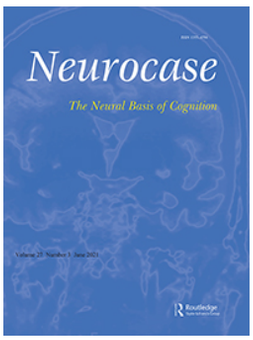

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An eleven-year history of Vanishing White Matter Disease in an adult patient with no cognitive decline and *EIF2B5* mutations. A case report

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ABSTRACT

Vanishing White Matter Disease (VWMD) is a rare autosomal recessive leukoencephalopathy . The classical presentation is characterized by a severe cerebellar ataxia, spasticity, neurological deterioration with a chronic progressive course and episodes of acute neurological deterioration after stress conditions.

We report a 52-year-old man with VWMD and atypical features who manifested two major events of transient aphasia eleven years apart with complete recovery in 48 hours. No cognitive decline was present. Brain MRI revealed typical aspects of VWMD including diffuse leukoencephalopathy with relative sparing of U-fibers. We identified the presence of c.592G>A (p.Glu198Lys) and c.1360 C>T (p.Pro454Ser) mutations in *EIF2B5*.

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KEYWORDS
Vanishing white matter disease; *EIF2B5*; leukoencephalopathy

Introduction

Vanishing White Matter Disease (VWMD; MIM#603896), a rare inherited leukoencephalopathy originally described in childhood, is an autosomal recessive disease caused by heterozygous loss of function in one of five genes coding for subunits of eukaryotic translation initiation factor 2b (EIF2B). EIF2B5 is involved in the initiation of proteins translation and in the regulation of the process, especially in stress conditions This may explain the vulnerability to stress conditions observed in VWMD patients (Pronk et al., 2006; Van der Knaap et al., 2006). It is well known that VWMD has a wide clinical spectrum, with age at onset inversely correlated with the clinical severity (Hamilton et al., 2018). The classical presentation is characterized by severe cerebellar ataxia, spasticity, variable optic atrophy, neurological deterioration with a chronic progressive course and episodes of acute neurological deterioration after stress conditions (Van der Knaap et al., 2003). The adult-onset form, which includes behavioral problems, cognitive decline, acute transient neurological symptoms, or headache, is usually milder and with slow progression than the early-onset form. Most cases are associated with mutations in *EIF2B5* which cause 65–70% of all the cases of VWMD regardless of age of onset (Pronk et al., 2006; Van der Knaap et al., 2003; Van Der Lei et al., 2010).

Women with VWMD leukodystrophy could be affected by ovarioleukodystrophy, an extremely rare condition characterized by premature ovarian failure or primary amenorrhea (Fogli et al., 2003).

Brain magnetic resonance imaging (MRI), usually diagnostic in VWMD, reveals diffuse leukoencephalopathy and, sometimes, relatively spared U-fibers. With disease progression MRI shows evidence of progressive rarefaction and cystic degeneration of the affected white matter. This change is best evidenced by using fluid attenuated inversion recovery (FLAIR) sequences. Presymptomatic and mildly symptomatic individuals, who undergo brain MRI, always present extensive cerebral white-matter abnormalities but not necessarily rarefaction or cystic degeneration at first (Van der Knaap et al., 2006).

Case report

A 41-year-old right-handed man came to our attention for an acute aphasia as he woke up in the morning. The night before, he had suffered from an episode of headache associated with a visual deficit lasting approximately 30 minutes. At the hospital admission, that morning, he was febrile. Neurological examination showed motor speech errors and phonemic paraphasias, anomia for few words without use of neologisms. Naming, repetition, and interpretation of grammar were preserved. No sensory deficit nor coordination problems were described, while positive bilateral Hoffmann's sign, positive bilateral Babinski sign and brisk deep-tendon reflexes at arms and legs were detected. No clear focal motor deficit was observed. The cranial nerves were preserved. Aphasia recovered within 48 hours.

