Unusual Clinical and Magnetic Resonance Imaging Findings in a Family With Proteolipid Protein Gene Mutation

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Background: Pelizaeus-Merzbacher disease (PMD) and a complicated form of familial spastic paraparesis (spastic paraplegia 2 [SPG2]) are X-linked development disorders of myelin formation caused by a mutation in the proteolipid protein (PLP) gene. Spastic paraplegia 2 is allelic to PMD. The wide range of PLP mutations results in a corresponding large spectrum of clinical severity in PMD, with a continuum of signs and symptoms to SPG2.

Objective: To report the results of genetic, neurophysiologic, and neuroimaging investigations performed in a child affected by a mild ataxic and spastic form of PLP-related disorder and in his relatives.

Results: A missense mutation in exon 6 of the PLP gene (Q233P) was found in the proband and in the female obligate carriers. In the proband, evoked potentials were altered and remained unchanged during the 7 years of follow-up. Magnetic resonance imaging of the child demonstrated patchy hyperintensities of the paraventricular white matter, with microcystic components. These latter findings, along with pallidal calcium deposition, were also present in 2 females heterozygous for PLP mutation.

Conclusion: The unusual genetic, magnetic resonance imaging, and clinical findings of this family confirm the wide variability of PLP-related disorders.

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THE PROTEOLIPID protein (PLP) gene, which maps to the Xq22 region, encodes 2 different proteolipids: PLP, produced by mature oligodendrocytes, and its spliced isoform, DM20, produced earlier in myelin development. The PLP gene was first identified as the causative locus for Pelizaeus-Merzbacher disease (PMD), an X-linked disease characterized by an early and severe impairment of motor development due to a lack of central nervous system myelination. More recently, PLP mutations have also been associated with X-linked spastic paraplegia 2 (SPG2), which involves early-onset progressive gait difficulties. A recent study of a large sample of families with PMD and SPG2 has attempted to correlate the genotype with the phenotype of PLP-related disorders.

In this study, we report the results of an extensive genetic, neurophysiologic, magnetic resonance imaging (MRI), and MR proton spectroscopy (1H-MRS) investigations of a family affected by a mild form of a PLP-related disorder.

REPORT OF CASES

Subjects included a male proband from a Tuscan Italian family (IV-1, 11 years old), the mother (III-2, 35 years old), the maternal grandmother (II-2, 64 years old), a maternal aunt (III-4, 37 years old) and uncle (III-3, 40 years old), a female maternal cousin (III-7, 22 years old), and a male maternal cousin (III-8, 31 years old) (Figure 1).

Molecular analysis of the PLP gene was carried out according to methods previously described. Electromyography, motor and sensory nerve conduction velocities of the lower limbs, and somatosensory evoked potentials of the upper limbs were performed in the carrier members. The proband underwent electroencephalography, brainstem auditory evoked potentials, electroretinogram, and flash and pattern reversal visual evoked potentials in addition.
Brain magnetic resonance imaging and single voxel 1H-MRS of the parieto-occipital white matter were performed in a single session on a 1.5-T MR scanner, according to previously described procedures and to the control data available in our MR laboratory.4–6

The child (IV-1) was born after a normal-term pregnancy. Nystagmus was noticed in the first weeks of life but decreased in intensity and disappeared at 1 year. Poor postural control due to generalized hypotonia was present during the first year, with only a mild delay in motor development: he could sit up unaided at age 10 months, stand at 12 months, and at 18 months, he was walking independently. By age 18 months, he developed mild spasticity of the lower limbs and mild ataxic symptoms that remained stable over time. At age 3 years, he could speak in sentences. Presently, the child (11 years old) has a fine tremor in his upper limbs, ataxia, and mild distal spasticity. His cognitive development is normal.

No clinical symptoms were observed in the other investigated subjects. The family includes a maternal male cousin (III-6) with SPG, with an uneventful prenatal and perinatal medical history, who refused to take part in investigations.

Proteolipid protein analysis of the proband’s DNA revealed a point mutation in exon 6 (CAA-CCA), resulting in a glutamine (Q) to proline (P) substitution of PLP/DM20 amino acid 233, as already described.3 The same mutation was found in 4 female obligate carriers in the same family as the male proband, whereas no abnormalities were found in the 2 healthy males.

Motor and sensory nerve conduction velocities and electromyograph results were normal in all subjects. Brainstem auditory evoked potentials of the proband showed normal wave I, increased latency of waves II and III (>3 SD), and absent IV and V components despite normal hearing acuity. Flash and pattern reversal visual evoked potentials could record either no identifiable response or a severe latency of the major components (P100 latency >3 SD, bilaterally). Somatosensory evoked potentials showed normal Erb point and cervical potentials and significant delay of scalp components (N20 latency >3 SD, N13-N20 central conduction time >3 SD, bilaterally). Electroencephalograph and electroretinogram results were normal. These electrophysiologic features, repeated every 2 years, remained stable during the 7 years of follow-up. The female carriers who were analyzed had normal somatosensory evoked potentials, except for the maternal cousin (III-7), who showed an absence of N20 components.

