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

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Authors contribution: 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.

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 one-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 TIWI cervical cord and some T2WI heterogenous cervical signals. **Figure 2A**. 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 (VLCFAs) 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 2B**. 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 two weeks. A contrast-enhanced brain MRI revealed two new enhancing lesions overlapping the pre-existing leukodystrophy pattern, raising suspicions of a demyelinating process, however, the lumbar cord MRI was normal. **Figure 2C**. 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 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.

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Four months following her previous relapse, in March 2023, she returned with left-sided weakness, while a repeat MRI brain and cord showed some supratentorial lesions with partial ring enhancement, they did not correlate with the patients' symptoms. **Figure 2D**. 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 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, carbamazepine and gabapentin were used for pain. More recently, Fingolimod 0.5 mg a day since 6th of September 2023.

Figure 1. Timeline of events

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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 (UMN) 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 (NCS) revealed peripheral axonal motor and sensory neuropathy.

The Romberg test was negative. Dysmetria and dysdiadochokinesia were present bilaterally, in addition to spastic and ataxic 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 (OCT) showed bilateral temporal retinal nerve fiber layer (RBFL) thinning and atrophy. Notably, our patient did not have typical features of retinitis pigmentosa.

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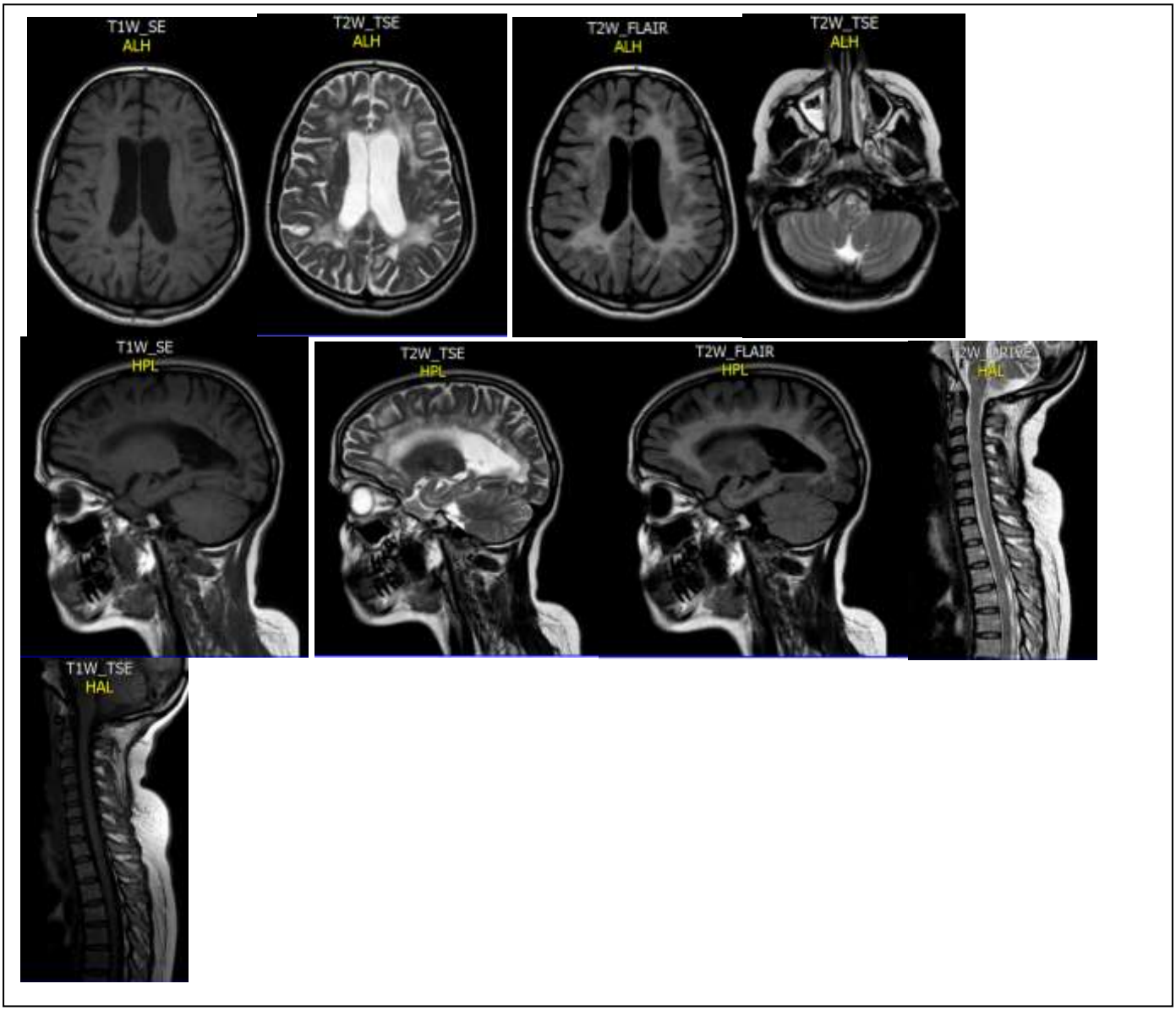