At that time lumbar puncture showed no pleocytosis (2/mm^3) and only a mild increase of proteins (700 mg/L; normal value 150–450 mg/L) in cerebrospinal fluid (CSF). The search for neurotropic viruses (cytomegalovirus, Epstein Barr virus, Herpes

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Simplex virus 1 and 2, human herpesvirus 6 and 3) on CSF was negative, instead blood cultures were not performed. Brain MRI showed, on Diffusion Weighted Imaging (DWI) sequences and Apparent Diffusion Coefficient (ADC) images, no areas of restricted diffusion consistent with acute ischemic lesions and, on T2-weighted images, a diffuse hyperintensity in the periventricular and deep white matter. MRI spectroscopy did not demonstrate a lactate peak nor other significant abnormalities. Due to the quick recovery of the patient, cognitive assessment was performed only by Mini Mental State Examination (MMSE), normalized for age and schooling of the patient, which did not show any impairment. There was no epileptiform activity at electroencephalogram (EEG). Family history was negative for neurological diseases and *NOTCH3* gene sequencing resulted normal at the ward discharge.

The episode resolved promptly without needing relevant interventions and no definite diagnosis was reached at that time.

In the following years, the patient reported sporadic headache episodes alike migraine without aura and one episode of headache headed by a 30-minute lasting visual deficit, resembling migraine with typical aura.

After 11 years, at the age of 52 years, he had an analogous event of acute aphasia while he was walking in the countryside.

At the hospital admission neurological examination showed deep-tendon brisk reflexes, positive bilateral Babinski and Hoffmann's signs, severe aphasia with verbal expression and repetition completely abolished, and preserved comprehension.

There were no motor deficits, no meningeal irritation signs, and a score of 4 at the National Institutes of Health Stroke Scale. His vital signs, ECG and routine blood exams were normal. Brain CT and CT-angiography showed no hemorrhages, no early ischemic signs and no occlusions of the large vessels but confluent hypodensity in the periventricular white matter and mild enlargement of lateral ventricles.

At the admission to our Stroke Unit intravenous thrombolysis (IV) was performed without complications. Few hours after the aphasia onset he became febrile (38°C) for 24 hours. No evidence of infection was found on blood and urine cultures. Lumbar puncture revealed no pleocytosis and mild increase of lactate (2.5 mmol/L; normal value 1–2.2 mmol/L), proteins (627 mg/L; normal value 150–450 mg/L), glucose (109 mg/dL; normal value 40–85 mg/dL), and albumin (39.2 mg/dL; normal value 10–30 mg/dL), suggesting a blood brain barrier damage. During this hospitalization, the search for neurotropic viruses (cytomegalovirus, Epstein Barr virus, Herpes Simplex virus 1 and 2, human herpesvirus 6 and 3) on CSF was negative. Assays of alpha-GAL and very long chain fatty acid enzyme activity on plasma, arylsulfatase-A enzyme activity on whole blood and pristanic acid, titanic acid, and sulphatides on urine sample were normal. An EEG, performed 24 h after the admission to the hospital, when the language disorder was still present, revealed transient delta activity without rhythmic activity over the anterior leads, corresponding to the frontal lobes, predominant on the left hemisphere.

The aphasia completely recovered within 48 hours. Brain MRI did not demonstrate areas of restricted diffusion indicating acute ischemic lesions. On T2-FLAIR images a symmetric, confluent high signal intensity in the cerebral white matter with corresponding hypo-intensity on T1-weighted images and no enhancement on postgadolinium T1-weighted images was described. There was relative sparing of the internal capsules and of the juxta-cortical U-fibers. Areas of low signal intensity on T2-FLAIR images in the white matter adjacent to the frontal horns of the lateral ventricles were suggestive of cystic degeneration (Figure 1).

Further investigations including echocardiogram, 24-hour Holter-ECG, carotid ultrasound, eye exam, and electroneurography were unremarkable. Somatosensory evoked potentials revealed a prolonged central sensory conduction time.

