American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2023; 24: e938569
DOI: 10.12659/AJCR.938569

Received: 2022.10.07
Accepted: 2023.01.28
Available online: 2023.02.02
Published: 2023.02.16

Juxtacortical White Matter Hypointensity on T2*Gradient Echo Image in Vanishing White Matter Disease: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Financial support: None declared
Conflict of interest: None declared

Patient: Female, 29-year-old
Final Diagnosis: Vanishing white matter disease
Symptoms: Weakness of upper and lower limb
Clinical Procedure: —
Specialty: Neurology

Objective: Congenital defects/diseases

Background: Vanishing white matter disease (VWMD) – also known as childhood ataxia with central nervous system hypomyelination – is one of the most commonly inherited white matter diseases in children. Notably, a course of chronic progressive disease with episodes of rapid and major stress-induced neurological deterioration, such as fever and minor head trauma, is a typical clinical feature of VWMD. The combination of clinical features with specific magnetic resonance imaging findings, including diffuse and extensive white matter lesions with rarefaction or cystic destruction, could recommend a genetic diagnosis. However, VWMD is phenotypically diverse and can affect individuals of all ages.

Case Report: A 29-year-old female patient presented with recent aggravation in gait disturbance. She had progressive movement disorder, with symptoms ranging from hand tremors to upper- and lower-extremity weakness, for 5 years. Whole-exome sequencing was performed to confirm the diagnosis of VWMD, and it revealed a mutation in homozygous eIF2B2 gene. The temporal evolution of VWMD observed in the patient for 17 years (from the age of 12 to 29 years) indicated an increased extent of T2 white matter hyperintensity in the cerebrum into the cerebellum and an increased amount of dark signal intensities in the globus pallidus and dentate nucleus. Moreover, a T2*-weighted imaging (WI) scan revealed diffuse, linear, and symmetrical hypointensity along the juxtacortical white matter on the magnification view.

Conclusions: This is the case report about rare and unusual finding of diffuse linear juxtacortical white matter hypointensity on T2*-WI scan as a potential radiographic marker for adult-onset VWMD.

Keywords: Leukoencephalopathies • Magnetic Resonance Imaging • Vanishing White Matter Leukodystrophy with Ovarian Failure

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/938569

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Background

Vanishing white matter disease (VWMD) – also known as childhood ataxia with central nervous system hypomyelination – is one of the most commonly inherited white matter diseases in children [1]. It is mainly diagnosed based on the clinical information of the patient and genetic testing for mutations in eukaryotic translational initiation factor 2B 1-5 (eIF2B1-5) gene, which comprises 5 subunits [2]. The mutation was initially thought to be related to cerebral white matter alone, but it has also been reported to be related to involvement of various organ, including ovarian failure, cataracts, hepatomegaly, pancreatitis, and renal hypoplasia [3,4]. Notably, a course of chronic progressive disease with episodes of rapid and major stress-induced neurological deterioration, such as fever and minor head trauma, is a characteristic clinical feature of VWMD [1,5]. Furthermore, the combination of clinical features with specific magnetic resonance imaging (MRI) findings, including diffuse and extensive white matter lesions with rarefaction or cystic destruction, could recommend a genetic diagnosis. However, VWMD is phenotypically diverse and can affect individuals of all ages.

In VWMD, mild mutations begin to appear in adolescence or adulthood, and such patients present with slow disease progression and varying imaging findings; thus, careful neuroimaging analysis is important [3,6,7]. Here, we present the case of a female patient with adult-onset VWMD who had progressive motor dysfunction with symptoms of bilateral hand tremors and weakness of the upper and lower extremities, congenital cataract, and primary ovarian failure. An MRI scan revealed diffuse and linear hypointensity in the bilateral juxtacortical white matter hypointensities on gradient recalled echo (GRE) T2*-weighted imaging (T2*-WI) scan. To the best of our knowledge, these radiographic findings on T2*-WI of an adult-onset VWMD patient have not yet been reported in the English literature. Thus, this report presents an unusual finding of diffuse linear juxtacortical white matter hypointensities on T2*-WI scan, indicating its potential pathophysiology in VWMD.

