The Canadian Journal of Neurological Sciences (2025), 1–4
doi:10.1017/cjn.2024.351

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Letter to the Editor: New Observation

FLVCR1 Gene Mutation in a Patient with an Atypical Multiple Sclerosis-Like Presentation

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Keywords: FLVCR1 gene; multiple sclerosis; posterior column ataxia with retinitis pigmentosa; retinitis pigmentosa; type 1 DM

A 25-year-old woman diagnosed with diabetes mellitus type 1 (DM1) since early childhood presented for the first time to the neurology clinic at Princess Basmah Teaching Hospital in Jordan with a 1-year history of progressive and disabling bilateral lower extremities weakness. The timeline of events is shown in Figure 1. Upon clinical and paraclinical investigation, brain and spinal cord MRI revealed a leukodystrophy pattern with normal T1-weighted Imaging (T1WI) cervical cord and some T2-weighted Imaging (T2WI) heterogenous cervical signals (Figure 2). Considering her history of DM1, adrenoleukodystrophy was initially considered, despite the fact that this entity tends to present later in life with mild neurological symptoms in most affected females.[1] Testing for the ABCD1 gene and very long-chain fatty acids were negative.

She was readmitted to our hospital 7 months later, in December 2021, for a brain MRI and further investigations only. The brain MRI was suggestive of a demyelinating process, and the cervical cord showed a heterogeneous cord signal with multifocal intrinsic high signal abnormality as seen in Figure 3. After 11 months of her latest admission, in November 2022, she was readmitted, this time presenting with worse left-sided weakness and a decrease in visual acuity for the past 2 weeks. A contrast-enhanced brain MRI revealed two new enhancing lesions overlapping the preexisting leukodystrophy pattern, raising suspicions of a demyelinating process; however, the lumbar cord MRI was normal (Figure 4). Accordingly, corticosteroid treatment (methylprednisolone 1 g/day intravenous for 5 days) yielded an excellent response, and she was discharged home with dramatic improvement.

Given the unusual overlap of different central nervous system (CNS) disease patterns, further investigations using genetic panels (targeted gene sequencing for leukodystrophy panel) revealed a likely pathogenic FLVCR1 gene mutation with a novel variant c.687_688de (p. Phe229LeufsTer37). Additionally, CSF quantitative analysis revealed positive oligoclonal bands, while serum myelin oligodendrocytes glycoprotein IgG and serum aquaporin-4 antibodies were negative. Finally, the vasculitis workup was negative.

Four months following her previous relapse, in March 2023, she returned with left-sided weakness. Although a repeat MRI brain and cord showed some supratentorial lesions with partial ring enhancement, they did not correlate with the patient's symptoms (Figure 5). In addition, this time symptoms did not respond to high-dose corticosteroid treatment, and her condition continued to deteriorate over time, leading her to be unable to stand unaided.

Importantly, at the time, symptoms presentation and progression did not align with the typical presentation of relapsing-remitting multiple sclerosis (MS) due to incomplete resolution of symptoms between attacks and variable response to corticosteroids.

Notably, she had no history of seizures, diplopia, urine or stool incontinence. Her vaccination records were up to date, and both antenatal and postnatal periods were uneventful, and there is no history of trauma, drug abuse, mood changes or psychosis. Family history was not informative. Apart from insulin for DM1, she had no significant medication history before symptoms onset. Since then, she was started on folic acid 5 mg, atorvastatin 40 mg, carbamazepine 400 mg and gabapentin 300 mg, with carbamazepine and gabapentin used for pain management. More recently, fingolimod 0.5 mg a day since September 6, 2023.

On examination, she was alert and oriented. The language was intact. Her pupils were equal and reactive, and extraocular movements were intact, though bilateral horizontal end-gaze nystagmus was observed without diplopia. The remaining cranial nerves examination was unremarkable.

The strength of her upper extremities was full, while her lower extremities were graded as 4 out of 5 on the right and 3 out of 5 on the left; her weakness was suggestive of an upper motor neuron pathology. She had an increased muscle tone in all limbs, with definite spasticity in her lower limbs. Brisk reflexes were noted in both upper limbs graded as 3. Also, the right patellar reflex was brisk, and the left patellar reflex was brisk with clonus graded as 3 and 4, respectively. Hoffmann and Babinski's signs were present bilaterally. The sensory examination did not reveal any impairment. A nerve conduction study revealed peripheral axonal motor and sensory neuropathy.