Neuropsychological examination included MMSE, Trail Making Test A and B, Symbol Digit Test, Stroop test (color, color word), Wisconsin card sorting test, Digit Span, Rey Auditory Verbal Learning Test, Clock drawing test, Semantic verbal fluency, and Phonological Verbal Test and Boston naming test. Based on the literature, all the results of the testing were normalized for age and schooling of the patient and compared to normal values. Neuropsychological testing did not reveal cognitive impairment: MMSE score was 29/30, and there only was a slightly reduced performance on executive functions (Trail Making Test B-A: 94, normal values ≤90) and Boston Naming Test (52, normal values ≥52) [Table 1].

Based on neuroradiological and clinical findings a diagnosis of VWMD was considered and direct sequencing of the *EIF2B5* gene revealed the presence of two heterozygous mutations in *EIF2B5*, namely, c.592G>A and c.1360C>T.

Discussion

The present report describes clinical features, neuroimaging, and genetic findings of a male patient with adult-onset VWMD. Our patient carried a compound heterozygosity for the *EIF2B5* gene mutations c.592G>A (p.Glu198Lys) and c.1360C>T (p.Pro454Ser). Both these mutations have been already described associated with VWMD (Fogli et al., 2004; Pronk et al., 2006) but, to the best of our knowledge, their association has not been already described. The c.592G>A missense mutation leads to a substitution within coding region from guanine to adenine, resulting from glutamic acid to lysine (p.Glu198Lys); instead the c.1360C>T missense mutation leads to a substitution from cytosine to thymine, resulting from proline to serine (p.Pro454Ser). Both the mutations are predicted to be pathogenetic and reported in the Human Gene Mutation Database (HGMD).

Indeed, this case represents an atypical presentation of VWMD with a stable long-standing mild symptomatic disease without significant cognitive and motor decline after eleven years of disease but showing classical MRI white matter alterations since the beginning of the disease history. This case further enlarges the wide VWMD clinical spectrum and highlights the importance of MRI technique in the diagnostic process. To the best of our knowledge no other patients with adult

