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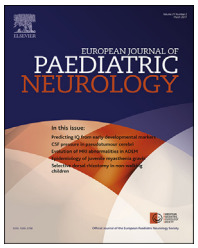

Case study

eIF2B-related multisystem disorder in two sisters with atypical presentations

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ABSTRACT

Background: Vanishing white matter disease (VWM) is a chronic progressive leukoencephalopathy that is characterized by cerebellar ataxia and spasticity, together with cystic degeneration of the cerebral white matter as evidenced by brain magnetic resonance imaging (MRI). Here, we report two sisters with *EIF2B2* variants, who presented with delayed development and failure to thrive before 1 year of age, developed cataracts, and showed diffuse leukoencephalopathy.

Case presentation: The index case had a history of hepatomegaly and intermittent vomiting after upper respiratory infection at 11 months of age. Her older brothers had died at an early age, one with similar symptoms and the other because of septic shock. Her older sister had similar presenting symptoms; she later suffered from both cataracts and primary amenorrhea, but showed neurological improvement. Her follow-up MRIs (at 21 years of age) revealed progressive diffuse brain atrophy with leukoencephalopathy, without cystic rarefaction. Whole-exome sequencing of the index case revealed the presence of the compound heterozygous variants, Val85Glu and Met226Lys in *EIF2B2*. The affected sister had the same compound heterozygous variants, and their unaffected parents were heterozygous carriers of each variant.

Conclusions: This study expanded the clinical and genetic spectrum of VWM with *EIF2B2* variants. It would be better to consider VWM as an eIF2B-related multisystem disorder, not just as a neurological disorder, on the basis that this is a family of housekeeping genes that affect multiple organs.

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1. Introduction

Vanishing white matter disease (VWM, OMIM #603896) is one of the most common inherited leukoencephalopathies in childhood and should be considered in cases showing progressive cystic degeneration of the cerebral white matter on brain magnetic resonance imaging (MRI).[1,2] The disease typically presents with ataxia and spasticity in early childhood (2–5 years of age) and shows progressive deterioration, with episodes aggravated by febrile illness or minor head trauma.[1,2] Mutations in five genes, *EIF2B1-5*, are associated with VWM. These genes encode the five subunits of eukaryotic translation initiating factor 2B (eIF2B), which is a guanine nucleotide-exchange factor (GEF); it catalyzes the exchange of GDP for GTP, bound to another initiation factor, eIF2. With this, eIF2B is indispensable for protein synthesis and its regulation.[3,4] As eIF2B is a house keeping factor, essential for all cells of the body, it is unclear why oligodendrocytes and astrocytes in the nervous system are almost exclusively vulnerable to reduced eIF2B activity.[4]

The characteristic neuroimaging features of VWM are very important clues. MRI criteria are usually helpful for the diagnosis of typical VWM.[2] However, the lack of specific neuroimaging findings, such as cystic rarefaction, or the presence of atypical presentations can be a diagnostic challenge for clinicians.[5,6]

Here, we report two sisters with VWM who presented with delayed development, hepatosplenomegaly, and failure to thrive with microcephaly before 1 year of age. They developed cataracts and showed diffuse leukoencephalopathy without cystic degeneration on the initial and follow-up brain MRI. We missed the diagnosis of VWM for several years because of their atypical clinical presentations and less specific neuroradiological findings. Using whole-exome sequencing (WES), we put an end to our diagnostic odyssey, as we figured out that the sisters had VWM associated with *EIF2B2* variants.