The Romberg test was negative. Dysmetria and dysdiadochokinesia were present bilaterally, in addition to spastic and ataxic

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Cite this article: Sa'di Q, Alsmadi S, Shtaiyat W, Qasaimeh M, and Munhoz RP. FLVCR1 Gene Mutation in a Patient with an Atypical Multiple Sclerosis-Like Presentation. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2024.351

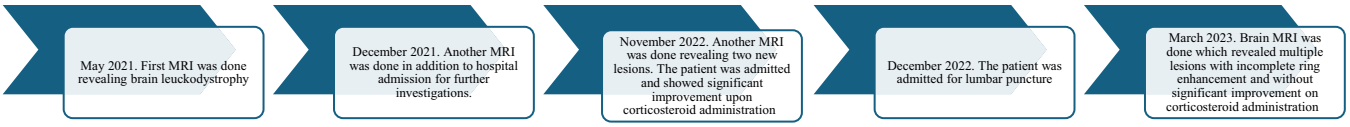

Figure 1. Timeline of events.

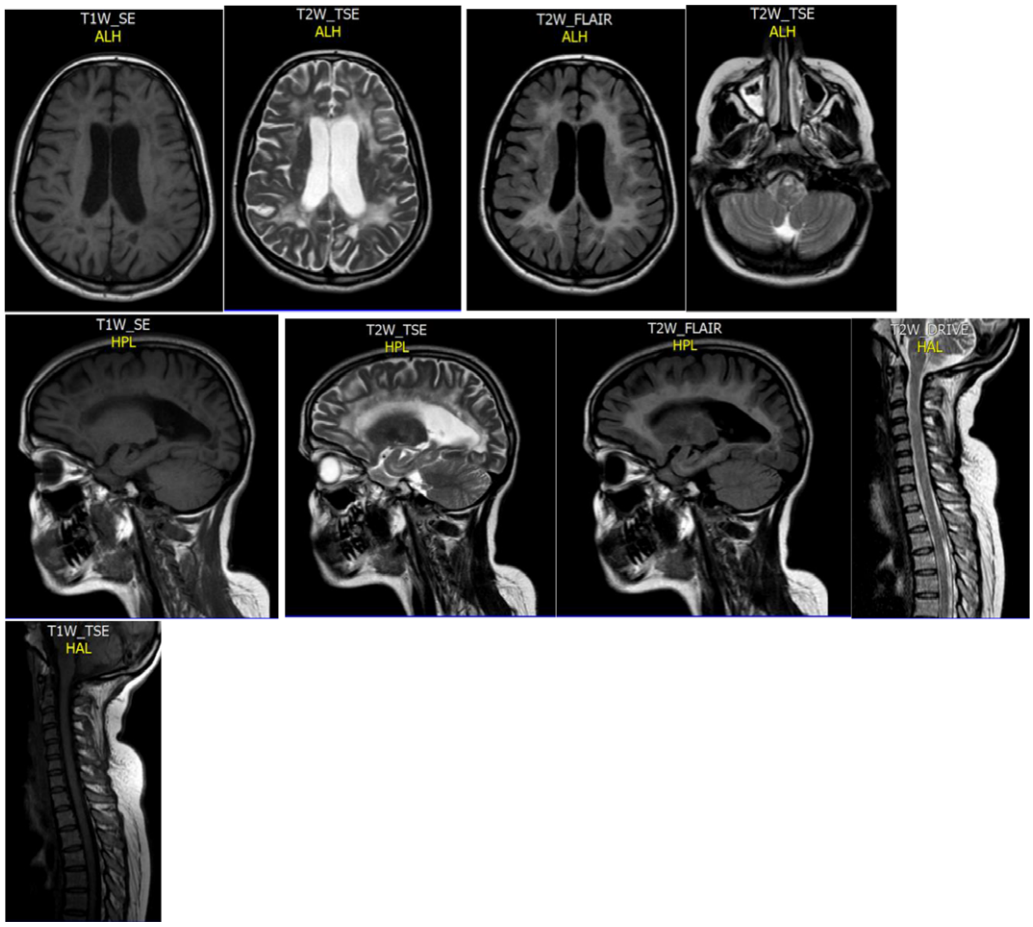

Figure 2. The brain and cervical spine MRI in May 2021 showed diffuse bilateral periventricular white matter hyperintensities on T2-weighted Imaging (T2WI) and Fluid-Attenuated Inversion Recovery (FLAIR) which were hypointense on T1-weighted Imaging (T1WI). There was a dilation of both the lateral and third ventricles, in addition to generalized atrophic changes. Regarding the sagittal cervical and upper dorsal spine MRI, the non-contrast T1WI showed normal cord size with no signal abnormality, while the T2WI image showed a heterogenous signal with multifocal intrinsic hyperintense lesions, more obviously opposite to C3–C4, C7–T1 and T4 levels.

gait, resulting in an inability to stand or walk unassisted at the time of relapses.