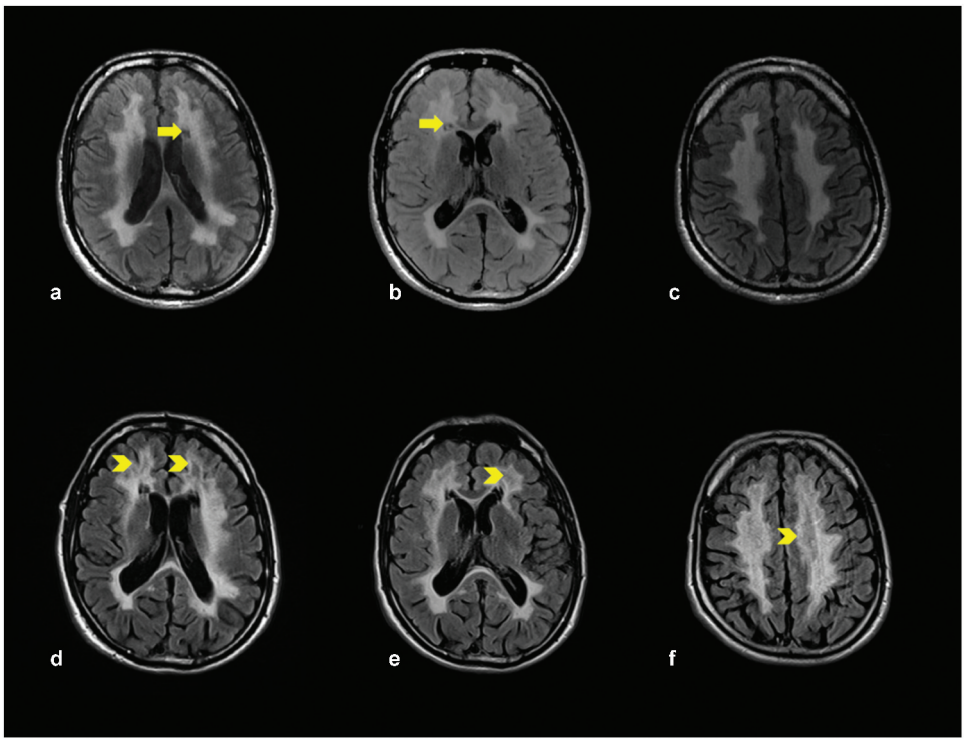

Figure 1. Comparison of axial T2 FLAIR images obtained at the time of the first clinical episode (upper row) and at the time of the most recent episode (lower row). Upper row T2-FLAIR sequences demonstrate diffuse and symmetric white matter hyperintensity with relative sparing of the outer rim of the corpus callosum and of the internal capsules (images A and B) and confluent and symmetric white matter involvement at the level of the centrum semiovale (image C). Minute areas compatible with cystic degeneration are present bilaterally in the periventricular white matter (arrows). Lower row T2-FLAIR sequences obtained at the same level (images D, E, and F) demonstrate in the frontal subcortical white matter, more on the left, slight attenuation of hyperintensity on T2-FLAIR, most consistent with increase of myelin rarefaction in the interval of time between the two acquisitions (arrows head).

Table 1. Neuropsychological examination of the patient 2 weeks after the last major event.

	Test	Raw score	Normalized score	Normal values
Mental state examination	MMSE	29	-	≥24
Attention and	TMT A	32	-	≤59
executive function	TMT B	126	-	≤155
	TMT B-A	97	-	≤90
	SYMBOL DIGIT	40	38.45	≥24
	STROOP color	40	16.65	≥30.08
	STROOP color word	18	16.65	≥15.8
	WISCONSIN CARD SORTING TEST (WCST)			
	Total score	78	79.2	≤90.5
	Perseverative errors	21	23.2	≤42.6
	Non-perseverative errors	27	27.2	≤29.9
	Interrupted series	2	2	≤2–3
Memory	Digit span – forward	6	5.75	≥4.26
	Digit span – backwards	4	3.79	≥2.45
	REY AUDITORY VERBAL LEARNING TEST			
	Immediate recall	53	49.5	≥28.56
	Delayed recall	9	8	≥4.69
	Babcock story recall test	14.5	14.5	≥8
Visualspatial	CDT	11	11	≥7.56
Language	Semantic verbal fluency	49	46	≥25
	Phonological verbal fluency	40	36	≥17
	BNT	52	52	≥52

MMSE = Mini Mental State Examination; TMT A = Trail Making Test A; TMT B = Trail Making Test B; TMT B-A = Trail Making Test B-A; CDT = Clock Drawing Test; BNT = Boston Naming Test

onset-disease, rapid recovery after major events and stable course for 11 years have been described before (Hamilton et al., 2018; Labauge et al., 2009; Van der Knaap et al., 2006; Wei et al., 2019). Only three other VWMD patients presenting with episodes of transient hemiparesis or aphasia with acute onset and complete recovery, have been described to date (La Piana et al., 2012; Ramaswamy et al., 2006; Robinson et al., 2014). These episodes recovered over several days or weeks and only in one 17-year-old girl, reported by Robinson and colleagues, the episodes were of short duration. In that case, the authors suggested that the episodes shared many features of sporadic hemiplegic migraine, although they did not meet the diagnostic criteria for the latter. In our patient's history, the first episode was preceded by a severe headache associated with visual deficits reminiscent migraine with aura (MA), one of the most frequent presentations of VWMD in adult patients. Sporadic headache attacks resembling migraine without aura were reported in the following years.

Identification of common pathomechanisms between VWMD and sporadic migraine is challenging. Cortical Spreading Depression (CSD) is often proposed in the literature as a pathophysiological substrate of both typical aura and hemiplegic migraine. In the latter several mutations have been described as cause of neuronal hyperexcitability and reduced CSD threshold (Russell & Ducros, 2011).