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93 **2A**: The brain and cervical spine MRI in May 2021 showed diffuse bilateral periventricular
94 white matter hyper-intensities on T2WI, FLAIR, hypointense on T1WI. There is a dilation of
95 both the lateral and third ventricles, in addition to generalized atrophic changes. Regarding the
96 sagittal cervical and upper dorsal spine MRI, the non-contrast T1WI showed normal cord size
97 with no signal abnormality, while the T2WI image showed heterogenous signal with multifocal
98 intrinsic hyperintense lesions, more obviously opposite to C3-C4, C7-T1, and T4 levels.

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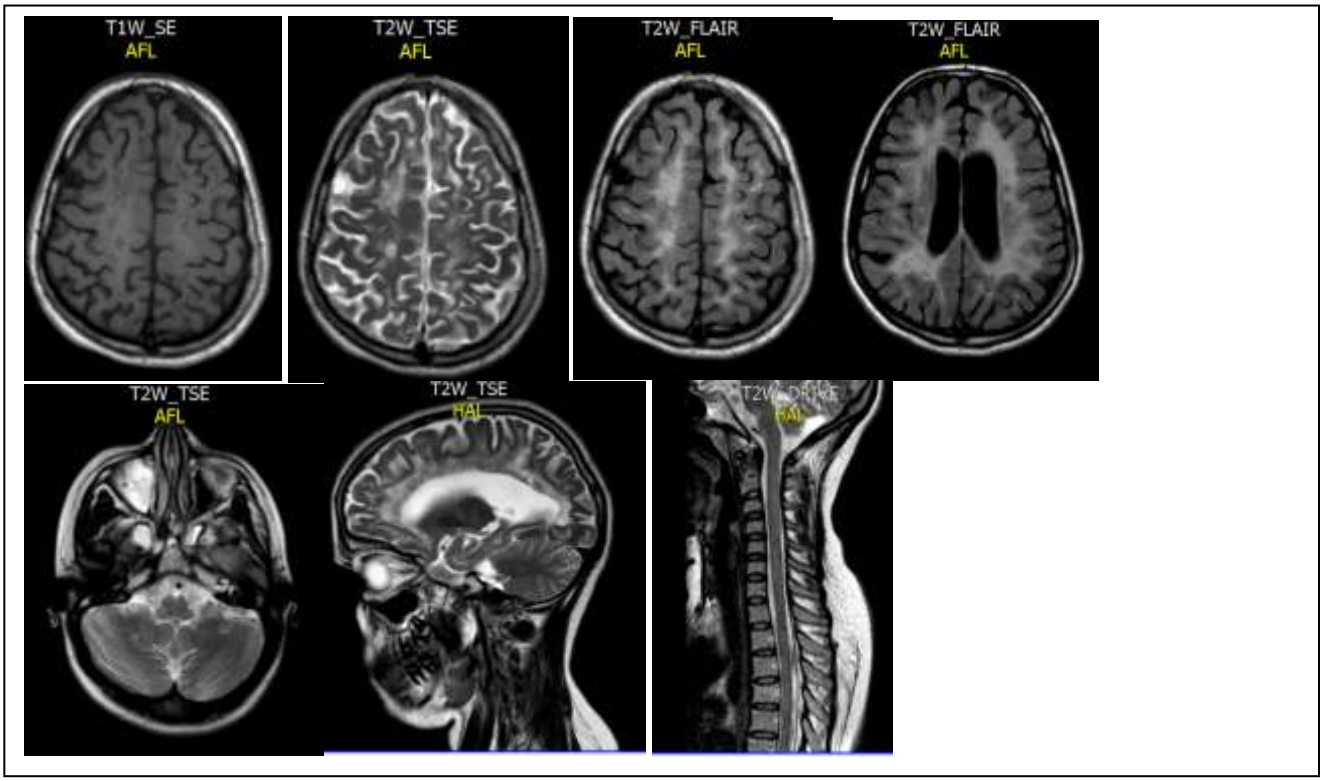

2B: The brain MRI in December 2021 showed bilateral periventricular abnormal high signal intensity foci on FLAIR T2WI, which were hypointense on T1WI, with multiple abnormal signal intensities seen in both cerebral hemispheres, pons, and cerebellum, some of these lesions on post contrast image showed incomplete ring enhancement which is suggestive of demyelinating process. The axial T2WI of the posterior fossa at the level of medulla oblongata showed two hyperintense signal abnormality 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.

