BMC Neurology

CASE REPORT

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A rare case of adult-onset vanishing white matter leukoencephalopathy with movement disorder, expressing homozygous *EIF2B3* and *PRKN* pathogenic variants

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Abstract

Background Vanishing white matter disease (VWMD) is a rare autosomal recessive leukoencephalopathy. It is typified by a gradual loss of white matter in the brain and spinal cord, which results in impairments in vision and hearing, cerebellar ataxia, muscular weakness, stiffness, seizures, and dysarthria cogitative decline. Many reports involve minors. Very few instances worldwide have been reported, with adult onset of vanishing white matter considered to account for 15% of cases. Clinical evaluation, MRI results, and confirmatory genetic testing are used to diagnose VWMD.

Case presentation A 39-year-old male from Hebron, Palestine, presented with a 7-month history of postural instability, imbalanced gait, and progressive deterioration of his lower extremities. Additionally, the patient suffered from ocular abnormalities and sphincteric issues. The patient's sibling showed comparable symptoms but was never diagnosed, as he passed away because of colon cancer. Reduced cognitive function, spastic quadriparesis, hyperreflexia, bradykinesia, and shuffling gait were found during a neurological examination. Normal results were obtained from routine laboratory tests, including cerebrospinal fluid (CSF), blood, and urine. Periventricular white matter hyperintensities, which are indicative of vanishing white matter leukoencephalopathy (VWML), were identified during an MRI. The diagnosis of adult-onset VWML with movement disability was substantiated by genetic testing, which named a homozygous pathogenic missense variant, *EIF2B3*, and a deletion in *PRKN/PARK2*. The patient's motor symptoms were temporarily alleviated following the administration of Levodopa/Carbidopa. Nevertheless, the long-term consequences are uncertain due to the illness's ongoing progression and the absence of a cure currently.

Conclusion This instance of vanishing white matter leukoencephalopathy (VWML) is particularly remarkable in adults because of its rarity and complexity. The diagnosis is further complicated by the coexistence of Parkinsonism

†Yazan Mohammad Abdullah Abufara, Mahmood Fayez Ali Aldrabeeh, Naela Ramadan Mohammad Tell and Ismail Abudaya contributed equally to this work.

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and VWML. Although a cure is not currently known. Early discovery is crucial to effectively manage symptoms. This example underscores the importance of more VWML research, particularly in Palestine, where studies on neurological disorders are limited. These findings underscore the importance of enhancing the region's diagnostic and therapeutic capabilities.

Keywords Vanishing white matter leukoencephalopathy (VWML), Vanishing white matter disease (VWMD), Movement disorder.

Background

Vanishing white matter disease (VWMD) is a rare autosomal recessive leukoencephalopathy. It is characterized by the progressive loss of white matter in the brain and spinal cord, which leads to cerebellar ataxia, muscle weakness, spasticity, seizures, dysarthria, cogitative decline, and vision and hearing impairments. It is mostly reported in children as a congenital form or early to late childhood-onset type, with an incidence ranging from 1.2 to 3 per 100,000 people per year or 1 in 80,000 live births [1, 2].

The adult onset of vanishing white matter is thought to account for 15% of cases, so only a few cases have been documented around the world [1]. However, cognitive decline and behavioral symptoms are more prominent in adults, and motor impairment is less severe. In addition, disease progression is slower, and acute episodes are less common but still possible [3].

Pathogenic variants in one of the five eukaryotic translation initiation factor 2B (eIF2B) genes, with eIF2B5 pathogenic variant being the most common, follow an autosomal recessive pattern. eIF2 starts the translation of mRNAs into polypeptides by forming a ternary complex with GTP and methionyl-transfer RNA (MettRNAi). One crucial stage in the regulation of protein synthesis under a range of stress conditions is the translation start point. The cellular stress response, a defensive mechanism that helps cells survive by limiting the accumulation of denatured proteins and preserving energy, involves the inhibition of protein synthesis. When eIF2B genes are altered, this mechanism is dysregulated, particularly impairing myelination and damaging oligodendrocytes and astrocytes while protecting neurons [1, 4].

Stressful situations such as head trauma, sudden terror, acute psychological stress, or infection provoke severe and rapid neurological deterioration [1]. VWMD is a combination of clinical assessment, MRI findings, and confirmatory genetic testing. MRI changes in white matter are key to suspecting VWMD, and genetic testing provides a definitive diagnosis [2].