It has also been observed, in experimental model of tissue deprived of glial function, that CSD can cause neuronal prolonged or permanent dysfunction (Lauritzen et al., 2011), and this could lead us to hypothesize that in VWMD white matter damage may expose to CSD injury.

Abnormal astrocyte morphology was already observed in primary cultures of VWMD patients' astrocytes (Dietrich et al., 2005) suggesting a glial involvement in the pathological process. Moreover, recently the role of glial pathology in VWMD was studied in a spontaneous mutant mouse of the *EIF2B5* gene (Terumitsu-Tsujita et al., 2020). In the latter study, the authors, based on their experimental findings, highlight that glial cell pathology in *EIF2B5* animal model is similar to that observed in VWMD patients. Therefore, we might speculate that dysfunction of glia could predispose to CSD and its related clinical manifestations in VWMD.

In conclusion, we present a patient with atypical manifestation of adult-onset VWMD with two events of acute onset aphasia and complete recovery over few hours. Interestingly, between the episodes, the patient was stable for eleven years without significant cognitive decline. Although for VWMD an early diagnosis does not significantly change the therapeutic approach, a definite diagnosis is very important for patients, particularly with atypical clinical presentation, to avoid useless therapies, as the i.v. thrombolysis in case of stroke mimic presentations. Moreover, a correct diagnosis has consequences in the genetic counseling of patients' family.

Statement of ethics

The authors state that no approval by ethics committee is required for the issue of this letter. Consent to participate not applicable. Informed consent of the patient for molecular test has been stated from genetic consultant. The participant has consented to the submission of the case report to the journal.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Dietrich, J., Lacagnina, M., Gass, D., Richfield, E., Mayer-Pröschel, M., Noble, M., Torres, C., & Pröschel, C. (2005, March). EIF2B5 mutations compromise GFAP+ astrocyte generation in vanishing white matter leukodystrophy. *Nature Medicine*, 11, 277–283. https://doi.org/10.1038/nm1195

Fogli, A., Rodriguez, D., Eymard-Pierre, E., Bouhour, F., Labauge, P., Meaney, B. F., Zeesman, S., Kaneski, C. R., Schiffmann, R., & Boespflug-Tanguy, O. (2003, June). Ovarian failure related to eukaryotic initiation factor 2B mutations. *The American Journal of Human Genetics*, 72, 1544–1550. https://doi.org/10.1086/375404

Fogli, A., Schiffmann, R., Bertini, E., Ughetto, S., Combes, P., Eymard-Pierre, E., Kaneski, C. R., Pineda, M., Troncoso, M., Uziel, G., Surtees, R., Pugin, D., Chaunu, M. P., Rodriguez, D., & Boespflug-Tanguy, O. (2004, May). The effect of genotype on the natural history of eIF2B-related leukodystrophies. *Neurology*, 62, 1509–1517. https://doi.org/10.1212/01.WNL.0000123259.67815.DB

Hamilton, E. M. C., Van Der Lei, H. D. W., Vermeulen, G., Gerver, J. A. M., Lourenço, C. M., Naidu, S., Mierzewska, H., Gemke, R. J. B. J., De Vet, H. C. W., Uitdehaag, B. M. J., Lissenberg-Witte, B. I., & van der Knaap, M. S. (2018 August). Natural history of vanishing white matter. *Annals of Neurology*, 84, 274–288. https://doi.org/10.1002/ana.25287

La Piana, R., Vanderver, A., van der Knaap, M., Roux, L., Tampieri, D., Brais, B., & Bernanrd, G. (2012). Adult-onset vanishing white matter disease due to a novel EIF2B3 mutation. *Archives of Neurology*, 69, 765–768. https://doi.org/10.1001/archneurol.2011.1942

