A did not belong to the same family.

### Table 3: Electrophysiologic and genetics characteristics of patients with intermediate electroneuromyographic finding (25-45 m/s)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Fam vs. Spo</th>
<th>Age at onset (years)</th>
<th>Age at diag</th>
<th>NCVm</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Familial</td>
<td>6</td>
<td>6</td>
<td>26</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>M</td>
<td>Familial</td>
<td>2.5</td>
<td>2.5</td>
<td>26</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>F</td>
<td>Sporadic</td>
<td>NA</td>
<td>NA</td>
<td>29</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>M</td>
<td>Familial</td>
<td>NA</td>
<td>8</td>
<td>29</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>M</td>
<td>Familial</td>
<td>4</td>
<td>7</td>
<td>31</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>M</td>
<td>Familial</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>F</td>
<td>Sporadic</td>
<td>3</td>
<td>8</td>
<td>32</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>M</td>
<td>Sporadic</td>
<td>8</td>
<td>9</td>
<td>34</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>F</td>
<td>Familial</td>
<td>10</td>
<td>10</td>
<td>36</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>F</td>
<td>Familial</td>
<td>5</td>
<td>6</td>
<td>39</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>M</td>
<td>Sporadic</td>
<td>NA</td>
<td>14</td>
<td>44</td>
<td>CMT1A (PMP22): dup</td>
</tr>
<tr>
<td>F</td>
<td>Sporadic</td>
<td>4</td>
<td>8</td>
<td>44</td>
<td>CMT2A (MFN2): p.Arg364Trp</td>
</tr>
<tr>
<td>M</td>
<td>Sporadic</td>
<td>3</td>
<td>3.5</td>
<td>44</td>
<td>CMT2A (MFN2): p.Val244Met</td>
</tr>
<tr>
<td>F</td>
<td>Familial</td>
<td>8</td>
<td>9</td>
<td>30</td>
<td>CMT4G (HK1): c.AltT2G &gt; C</td>
</tr>
<tr>
<td>F</td>
<td>Familial</td>
<td>10</td>
<td>12</td>
<td>33</td>
<td>CMT4G (HK1): c.AltT2G &gt; C</td>
</tr>
<tr>
<td>M</td>
<td>Familial</td>
<td>1.5</td>
<td>7</td>
<td>37</td>
<td>CMT1X: p.Ile93Val</td>
</tr>
<tr>
<td>M</td>
<td>Familial</td>
<td>1.5</td>
<td>2</td>
<td>26</td>
<td>CMT1B (PO): p.Asn131Tyr</td>
</tr>
<tr>
<td>M</td>
<td>Sporadic</td>
<td>1.1</td>
<td>12</td>
<td>36</td>
<td>CMT2N (AARS): p.thr385Ile</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; Fam, familial; M, male; NA, no data available; Spo, sporadic.
Note: CMT1A represents the majority of pediatric intermediate electroneuromyographic finding. This group of intermediate HSMNs is the most genetically heterogeneous. The two patients with CMT4G belong to the same family. Among CMT1A, only two patients belong to the same family.

**CMT2A**

Among the 12 CMT2A cases, nine had an ENMG. Five had axonal finding, two had intermediate finding, and two a non-excitable median nerve.

The five CMT2A subjects with axonal finding had a disease onset before the age of 10 years. On average, the family noticed the first signs of the pathology at around 3.7 years of age. The illness predominantly started with a steppage gait, swaying gait, or gait ataxia. The clinical examinations confirmed steppage gait and amyotrophy, falls and deformations.
of the feet, such as pes cavus and fatigue when walking. Sensory impairment revealed by pain and sensory ataxia was not unusual. Upper limbs were also involved, most symptoms were once again motor impairment, amytrophy and fatigue, and deformations of the hands. The two patients with the worst outcome were unable to walk autonomously by 10 years of age.

The two patients with intermediate finding did not differ from the other CMT2A children. They had a stable disease progression during childhood and they retained their ability to walk autonomously.

Clinical Characteristics of Rare Subgroups
Clinical characteristics of CMT1B, CMT1X, CMT2B, CMT2N, CMT2Z, and CMT4G patients were reported in the

- Supplementary Table 1 (available in the online version only).

Discussion
This study showed that in children when NCV is in intermediate range, CMT1A is the most frequent diagnosis and when it is in axonal range CMT2A is the most frequent diagnosis.

The distribution of HMSN subtypes differs in children compared to adults and children. In our population and that of Cornett et al., we find a higher frequency of CMT1A and CMT2A in children and fewer in CMT1X. This can be explained by the earlier age of onset in these first two subtypes. The main forms of HSMNs and related pathologies are CMT1A, CMT1B, CMT2A, and CMT1X. However, regional and ethnic variations exist and have to be taken into account.

Genetic and electroneuromyographic classifications are not completely overlapping. The CMT1A, typically representing demyelinating CMTs, present mostly demyelinating NCV values but can also have intermediate values with NCV up to 44 m/s in our study. Thus, the search for PMP22 (CMT1A) duplications, which is systematically performed before NGS, seems particularly important when NCV is below 45 m/s.

