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A Case Report on Ataxia Neuropathy Spectrum Disorder

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Abstract

Ataxia Neuropathy Spectrum (ANS) represents a complex array of neurological disorders primarily associated with POLG gene mutations. This case report examines a young male patient presenting with a compound homozygous POLG1 mutation c.2243G>C, encoding p.Trp748Ser. Despite lacking typical clinical features of Mitochondrial Autosomal Recessive Ataxia Syndrome (MIRAS) or Sensory Ataxia Neuropathy Dysarthria and Ophthalmoplegia (SANDO), the patient exhibited progressive neurological symptoms including behavioural abnormalities, seizures, and motor deficits. Notably, MRI imaging revealed atypical hyperintensities in multiple brain regions, including the frontal and parietal lobes, rarely reported in ANS cases. Molecular genetic analysis highlighted a less common mutation variant, emphasizing the genetic heterogeneity within ANS.

Introduction

The Ataxia Neuropathy Spectrum (ANS) constitutes a diverse range of clinical conditions centered around ataxia and neuropathy, devoid of significant muscle weakness or myopathy [1]. This spectrum encompasses conditions such as Mitochondrial Recessive Ataxia Syndrome (MIRAS) and Sensory Ataxia Neuropathy Dysarthria and Ophthalmoplegia (SANDO) [2]. ANS is a subset within the broader spectrum of POLG-related disorders, with the prevalent variants being the p.A467T and p.W748S mutations [3]. Characteristic MRI findings, including bright T2 lesions in the thalamus, cerebellum, and inferior olivary nucleus [4], serve as pivotal indicators prompting screening for POLG mutations and related ANS disorders. These radiological features may manifest in patients harboring homozygous W748S or heterozygous W748S/A467T POLG mutations [4]. Notably, in the Indian population, the predominant pathogenic mutations identified are p.L304R, followed by p.W748S, as reported by Deepha et al [5]. Additionally, previous studies have linked ANS to the gene mutation c.2243G>C encoding p.W748S [2]. POLG1 mutation c.2243G>C, resulting in the p.Trp748Ser variant was previously reported in a European population [6].

In this report, we present a unique case involving a young male individual who harbours compound homozygous POLG1 mutation c.2243G>C, resulting in the p.Trp748Ser variant. This patient

exhibits the hallmark features of Ataxia Neuropathy Spectrum (ANS); however, the clinical presentation, disease progression, and MRI findings demonstrate notable variations.

Case report

A young male born to non-consanguineous parents, initially presented with a prolonged history of headaches. Subsequently, he exhibited behavioural abnormalities characterized by apathy, suicidal tendencies, and reduced motivation, followed by a focal seizure progressing to generalized seizures. Over the course of the next year, the patient experienced progressive symptoms, including easy fatigability, sensory disturbances in the extremities, dysarthria, and gait ataxia. Eventually, he became bedridden, primarily due to ataxic symptoms and refractory seizures. Physical examination revealed hypotonia, symmetric pyramidal signs, cerebellar signs, loss of superficial sensations in all extremities, and episodic memory and attention deficits. Notably, there was no reported family history of similar illness (**Figure 1)**

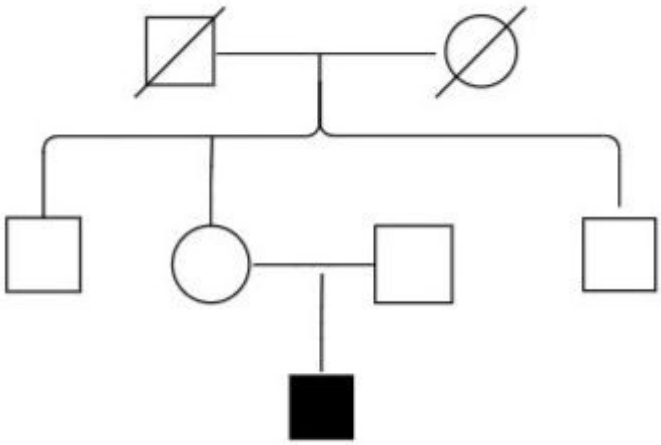

Figure 1: Pedigree chart. The affected member is indicated by black mark in the pedigree chart

Clinical laboratory investigations yielded normal results, while cerebrospinal fluid (CSF) analysis and autoimmune encephalitis panel returned negative findings. Serum testing for Neuromyelitis Optica (NMO) and Myelin Oligodendrocyte Glycoprotein (MOG) antibodies also yielded negative results. Electroencephalogram (EEG) displayed diffuse delta wave slowing, indicative of moderately diffuse cerebral dysfunction. MRI imaging, particularly axial FLAIR sequences, revealed hyperintensities in the bilateral thalamus, midbrain tegmentum, left frontal lobe, left parietal lobe, and right cerebellar hemisphere, accompanied by mildly elevated choline and lipid lactate levels in the left frontal lobe (**Figure 2**). Molecular genetic analysis, focusing on DNA sequencing of the POLG1 gene, identified a homozygous missense variant in exon 13 (chr15:g.89323426C>G), resulting in the amino acid substitution of tryptophan to serine at codon p.Trp748Ser.

