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Clinical Letter

Confirmation of Atypical Presentation With Nonprogressive Leukodystrophy in eIF2B-Related Disorders

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Mutations in the *EIF2B1–5* genes encoding the subunits of the ubiquitously expressed eukaryotic initiation factor 2B (EIF2B)[1] have been reported in a group of clinically heterogeneous autosomal recessive multisystem diseases, frequently including leukodystrophy, termed EIF2B-related disorders.[2] Childhood ataxia with central hypomyelination and vanishing white matter disease were first described in the 1990s.[3,4] Onset is most often in childhood, but vanishing white matter disease may also start at adulthood.[5,6] Classically, neurological signs are predominant, dominated by cerebellar ataxia and spasticity with a chronic progressive course and additional episodes of rapid deterioration after minor head trauma and febrile infections that may lead to coma.[7] Brain magnetic resonance imaging (MRI) shows abnormal hyper-T2 signal of all or almost all cerebral white matter. Progressively, there is a rarefaction and cystic degeneration of the affected white matter, which is replaced by cerebrospinal fluid.[4,7] Later, initial symptoms such as psychiatric manifestations or primary ovarian failure were also described, as well as oligohydramnios, intrauterine growth retardation, cataracts, pancreatitis, hepatosplenomegaly, and hypoplastic kidneys.[2,5]

Recently, Lee et al. described a family with an original multisystem phenotype including vanishing white matter disease related to compound heterozygous mutations in *EIF2B2*.[8] The index case had a history of hepatomegaly, bilateral congenital cataract, and delayed development with ataxia. Brain MRI showed nonprogressive diffuse atrophy and leukoencephalopathy without cystic degeneration at age seven years. Her older sister developed febrile status epilepticus around age 12 months and exhibited ataxia and spasticity until age five years. She had intellectual deficiency, bilateral cataracts, and primary amenorrhea. Brain MRI at age 21 years showed diffuse atrophy and overall stable bilaterally symmetric T2 high signal in the cerebral deep white matter (Fig).

Here, we describe a 26-year-old Caucasian man born after uneventful pregnancy and delivery. Family history was negative for neurological disease or other conditions. He was the third child of healthy nonconsanguineous parents. His birth weight was 3.8 kg and his height was 52 cm. Developmental milestones were initially normal: he sat at six months and walked alone at 18 months. From age 18 months, ataxia and spasticity were noted. Although early

