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Radiologically isolated syndrome accompanying hereditary neuropathy with liability to pressure palsies: A case report of a new demyelinating phenotype

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Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder caused by peripheral myelin protein 22 (PMP22) gene deletion on chromosome 17p11.2-p12.[1] It leads to peripheral nerve susceptibility to mechanical stress, typically presenting as recurrent mononeuropathies.

Radiologically isolated syndrome (RIS) is considered a preclinical stage of multiple sclerosis (MS), defined by incidental magnetic resonance imaging (MRI) findings of central nervous system (CNS) demyelination without accompanying clinical symptoms.[2]

To our knowledge, the coexistence of genetically confirmed HNPP and RIS has not been previously reported. Documenting such a case may help uncover potential shared mechanisms underlying both peripheral and central myelin vulnerability. This report aims to highlight this novel overlap and emphasize the need for integrated genetic and neuroimaging evaluation in atypical demyelinating presentations.

A 28-year-old woman presented to our clinic with complaints of intermittent numbness, tingling, weakness in both hands and feet, and difficulty lifting her left foot. Her symptoms were triggered during periods of increased use of her extremities and subsided with rest. Her medical history revealed a prior surgery for carpal tunnel syndrome (CTS) on the left wrist. Cranial nerve examination was unremarkable.

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On motor examination, dorsiflexion strength of the left ankle and great toe was graded as 1/5, while strength in the other extremities was preserved at 5/5. Sensory examination revealed a deficit along the lateral aspect of the left leg. Deep tendon reflexes were diffusely hyperactive.

Electromyography (EMG) revealed markedly slowed nerve conduction, particularly at entrapment sites, along with conduction blocks ranging from 30% to 50% in some motor compound muscle action potentials (CMAPs). Motor latencies of the median nerve were prolonged. Sensory nerve conduction was also slowed, suggestive of demyelination. These findings were consistent with a sensorimotor demyelinating polyneuropathy. Additionally, visual evoked potentials (VEPs) demonstrated bilateral prolongation of P100 latencies (left: 120 ms, right: 146 ms).

Brain MRI revealed multiple T2 and fluid attenuated inversion recovery (FLAIR) hyperintense lesions in the periventricular and juxtacortical regions, oriented perpendicular to the corpus callosum. One gadolinium-enhancing lesion was present in the left centrum semiovale (Figure 1). These findings were consistent with RIS based on the 2023 McDonald criteria. Cervical spine MRI was normal.

The patient tested negative for both neuromyelitis optica (NMO) and myelin oligodendrocyte glycoprotein (MOG) antibodies, and cerebrospinal fluid (CSF) analysis via lumbar puncture revealed no evidence of oligoclonal bands (OCBs). Due to her history of recurrent peripheral entrapment neuropathies, HNPP was considered in the differential diagnosis, and genetic testing was performed. This analysis identified a heterozygous deletion encompassing the entire PMP22 gene, confirming the clinical diagnosis of HNPP at the molecular level. These combined findings support the diagnosis of RIS under the 2023 McDonald criteria and confirm HNPP based on clinical features, characteristic EMG abnormalities, and PMP22 gene deletion, while acknowledging that CSF OCB negativity does not exclude RIS.

Physical therapy was recommended to improve distal weakness and preserve functional mobility. Annual brain MRI follow-up was planned to monitor demyelinating lesion burden and assess for new active disease, as yearly intervals are considered sufficient for RIS surveillance. At short-term follow-up, the patient remained clinically stable without new neurological symptoms.

"I felt relieved to have an explanation for my symptoms and appreciated the thorough evaluation and follow-up plan."

HNPP is a peripheral demyelinating disorder classically attributed to PMP22 gene deletion.[3] However, increasing evidence suggests that PMP22 may also play a role in the CNS, challenging the traditional dichotomy between peripheral and central demyelination. Expression of PMP22 messenger ribonucleic acid (mRNA) and protein in oligodendrocytes has been documented, suggesting a broader biological function.[4,5]

Additionally, neuroimaging studies in patients with HNPP have shown subcortical white matter abnormalities and decreased total white matter volume, even in the absence of clinical CNS symptoms.[4] Electrophysiological data further support central involvement, with delayed central conduction observed in auditory and blink reflex pathways.[4]