Discussion

Within this spectrum lies Ataxia Neuropathy Spectrum (ANS), encompassing entities like Mitochondrial Autosomal Recessive Ataxia Syndrome (MIRAS) and Sensory Ataxia Neuropathy Dysarthria and Ophthalmoplegia (SANDO) [1]. Interestingly, our patient displayed pyramidal signs, an uncommon finding, and lacked ophthalmoparesis, making the clinical presentation inconsistent with classic MIRAS or SANDO phenotypes.

The most common mutation variants observed in Ataxia Neuropathy Spectrum (ANS) patients are p.A467T, p.W748S, and G848S [1]. Indian studies highlight the prevalence of the p.L304R

mutation, especially among younger patients, followed by the p.W748S mutation [5]. A previous study by Wong et al. linked ANS to the mutation c.2243G>C encoding p.A467T [2].

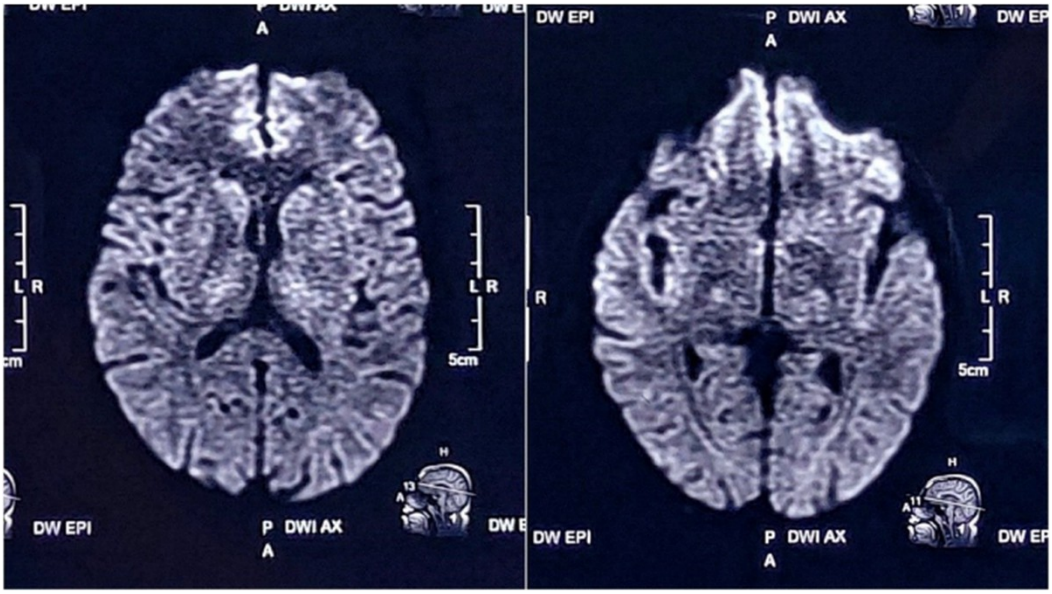

Figure 2: MRI axial FLAIR sequences revealed hyperintensities in bilateral thalamus, tegmentum of mid-brain, left frontal lobe, left parietal and right cerebellar hemisphere with mildly elevated choline and lipid lactate in the left frontal lobe.

Contrasting these findings, our study identified the mutation c.2243G>C encoding p.Trp748Ser in our patient, a variant less frequently associated with ANS according to available data. The involvement of the frontal and parietal lobes, particularly in ANS cases, is rarely reported to the best of our knowledge. These distinctive MRI findings underscore the importance of considering POLG mutation and related ataxia-neuropathy spectrum disorders in patients exhibiting such radiological anomalies, especially in cases with atypical genetic variants like the one observed in our study

Conclusion

This case highlights the complex genetic and clinical diversity in Ataxia Neuropathy Spectrum (ANS). Despite a rare POLG1 mutation, the patient showed varied neurological symptoms different from typical ANS cases. Unusual MRI findings in the frontal and parietal lobes further emphasize ANS variability. Comprehensive genetic and radiological evaluations are crucial for understanding ANS fully, especially in unusual cases. Future research should aim to uncover the mechanisms behind this variability for better diagnosis and management.

Disclosures

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