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Severe Epilepsy and Movement Disorder May Be Early Symptoms of *TMEM106B*-Related Hypomyelinating Leukodystrophy

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Abstract

Objective

To report the clinical presentation of the first Italian child affected by hypomyelinating leukodystrophy (HLD) associated with the recurrent variant p.Asp252Asn in the *TMEM106B* gene.

Methods

The methods included clinical case description, neurophysiologic assessment, brain MRI, and whole-exome sequencing (WES).

Results

The child presented soon after birth with nystagmus and hyperkinetic movement disorder. Focal seizures appeared from 2 months of age and recurred at high frequency, despite several antiseizure medications, and focal epileptic status frequently required IV phenytoin. Control of seizures was achieved at the age of 8 months by the association of high doses of sodium blockers. Clinical picture worsened over time and was characterized by axial hypotonia, failure to thrive requiring gastrostomy, pyramidal sings, and severe secondary microcephaly. MRI performed at ages 2, 6, and 20 months showed diffuse supratentorial and subtentorial hypomyelination; multimodal evoked potentials showed increased latency. WES performed at 6 months of age identified the p.Asp252Asn de novo variant in the *TMEM106B* gene.

Discussion

Hyperkinetic movement disorders and seizures may be early symptoms of *TMEM106B*-HLD. Our observation, supported by video EEG recordings, emphasizes that seizures may be difficult to recognize from movement disorders and that epilepsy may be a severe and prominent symptom of the disease. *TMEM106B*-HLD should be considered in the genetic screening of infants with early-onset seizures and movement disorders.

MORE ONLINE

Video

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TMEM106B gene codifies for a transmembrane protein affecting lysosomal function (Video, links.lww.com/NXG/A538). Variants of this gene have been initially described as a disease risk modifier in frontotempolar lobar degeneration.[1] More recently, the recurrent *TMEM106B* variant c.754G>A (p.Asp252Asn) has been reported in association with a rare and mild form of hypomyelinating leukodystrophy (HLD)[2-5] in 7 patients. We described the first Italian case of *TMEM106B*-related HLD, whose clinical picture includes congenital nystagmus, hyperkinetic movement disorder, and severe early-onset epilepsy with intractable focal seizures. We provided a detailed characterization of the patient's phenotype, supported by video documentation, neuroimaging, and neurophysiologic data. This case description highlights that severe epilepsy and movement disorders may figure among the presenting symptoms of the disease and may dominate the course of disease at least in early infancy.

Case Report

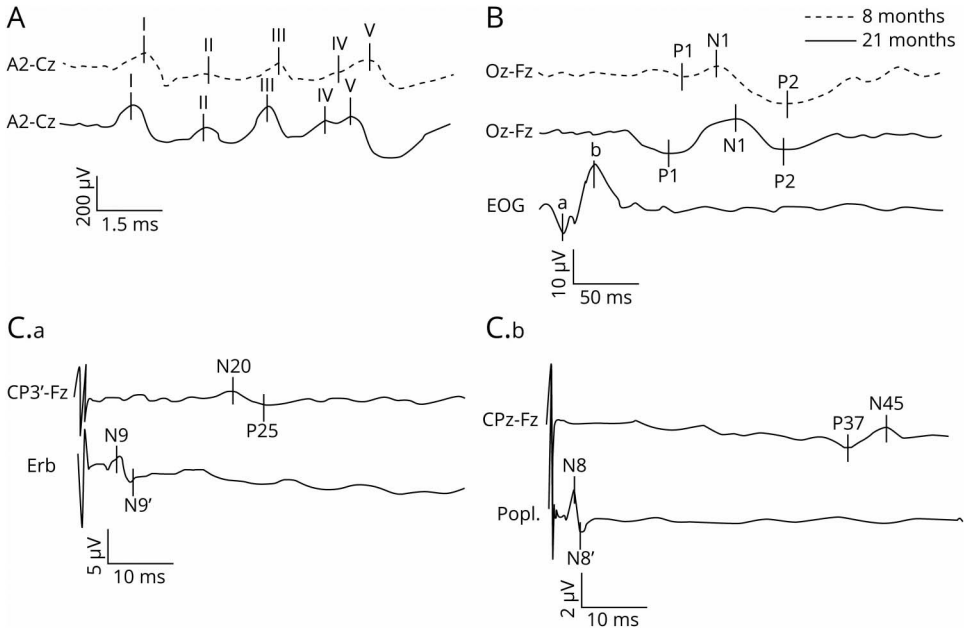
The child now aged 20 months is a female who presented soon after birth with continuous nystagmus of both eyes and a hyperkinetic movement disorder. From 2 months of age, the infant experienced brief paroxysmal events characterized by sudden opisthotonos, limb hypertonus, desperate crying, flushing, and labial cyanosis. The episodes rapidly increased until they occurred several times a day. Initial EEG recordings did not show obvious ictal change during the attacks, which were therefore misdiagnosed as dystonic.