Case Report

A 29-year-old female patient presented to the neurological outpatient department with a concern of recent aggravation in gait disturbance. She also had progressive movement disorder, with symptoms ranging from hand tremors to upper- and lower-extremity weakness, for 5 years. Notably, she reported no signs of developmental delay in childhood. Twenty years ago, at the age of 9 years, she underwent phacoemulsification with posterior chamber lens insertion for a binocular congenital cataract. She first experienced a headache at the age of 14 years and underwent imaging at another hospital, where white matter abnormality was incidentally found for the first time. However, at that time, she did not receive a clear diagnosis. She was diagnosed with ovarian failure owing to the absence of menarche until the age of 23 years; subsequently, she underwent hormone replacement therapy until the presentation to our institution, but had experienced oligomenorrhea. She had no family history of these symptoms, and her mother was the only family member still alive. Her neurological examination revealed that muscle strength of upper and lower extremities was reduced, with overall strength of Medical Research Council grade 3; further, the deep tendon reflex of the knee was 4+, and she presented with positive Tromner and Hoffman phenomenon. Notably, the finger-to-nose and heel-to-shin tests were considered inaccurate owing to muscle weakness. The following basic blood tests were within normal range in our hospital: complete blood count, liver function test, blood sugar test, inflammatory markers, lipid profile test, and blood electrolyte test. CSF analyses was unremarkable except for total protein, 56.2 mg/dL (normal range: 15-45 mg/dL).

Neuroimaging findings revealed diffuse and bilateral symmetric hyperintensities of the cerebral white matter on T2-WI scan and fluid-attenuated inversion recovery (FLAIR) image using a 3.0 T MR machine (GE Discovery MR750, GE Healthcare, Waukesha, WI). The region identified to be primarily involved was the frontoparietal white matter. Moreover, we identified no evidence of cystic degeneration or rarefaction of abnormal white matter. Furthermore, bilateral intraocular lens implantation for congenital cataract was detected at the level of the pons. Notably, T2-WI scan revealed diffuse and linear juxtacortical white matter hypointensity on the magnification view (**Figure 1**). The globus pallidus, thalamus, and dentate nucleus were observed as distinct dark signal intensities on T2*-WI scan after the symptoms of muscle weakness appeared (**Figure 2**). Adult-onset VWMD was suspected based on clinical features, history of ovarian failure, and white matter change on magnetic resonance imaging. Whole-exome sequencing (NextSeq, illumine) was performed to confirm the diagnosis, and it revealed a homozygous variant of eIF2B2 gene, c.254T>A (p.Val85Glu, NM_014239.3). Furthermore, the presence of heterozygous carrier was confirmed by the base sequence analysis of the patient's mother.

Discussion

In 2017, a new classification of genetic white matter disorders based on neuropathology was presented, and VWMD was accordingly classified as a strocytopathy, which is mainly characterized by white matter rarefaction, cystic degeneration, and meager astrogliosis without glial scarring and dysplastic immature astrocyte, as well as increased numbers of oligodendrocyte progenitors that inhibit maturation to myelin-forming cells [8]. A recent study reported that the predominant

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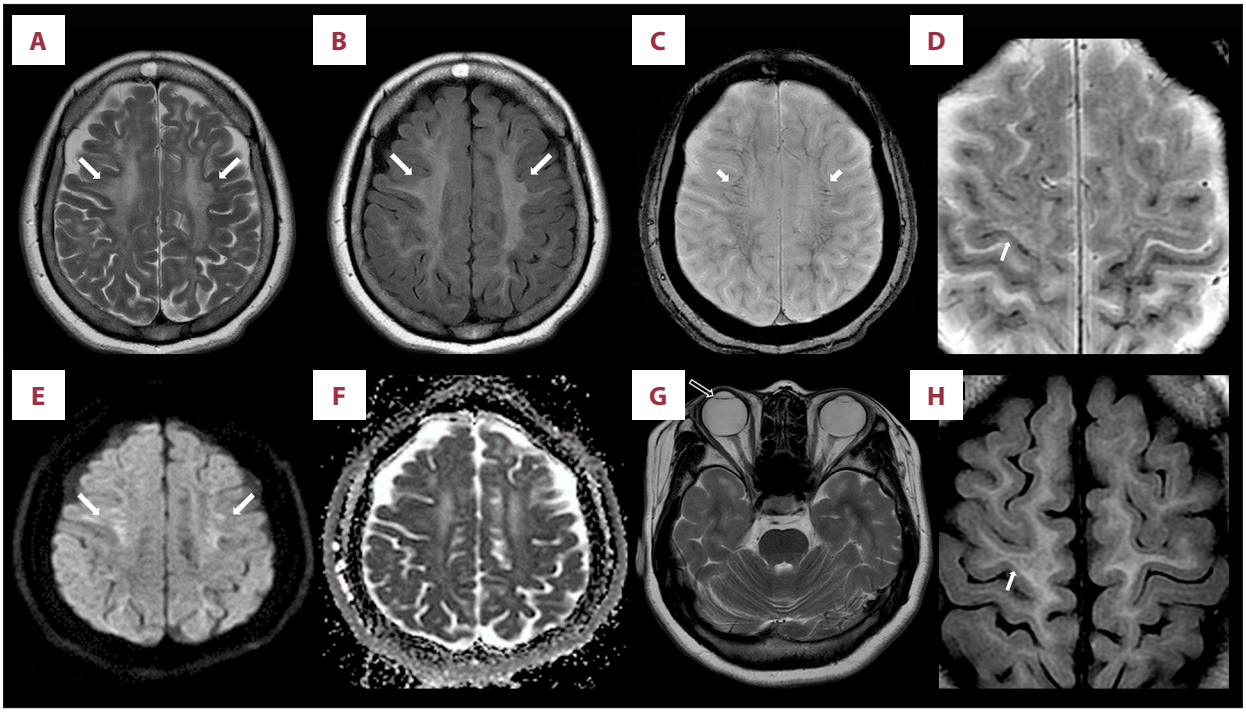