Early-onset parkinsonism, also known as juvenile parkinsonism, is characterized by the beginning of parkinsonism of any etiology at or before the age of 40, however, other definitions extend the upper age limit to 50 years. Juvenile parkinsonism (JP) is an uncommon, heterogeneous, and often family condition. JP has multiple etiologies, but the genetic cause is the most notified and the most common pathogenic variant expressed is *PRKN/PARK2*. Many patients fail to satisfy the clinical or pathological criteria for Parkinson's disease, as they frequently exhibit atypical characteristics, including disproportionate severity of alternative movement disorders (e.g., dystonia, ataxia, spasticity), early cognitive deterioration, significant behavioral disturbances, or pertinent medical histories such as exposure to dopamine receptor antagonists, head trauma, brain tumors, and other secondary etiologies. JP typically reacts to the standard treatment for Parkinsonism, which is Levodopa/Carbidopa [5].

We report a case of a 39-year-old male who presented to our clinic with lower limb weakness, postural instability, cognitive decline, and other symptoms. Imaging and genetic studies were performed on the patient, confirming the diagnosis of adult-onset vanishing white matter leukoencephalopathy with movement disorders, presenting Homozygous *EIF2B3* and *PRKN* pathogenic variants. This case is believed to be the first case reported in Palestine.

Case presentation

A 39-year-old male from Palestine lived in Hebron. The patient presented to our clinic with a 7-month history of progressive worsening of lower limb weakness, gait imbalance, and postural instability. The patient had no significant medical or surgical history. The patient reported that he had a brother who died recently due to colon cancer, for which he had the same presenting symptoms as our patient but had never been diagnosed. The symptoms of our patient started subtly and started to progressively worsen slowly over time. The patient also complained of visual disturbances that occurred over time; in addition, the patient complained of sphincteric disorders that occurred during the period of disease progression.

On neurological examination, the patient had a stooped posture, bradykinesia, a shuffling gait, and rigidity. In addition, the patient also had spastic weakness in both the upper and lower limbs (spastic quadriparesis) with hyperreflexia and a positive Babinski sign. On a mental examination, the patient had decreased mental ability and cognition. Cranial nerve examination and sensation were normal.

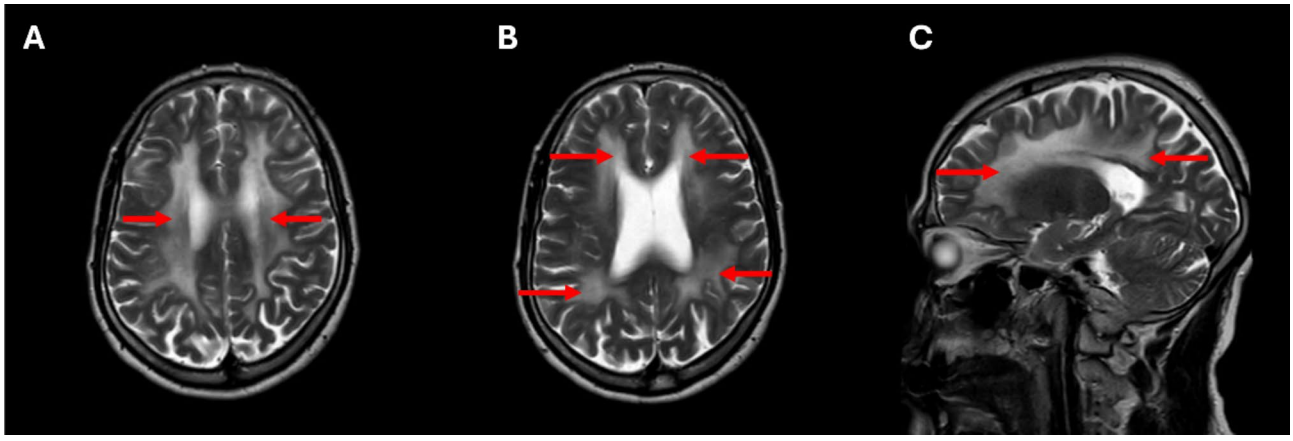

Fig. 1 (**A**), (**B**), and (**C**) Axial and sagittal view of MRI revealed white matter that was diffusely involved with T2-FLAIR hyperintensity, extending from the periventricular white matter to the subcortical arcuate fibers (Red arrows)

Table 1 Primary findings

Gene	Nomenclature	Consequence	Genotype	Classification
EIF2B3	c.687T > G, p.(Ile229Met)	Missense variant	Homozygous	Likely pathogenic
PRKN	c.(412 + 1_413-1)_(534 + 1_535-1)del	Deletion	Homozygous	pathogenic

This table represents the primary findings that are seen in the whole exome test, which consists of a sequence analysis of all protein-coding genes in the genome for the proband, coupled with whole exome deletion/duplication analysis.