Her eye exam showed a relative afferent pupillary defect on the left, the distance vision test showed 6/9 in the left eye and 6/36 in the right eye and her optical coherence tomography showed bilateral temporal retinal nerve fiber layer thinning and atrophy. Notably, our patient did not have typical features of retinitis pigmentosa.

Considering FLVCR1, it is a transmembrane heme and choline transport that plays a crucial role in protecting against the toxic effects of heme.[2,3] The effect of the FLVCR1 gene mutation is mediated by disturbing heme hemostasis, leading to elevated intracellular heme levels, ultimately resulting in cell toxicity and apoptosis.[3] Moreover, heme is also known to cause neurotoxicity and neurodegeneration, leading to the development of such disorders.[3]

The FLVCR1 gene mutation has been linked to some diseases, including posterior column ataxia with retinitis pigmentosa (PCARP), hereditary sensory and autonomic neuropathy, Diamond–Blackfan anemia and Walker–Warburg syndrome.[4,5]

In the context of PCARP, the most commonly reported mutation involves the FLVCR1a isoform. PCARP is a rare autosomal recessive disorder marked by the combination of retinitis pigmentosa and loss of proprioception with sensory ataxia and is linked to a hyperintense signal of the dorsal spine on MRI of affected individuals.[3] Case reports of PCARP are scarce in the literature.[6] Our report stands out due to the association of DM1, leukodystrophy and CNS demyelinating processes with positive oligoclonal bands, which increase the possibility of MS diagnosis There have been no reports of PCARP associated with MS or DM1.

Regarding the association between FLVCR1 mutation and DM, excess heme has been implicated as a risk factor for the development of glucose intolerance and type 2 DM,[7] as excess heme generates an environment rich in oxidative stress that induces beta cell death, insulin resistance and disturbing hepatic function, ultimately leading to DM.[8] Thus, we can propose that the patient FLVCR1 mutation might be linked to her DM. Moreover, in a family with a similar presentation of PCARP, four individuals were diagnosed with maturity-onset diabetes mellitus (DM), suggesting a possible, though unproven, genetic link between PCARP and DM.[9] Nevertheless, this theory needs further investigation to confirm. Furthermore, MS and DM1 are both presumed autoimmune

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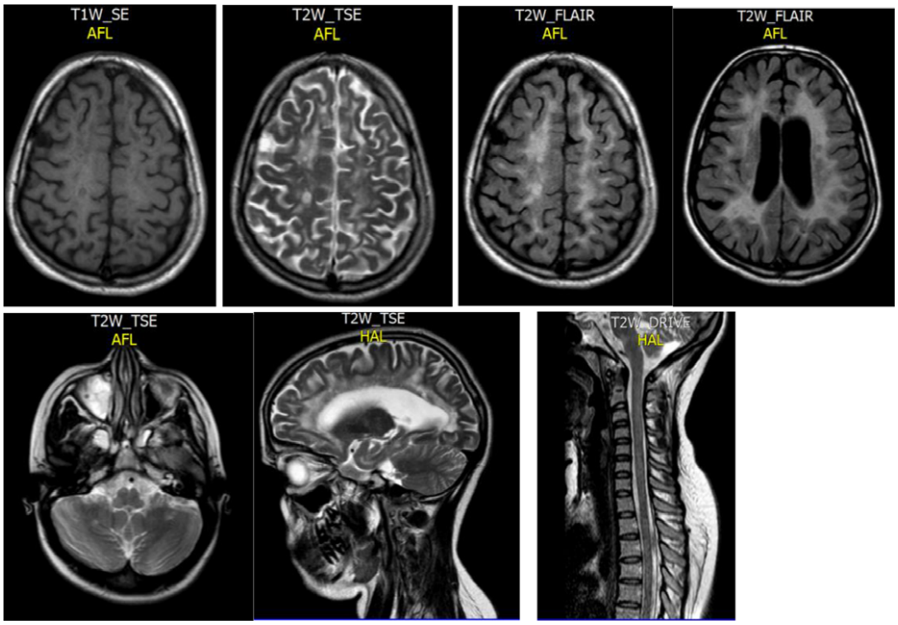