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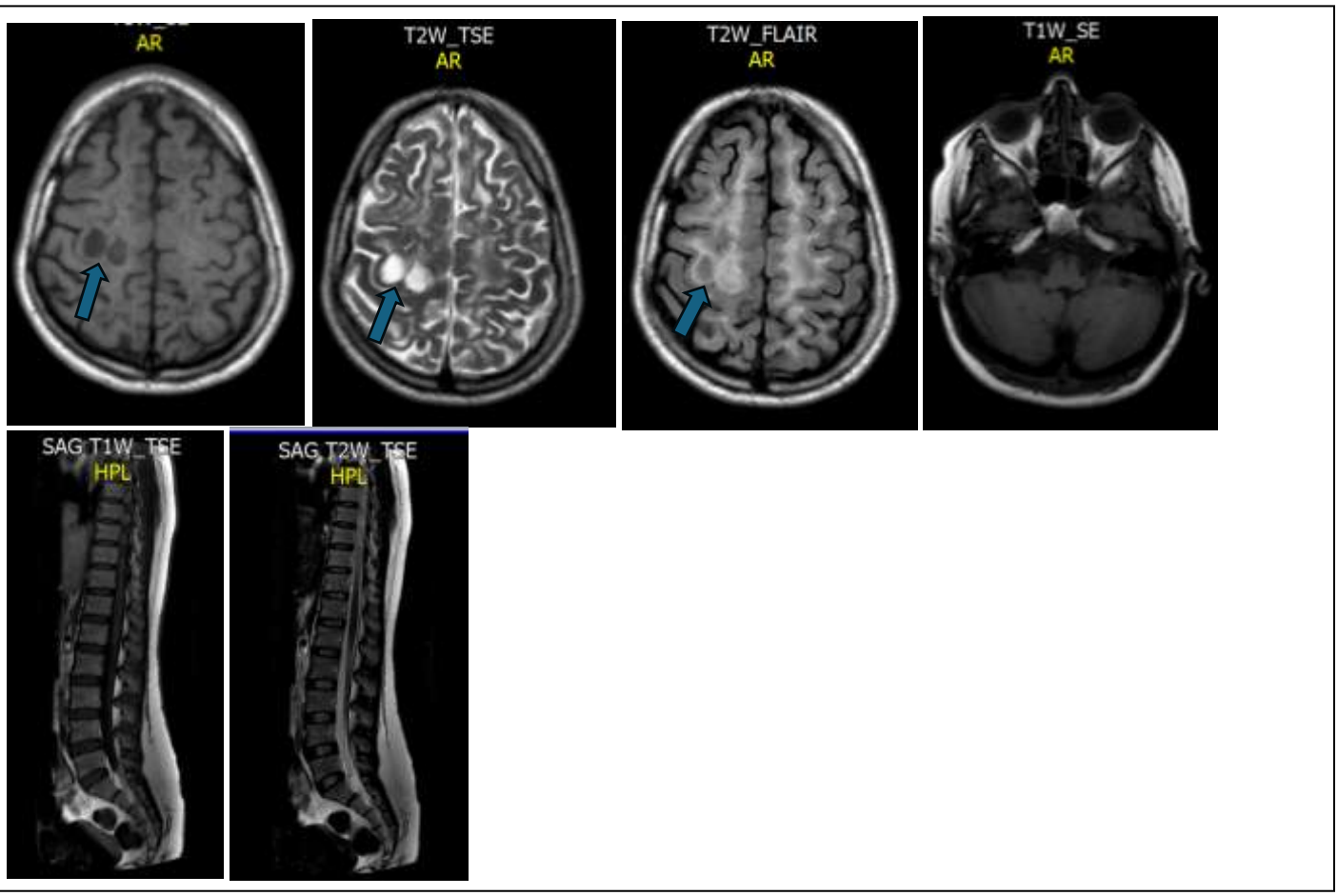

2C: The brain and whole spine MRI in November 2022 showed two periventricular lesions hyperintense lesions on T2WI and two hypointense lesions on T1WI, the lesions are typical for demyelination (blue arrows). Regarding the sagittal lower lumbar and dorsal spine MRI, the T1WI and T2WI showed no signal abnormality in the visualized lower cord or conus medullaris.