Owing to worsening symptoms, the patient was admitted to our hospital, and an extensive range of tests was performed. Routine laboratory tests, including blood, urine, and cerebrospinal fluid (CSF) tests, were performed, and the results were within normal limits. The screening results for endocrine and immunologic disorders were negative. Neuroimaging was performed with magnetic resonance imaging (MRI), which revealed confluent areas of periventricular white matter hyperintensities in T2 and fluid-attenuated inversion recovery (FLAIR) sequence (Fig. 1). These findings were consistent with vanishing white matter leukoencephalopathy (VWML). Genetic testing revealed an *EIF2B3* and a *PRKN/PARK2* pathogenic variants (Table 1).

Based on the patient's history, physical examination, neurological imaging, and genetic testing, a diagnosis of vanishing white matter leukoencephalopathy (VWML) with a movement disorder was confirmed. The patient was discharged only on Levodopa/Carbidopa since there is no cure for vanishing white matter leukoencephalopathy (VWML). The patient's motor symptoms improved in the short term, but we cannot suspect long-term outcomes as the patient's disease is progressive and there is no available curative treatment for his condition.

Discussion and conclusion

Our case report involves a 39-year-old gentleman from Palestine who was diagnosed with adult-onset vanishing white matter disease (VWMD) with movement disorders. Over seven months, he experienced a gradual decline in weakness in his lower limbs, difficulties with balance, visual disturbances, and issues related to sphincter control.

Owing to their relative rarity, varied presentations, and perceived diagnostic challenges, the adult leukodystrophy spectrum is less understood than the child spectrum because of the greater proportion of confounding mimics such as multiple sclerosis and small vessel disease. The epidemiology of adult leukodystrophies also differs. In a cohort study performed in Europe in 2015 with 154 patients, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was the most common diagnosis (33%), followed by vanishing white matter disease (VWMD), X-linked adrenoleukodystrophy (X-ALD), and Collagen type IV alpha 1 chain (COL4A1) related disorders [6]. Currently, VWMD is increasingly recognized in adulthood, manifesting large phenotypical and severe variability, with the latest known onset of disease being 55 years. Late-onset VWMD corresponds to 15% of all described cases [7]. In the context of Palestine, this case is exceptionally rare, as studies addressing VWMD and its manifestations in the adult population are scarce. The limited research on neurological disorders in Palestine underscores the need for more comprehensive studies to understand the prevalence and characteristics of such conditions within the region.

VWMD in adults is defined as rare progressive leukodystrophy that affects only the white matter of the brain via autosomal recessive pathogenic variant in one of the five eukaryotic translation initiation factor 2B (EIF2B) genes, particularly EIF2B5, that are responsible for this

condition, leading to defects in protein translation initiation and the regulation of protein synthesis. Myelination is impaired because of the disruption of the cellular stress response, which affects astrocytes and oligodendrocytes but not neurons. This frequently leads to a rapid and severe neurological decline that is induced by stressors such as infection, minor head trauma, acute psychological stress, or sudden fright [8, 9]. Adult-onset VWM typically presents with milder symptoms and a slower decline in neurological function, with a focus on cognitive impairments rather than the motor disabilities prevalent in early-onset cases. Seizures and episodic exacerbations are crucial to disease progression in all patients, underscoring the need for effective seizure management and prevention strategies, including infection control, head injury prevention, and keeping emotional stability [10].

The E3 ubiquitin ligase parkin, which is encoded by the gene *PRKN*, also referred to as *PARK2*, is essential for mitophagy-mediated mitochondrial quality regulation. By selectively destroying damaged mitochondria, this procedure stops the buildup of malfunctioning organelles that can cause oxidative stress and cellular degeneration, two conditions linked to neurodegenerative illnesses including Parkinson's disease (PD). Pathogenic variants in the PRKN gene are primarily associated with Autosomal Recessive Juvenile Parkinsonism (AR-JP), where the absence or malfunction of parkin disrupts its ability to tag damaged mitochondria for degradation, resulting in mitochondrial dysfunction and subsequent neuronal degeneration, particularly in dopaminergic pathways [11]. Motor symptoms that closely match those of classic Parkinson's disease, such as bradykinesia, rigidity, and postural instability, are frequently found in patients with *PRKN* pathogenic variants. But what's most remarkable in this instance is the rare instance of a patient who has both *PRKN* and *EIF2B3* pathogenic variants. Although leukoencephalopathy is mainly associated with *the EIF2B3* pathogenic variant, the combination of these two genetic changes may point to a new pathogenic pathway. The *EIF2B3* pathogenic variant leads to impaired protein synthesis and oligodendrocyte dysfunction, while the *PRKN* pathogenic variant contributes to mitochondrial impairment and neuronal degeneration [12]. The combination of these pathogenic variants could exacerbate motor symptoms, as the disruption of white matter integrity due to the *EIF2B3* pathogenic variant may compound the dopaminergic deficits caused by the *PRKN* pathogenic variant, resulting in a more complex clinical presentation. Recent studies have highlighted the role of mitochondrial dysfunction in various forms of leukoencephalopathy, suggesting that the presence of a *PRKN* pathogenic variant could further aggravate white matter injury through increased oxidative stress or disrupted neuron-glial interactions [12, 13]. This emphasizes how crucial it is to target mitochondrial function in treatment plans for individuals who have two or more genetic abnormalities. Additionally, the discovery of *PRKN* pathogenic variants in people with mixed or atypical symptoms highlights the need for thorough genetic testing in the diagnosis of complex neurodegenerative diseases, going beyond the conventional emphasis on genes linked to EIF2B. This dual pathogenic variant scenario not only complicates the clinical picture but also highlights the need for a broader approach to genetic screening and potential therapeutic interventions aimed at mitochondrial health and neuronal integrity.