In our pediatric population, we used median nerve conduction velocity, a validated adult criterion, to differentiate the subgroups. However, conduction velocities increased during childhood, with mean values for the median motor nerve, from 25 m/s in newborns, to 47 m/s between 1 and 2 years, to reach adult values around 50 to 6 years (56 m/s). So, it is possible that we have misclassified because of an underestimation of conduction velocities in children who performed an ENMG before 5 years. For example, the two children with CMT2A classified in the intermediate group according to their NCV values (44 m/s) had an ENMG at 3 and 4 years. At this age, the mean median nerve NCV is 51 m/s (SD = 6), with pathological values below 39 m/s. So this patient had normal range NCV values for age. Age at the time of the ENMG and action potential values should be taken into account when interpreting ENMG results according to age-appropriate standards.

While the group of axonal NCV values is small (11% of HMSN in our population) with a predominance of CMT2A (71%), the group of intermediate NCV values is more important and heterogeneous, including half CMT1A, common subtypes of intermediate CMT by mutation in GJB1, DNM2 and AARS genes, and less common CMT1 or CMT2 subtypes. In a large North American and European cohort of 1,652 adult and pediatric patients, Fridman et al identified 237 patients with axonal HMSN (14%), 70 CMT2A (30%), 15 subgroups of axonal HMSN (CMT2C, D, F, K; 6%), 17 (7%) subgroups of HMSN (CMT1A, CMT1X, CMT1B), 135 without any detected mutations (57%). The frequency of the different subgroups varies according to geographical location, with, for example, a larger proportion of patients carrying the NEFL gene mutation than MNF2 in the Taiwans’ Lin et al cohort.

We used broad NCV limits for intermediate group that lead to the inclusion of patient who had axonal or demyelinated CMT syndromes. It led to a restricted definition of axonal form, including only NCVm above 45 m/s while other studies included patients with NCV above 38 m/s that could explain why our axonal group was smaller and excluded some CMT1A or CMT2B with NCV between 38 and 45 m/s. Restricting the limits of NCV values in intermediate group will allow to specify patients with typically intermediate CMT (with NCV between 35 and 40 m/s in our cohort) but will lead to the inclusion in axonal group of patients with demyelinated CMT1A.

Clinically, in our population, the signs of neuropathy seem more important in CMT2. In our axonal subgroup, there is a common symptomatology starting with a progressive motor impairment of the lower limbs, than a sensitive impairment. The deficit of upper limbs began later. CMT2As are distinguished by an earlier onset, a faster progression, and a functional repercussion (FDS score) which seems more important compared with other patients with axonal CMT. Functional impairment was further investigated by the CMTPed score in the Cornett et al study. They found in participants with CMT2A that grip strength, plantar flexion, and dorsi flexion of the ankle, longer than 6-minute jump test and walking distances get worse than other CMT patients.

The retrospective nature of this study resulted in a lack of ENMG data for 45% of the cohort but it was a reflect of what is performed in our clinical practice. The proportion of common HMSN subgroups with intermediate and axonal NCV values may thereby have been underestimated in our study by the low level of ENMG, particularly in the CMT1A and CMT1X groups. Many parents are apprehensive about accepting an ENMG for their child, because of the pain factor. This leads to suspend this examination in favor of first pursuing a search for familial mutations. However, current techniques allow ENMG to be performed in the best possible conditions, even in young children and ENMG results contribute significantly to the diagnosis.

Before NGS, ENMG played a major role to orient the clinician and the geneticist to one or more genes to be explored by SANGER sequencing. Today, NGS panel analysis which includes genes involved in demyelinating, intermediate and axonal HSMNs allows a clear improvement in the diagnosis and its lag time. Nevertheless, ENMG remains an examination of interest in HMSN. Firstly, because it allows to
perform the diagnosis of a sensory and motor neuropathy. In atypical cases, such as CMT1X involving a combination of central nervous sign, ENMG is particularly important to orient the diagnosis. Secondly, it may help the clinician to interpret variants of unknown significance as some subtypes have preferential ENMG forms. A better understanding of clinical, genetic, and electrophysiological features of rare HMSN subtypes is still important, particularly as such rare subtypes may have gone undiagnosed prior to the advent of NGS. Finally, as explained previously, in terms of function and prognostic, CMAP reflects clinical severity. So, ENMG evaluation must remain an element of the initial evaluation associated with the clinical picture.

Conclusion

CMT1A is the main CMT subgroup when demyelinating or intermediate NCV values are found and CMT2A is the main CMT subgroup for axonal NCV values. Taking intermediate NCV values with broad limits (25–45 m/s) leads to the inclusion of non-typically “intermediate” group of CMT such as CMT1A or CMT2A. We highlighted the broad spectrum of NCV in CMT1A, that reinforces the systematic search of a duplication of PMP22 gene when planning molecular diagnostics in a child with CMT. The NCV threshold of 45 m/s after 5 years old, used in our population seems to be interesting to unify the axonal group, that is the only in which searching of MFN2 mutation seems to be more profitable than a duplication of PMP22.

Moreover, gene panels used for HSMN testing are increasingly allowing us, to diagnose rare pathology subgroups. The characterization of the different electrophysiologic patterns remains important alongside NGS analyses because it contributes to the diagnosis and may sometimes help interpret the clinical significance of novel pathogenic gene variants.

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Conflict of Interest
None declared.

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Ethical Publication Statement
We declare that we have read the journal’s position relating to ethical publication issues and confirm that this report is consistent with those guidelines.

Author’s Contribution
E.B. wrote the first draft of the manuscript, tables, and figure. C.C., U.W.L., and F.R. followed patients included in this study. They all made critical amendments and essential feedback to this manuscript. C.M. and P.L. performed genetic analysis. R.J.-m. and P.C. performed and discussed electrophysiological analysis. P.C. made essential feedback to the manuscript. All authors have approved the final article.

References