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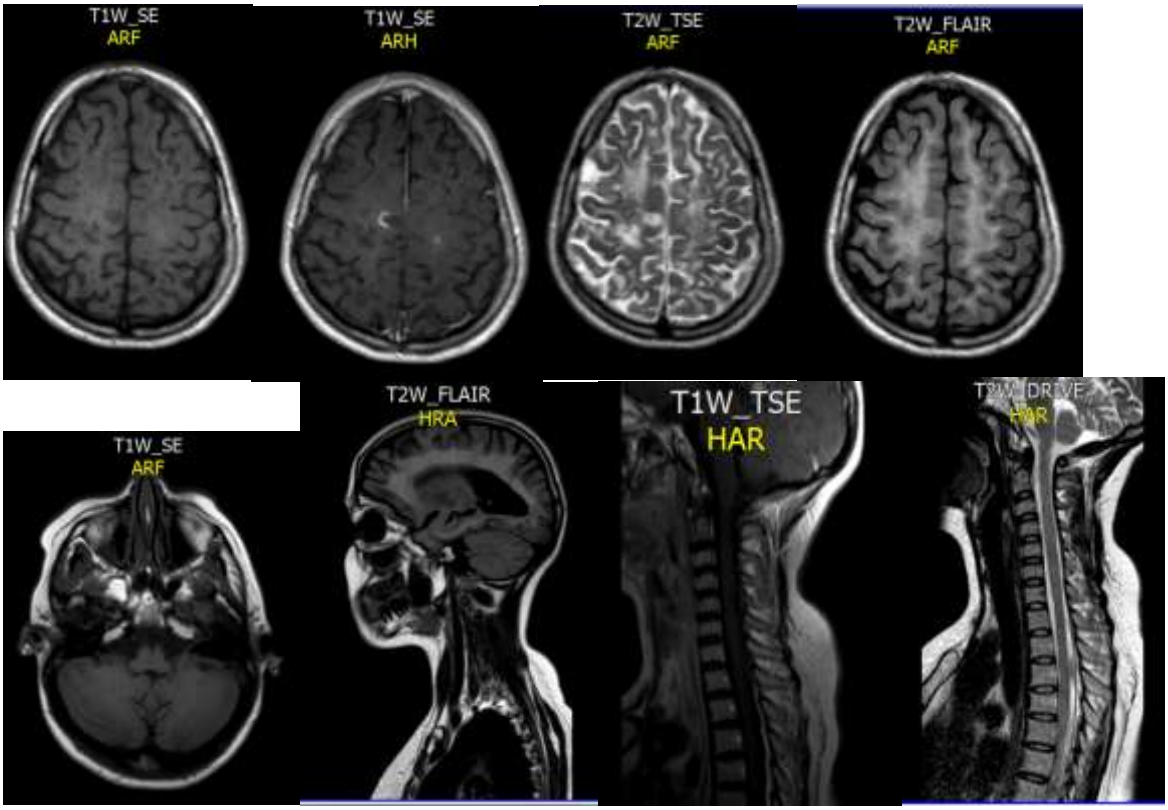

2D: The brain and cervical spine MRI in March 2023 showed diffuse supratentorial white matter abnormal high signal with severe volume loss along with multiple supra and tentorial white matter lesions, some of them showed incomplete ring enhancement. Regarding the cord there are patchy signal abnormalities with cord atrophic changes. Overall findings are suggestive of advanced white matter disorder involving brain, brain stem as well as the cord

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

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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 (HSAN), Diamond Balckfan anemia (DBA), and Walker–Warburg syndrome. [4,5]

In the context of posterior column ataxia with retinitis pigmentosa (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 PCARP similar presentation, four individuals were diagnosed with maturity-onset diabetes mellitus, suggesting a possible unproven genetic link between PCARP and DM. [9] Nevertheless, this theory needs further investigation to confirm. Furthermore, MS and DM1 are both presumed autoimmune 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

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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 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 probably due to the brain, brainstem, and cerebellar white matter lesions as posterior column abnormalities, as those seen in cases of FLVCR1 gene mutations, were not found, in keeping with the absence of deep sensory deficits on the exam. In addition, we did not have specific oligoclonal bands levels, which keeps 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.

Consent for publication

Written informed consent was obtained from the patient herself for 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.

Availability of data and material

Relevant genetic data can be made available when it is requested by the authors.

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Declaration of Competing Interest: The authors confirm that they have no any competing interests.

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