Adult Vanishing White Matter Disease with a Novel EIF2B4 Mutation

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ABSTRACT

Vanishing white matter disease (VWMD) is an autosomal recessive genetic disease characterised by progressive loss of white matter in both cerebral hemispheres. VWMD is caused by mutations in eukaryotic translation initiation factor 2B (EIF2B). The disease typically occurs in children. Ovarioleukodystrophies disease (OLD) is a special type of adult VWMD, associated with primary ovarian insufficiency. Herein, we report an adult woman with VWMD who had a novel EIF2B4 mutation. A 27-year woman presented with complaints of intermittent movement disorder of both upper extremities for 5 years and walking instability for 1 year. She had primary amenorrhea and infertility, low sex hormones, and a primordial uterus. MRI showed progressive loss of white matter in the brain. Whole-exome sequencing showed a novel *EIF2B4* gene mutation: c.1441 (exon13) T>C. Therefore, a diagnosis of OLD, a special type of adult VWMD, was established. To our knowledge, this is a novel mutation and has not been reported till date. This report extends the mutation spectrum and phenotypic heterogeneity of VWMD.

Key Words: *Vanishing White matter, EIF2B, Primary ovarian insufficiency.*

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INTRODUCTION

Vanishing white matter disease (VWMD) is an autosomal recessive genetic disease characterised by progressive loss of white matter in both hemispheres of the brain. It is caused by mutations in eukaryotic translation initiation factor 2B (*EIF2B*).[1] Patients with VWMD typically present with spasticity, microcephaly, gradual cognitive decline, and characteristic episodes of acute deterioration following an inciting event. The condition usually occurs in children. Ovarioleukodystrophies disease (OLD) is a special type of adult VWMD, which is associated with primary ovarian insufficiency. Here, we report a female patient with OLD who had a novel EIF2B4 mutation.

CASE REPORT

A 27-year woman came to this hospital with chief complaints of intermittent movement disorder of both upper extremities for 5 years and walking instability for 1 year. She often fell and was afraid to walk at night.

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In past, she had craniocerebral trauma at the age of 3 years. She had a history of fever and convulsions at an early age. Considering the possibility of meningitis, the exact treatment was unclear. She had a history of carbon monoxide poisoning more than 10 years ago with a loss of consciousness for about 5-10 minutes and without treatment. On July 27, 2017, she took the "dichlorvos" by herself and was sent to the hospital for gastric lavage treatment. The patient had a history of poor vision, poor tooth development, tooth debris loss, and darker skin, without diagnosis and treatment.

The patient had no natural menarche and had a diagnosis of abnormal development in the hospital. There was a history of long-term intermittent taking of "complex packing estradiol valerate tablets, estradiol valerate and cyproterone acetate tablets (CLIMEN)", and she had irregular menstruation. She got married at the age of 23 years without childbearing.

Her parents were not close relatives. She had a younger brother. Both her parents and younger brother were normal. On physical examination, she was conscious, coherent, and speaking fluently. Her bilateral pupils were equal in size and shape, with a diameter of about 3 mm. Both eyes were sensitive to light, eye movements are acceptable, and nystagmus was absent. She had symmetrical forehead lines, fair tongue extension, and fair nasolabial sulci on both sides. Muscle strength of the right lower limb was 4 to 5 grade, and muscle strength of the remaining limbs was acceptable. The sensory examination was normal. Tendon reflexes were brisk. Rotation test, finger-nose test and heel-knee-nose test of both sides were not coordi-

nated. Open eyes Romberg test was positive. The right side Babinski sign was positive, the left side was suspected positive.

Abdominal ultrasound showed a primordial uterus. Magnetic resonance imaging (MRI) showed extensive white matter lesions in bilateral cerebral hemispheres and brain atrophy (Figure 1A-1D). Magnetic resonance spectroscopy (MRS) showed the appearance of Lac peak in bilateral basal ganglia (Figure 1E-1F). No clear abnormally enhanced lesions were observed in the brain parenchyma. Whole-exome sequencing result showed a homozygous mutation in the *EIF2B4* gene: c.1441 (exon13) T>C/p.S481P (nm_001034116) (Figure 2A). The gene test results of her mother, her father and her mother were shown in Figure 2B-D.

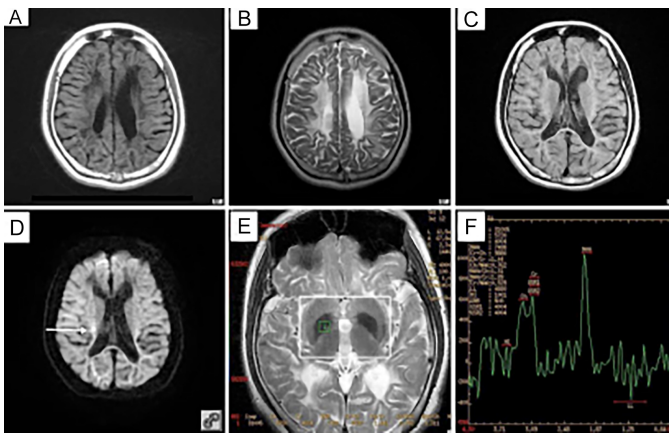

Figure 1: Magnetic resonance image showing extensive white matter lesions in the bilateral cerebral hemispheres. The lesions are hypointense in T1-weighted images (A) and hyperintense in T2-weighted images (B). Signs of brain atrophy are seen (C). White arrow in the diffusion weighted imaging sequence indicates white matter lesions (D). Magnetic resonance spectroscopy indicates normal peaks of NAA, Cr, and CHO in the bilateral basal ganglia; however, there is appearance of lac peak (E, F).