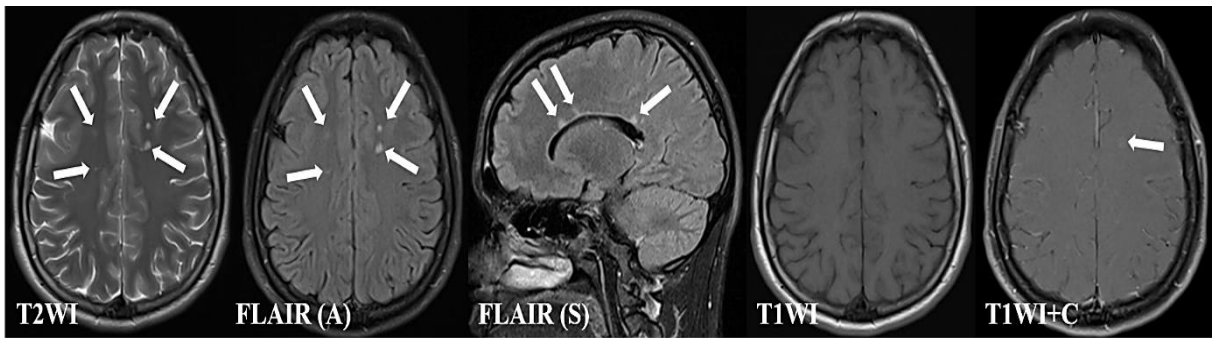

Figure 1. Brain magnetic resoance imaging (MRI) demonstrates multiple white matter lesions (white arrows) in the juxtacortical and periventricular regions at the level of the centrum semiovale, extending perpendicularly to the corpus callosum, as seen on T2-weighted (T2WI) and fluid attenuated inversion recovery (FLAIR) sequences – findings that may be consistent with radiologically isolated syndrome (RIS)/multiple sclerosis (MS). On post-contrast T1-weighted imaging (T1WI + C), a demyelinating plaque measuring 5 mm in diameter with mild contrast enhancement is observed in the left centrum semiovale (white arrow).

RIS, on the other hand, is typically identified as part of the preclinical spectrum MS and is thought to result from autoimmune mechanisms in genetically susceptible individuals.[6] The presence of RIS findings in a patient with genetically confirmed HNPP raises the question of whether PMP22 deletion could contribute not only to peripheral demyelination but also to central myelin vulnerability.

Combined central and peripheral demyelination (CCPD) is a rare but recognized syndrome often associated with autoimmune antibodies such as anti-neurofascin-155 (NF155), aquaporin 4 (AQP4), or MOG, and may respond to immunosuppressive therapy.[7,8] Current knowledge on CCPD is largely based on case reports and small case series. A review of the literature revealed a two-center retrospective study evaluating a cohort of 31 patients, in which the clinical spectrum, diagnostic characteristics, treatment responses, and disease course of CCPD were analyzed. The findings indicated that CCPD typically presented following an infectious trigger, affected both the CNS and peripheral nervous system (PNS), and manifested as a heterogeneous and treatment-resistant condition that could not be fully explained by existing diagnostic criteria for MS or chronic inflammatory demyelinating polyneuropathy (CIDP).[9] Case reports have described the co-occurrence of Charcot-Marie-Tooth disease type 1A (CMT1A) and MS, suggesting a potentially shared demyelinating mechanism despite differing genetic origins.[8] In a nationwide study conducted in Japan, 40 cases of CCPD were evaluated. The findings revealed that sensory and motor symptoms were predominant, CSF protein levels were generally elevated, but the rate of OCB positivity was low.[10] OCB positivity in patients with RIS ranges from approximately 30% to 50%, and its presence is associated with an increased risk of progression to clinical MS. In our patient, OCB was negative; notably, OCB positivity is not mandatory for RIS diagnosis but serves as an important risk factor for progression to clinical MS. Unlike immune-mediated CCPD cases, our observation raises the possibility of a shared genetic predisposition underlying both conditions, although a coincidental coexistence cannot be ruled out.

We propose the term ''Potential PMP22-Associated Dual Demyelination'' to describe this phenotype, where a single genetic abnormality might predispose to both central and peripheral demyelination. Recognition of such cases may prompt more comprehensive diagnostic evaluations and support research exploring the broader role of PMP22 in myelin biology.

This case documents the first known coexistence of RIS and genetically confirmed HNPP, suggesting a potential but preliminary association involving PMP22 beyond the PNS. Given the limitations inherent to a single-case observation, these findings should be viewed as hypothesis-generating, necessitating further research and validation through additional clinical and molecular studies. Broader recognition and investigation of such overlap syndromes could enhance diagnostic precision and guide future research into demyelinating disorders.

Conflict of Interests

The authors declare no conflict of interest in this study.

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None.

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