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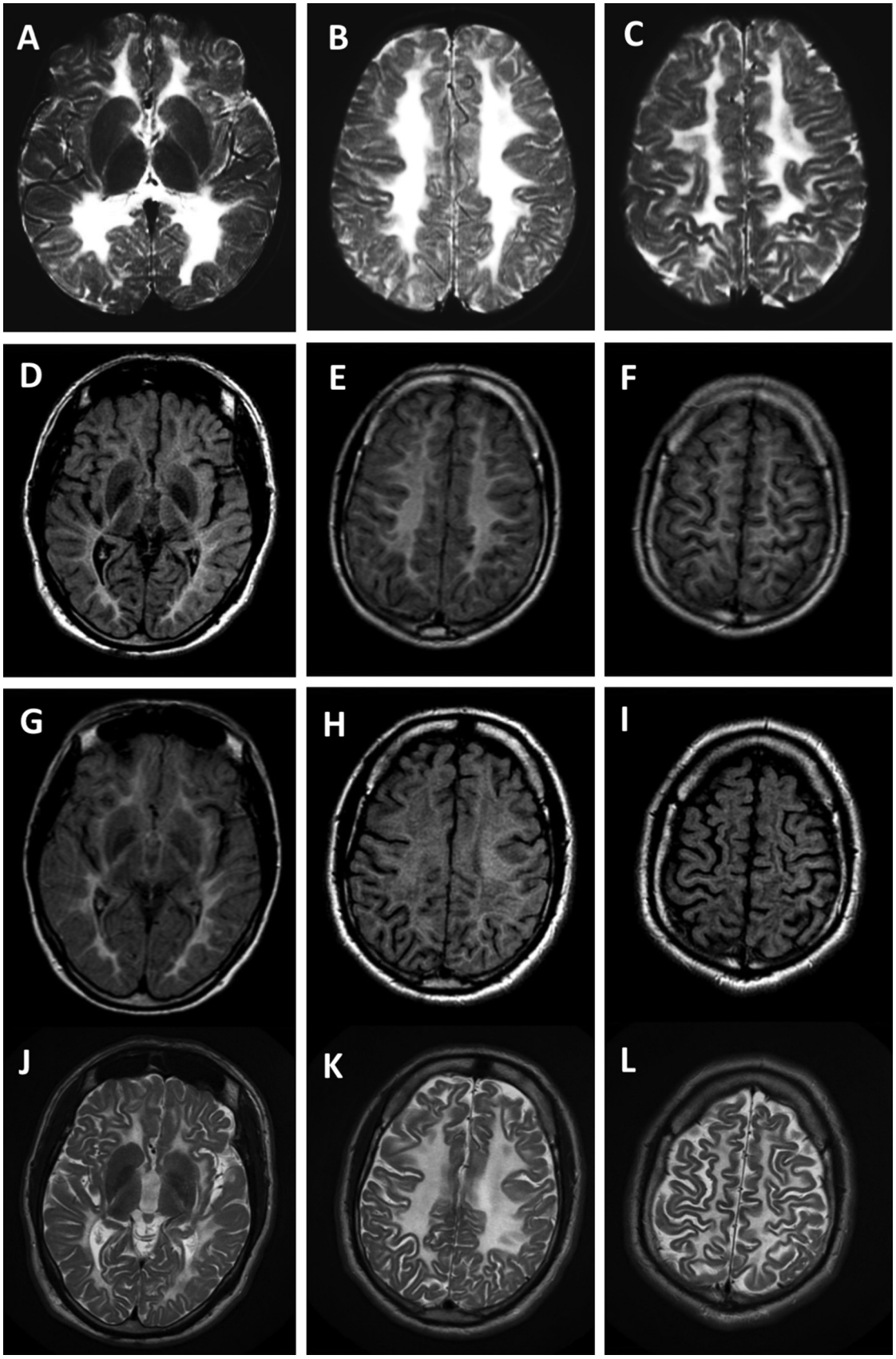

FIGURE. Brain magnetic resonance imaging of the proband at age three years (A–C), 19 years (D–F), and 26 years (G–L). Axial T2 images (A–C and J–L) and axial fluid-attenuated inversion recovery images (D–I) showed diffuse hypersignal of the cerebral white matter with diffuse cerebral atrophy but without progression or cystic changes.

development of language was considered normal during childhood, he never learnt to write and read. He progressively needed support for walking and used a walker since age four years. At age six years, he required a wheelchair. His progression was extremely slow with minimal clinical worsening. At age 26, examination showed mild cerebellar ataxia with nystagmus, dysmetria, and saccadic ocular pursuit. He had pyramidal signs in the four limbs with severe spasticity, brisk tendon reflexes, and left Hoffmann's reflexes. He had occasional seizures at age four, 18, and 26 years efficiently treated with levetiracetam. Bilateral cataract was noted at age 16 years, corrected by surgery at age 24 years. Routine hematology and chemistry assessments were normal. Extensive searches for metabolic abnormalities including urine gas chromatography and mass spectrometry, very-long-chain fatty acid dosage, dosage of lysosomal enzymes activities, and dosage of urine mucopolysaccharides, oligosaccharides, and glycosphingolipids were negative.

Brain MRI performed at ages three, 19, and 26 years showed diffuse hyper-T2 signal of the cerebral white matter affecting corpus callosum and U-fibers as well as diffuse cerebral atrophy. There was no progression and no cystic degeneration. Genetic analysis using targeted next-generation sequencing of 131 genes implicated in common leukodystrophies and early-onset hereditary spastic paraplegias led to identify previously described compound heterozygous mutations: c.547C>t, p.Arg183* and c.638A>C, p.Glu213Gly in *EIF2B2* (NM_014239.3).[9,10] Genetic analysis of parents confirmed biallelic segregation consistent with autosomal recessive inheritance.

Our observation confirms the large clinical spectrum of eIf2B disorders including early-onset cataract and apparently nonprogressive leukodystrophy without the classical evolution to cystic degeneration. Moreover, our patient displayed extremely slow worsening of his neurological troubles, which is particularly infrequent in such disorders.

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