Figure 1. A 29-year-old female patient with VWMD. (**A, B**) Axial T2-weighted and fluid-attenuated inversion recovery (FLAIR) images shows diffuse and bilateral symmetrical hyperintensity in the cerebral white matter. (**C**) T2* gradient echo image shows a diffuse, linear, and symmetrical hypointensity in the affected white matter (short arrow). (**D**) Magnification of an axial GRE T2*-WI apparently reveals diffuse linear juxtacortical white matter hypointensities. (**E, F**) Diffusion-weighted image reveals diffuse hyperintensity without diffusion restriction on the apparent diffusion coefficient map. (**G**) Axial T2-WI scan reveals bilateral intraocular lens insertion for congenital cataract (blanked arrow). (**H**) Magnification of an axial FLAIR image shows relatively spared juxtacortical white matter in the cerebral hemisphere.

pathophysiology of VWMD is astrocyte immaturity caused by eIF2B mutation. Stress-inducing factors, such as heat or minor trauma, promote immature apoptosis via an imbalance in the response of unfolded protein and have secondary effects on oligodendrocytes and axons [9,10].

The classic MRI findings of VWMD include the following: symmetric cerebral white matter and diffuse hyperintensities on T2-WI scan; some or all of the affected white matter showing a hypointensity close to that of cerebrospinal fluid (CSF) on FLAIR image; and dot-like lesions among the axial and radiating lesions identified on the sagittal images within the areas of CSF-like white matter. However, a recent study described a spectrum of radiologic findings based on the age of onset in cases of VWMD [1,3,5]. Early onset was found to be correlated with faster and more cystic degeneration, whereas late onset type was predominantly correlated with atrophy and gliosis [11]. Radiologic features identified on MRI scan and the progression rate of VWMD vary depending on the age of onset, thereby suggesting a difference in pathophysiology depending on the age of onset.

T2*-WI findings of the present case revealed diffuse and linear juxtacortical white matter hypointensities at the gray–white matter junction of the frontoparietal lobe. Hemorrhage, iron accumulation, and calcification are depicted in diverse tissues using GRE sequences with T2*-based contrast [12]. A recent study matched the observed changes with neuropathological findings and suggested that susceptibility changes are correlated with iron accumulation in macrophages [13]. Additionally, similar findings have been reported in progressive multifocal leukoencephalopathy and multiple sclerosis, suggesting blood–brain barrier dysfunction, decreased iron clearance owing to axonal dysfunction, and dysregulation of iron transport proteins as causes of iron deposition [14,15]. Notably, recent studies on brain ion deposition used susceptibility-weighted imaging sequences, which are more sensitive to paramagnetic effect than T2*-WI, or quantitative susceptibility mapping, which can be quantitatively evaluated; these methodological differences limitations of the present study. However, a relatively clear linear hypointensity along the juxtacortical white matter was observed in our case, even on T2*-WI scan; thus, it was thought to be a meaningful finding.

The pathological finding of VWMD is known to be early juxtacortical white matter preservation; however, our patient eventually presented with juxtacortical white matter involvement.

