Adult-Onset Vanishing White Matter Disease Due to a Novel EIF2B3 Mutation

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Objective: To report a novel mutation in the gene EIF2B3 responsible for a late-onset form of vanishing white matter disease.

Design: Case report.

Setting: University teaching hospital.

Patient: A 29-year-old pregnant woman with a history of premature ovarian failure and hemiplegic migraines presented with a 10-week history of progressive confusion and headaches. Magnetic resonance imaging of the brain revealed a diffuse leukoencephalopathy.

Results: Sequencing of the exons and intron boundaries of EIF2B3 uncovered 2 missense mutations: c.260C>T (p.Ala87Val) and c.272G>A (p.Arg91His). To our knowledge, the latter missense mutation has never been previously reported.

Conclusion: This is the second report of adult-onset vanishing white matter disease due to mutations in EIF2B3 and the first report of the c.272G>A (p.Arg91His) missense mutation.


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OBSERVATION

Vanishing white matter disease (VWM; OMIM 603896),\(^1\) also called childhood ataxia with central hypomyelination, is one of the most common leukodystrophies.\(^2\) It is an autosomal recessive leukoencephalopathy with typical onset in the pediatric age group. It is estimated that adulthood-onset VWM represents 15% of cases.\(^3\) The classic phenotype is characterized by an onset between the first and fifth years of life, with prominent cerebellar ataxia and spasticity. The disease is typically slowly progressive with episodes of neurological deterioration classically triggered by stressful events (eg, fever, infections, mild head trauma, or even fright).\(^1,4\) The evolution of the disease is highly variable, from patients dying within 1 to 5 years of disease onset to a much slower progression.\(^5\)

Patients with the adult-onset form of the disorder typically have a milder and more insidious clinical course characterized by behavioral changes, dementia, and seizures.\(^6,7\) A few cases have presented with complicated migraines.\(^8,9\) The typical stress-related acute neurological deteriorations are less frequent in adult-onset cases.\(^3\) Ovarian failure is frequently reported in women with VWM and can precede the neurological symptoms,\(^10,11\) leading to the name ovarioleukodystrophy.\(^10,12\) Interestingly, gene mutations in EIF2B1, EIF2B2, EIF2B3, EIF2B4, and EIF2B5 are extremely rare among subjects with premature ovarian failure.\(^13\)

Neuroradiological findings of VWM are specific.\(^1,14\) Brain magnetic resonance imaging typically shows diffuse and symmetric white matter hyperintensities on T2-weighted imaging, with possible sparing of the U fibers, the outer rim of the corpus callosum, the anterior commissure, and the internal capsule.\(^15\) The cerebral white matter typically progresses to cystic degeneration and rarefaction, best visualized in fluid-attenuated inversion recovery or proton density sequences.\(^1\) The cerebellar and brainstem white matter can be affected as well, but no cystic degeneration has been reported.\(^16\) Magnetic resonance spectroscopy may show a global reduction of all metabolites.\(^16,17\)

Mutations in any of the 5 genes encoding the eukaryotic translation initiation factor 2B (EIF2B1, EIF2B2, EIF2B3, EIF2B4, and EIF2B5) are responsible for the disease.\(^18,19\) Patients usually have a compound heterozygous status.\(^20\) Mutations in EIF2B3 are the most common, accounting for approximately 60% to 70% of all cases of VWM.\(^19,20\) The Arg113His mutation in EIF2B3 presented in this report has not been described previously.
mutation is the most frequent and is usually associated with the adult-onset form.21

Figure 1. Axial fluid-attenuated inversion recovery magnetic resonance images. A, Symmetric involvement is noted at the level of the cerebellar white matter. B, Diffuse and symmetric leukodystrophy is evident: the U fibers, the outer rim of the corpus callosum, and the internal capsule are relatively spared. Small areas of cystic degeneration (arrow) are noted bilaterally in the periventricular white matter. The typical widespread white matter rarefaction is lacking. C, Diffuse and symmetric white matter involvement is noted at the level of the centrum semiovale.

Figure 2. Sagittal T1-weighted magnetic resonance image shows the diffuse and homogeneous white matter hypointense signal in the deep cerebral white matter, relatively sparing the U fibers (arrow).

We report an atypical case of adult-onset VWM carrying a novel mutation in EIF2B3 (GenBank NM_020365.2).

