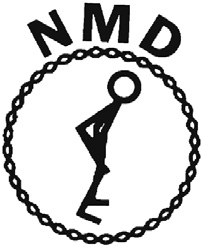
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Case report



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MRI findings in SANDO variety of the ataxia-neuropathy spectrum with a novel mutation in POLG (c.3287G*>T*): A case report

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**Abstract**

Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO) is an adult onset sensory ataxic neuropathy, dysarthria and chronic progressive external ophthalmoplegia associated with mutations in POLG1. We report a 38-year-old woman with a history of progressive gait instability and bilateral ptosis. Neurological examination found ataxia, ophthalmoplegia, and dysarthria. MRI showed bilateral thalamic and cerebellar lesions. A POLG related disorder was suspected and after DNA sequencing a SANDO with a novel mutation in POLG was confirmed.

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*Keywords:* Ataxia-neuropathy spectrum; CPEO; Mitochondrial disease; POLG gene; POLG mutation; Ophthalmoparesis; SANDO.

# Introduction

In patients with mitochondrial diseases, the most frequent clinical symptom is chronic progressive external ophthalmoplegia (CPEO), the latter is often associated with multisystem presentations, so the term CPEO-plus has been employed to include all patients within the spectrum. Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO) is one of the most common chronic progressive external ophthalmoplegia-plus (CPEO-plus) syndromes [[1](#_bookmark11),[2]](#_bookmark12). The POLG gene, which is located in chromosome 15q25.7 encodes the polymerase gamma enzyme that participates in the replication and repair of mitochondrial DNA. Certain mutations in this gene give rise to the so-called "POLG- related disorders", which include CPEO itself, epilepsy, parkinsonism, infertility in men, Alpers syndrome and ataxia- neuropathy spectrum (SANO, SANDO and MIRAS)[[1](#_bookmark11)–[3]](#_bookmark4).

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Here we describe a patient with SANDO diagnosis, who present characteristic findings in MRI and a novel POLG gene c.3287G*> T* heterozygous mutation.

# Case report

We present a 38-year-old woman, with no relevant prior clinical history or consanguinity in family members. Her condition began at age 27, with progressive gait instability that slowly worsened and after 5 years of onset progressive bilateral ptosis was developed. She began the evaluation in our hospital 11 years after the onset of symptoms, at first evaluation we noted an ataxic gait and the presence of bilateral ptosis.

Neurological examination revealed, normal mental state, pupils without abnormalities, bilateral complete ophthalmoplegia, dysarthria, normal strength with global areflexia, normal sensitive examination, wide-based gait and positive Romberg test.

General laboratory studies were unremarkable. Targeted studies including rheumatoid factor, C-reactive protein levels, serologies for HIV and syphilis, vitamin B12 levels and

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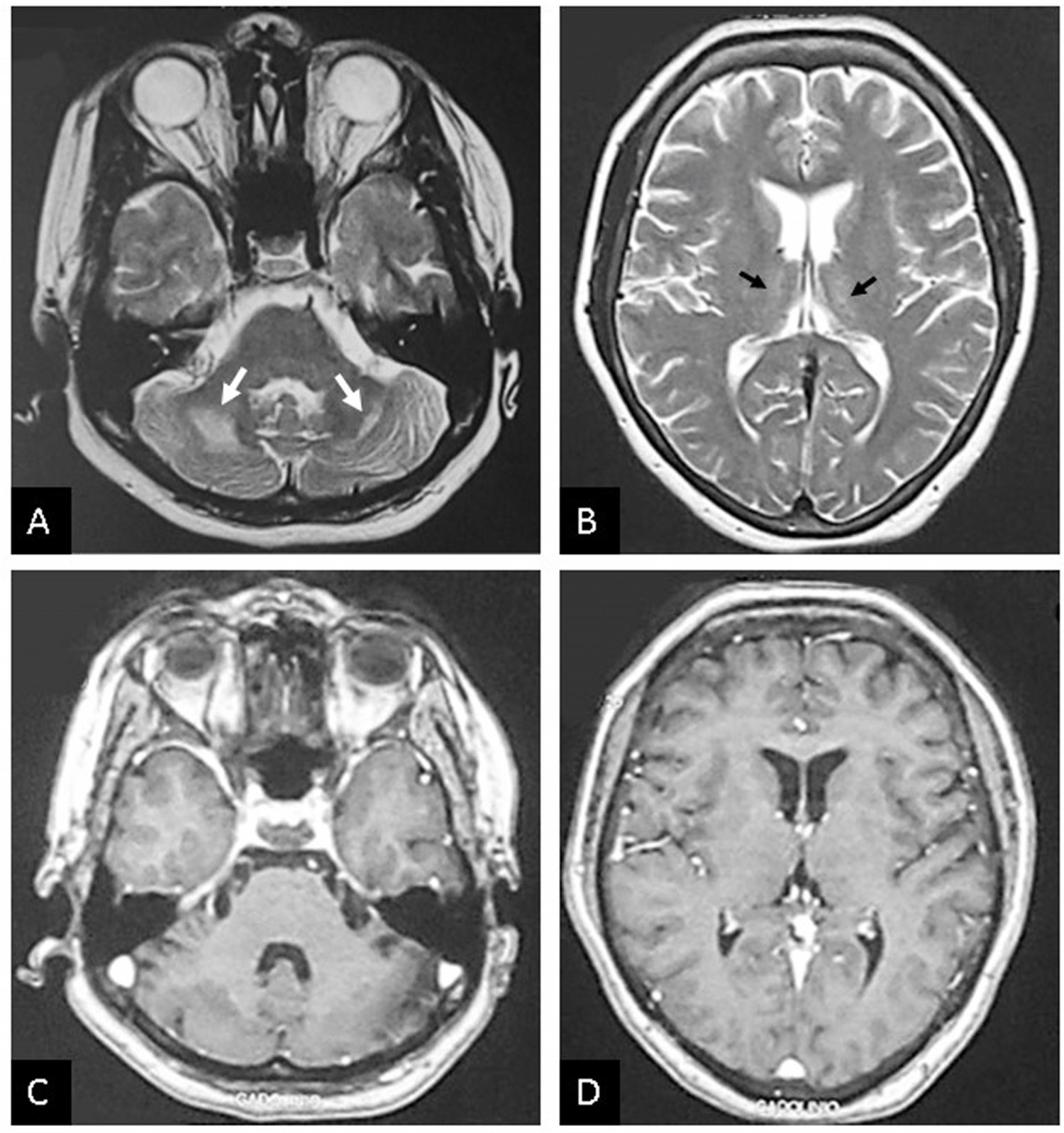


