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Hereditary Spastic Paraparesis Mimicking Primary Progressive Multiple Sclerosis Due to CYP7B1 Gene Mutation: A Case Report

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ABSTRACT

The hereditary spastic paraplegias (HSPs) are a group of disorders characterised by progressive lower limb weakness and spasticity. This report presents the a case of a 49-year-old female with spastic paraparesis, initially suspected to be primary progressive multiple sclerosis (PPMS). Genetic testing later identified two mutations in the CYP7B1 gene that was associated with the SPG5 form of HSP. This case highlights the challenge of distinguishing HSP from other chronic spinal cord diseases and emphasizes the role of genetic analysis in rare cases of spastic paraplegia.

Keywords: Hereditary spastic paraplegia, Spastic paraparesis, Primary progressive multiple sclerosis, CYP7B1 gene mutation, Genetic testing.

I. INTRODUCTION

Hereditary spastic paraplegia defines genetically and clinically heterogeneous group of disorders which is mainly characterized by progressive weakness of lower limbs and spasticity. The HSPs can be classified as either 'pure' (uncomplicated) or 'complex' (complicated). Pure forms involve lower limb spastic paraplegia and may include bladder involvement and subtle sensory signs such as impaired vibration sense. Complicated forms include additional neurological and non-neurological manifestations, such as cognitive impairment, dysarthria, optic atrophy and peripheral neuropathy. Due to overlapping clinical features, HSP may sometimes lead to misdiagnosis of other neurodegenerative or neuroinflamative diseases including primary progressive multiple sclerosis (PPMS). In this case, we report a patient of HSP due to a CYP7B1 gene mutation who presented with spastic paraparesis, initially misdiagnosed as PPMS.

II. CASEPRESENTATION

A 49-year-old female was admitted in July 2024 for bilateral lower limb weakness and spasticity, progessively worsening over the past 10 years. Her symptoms initially manifested as a sensation of tightness in the legs and rapid fatigue, limiting her ability to walk more than 20 meters before needing to rest. She also reported urinary urgency but no sensory disturbances, spinal pain, or radicular symptoms. There were no visual impairments or other non-neurological symptoms.

The patient's family history revealed similar symptoms in one of her a sister with similar symptoms, suggesting a hereditary condition.

Clinical examination showed a spastic gait with lower limb muscle strength reduced to 3/5 at the hips and 4/5 at the feet. Hyperreflexia was present, along with bilateral clonus and positive Babinski signs.

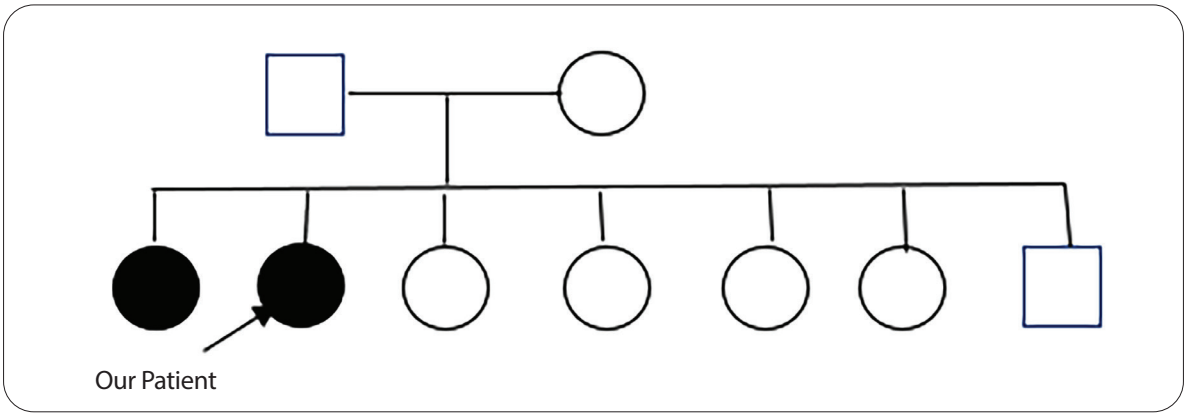

***Figure 1**. Pedigree of the Patient's Family The family pedigree shows a sister of the patient with a similar condition, suggesting a hereditary spastic paraplegia pattern. The patient's sixth sibling, a younger brother, died at age one, with no clear diagnosis available.*

III. INVESTIGATIONS

• Blood tests and routine biochemistry: All within normal limits. Cerebrospinal fluid (CSF) analysis: No abnormal cell counts; protein, glucose, and chloride levels were normal. However, oligoclonal bands (OCBs) were positive, Type 2.

• Spinal MRI (cervical and thoracic): No significant abnormalities were detected.

• Brain MRI: Showed non-specific white matter lesions in the periventricular area and centrum semiovale.

• Genetic testing: Using next-generation sequencing (NGS), the patient was found to carry two heterozygous mutations in the CYP7B1 gene (C.259T>C and C.187C>T), confirming the diagnosis SPG5 form of HSP.

IV. DIAGNOSIS

Based on the clinical presentation and genetic testing results, the patient was diagnosed with hereditary spastic paraplegia type 5 due to two heterozygous mutations in the CYP7B1 gene.

