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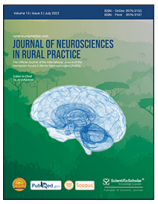

Letter to Editor

Vanishing white matter leukodystrophy due to novel EIF2B4 mutation in an adult female

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Dear Editor,

The vanishing white matter leukodystrophy (VWM) is an autosomal recessive leukodystrophy which can present in childhood (1–5 years) as well as adulthood (15%).[1] They present with behavioral changes, dementia, migraine, and seizures.[1] Premature ovarian insufficiency and stress (fever, trauma, and infections) related clinical worsening are the characteristic features. Mutation in the genes encoding eukaryotic translation initiation factor 2B (EIF2B1-EIF2B5) is the culprit. The EIF2B5 mutation accounts for the majority of cases.[2-5] To the best of our knowledge, there are no genetically proven cases of adult-onset VWMD with EIF2B4-related mutations reported from India.

A 52-year-old lady, born out of non-consanguineous parents, presented with 2-year history of slowly progressive dragging of the right foot, 1-year history of bladder urgency, 6-month history of the right-sided abnormal posturing of limbs, swaying, and behavioral disturbances. Two months before presentation, she had high-grade fever followed by which she became bed-bound and double incontinent. She attained menopause at the age of 35 years. No significant family history.

On examination, she was opening eyes spontaneously, but could not obey simple commands. Cognitive examination revealed perseveration, repetition, echolalia, and emotional incontinence. There was a relative paucity of the right upper and lower limb with contractures and bilateral spasticity. Deep tendon reflexes were exaggerated with extensor plantar response bilaterally.

On evaluation, she was detected to have anemia (8.1 g/dl). Liver and kidney function tests, and thyroid function test, lactate, and ammonia were normal. Her urine for abnormal metabolites, serum aryl-sulfatase levels, and tandem mass spectrometer were negative. Serology for human immunodeficiency virus and venereal disease research laboratories tests were negative. Nerve conduction studies and cerebrospinal fluid study were unremarkable. Magnetic resonance imaging (MRI) brain demonstrated diffuse white matter involvement with radiating strips of preserved white matter [Figure 1a]. External capsule involvement and sparing of the basal ganglia and thalamus [Figure 1b] were seen. Cysts were present in both anterior frontal regions [Figure 1c] with no diffusion restriction [Figures 1d and e] and no contrast enhancement [Figure 1f]. Thinning of the corpus callosum [Figure 2a], selective involvement of posterior limb of the internal capsule [Figure 2b], central tegmental tract hyperintensities [Figure 2c], and mineralization of globus pallidus [Figure 2d] were seen. Based on clinical and imaging characteristics, diagnosis of adult-onset VWM was made.

Genetic testing revealed a homozygous missense mutation in exon-12 of the EIF2B4 gene.

The VWM was first described in young children by Hanefeld *et al.* as myelinopathia centralis diffusa and by Schiffmann *et al.* as childhood ataxia with CNS hypomyelination (CACH).[6,7]

The eIF2B is the guanine exchange factor for eIF2 and helps in translation initiation and regulation of protein synthesis under different conditions, including cell stress.[8] Mutations in EIF2B genes alter the cellular response to stress and thus lead to worsening of clinical symptoms. Mutations in EIF2B5 are the most common (60%) followed by EIF2B2 mutation.[2,9,10] In 1997, van der Knaap introduced the term "vanishing white matter disease."[11] Since then, multiple isolated cases have been reported. In 2001, Japanese authors reported the first Asian girl with vanishing white matter disease.[12] The disease presents in young children with cerebellar ataxia

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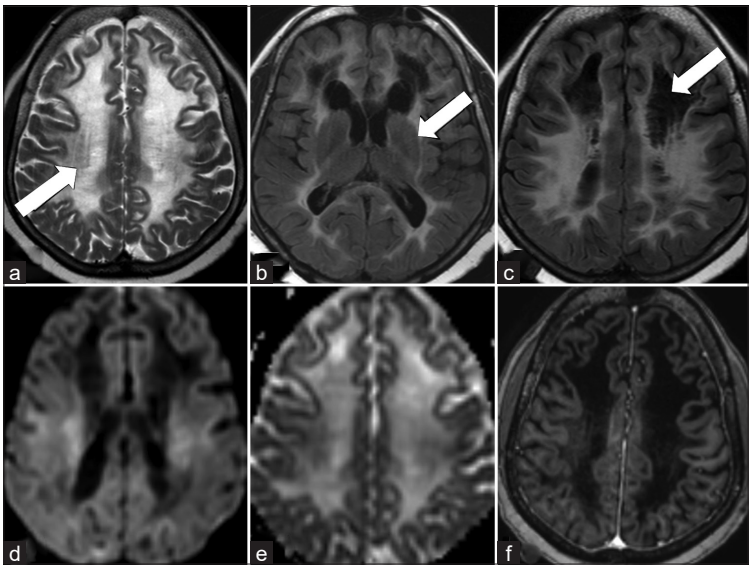

Figure 1: Magnetic resonance imaging (MRI) brain – A}XIAL T2-weighted imaging (T2WI) shows diffuse hyperintense signal with hypointense radiating strips of preserved white matter (a). Axial FLAIR image depicts the involvement of an external capsule with sparing of the basal ganglia and thalamus (b), suppression of signal of affected white matter in anterior bifrontal region s/o cyst formation, white matter in the parietal and posterior frontal region is hyperintense (c). Diffusion-weighted imaging and apparent diffusion coefficient (d and e) reveal no diffusion restriction. Post-contrast FLAIR image of the brain showing no enhancement in the areas of signal alteration (f). Arrows showing the abnormalities.