The final diagnosis was VWMD. At the two-year follow-up, there was a slight aggravation of the patient's walking instability; in addition, the walking instability was more obvious at night. She had no cognitive deficit or epilepsy. She was able to take care of herself. Physical examination showed rotation test, finger-nose test, and heel-knee-nose test of both sides were not coordinated, the right side was obvious. Bothe Romberg test and the right side Babinski signs were positive, and the left side Babinski sign was suspected positive. The ataxia was worse than before. She refused to reexamine MRI. Her parents and younger brother were still normal.

DISCUSSION

VWMD is an autosomal recessive genetic disease caused by mutations in subunits of eukaryotic translation initiation factor 2B (*EIF2B*). Craniocerebral trauma, infection, fever, stress, fear, pregnancy, or childbirth may induce or aggravate the disease.[2] These factors such as traumatic brain injury, fever and convulsions, CO poisoning, and long-term intermittent administration of CLIMEN may have caused or exacerbated this patient's disease. Patients with the onset of VWMD in adolescence or adulthood have relatively mild disease characterised by slow disease progression.[3] Female adult VWMD patients typically have motor symptoms.[4] Some adult female VWMD patients present with abnormal menstruation, primary amenorrhea, secondary amenorrhea, and infertility, which are suggestive of ovarian failure.[4] This is a special type of VWMD, called OLD. Our VWMD patient was diagnosed with OLD because she had primary amenorrhea and infertility.

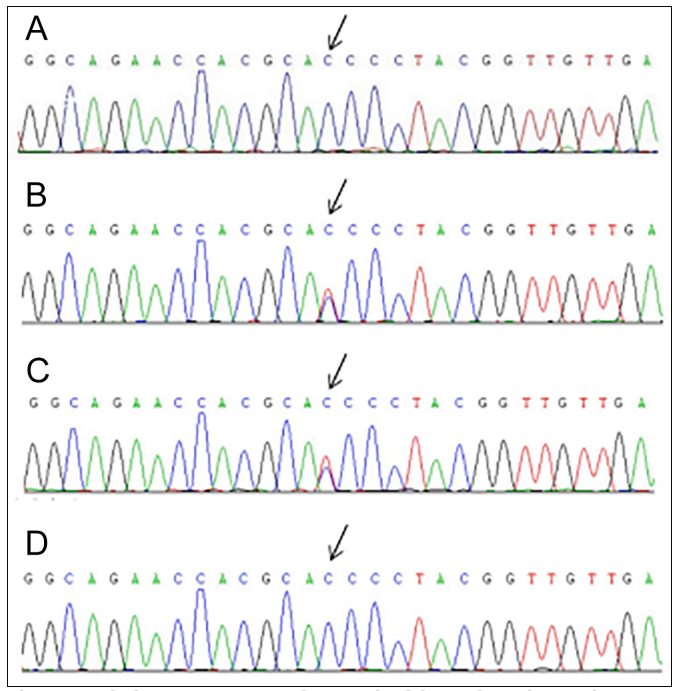

Figure 2: Whole-exome sequencing result of the patient shows a homozygous mutation in the *EIF2B4* gene: c.1441 (exon13) T>C/p.S481P (nm_001034116) (A). Her father (B) and her mother (C) had heterozygous mutations c.1441 (exon13) T>C, while her younger brother had a homozygous mutation c.1441 (exon13) T>C (D). The black arrow stands for mutation site.

MRI characteristics of this patient were consistent with typical signs of VWMD, *i.e.*, diffuse and symmetrical liquefaction of the brain white matter, which is also referred to as "white matter ablation". In previous studies, MRS of the involved white matter showed a phased decrease in the peak value of normal metabolites, and accumulation of glucose and lactate in cerebrospinal fluid-like signals, these findings are consistent with our report.

Genes *EIF2B1-5* encode 5 subunits (α - ε) of the EIF2B protein. Mutations of all these five subunits can cause VWMD. More than 120 *EIF2B1-5* gene mutations have been reported. *EIF2B5* subunit mutations are most common, accounting for 60%–70%,[5] while *EIF2B4* mutations account for 4-14%.[6] Whole-exome sequencing results of our patient showed a homozygous mutation in the *EIF2B4* gene: c.1441 (exon13) T>C/p.S481P. Her father and mother had heterozygous mutations c.1441 (exon13) T>C, while her younger brother had a homozygous mutation c.1441 (exon13) T>C (D). To the best of our knowledge, this mutation is a novel mutation and has not been reported till date.

Clinically, there is no radical treatment for VWMD. However, early identification is of great significance as it provides an

opportunity for genetic consultation and treatment. Avoidance of aggravating factors is a potential preventive strategy.

In conclusion, we reported an adult woman with VWMD who had a novel *EIF2B4* gene mutation: c.1441 (exon13) T>C. This report extends the mutation spectrum and phenotype heterogeneity of VWMD.

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PATIENT'S CONSENT:
The patient agreed to her medical records and images to be published.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
TS, HY: Drafted the manuscript.
TS, WG: Contributed to the diagnosis and treatment of the patient.
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All authors have read and approved the manuscript and contributed to the design of the study and interpretation of data.

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