Figure 3. The brain MRI in December 2021 showed bilateral periventricular foci with abnormal high signal intensity on Fluid-Attenuated Inversion Recovery (FLAIR), T2-weighted Imaging (T2WI), which were hypointense on T1-weighted Imaging (T1WI), with multiple abnormal signal intensities seen in both cerebral hemispheres, pons and cerebellum; some of these lesions on post-contrast image showed incomplete ring enhancement, which is suggestive of a demyelinating process. The axial T2WI of the posterior fossa at the level of medulla oblongata showed two hyperintense signal abnormalities seen in both cerebellar hemispheres. Additionally, there was an opacification of the right maxillary sinus. Regarding the sagittal T2WI cervical and upper dorsal cord MRI, there were heterogeneous cord signals with multifocal intrinsic high signal abnormality.

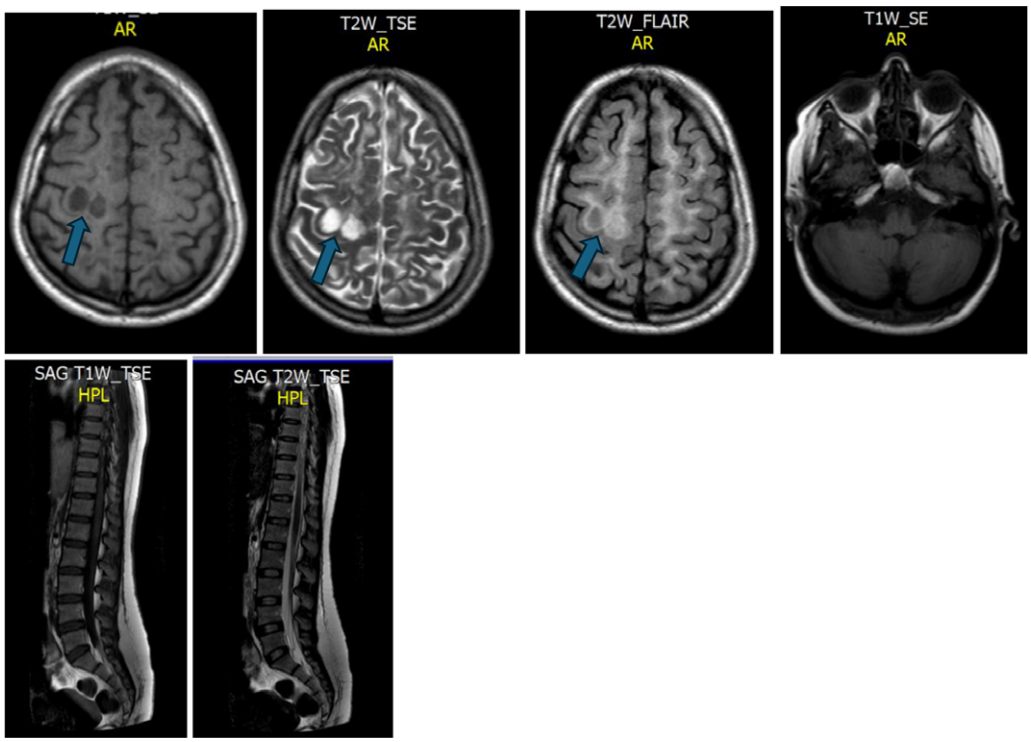

Figure 4. The brain and whole spine MRI in November 2022 showed two periventricular hyperintense lesions on T2-weighted Imaging (T2WI) and two hypointense lesions on T1-weighted Imaging (T1WI); these lesions are typical for demyelination (blue arrows). Regarding the sagittal lower lumbar and dorsal spine MRI, the T1WI and T2WI showed no signal abnormality in the visualized lower cord or conus medullaris.

conditions that share some immunological and etiological characteristics,[10] although further study is needed. This patient's MS-like presentation may have been coincidental or possibly modulated by DM1 or the FLVCR1 mutation. In summary, we are presenting a case with DM1, PCARP and a possible MS diagnosis. The complex overlapping pathophysiology between these disorders supports continued research and expanding investigations to understand the potential association between them.

This report faced some limitations, including the inability to verify the association between PCARP and DM from one side and the inability to confirm MS diagnosis from the other side. Additionally, due to a lack of sensory deficit and typical hyperintense lesions of PCARP on dorsal spinal MRI, we cannot confirm her PCARP diagnosis; this case might be an atypical PCARP presentation that would further extend the spectrum.