2. Case study

A 31-month-old girl (II-4, Fig. 1) was referred to the Neurology Department for developmental delay. She was born at 38 weeks of gestation by cesarean section and weighed 2.18 kg. She was the fourth baby of nonconsanguineous Korean parents. The older brother of the proband (II-2), who had hepatosplenomegaly and seizures at the age of 1 year, died at the age of 3 years. Another older brother of the proband (II-3) suffered and died from septic shock at the age of 50 days. She failed to thrive from 4 months of age. Hepatomegaly with intermittent vomiting was noted at the age of 11 months, which developed after upper respiratory infection. On admission to the Gastroenterology Department at the age of 12 months, her weight, height, and head circumference were 5.1 kg (<3rd percentile), 62 cm (<3rd percentile), and 38 cm (<3rd percentile), respectively. The liver was palpated with 4.5 finger breadth below the right costal margin and the level of aspartate transaminase (AST) and alanine transaminase (ALT) was 64 and 34 IU/L (normal, 0–40 IU/L), respectively. Her serum creatine kinase and lactate levels were 36 IU/L (normal, 20–270 IU/L) and 3.9 mmol/L (normal, 0.7–2.5 mmol/L), respectively. At that time, she could roll over, sit alone, and stand with assistance, although she did not crawl. A liver biopsy showed marked macrovesicular fatty changes with fibrosis. Brain MRI performed at the age of 12 months showed diffuse brain atrophy with diffuse high-signal changes in the bilateral globus pallidus, internal capsule, and white matter (Fig. 2A–D). Bilateral cataracts were noted at the age of 30 months, which were surgically corrected thereafter. When she came to our department, at the age of 31 months, she could walk with assistance, but her expressive and receptive language was poor. Neither ataxia nor spasticity was noted. A neurological examination found no remarkable abnormalities. Comprehensive tests, including a metabolic work-up, failed to identify an etiology. At the time of this report, she is 7 years old and the hepatomegaly has resolved itself. There was only one attack of afebrile seizure, which did not aggravate her symptoms. She still has microcephaly and growth retardation. She can walk without assistance, but ataxia is noted. She cannot make two-word sentences, but speaks many single words. Follow-up MRI performed at the age of 32 months and at 7 years showed diffuse atrophy and leukoencephalopathy, without cystic degeneration (Fig. 2E–H).

The older sister of the proband (II-1, Fig. 1) was born at 39 weeks of gestation by cesarean section because of cephalopelvic disproportion, and weighed 2.6 kg. She controlled her head at 4 months of age, but could roll over only at 12 months of age. She developed febrile status epilepticus around 12 months of age; thereafter, spasticity with dystonia was noted. She could walk independently and speak meaningful words at 4 years of age. She did not have afebrile seizures, but febrile seizures sometimes occurred until 5 years of age. Bilateral cataracts were noted and corrected at the age of 15 years. At the age of 16 years, she was referred to our department together with her younger sister, the index case (II-4, Fig. 1). She had microcephaly and mental retardation. Ataxia was prominently observed. Brain MRI showed diffuse cerebral atrophy and bilaterally symmetric T2 high-signal changes in the cerebral deep white matter, which spared the subcortical white matter and internal capsule relatively. She is currently 21 years of age and the ataxia and spasticity have resolved themselves. She speaks two-word sentences and obeys simple orders. Her weight, height, and head circumference are 38.5 kg (<3rd percentile), 144.4 cm (<3rd percentile), and 48 cm (<3rd percentile), respectively. She has suffered from primary amenorrhea. Hormone tests showed a high basal gonadotropin level (FSH at 124.32 mIU/mL and LH at 44.21 mIU/mL) with low estrogen (<10 pg/mL) levels. Her bone age was 132 months, indicating delayed skeletal maturation. Pelvic sonography showed a small tubular prepubertal-shaped uterus and small-sized, barely detectable ovaries. A follow-up brain MRI performed at the age of 21 years showed diffuse brain atrophy without significant change in the bilateral symmetric white matter abnormality (Fig. 2I–L).

Blood samples were obtained from the two patients (II-1 and II-4) and their unaffected parents, who provided informed consent. We performed WES in the proband (II-4), followed by the validation of genetic variants using Sanger sequencing (see Supplementary methodology and Supplementary Tables 1 and 2). WES revealed the presence of the compound