The epileptic origin of these episodes was defined in the following weeks, when more clear focal signs associated (forced conjugate eye and head deviation and ipsilateral eyelid myoclonias) and the EEG showed ictal theta activity (video sequence). Epilepsy rapidly worsened: seizures recurred up to 50 episodes a day, despite several trials with antiseizure medications, and focal epileptic status frequently required IV phenytoin. Seizures control was achieved at 8 months, after the association of high doses of sodium blockers (phenytoin 12 mg/kg/d, carbamazepine 24 mg/kg/d, and lacosamide 7 mg/kg/d). At the age of 14 months a gastrostomy tube was placed for failure to thrive. At our last examination, at 20 months, the clinical picture was characterized by nystagmus, severe axial and limb hypotonia, poor motricity, brisk deep tendon reflexes, and ankle clonus. Speech was absent, despite a good communicative intent. Moreover, severe secondary microcephaly became evident.

EEG now shows sporadic epileptiform elements during sleep. Multimodal evoked potentials showed increased latency with a more severe impairment of visual and somatosensory responses both at ages 6 and 20 months (Figure 1). Diffuse supratentorial and subtentorial hypomyelination, which was suspected at the first MRI at the age of 2 months, was confirmed at ages 6 and 20 months (Figure 2).

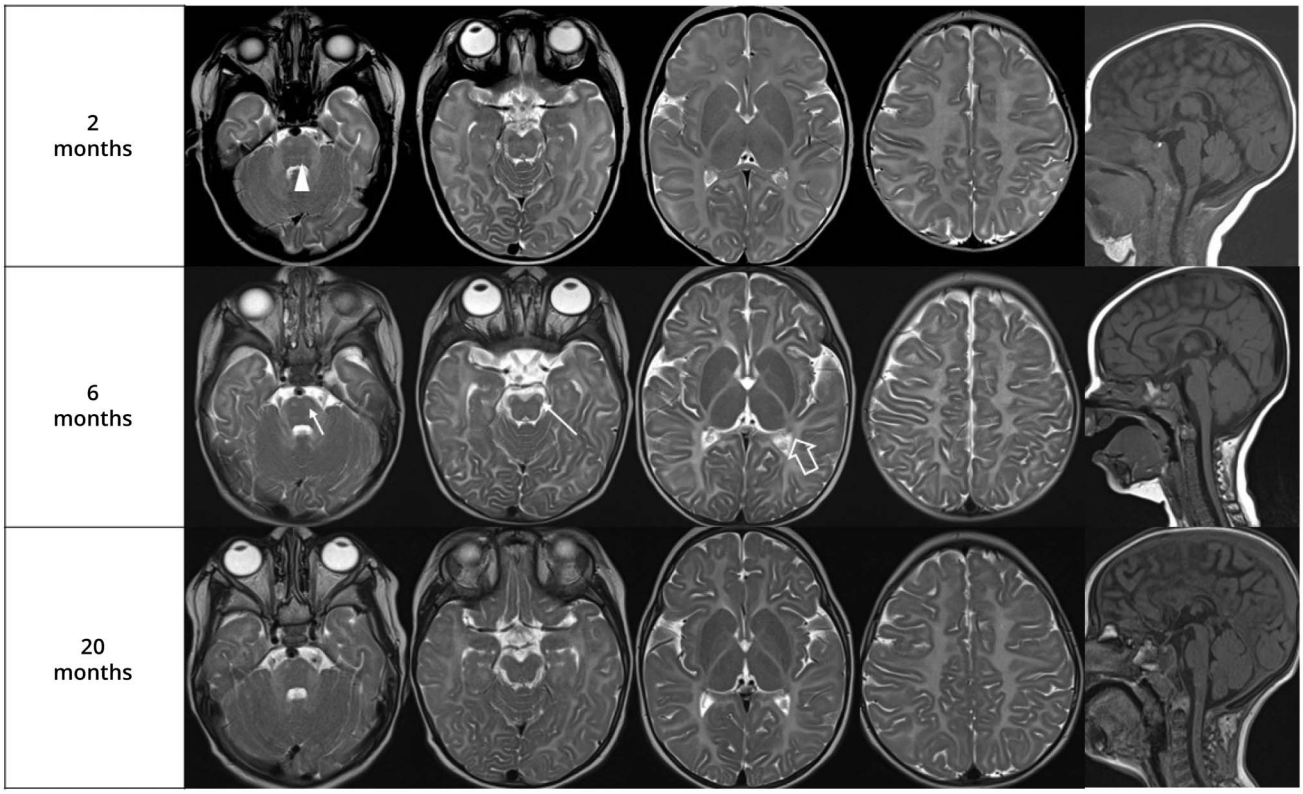
The diagnostic workup that included metabolic screening and arrayCGH was unrevealing. At the age of 6 months, genomic DNA was extracted from peripheral blood samples of proband and parents using standard procedures. The exonic regions and flanking splice junctions of the genome were captured using the