Magnetic resonance imaging of the proband at age 3 years demonstrated a patchy hyperintensity on T2-
weighted images of the paraventricular white matter, containing rare microcystic components filled with fluid similar to cerebrospinal fluid (Figure 2A). These features remained unchanged in 2 follow-up scans at the age of 6 and 8 years, while in the last examination at age 11 years, signal abnormalities were sharper and smaller, with no sign of brain atrophy (Figure 2B). A brain MRI of the mother (III-2), performed at age 35 years, revealed a microcystic lesion in the left lentiform nucleus and calcium deposits in both pallidal nuclei (Figure 3A), confirmed by a computed tomographic scan (Figure 3B). The same MRI abnormalities were found in the 64-year old grandmother (II-2) (Figure 3C). In addition, she showed shaded paraventricular white matter hyperintensity, some of which contained microcysts (Figure 3D). Magnetic resonance images of other family members, including 2 other female carriers analyzed at age 37 and 22 years, respectively, and 2 normal males, were normal. Magnetic resonance proton
Proteolipid protein–related disorders are inborn errors of myelin formation with a wide clinical and pathologic spectrum. Pelizaeus-Merzbacher disease is characterized by early motor impairment, possibly related to the apoptosis of maturing oligodendrocytes, whereas the SPG2 phenotype, characterized by progressive walking impairment, results from abnormal myelin compaction without oligodendrocyte death. As more PLP mutations are discovered, the nosology of PLP-related disorders is changing, and a clinical continuum is hypothesized, from the most severe forms of PMD to the mildest SPG2.

Our proband, with a missense mutation in a non-conserved amino acid of the DM20 protein, expressed a mild form of PLP-related disease with predominant tremor and atactic symptoms of the upper limbs that improved progressively during the 7 years of follow-up, similar to a family recently reported with a PLP mutation in exon 3B.

The neurophysiologic results are in agreement with previously published data on PMD; in particular, they confirm the diagnostic value of brainstem auditory evoked potentials, which typically show abnormal waves II to V in contrast with the normal wave I latency and the normal latencies of the cortical evoked potential found in the carriers.

Magnetic resonance imaging is preferred for assessing central nervous system myelin formation and breakdown in leukodystrophies. In patients with PMD, it shows diffuse white matter signal abnormalities—hypersignal on T2 contrasting with normal or isosignal on T1—that reflect the underlying hypomyelinating process. According to MRI criteria, PMD is usually classified into 3 main subtypes8 that seem to be independent of clinical severity. Very mild white matter signal abnormalities or even normal MRI results have been reported in some cases of phenotypic SPG2.9 In addition to typical findings, the MRI of the proband and of the mother and grandmother carriers showed white matter and basal ganglia abnormalities, findings not previously reported in patients with a PLP mutation. The images suggest a vacuolization process within the abnormal white matter.

These atypical brain MRI findings may not be specific for the disease caused by Q233P mutation. Animal models of SPG2, such as rumpshaker and PLP knock-out mice, have demonstrated abnormalities in myelin compaction associated with progressive axonal swelling.10 In our family, additional factors could result in focal disruption of the myelin sheath and basal ganglia involvement. Cystic changes of the white matter have been described in diffuse and severe demyelinating leukodystrophies, such as Alexander disease, megalencephaly with leukodystrophy and cysts, cerebellar ataxia with cerebral hypomyelination syndrome, or vanishing white matter disease.2 Basal ganglia involvement has been observed with white matter change in Alexander disease, Canavan disease, Krabbe disease, L-2-OH glutaric aciduria, and GM1 gangliosidosis.2 Patchy white matter changes with focal microcystic lesions involving basal ganglia, with calcifications, are usually found in energy metabolism dysfunction, such as mitochondrial disorders. Dysfunction of respiratory chain metabolism was described in a patient with PMD with a PLP duplication.11 However, the clinical findings and normal lactate concentrations on brain 1H-MRS were not in favor of such a pathologic process in our cases.

The absence of axonal degradation on clinical and MRI examination of the affected male, the absence of clinical signs in a female carrier of an advanced age, and the absence of N-acetylaspartate change on 1H-MRS suggest that the particular MRI signs in our cases do not indicate the high severity of axonal degeneration that is typical of PLP disorders.12 The signs we observed could be the results of the PLP/DM20 mutated proteins13 in association with other genetically determined factors, such as adhesion molecules, or those involved in energy metabolism or astrocyte functions. Further descriptions of patients with PLP carrying the Q233P mutation are needed to confirm the specificity of MRI changes. The unusual genetic, MRI, and clinical findings of our family confirm the wide variability of PLP-related disorders.

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