The case presented here presented features in keeping with MS, namely, the presence of enhancing periventricular lesions, positive oligoclonal bands and response to high-dose steroids in her first episode. Nevertheless, MS diagnosis became uncertain following genetic test results, which revealed likely pathogenic biallelic

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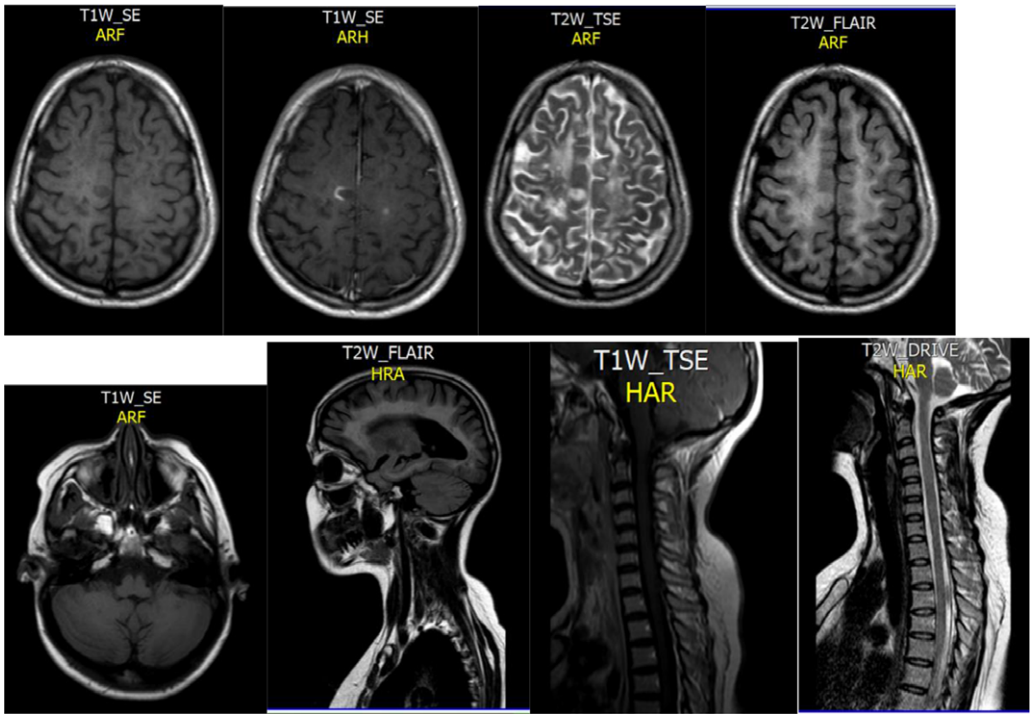

Figure 5. The brain and cervical spine MRI in March 2023 showed diffuse supratentorial white matter abnormalities with high signal intensity and severe volume loss, along with multiple supratentorial white matter lesions, some of which showed incomplete ring enhancement. Regarding the cord, there were patchy signal abnormalities with cord atrophic changes. Overall findings are suggestive of an advanced white matter disorder involving the brain, brainstem and cord.

FLVCR1 gene mutations. The mutation is characterized by a novel variant c.687_688del (p. Phe229LeufsTer37). In this context, we speculate that her ataxia is most likely due to the brain, brainstem and cerebellar white matter lesions as posterior column abnormalities, such as those seen in cases of FLVCR1 gene mutations, were not found, which is consistent with the absence of deep sensory deficits on the examination. In addition, we did not have specific oligoclonal band levels, which leaves the MS diagnosis open to doubt.

In summary, this case report is the first presenting possible PCARP and MS in the same patient, thus highlighting a distinctive and unusual presentation, underscoring the importance of careful diagnosis and symptom monitoring. A key message from this case is the necessity of considering in-depth screening for rare disorders when faced with patients exhibiting atypical neurological symptoms, especially those not improving with standard medical therapy.

Availability of data and material. Relevant genetic data can be made available when it is requested by the authors.

Acknowledgments. The authors wish to thank the patient and her next of kin as well as the reviewers of the paper.

Author contributions. QS[1] and MQ[3] were involved in conceptualization, editing and supervision. RPM[4] was involved in manuscript revision, drafting, writing and supervision. SA[2] and WS[2] were involved in manuscript writing, editing and case follow-up. WS[2] was the one who brought this case to light.

Funding statement. The authors did not receive any form of funding for this case report production.

Competing interests. The authors confirm that they have no any competing interests.

Consent for publication. Written informed consent was obtained from the patient herself for the publication of this case report and any accompanying data and images. A copy of the signed written consent is available for review by the editor of the journal.

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