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Case Report

Adult-onset vanishing white matter disease as differential diagnosis of primary progressive multiple sclerosis: A case report

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Marina Herwerth, Benedikt J Schwaiger, Kornelia Kreiser, Bernhard Hemmer and Rüdiger Ilg

***Abstract*:** We report the case of a 42-year-old woman with a slowly progressive cerebellar syndrome. In contrast to a relatively mild clinical presentation, the magnetic resonance imaging (MRI) showed extensive leukencephalopathy with cystic degeneration. Initially primary progressive multiple sclerosis (PPMS) was suspected. Additional diffusion-weighted imaging revealed restricted diffusion in the white matter lesions with a reduced apparent diffusion coefficient. Genetic testing showed vanishing white matter disease (VWM) with c.260C>T EIF2B3 mutation. In conclusion, in cases with relatively mild symptoms and extensive white matter lesions, adult-onset VWM should be considered as differential diagnosis of PPMS and diffusion-weighted imaging may be helpful to identify suspected cases.

***Keywords*:** Primary progressive multiple sclerosis, diffusion-weighted imaging, vanishing white matter disease, EIF2B3

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Introduction

Vanishing white matter disease (VWM), first described in 1962 as 'atypical diffuse sclerosis', is a rare autosomal recessive disease. It is caused by a mutation in any of the five genes of the eukaryotic translation initiation factor eIF2B[1–5] that is involved in the initiation of protein translation.[1] Neuropathological features are increased density of 'foamy' oligodendrocytes and dystrophic astrocytes.[2] Over the last 15 years a large variation of the age of onset has become apparent. In adults, disease onset was reported up to the age of 60 years with slowly progressive spastic paraparesis, cerebellar symptoms and ataxia. In affected women, premature ovarian failure can occur. Here, we report the clinical and radiological features of a patient with late adult-onset homozygous p.Ala87Val EIF2B3 VWM and demonstrate the potential role of diffusion-weighted imaging (DWI) for distinguishing VWM from primary progressive multiple sclerosis (PPMS).

Case report

A 43-year-old woman presented with a 2-year history of a slowly progressive impairment of her gait and coordination. The neurological examination showed a mild cerebellar syndrome. Due to her age and the slow clinical progression PPMS was considered. Magnetic resonance imaging (MRI) showed extensive bihemispherical FLAIR-hyperintense signal changes of the white matter (Figure 1(a), (b)) with areas of cerebrospinal fluid (CSF)-isointense cystic degeneration. DWI showed diffusion restriction throughout the white matter lesions with corresponding apparent diffusion coefficient (ADC) loss (Figure 1(c), (d)). The MRI of the spinal cord showed no signal alteration. Examination of the CSF revealed a high protein level but no CSF-specific oligoclonal IgG bands were detected. The somatosensory evoked potentials were unremarkable. The neuropsychological examination showed moderate global cognitive deficits. The family history revealed that her 49-year-old sister suffered from spastic paraparesis and premature ovarian failure. Due to the positive family history and extensive white matter lesions with diffusion restriction we considered adult-onset VWM as differential diagnosis. Gynaecological examination of our patient also revealed a premature ovarian failure. Genetic testing finally confirmed a homozygous point mutation c.260C>T (p.Ala87Val) in the EIF2B3 gene.

Correspondence to:
Marina Herwerth
Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Strasse 22, 81675 Munich, Germany.
herwerth@lrz.tum.de

Marina Herwerth
Benedikt J Schwaiger
Kornelia Kreiser
Bernhard Hemmer
Rüdiger Ilg
Klinikum rechts der Isar, Department of Neurology and Neuroradiology, Technische Universität München, Munich, Germany