Figure 1 Brainstem Auditory Evoked Potentials, Flash Visual Evoked Potentials, and Somatosensory Evoked Potentials of the Upper and Lower Limbs



Brainstem auditory evoked potentials, flash visual evoked potentials, and somatosensory evoked potentials of the upper and lower limbs are shown in A, B, C.a, and C.b, respectively. All these data are elicited by the stimulation of the right ear, eye, median nerve, and tibial nerve. In each of them, the latency of the brainstem and cortical responses are increased, especially for the flash visual evoked potentials, whose P2 component peaked at 192 ms.

Figure 2 Axial T2w images and Sagittal T1w at the Midline



MRI shows diffuse hypomyelination with a slight hyperintense T2-signal throughout the white matter, stable at different ages. On sagittal images, corpus callosum is very thin. Basal ganglia are normal. Both supratentorial and infratentorial white matter are affected, note the involvement of cortico spinal tract (arrow), the medial lemniscus (arrow head), and the caudate tail (open arrow) well contrasted by adjacent hypomyelinated white matter.

Clinical Research Exome v.2 kit (Agilent Technologies, Santa Clara, CA). Sequencing was performed on a NextSeq500 Illumina system with 150 bp paired-end reads. Reads were aligned to human genome build GRCh37/UCSC hg19 and analyzed for sequence variants using a custom-developed analysis tool.[6] Additional sequencing technology and variant interpretation protocol have been previously described.[6] Coverage on target for the index was ≥10× for 98.4% with a mean coverage of 233×. Trio-WES analysis identified the de novo variant NM_018374.4: c.754G>A, p.Asp252Asn in the *TMEM106B* gene. No significant variants in other genes were detected.

Discussion

We reported the first Italian child affected by HLD associated with the recurrent mutation p.Asp252Asn in the *TMEM106B* gene.

The clinical picture in our patient was characterized, since the early months of life, by hyperkinetic movement disorder and focal seizures. Both early-onset MD and seizures have already been described in *TMEM106B*-HLD: episodes of choreoathetosis are described in one of the patients originally reported, and seizures responsive to first-line ASM are described in 2 of the 7 patients published so far.[2] In our case, movement disorder and seizures coexisted, and repeated video-EEG monitoring was required to correctly differentiate from each other. Moreover, the epilepsy course was extremely severe, it was characterized by prolonged focal seizures and focal status epilepticus, refractory to IV benzodiazepine, and required prolonged hospitalization. Our report underscores that early-onset severe epilepsy may be among the major symptoms of HLD. As already suggested in other rare forms of HLD (*ARV1* and *UFM1*-related HLD[7,8]), we think that *TMEM106B*-HLD should be included in the differential diagnosis of genetic early-onset encephalopathies with epilepsy.

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Disclosure

Relevant conflicts of interests/financial disclosures: nothing to report. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

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