REPORT OF A CASE

This patient was first seen by our neurogenetics team at age 29 years for an acute episode of migraine, fever, and encephalopathy. She had been pregnant for 10 weeks at the time and had constant headache with intermittent left hemibody paresthesias, aphasia, nausea, and vomiting since the beginning of her pregnancy. The patient was the second daughter of nonconsanguineous French Canadian parents. The family history was unremarkable. Her medical history was significant for hemiplegic migraines since age 20 years as well as secondary amenorrhea and premature ovarian failure. Magnetic resonance imaging of the brain performed at age 21 years revealed a diffuse leukoencephalopathy; magnetic resonance spectroscopy showed a reduction of all metabolites. The investigations performed at the time did not uncover the cause of her leukoencephalopathy. On arrival to the emergency department, the degree of her encephalopathy limited the neurological examination. Laboratory investigations failed to show any abnormality except mild leukocytosis. Electroencephalography revealed a slow background without epileptic abnormality. During the course of her admission, the patient's encephalopathy subsided and, as she became more collaborative, mild cerebellar signs were noted. In the following month, she gradually improved but did not recover completely; she remained with impaired cognitive status and behavioral disturbances. Magnetic resonance imaging of the brain confirmed the known diffuse and symmetric cerebral and cerebellar white matter abnormalities, with hyperintense signal on T2-weighted images (Figure 1) and hypointense signal on T1-weighted images (Figure 2). Small cystic areas were seen bilaterally at the frontal horns on a fluid-attenuated inversion recovery sequence (Figure 1B). Otherwise, there was no evidence of white matter rarefaction or cystic degeneration.

On the basis of the clinical features, the history of ovarian failure, and the magnetic resonance imaging pattern, adult-onset VWM was suspected. Genetic testing for the 5 EIF2B genes was performed (PreventionGenetics) and uncovered 2 mutations in EIF2B3: c.260C>T (p.Ala87Val) and c.272G>A (p.Arg91His) (Figure 3). To our knowledge, the second mutation in exon 3 has never been reported but is thought to be pathogenic because it leads to an amino acid substitution (p.Arg91His).
in a highly conserved region across species and is predicted to be probably damaging by the experimental program Polymorphism Phenotyping version 2.22

**COMMENT**

This is the second report of adult-onset VWM with mutations in EIF2B3.23 Mutations in EIF2B3 are thought to account for approximately 4% to 7% of all VWM cases.20,24 We report a novel missense mutation in this gene in an adult-onset case. Wu et al25 reported that mutations in EIF2B3 account for 20% of the Chinese pediatric cases, raising the hypothesis that mutations in this gene may be more prevalent than previously thought, particularly in the Chinese population, although this was a small patient sample. Moreover, they identified 2 novel missense mutations in the gene: c.140G>A in exon 2 and c.1037T>C in exon 9, the latter being a common mutation present in 4 of 5 patients. Until recently, mutations in EIF2B3 have never been reported in patients with adult-onset VMW or ovarioleukodystrophy.10,11,18 A recent article26 reports a new homozygous mutation (c.80T>A) in EIF2B3 resulting in the substitution of leucine by glutamine (p.Leu27Gln) in an adult-onset case of VWM and ovarian failure. Our case is thus the second report of late-onset VWM and ovarian failure due to mutations in EIF2B3.

Some clinical features in our patient are of particular interest. The hemiplegic migraine as the presenting neurological sign has been rarely reported in VWM.8,9 In a case of pediatric-onset VWM reported by Ramaswamy et al8 in 2006, episodes of periodic hemiparesis and headache were described in the course of the disease. Ramaswamy and colleagues discussed the fact that the episodes of hemiplegia and headaches could fulfill the criteria for hemiplegic migraines. They emphasized that in both conditions, the episodes can be triggered by stressful events.8 This was also observed in our patient; in fact, the patient, who has had hemiplegic migraines for years, experienced an exacerbation of her migraines culminating in an encephalopathy in the context of her acute febrile disease and pregnancy. The known correlation between the age at onset of the neurological deterioration and the severity of ovarian failure was observed in our case; despite the previous diagnosis of early menopause, the patient became pregnant unexpectedly without any hormone replacement therapy or in vitro fertilization. This event can be explained only by considering residual ovarian functionality.

The trigger event for the rapid deterioration in our patient is not completely established, but the role of the pregnancy should be taken into account. Another case of rapid neurological deterioration was described in a patient who had undergone in vitro fertilization and had been pregnant for 4 weeks.27 The important physical and psychological changes occurring in the first trimester as well as in the last weeks of gestation, especially the labor, may be considered potentially stressful events.27 Both the case reported by Peter et al27 and our case had a history of leukoencephalopathy and premature ovarian failure when the acute neurological deterioration occurred during pregnancy, suggesting the diagnosis of VWM.

In conclusion, our patient is the second adult-onset case of VWM with mutations in EIF2B3 reported in the literature and the first, to our knowledge, with the c.272G>A (p.Arg91His) missense mutation in exon 3. Hemiplegic migraines are an unusual but possible presenting manifestation of this disorder, and it is important to consider the diagnosis of adult-onset VWM disease in patients with leukoencephalopathy and premature ovarian failure with or without neurological deterioration.

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REFERENCES