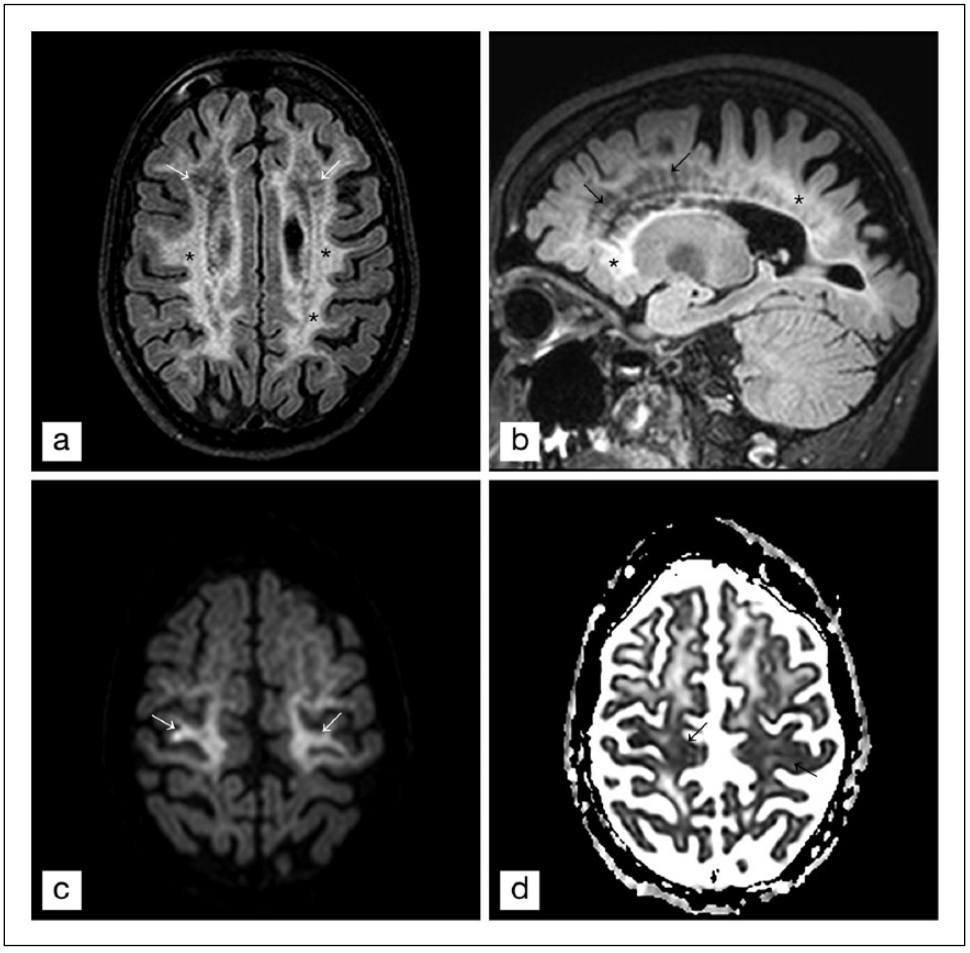

Figure 1. Axial (a) and sagittal (b) FLAIR showing extensive hyperintense white matter changes, partially affecting U fibres (asterisks), cystic degeneration with CSF-similar signal (white arrows) and a radiating pattern of remaining tissue in cystic degenerated tissue (black arrows); DWI showing B1000-hyperintense areas (c) with corresponding ADC signal loss (d) in non-cystic degenerated WM as a correlate of diffusion restriction.

Discussion

The c.260C>T EIF2B3 mutation is a rare adult variant of VWM. To our knowledge, this mutation has only been described twice, in a 66-year-old woman with progressive gait impairment,[4] and in a 29-year-old woman with a mild cerebellar syndrome (as part of a compound mutation c.260 C>T and c.272 G>A in the EIF2B3 gene).[5] While cystic lesions have also been described in PPMS,[3] diffusion restriction of white matter lesions with reduced ADC has not been reported in PPMS so far.[6] In contrast, studies investigating the role of ADC in MS lesions found significantly higher ADC values than in controls.[6–8] Thus, in cases with mild clinical symptoms and unusual extensive white matter lesions DWI may help to identify suspected cases of late adult-onset VWM. Furthermore, MRI of the spinal cord, which is usually unremarkable in VWM disease, and the absence of oligoclonal IgG bands might be helpful to discriminate the disease from PPMS.

So far, there is no clear phenotype correlation in the EIF2B3 variant of VWM. The reported cases with EIF2B3 mutations presented with relatively mild neurological deficits including cerebellar symptoms and spastic paraparesis. The age at onset of all reported EIF2B cases varied between 29 and 61 years.[4,5,9] That raises the question whether EIF2B3 genotype is a variant of VWM with later onset and better outcome. To summarize, adult-onset EIF2B3 VWM should be particularly considered as differential diagnosis in suspected cases of PPMS with a striking discrepancy between relatively mild clinical symptoms and extensive confluent white matter lesions with cystic degeneration and diffusion restriction.

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Conflict of interest

None declared.

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References

1. van der Knaap MS, Pronk JC and Scheper GC. Vanishing white matter disease. *Lancet Neurol* 2006; 5: 413–423.
2. Rodriguez D, Gelot A, Gaspera della B, et al. Increased density of oligodendrocytes in childhood ataxia with diffuse central hypomyelination (CACH) syndrome: Neuropathological and biochemical study of two cases. *Acta Neuropathol* 1999; 97: 469–480.
3. Renard D, Brochet B, Vukusic S, et al. Clinical and radiological characteristics in multiple sclerosis patients with large cavitary lesions. *Eur Neurol* 2012; 68: 156–161.
4. Ghezzi L, Scarpini E, Rango M, et al. A 66-year-old patient with vanishing white matter disease due to the p.Ala87Val EIF2B3 mutation. *Neurology* 2012; 79: 2077–2078.
5. Vanderver A. Adult-onset vanishing white matter disease due to a novel EIF2B3 mutation. *Arch Neurol* 2012; 69: 765.
6. Natarajan R, Hagman S, Wu X, et al. Diffusion tensor imaging in NAWM and NADGM in MS and CIS: Association with candidate biomarkers in sera. *Mult Scler Int* 2013; 2013: 265259.
7. Horsfield MA, Lai M, Webb SL, et al. Apparent diffusion coefficients in benign and secondary progressive multiple sclerosis by nuclear magnetic resonance. *Magn Reson Med* 1996; 36: 393–400.
8. Larsson HB, Thomsen C, Frederiksen J, et al. In vivo magnetic resonance diffusion measurement in the brain of patients with multiple sclerosis. *Magn Reson Imaging* 1992; 10: 7–12.
9. Matsukawa T, Wang X, Liu R, et al. Adult-onset leukoencephalopathies with vanishing white matter with novel missense mutations in EIF2B2, EIF2B3, and EIF2B5. *Neurogenetics* 2011; 12: 259–261.