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► **To cite this version:**

Clémence Scappaticci, Julien Van-Gils, Simon Samaan, Pierre Bessou, Didier Lacombe, et al.. Confirmation of Atypical Presentation With Nonprogressive Leukodystrophy in eIF2B-Related Disorders. *Pediatric Neurology*, 2019, 100, pp.97 - 99. <10.1016/j.pediatrneurol.2019.02.005>. <hal-03488853>

HAL Id: hal-03488853

<https://hal.science/hal-03488853v1>

Submitted on 20 Jul 2022

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Confirmation of atypical presentation with non-progressive 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 (CACH) and Vanishing White matter Disease (VWH) were first described in the nineties.^{3,4} Onset is most often in childhood but VWH 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 MRI shows abnormal hyper-T2 signal of all or almost all cerebral white matter. Progressively, there is a rarefaction and a cystic degeneration of the affected white matter, which is replaced by CSF.^{4,7} Later, initial symptoms as psychiatric manifestations or primary ovarian failure were also described, as well as oligohydramnios, intrauterine growth retardation, cataracts, pancreatitis, hepatosplenomegaly and hypoplastic kidneys.^{2,52} Very recently, Lee et al, described in this journal an interesting family displaying an original multisystem phenotype including VWH 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 non progressive diffuse atrophy and leukoencephalopathy without cystic degeneration at 7 years of age. Her older sister developed febrile status epilepticus around 12 months of age until 5 years of age with ataxia and spasticity noted at the examination which are currently resolved at 21 years of age. She had intellectual deficiency, bilateral cataract and primary amenorrhea. Brain MRI showed diffuse atrophy and overall stable bilaterally symmetric T2 high-signal in the cerebral deep white matter.

Here, we report a Caucasian 26-year-old boy born after uneventful pregnancy and delivery. Family history was negative for neurological disease or other condition. He was the third child of healthy non-consanguineous parents. At birth, weight was 3.8kg and height 52cm. Developmental milestones were initially normal: he sat at 6 months, and walked alone at 18 months. From the age of 18 months, ataxia and spasticity were noted. Although early 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 4 years. At age 6, a wheelchair was required. The 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 of 4, 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 included 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 age 3, 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 elf2B-disorders including early-onset cataract and apparently non-progressive 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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LEGENDS

Fig. 1 – Brain MRI of the proband at age 3 yrs (A-C), 19 yrs (D-F) and 26 yrs (G-L). Axial T2 images (A-C and J-L) and axial FLAIR images (D-I) showed diffuse hyper signal of the cerebral white matter with diffuse cerebral atrophy but without progression or cystic changes.