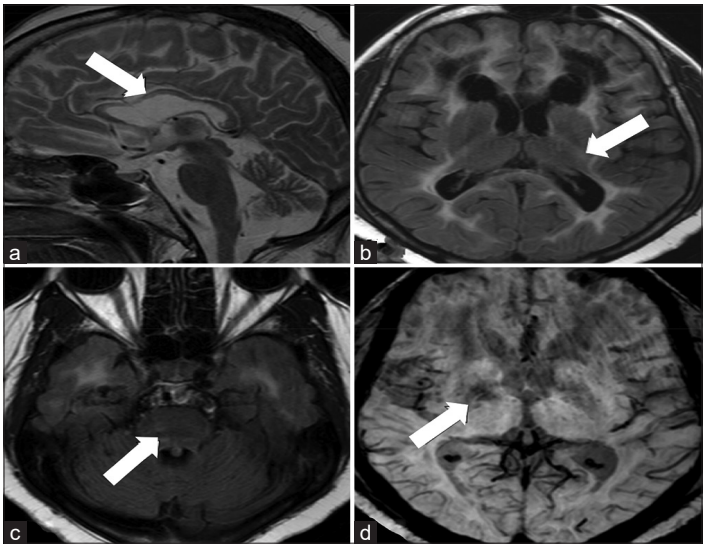

Figure 2: MRI brain – sagittal T2WI image of the brain shows the involvement of inner layer of the corpus callosum with thinning of corpus callosum (a), axial FLAIR image at the level of basal ganglia demonstrates the involvement of posterior limb of the internal capsule with sparing of anterior limb (b), axial FLAIR image at the level of pons illustrates hyperintense signal along central tegmental tract (c), and axial SWI image shows hypointensity in bilateral globus pallidus suggestive of mineralization (d). Arrows showing the abnormalities.

and less prominent spasticity. Optic atrophy with loss of vision and epilepsy may occur rarely.[6,11,13] In adults, it presents with behavioral changes, dementia, migraine, and seizures. Premature ovarian failure is reported in females and can precede the neurological symptoms by decade.[5] Both childhood and adult-onset forms witness stress-related exacerbations. MRI shows diffuse and symmetric involvement of the cerebral white matter that spares U-fibers, the outer part of the corpus callosum, the internal capsule, and anterior commissure. Gradually cystic degeneration occurs. Our patient has cystic degeneration of the white matter, sparing U fibers, and no contrast enhancement.

There is no specific treatment for VWM. The avoidance of stressful events may help in prolonged survival.[8] These measures include avoiding contact sports, liberal use of antipyretics, and antibiotics for suspected infections. Patients must be vaccinated up-to-date.[8]

Possibility of VWMD needs to be considered in adult patients who present with features of leukodystrophy and stress-related neurological worsening and associated with premature ovarian failure. Imaging features of progressive rarefaction, cyst formation, and shrinkage of the white matter support the diagnosis. Genetic testing helps in prognostication and initiation of preventive measures.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Labauge P, Horzinski L, Ayrignac X, Blanc P, Vukusic S, Rodriguez D, *et al*. Natural history of adult-onset eIF2B-related disorders: A multi-centric survey of 16 cases. Brain 2009;132:2161-9.
2. Bugiani M, Boor I, Powers JM, Scheper GC, van der Knaap MS. Leukoencephalopathy with vanishing white matter: A review. J Neuropathol Exp Neurol 2010;69:987-96.
3. La Piana R, Vanderver A, van der Knaap M, Roux L, Tampieri D, Brais B, *et al*. Adult-onset vanishing white matter disease due to a novel EIF2B3 mutation. Arch Neurol 2012;69:765-8.
4. Hamilton EM, van der Lei HD, Vermeulen G, Gerver JA, Lourenço CM, Naidu S, *et al*. Natural history of vanishing white matter. Ann Neurol 2018;84:274-88.
5. Scali O, Di Perri C, Federico A. The spectrum of mutations for the diagnosis of vanishing white matter disease. Neurol Sci 2006;27:271-7.
6. Hanefeld F, Holzbach U, Kruse B, Wilichowski E, Christen HJ, Frahm J. Diffuse white matter disease in three children: An encephalopathy with unique features on magnetic resonance imaging and proton magnetic resonance spectroscopy. Neuropediatrics 1993;24:244-8.
7. Schiffmann R, Moller JR, Trapp BD, Shih HH, Farrer RG, Katz DA, *et al*. Childhood ataxia with diffuse central nervous system hypomyelination. Ann Neurol 1994;35:331-40.
8. van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. Lancet Neurol 2006;5:413-23.
9. Moon SL, Parker R. EIF2B2 mutations in vanishing white matter disease hypersuppress translation and delay recovery during the integrated stress response. RNA 2018;24:841-52.
10. Fogli A, Boespflug-Tanguy O. The large spectrum of eIF2B-related diseases. Biochem Soc Trans 2006;34:22-9.
11. van der Knaap MS, Barth PG, Gabreëls FJ, Franzoni E, Begeer JH, Stroink H, *et al*. A new leukoencephalopathy with vanishing white matter. Neurology 1997;48:845-54.
12. Sugiura C, Miyata H, Oka A, Takashima S, Ohama E, Takeshita K. A Japanese girl with leukoencephalopathy with vanishing white matter. Brain Dev 2001;23:58-61.
13. van der Lei HD, van Berkel CG, van Wieringen WN, Brenner C, Feigenbaum A, Mercimek-Mahmutoglu S, *et al*. Genotype-phenotype correlation in vanishing white matter disease. Neurology 2010;75:1555-9.

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