Diagnosing VWMD can be quite challenging because its symptoms overlap with those of various neurological disorders. In this case, we had to consider differential diagnoses such as multiple sclerosis and other leukodystrophies. Advanced neuroimaging techniques, particularly MRI, play a pivotal role in revealing the characteristic periventricular white matter hyperintensities associated with VWMD [14]. Confirmation through genetic testing further emphasizes the necessity of a thorough diagnostic approach, especially for atypical presentations.

To manage this case, we opted for symptomatic treatment with Levodopa/Carbidopa, which led to noticeable improvements in the patient's motor symptoms. This choice aligns with the literature suggesting that dopaminergic treatment can be beneficial for patients with movement disorders linked to the *PRKN* pathogenic variant [15]. , While we did not explore alternative treatments targeting the integrated stress response, such avenues are still promising for future management strategies. Following treatment, the patient showed short-term improvements in motor function. However, long-term outcomes stay uncertain, as VWMD is a progressive disorder with a highly variable prognosis. The literature states that early intervention and a multidisciplinary approach can significantly enhance quality of life and functional independence. Factors such as the extent of neurological involvement and the presence of genetic pathogenic variants are likely to influence a patient's prognosis [16].

Our case report contributes valuable insights into the recognition of adult-onset VWMD and the implications of genetic pathogenic variants in its clinical presentation. This underscores the importance of considering genetic testing for patients showing atypical neurological symptoms, particularly when there is a family history of similar conditions. Furthermore, this case highlights the necessity of a multidisciplinary approach to improve patient care and management.

This case is particularly noteworthy because of the rarity and complexity of vanishing white matter leukoencephalopathy (VWML), particularly in adult populations. Vanishing white matter leukoencephalopathy (VWML) is

often associated with children; however, when it occurs in adults and is characterized by added symptoms such as parkinsonism, it becomes even rarer and more challenging to diagnose. Although there is currently no treatment, early discovery is imperative to manage symptoms and prevent the occurrence of more issues. The importance of giving information about vanishing white matter leukoencephalopathy (VWML) is underscored by this narrative, particularly in regions such as Palestine where there is a chronic shortage of neurological disease research. The need for more comprehensive investigations in this field is underscored by the scarcity of research on vanishing white matter leukoencephalopathy (VWML) in adult Palestinians. This paper advances knowledge about vanishing white matter leukoencephalopathy (VWML) and encourages the development of more medical resources and research in Palestine to improve the capacity for diagnosis and treatment of neurological disorders in patients by focusing on this unique occurrence.

Abbreviations

VWMD	Vanishing white matter disease
VWML	Vanishing white matter leukoencephalopathy
eIF2B	Eukaryotic translation initiation factor 2B
MRI	Magnetic resonance imaging
CSF	Cerebrospinal fluid
FLAIR	Fluid-attenuated inversion recovery

Acknowledgements
We thank the patient for giving consent for publication. The authors would like to thank Al-Quds University for proofreading and revising our manuscript.

Author contributions
BD contributed to handling manuscript formation and data collection. YA, NA & MA contributed to the study design and analyzing data. IA contributed to the supervision of the case report. All authors read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
The data generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval for this study was obtained from the ethics committee of Al-Quds University, and informed consent was provided by the patient involved.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report.

Competing interests
The authors declare no competing interests.

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Received: 10 October 2024 / Accepted: 31 December 2024
Published online: 04 January 2025

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