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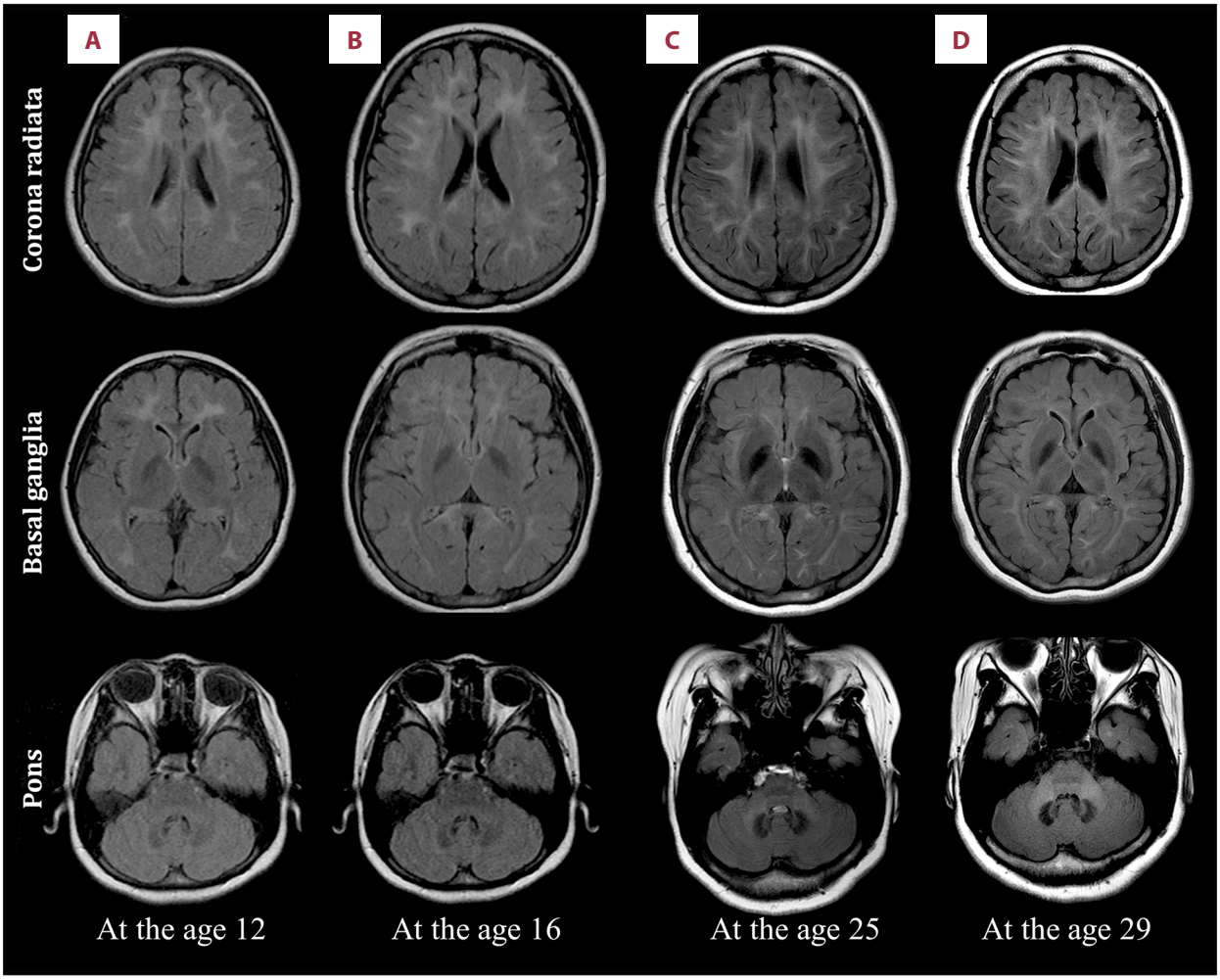

Figure 2. Temporal evolution of VWMD in the patient for 17 years. Serial T2-WI scans of a patient with VWMD. Columns **A and B** show initial and follow-up MRI images obtained at the ages of 12 and 16 years with symptoms of headache and syncope, respectively. Column **C** shows images obtained after the onset of motor neurological symptoms, such as hand tremor and upper-extremity weakness, at the age of 25 years, and the column **D** image was obtained at the age of 29 years due to lower-extremity weakness and severe gait disturbance. Changes in the extent of the lesion over time can be seen at the corona radiata, basal ganglia, and pons levels. In column **C**, the extent of white matter hyperintensity increased at the corona radiata level, and the invasion of the splenium of the corpus callosum was found. At the level of basal ganglia, there is a distinct dark signal intensity due to iron deposition in the globus pallidus and thalamus. At the level of the pons, dark signal intensity was prominent in the dentate nucleus, and white matter hyperintensity was seen in the cerebellar peduncle in column **D**.

Therefore, adult-onset VWMD should be included in the differential diagnosis during the initial examination of leukodystrophy disease associated with juxtacortical white matter invasion. In addition, an accurate diagnosis should be made considering the clinical symptoms and course of the disease. Moreover, the dark signal intensity in the globus pallidus and dentate nucleus was a striking feature. Notably, this finding has been reported in cases of neurogeneration with brain iron accumulation, such as neuroferritinopathy and aceruloplasminemia [16]. The presence of dark signal intensity due to iron accumulation on T2*-WI scan can indicates that microglia, which plays an important role in brain iron metabolism, is possibly involved in the pathophysiology of adult-onset VWMD as much as astrocytes and oligodendrocytes.

Conclusions

This is a case report of rare and an unusual finding of diffuse linear juxtacortical white matter hypointensity on T2*-WI scan as a potential radiographic marker for adult-onset VWMD. This finding may provide useful clues in assessing differential pathophysiology and disease progression by the age of onset, although additional cases need to be investigated to validate this.

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Statement

This study protocol was approved by the Institutional Review Board of Kyungpook National University Hospital (File No. KNUH 2022-06-024-001).

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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