Labauge, P., Horzinski, L., Ayrignac, X., Blanc, P., Vukusic, S., Rodriguez, D., Mauguiere, F., Peter, L., Goizet, C., Bouhour, F., Denier, C., Confavreux, C., Obadia, M., Blanc, F., De Sèze, J., Fogli, A., & Boespflug-Tanguy, O. (2009, August). Natural history of adult-onset eIF2B-related disorders: A multicentric survey of 16 cases. *O Brain*, 132, 2161–2169. https://doi.org/10.1093/brain/awp171

Lauritzen, M., Dreier, J. P., Fabricius, M., Hartings, J. A., Graf, R., & Strong, A. J. (2011). Clinical relevance of cortical spreading depression in neurological disorders: Migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *Journal of Cerebral Blood Flow & Metabolism*, 31, 17–35. https://doi.org/10.1038/jcbfm.2010.191

Pronk, J. C., Van Kollenburg, B., Scheper, G. C., & van der Knaap, M. S. (2006). Vanishing white matter disease: A review with focus on its genetics. *Mental Retardation and Developmental Disabilities Research Reviews*, 12, 123–128. https://doi.org/10.1002/mrdd.20104

Ramaswamy, V., Chan, A. K., & Kolski, H. K. (2006). Vanishing white matter disease with periodic (Paroxysmal) hemiparesis. *Pediatric Neurology*, 35, 65–68. https://doi.org/10.1016/j.pediatrneurol.2005.12.014

Robinson, M. E., Rossignol, E., Brais, B., Rouleau, G., Arbour, J. F., & Bernard, G. (2014). Vanishing white matter disease in French-Canadian patients from Quebec. *Pediatric Neurology*, 51, 225–232. https://doi.org/10.1016/j.pediatrneurol.2014.05.006

Russell, M. B., & Ducros, A. (2011, May). Sporadic and familial hemiplegic migraine: Pathophysiological mechanisms, clinical characteristics, diagnosis, and management. *The Lancet Neurology*, 10, 457–470. https://doi.org/10.1016/S1474-4422(11)70048-5

Terumitsu-Tsujita, M., Kitaura, H., Miura, I., Kiyama, Y., Goto, F., Muraki, Y., Ominato, S., Hara, N., Simankova, A., Bizen, N., Kashiwagi, K., Ito, T., Toyoshima, Y., Kakita, A., Manabe, T., Wakana, S., Takebayashi, H., & Igarashi, H. (2020). Glial pathology in a novel spontaneous mutant mouse of the Eif2b5 gene: A vanishing white matter disease model. *Journal of Neurochemistry*, 154, 25–40. https://doi.org/10.1111/jnc.14887

van der Knaap, M. S., Fogli, A., Boespflug-Tanguy, O., Abbink, T. E. M., & Schiffmann, R. (2003 February 20). Childhood Ataxia with central nervous system hypomyelination/vanishing white matter. [Updated 2019 Apr 4] M. P. Adam, H. H. Ardinger, R. A. Pagon, et al., Eds. *GeneReviews® [Internet]*. University of Washington, Seattle. 1993–2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1258/

van der Knaap, M. S., Pronk, J. C., & Scheper, G. C. (2006, May). Vanishing white matter disease. *The Lancet Neurology*, 5, 413–423. Review. https://doi.org/10.1016/S1474-4422(06)70440-9

Van Der Lei, H. D. W., van Berkel, C. G. M., van Wieringen, W. N., Brenner, C., Feigenbaum, A., Mercimek-Mahmutoglu, S., Philippart, M., Tatli, B., Wassmer, E., Scheper, G. C., & van der Knaap, M. S. (2010, October). Genotype–phenotype correlation in vanishing white matter disease. *Neurology*, 75, 1555–1559. https://doi.org/10.1212/WNL.0b013e3181f962ae

Wei, C., Qin, Q., Chen, F., Zhou, A., Wang, F., Zuo, X., Chen, R., Lyu, J., & Jia, J. (2019, August 22). Adult-onset vanishing white matter disease with the EIF2B2 gene mutation presenting as menometrorrhagia. *BMC Neurology*, 19, 203. https://doi.org/10.1186/s12883-019-1429-9