V. DISCUSSION

This case initially raised concerns about for primary progressive multiple sclerosis (PPMS), due to the progressive nature of the spasticity

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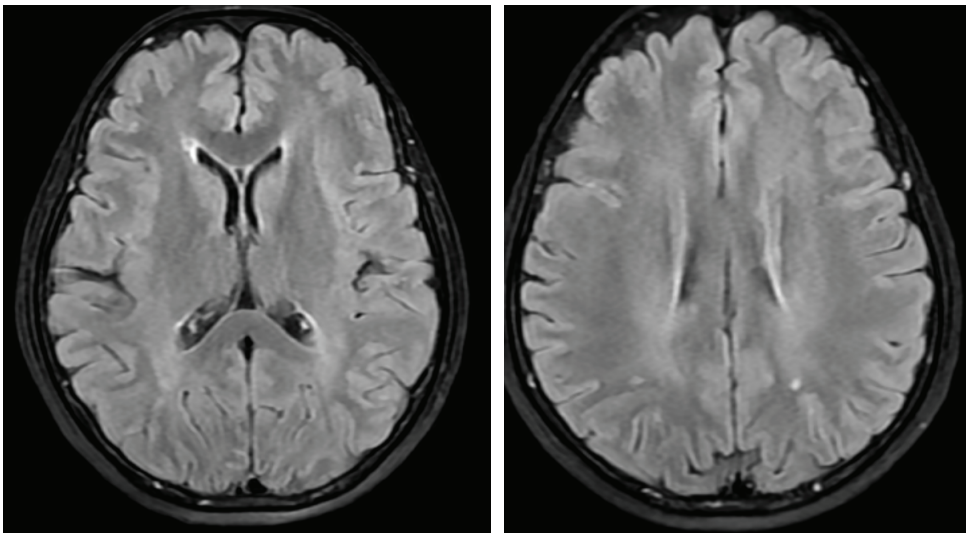

***Figure 2**. White Matter Lesions on Brain MRI (Lynx Ear Sign)*
The brain MRI of the patient shows non-specific white matter lesions in the periventricular region, particularly near the frontal horns of the lateral ventricles. These lesions exhibit the characteristic " ears of the lynx sign", which is a suggestive feature observed in hereditary spastic paraplegia.

limited to lower limbs begining at late adulthood and the presence of oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF). Although, the absence of demyelinating lesions as typical MRI features in PPMS, especially in the presence of documented family history gave us a clue to diagnose HSP. The results of genetic testing later confirmed the diagnosis SPG5 form of HSP. It is important to differentiate HSP from other chronic spinal cord diseases, as the management strategies differ significantly.

Although the presence of OCBs in the CSF is typically associated with multiple sclerosis, it has also been observed in a minority of HSP cases, particularly in patients with more severe and chronic presentations. This underscores the need for comprehensive diagnostic approaches, including genetic testing, especially when standard imaging and CSF analysis yield inconclusive results. However, an increasing number of cases of comorbid hereditary spastic paraplegia (HSP) and possible multiple sclerosis (MS), including the PPMS have been described.

Hereditary spastic paraplegia type 5 (SPG5) is an extremely rare subtype, with an estimated prevalence of 1 per million individuals, usually a pure hereditary spastic paraplegia although complex type features have been reported in some individuals. In addition to spasticity and weakness, people with Hereditary spastic paraplegia type 5 can present deep sensory disturbance, sphincter disorder or high arches of the feet. Symptoms can begin at any age from childhood through late adulthood. Most patients experience onset of symptoms in the second – fourth decades of life.

SPG5 due to mutations in the CYP7B1 gene encoding a distinct microsomal oxysterol-7α-hydroxylase. This enzyme is involved in the

degradation of cholesterol into primary bile acids. CYP7B1 deficiency results in accumulation of neurotoxic oxysterols, with elevation of 25-hydroxycholesterol (25-OHC) and 27-hydroxycholesterol (27-OHC) in the plasma and a much higher increase of 27-OHC in the CSF. However, it is important to note that two trials have demonstrated a reduction in cholesterol/bile acid biomarkers, but without benefit in terms of clinical, imaging, or electrophysiological outcome measure.

VI. CONCLUSION

This case of HSP type 5 due to mutations in the CYP7B1 gene highlights the clinical challenges in distinguishing hereditary spastic paraplegia from other conditions such as primary progressive multiple sclerosis. Genetic testing plays a crucial role in confirming the diagnosis of rare neurodegenerative disorders and guiding appropriate treatment and management.

REFERENCES

1. Harding AE. Hereditary spastic paraplegias: clinical features and classification. J Neurol Neurosurg Psychiatry. 1983.
2. Coutinho P, et al. Hereditary spastic paraplegia type 5: clinical manifestations and genetic findings. Ann Neurol. 1999.
3. Cardona J, et al. Hereditary spastic paraparesis due to SPG5 (CYP7B1 mutation): Clinical, genetic, and imaging findings. Neurología (English Edition). 2023;38(7):495-501.
4. Kumar KR, et al. Spastic paraplegia: advances in genetic understanding and disease management. Journal of Biological Chemistry. 2020;295(45):15100-15109.
5. Tessa A, et al. SPG5: A rare cause of hereditary spastic paraplegia due to mutations in CYP7B1. Brain. 2009;132(6):1589-1600.
6. Lydia Saputra, et al: Challenges and Controversies in the Genetic Diagnosis of Hereditary Spastic Paraplegia, Curr Neurol Neurosci Rep. 2021; 21(4): 15