Fig. 1. Axial T2-weighted images (A, B) show hyperintense lesions in cerebellar white matter (white arrows) and dorso-medial thalami (black arrows). Post-contrast T1- weighted MRI (C, D) does not show contrast enhancement.

antibodies against the acetylcholine receptor were reported normal. Positive antinuclear antibodies in 1:1280 dilution with a centromeric fluorescence pattern were reported. The electrodiagnostic studies showed sensory axonal neuropathy and negative repetitive stimulation test.

Brain MRI revealed T2 and FLAIR hyperintense bilateral lesions in the dorso- medial thalami and cerebellar white matter. Diffusion-weighted and contrast-enhanced MRI were normal ([Fig. 1](#_bookmark3)A-D). Based on these results the suspicion of a "POLG related disorder" increased. Molecular genetic investigation with DNA sequencing of the POLG1 gene discovered two heterozygote mutations c.264C*> G* and c.3287G*> T*, thus a SANDO variety of the ataxia-neuropathy spectrum was diagnosed.

# Discussion

The clinical evolution with initial predominant ataxia and late CPEO (which invariably develops during the first decade

of the disease) of our case is consistent with previous reports in SANDO case series [[1]](#_bookmark11).

According to prior reports, in cases of ataxia-neuropathy spectrum, the MRI findings such as the hyperintense lesions in cerebellar white matter, inferior olivary nucleus and dorso- medial thalami have been the pivot signs for the initial diagnosis and an indication to proceed with a sequencing of POLG gene, just as happened in this case [[2]](#_bookmark12). The most common MRI findings in these patients are the with matter lesions in 26%, cerebellar lesions in 19% and thalamic lesions in 15% of cases [[1]](#_bookmark11). Therefore, knowledge of this signs in the ataxia-neuropathy spectrum related to POLG mutation is useful to facilitate the diagnosis.

The sequence variant c.264C*>G* p.Phe88Leu replaces phenylalanine with leucine at codon 88 of the POLG protein. The phenylalanine residue is highly conserved and there is a small physicochemical difference between phenylalanine and leucine. This variant has been observed in individuals with POLG related disease and is classified as a variant of uncertain significance [[4](#_bookmark5),[5]](#_bookmark6). c.3287G*>T* is the second

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sequence variant presented by our patient, it is predicted that it will result in amino acids substitution p.Arg1096Leu in the exon 21 of the POLG gene. The R1096L mutation is a non-conservative amino acid substitution, which is likely to impact secondary protein structure as these residues differ in polarity, charge, size and/or other properties. Previously, a different amino acid change was reported in this position (p.Arg1096Cys by 3286C*>T*) as pathogenic in a patient with a "POLG-related disorder" diagnosis with CPEO [[4]](#_bookmark5). Therefore, the clinical significance of p.Arg1096Leu interprets as likely pathogenic[[6](#_bookmark7),[7](#_bookmark8),[8](#_bookmark9)].

The most frequent POLG mutations that are reports to cause of SANDO include A467T, T748S, R627W, H932Y and G1051R [[9]](#_bookmark10). However, the same mutation can give rise to different clinical pictures and vice versa, so this are genetically heterogenous diseases.

# Conclusion

In this case report, the MRI findings were essential for the diagnostic approach, and a further sequencing of the POLG gene. The ever-expanding molecular and clinical spectrum of mitochondrial DNA polymerase gamma mutations, now enriches with the c.3287G*>T* mutation with a clinical spectrum consisting with ophthalmoplegia, ataxia and sensory neuronopathy.

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