Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO) syndrome associated with two heterozygous POLG mutations

Seetal Sasikumar[1], **Jaisurya Jaisukhalal**[2]

[1,2]Department of Neurology, Pushpagiri institute of medical sciences, Kerala, India

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Abstract

Polymerase gamma is a mitochondrial DNA polymerase, that is responsible for the replication of the mitochondrial DNA (mtDNA). It is encoded by the POLG gene, on chromosome 15q25. Various mutations in this gene have been described, with varied phenotypic manifestations. The triad of sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO) has been reported only in a small group of patients with POLG mutations. We report the case of a male, who presented with phenotype of SANDO syndrome and and was found to have two pathogenic, heterozygous mutations in the POLG gene.

Key words: Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO), POLG, mitochondrial, heterozygous

Introduction

The mitochondrial DNA polymerase gamma, Pol γ, is responsible for replication of the mitochondrial genome and is coded by the POLG gene. Mutations in POLG can cause a wide spectrum of neurological diseases, which are phenotypically heterogenous. [1] Among the various phenotypes, ataxia neuropathy spectrum (ANS) includes mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).The classical clinical triad of sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO) has been reported only in a small subset of patients with POLG mutations.[3] We report the case of a 36-year-old male, who presented with features of SANDO, associated with 2 heterozygous pathogenic POLG variants.

Case report

A 36-year-old male presented with a history of progressive drooping of eyelids and swaying on walking, for the past 5 years. He had progressive drooping of eyelids, with no diurnal variation, and reported no double vision. However, over the years he noticed than he had to turn his head to view targets on either sides. He also developed a nasal twang to his voice. He would sway to either sides on walking, which increased on closing his eyes. There was no history of similar illness for anyone in the family. On examination, he had bilateral ptosis and his horizontal and vertical extraocular movements were grossly restricted. He had a flaccid type of dysarthria, with reduced palatal movements and absent gag reflex. Motor power was normal in all limbs, deep tendon reflexes were absent in lower limbs and plantars were bilaterally flexor. He had impairment in touch, and pinprick sensation and loss of position and vibration senses, in the lower limbs. He had a wide based, ataxic gait and had positive Romberg sign. His serum biochemistry values were normal. Repetitive nerve stimulation test was also normal. Nerve conduction study was suggestive of severe sensory motor axonal neuropathy involving bilateral upper and lower limb nerves. Clinical exome sequencing was done, which revealed two novel heterozygous pathogenic variants in exome 4 and exome 13 of the POLG gene. (Figure 1)

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Address for correspondence:
Dr. Seetal Sasikumar
Associate Professor, Department of Neurology, Pushpagiri institute of medical sciences and research centre, Thiruvalla, Kerala
Phone no: 91-9446417979
Email: sheetalrehaan@gmail.com

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Previous reports	Gene	Zygosity	Variant
Present case- Sheetal et al	POLG	Heterozygous	c.911T>G c.2243G>C
Goethem et al[2]	POLG	Heterozygous	c.1879 C>T
Weiss et al3	POLG	Heterozygous	c.752C>T, c.1760C>T and c.2542G>A
Gáti I 4	POL G	Heterozygous Heterozygous	c.1399G > A and c.2243G > C c.752C > T and c.2542G > A
Crespo et al[5]	POLG	Heterozygous	c.3614G>C
Kurt et al6	POLG	Heterozygous	c.1774C>T c.3286C>T

Table 1: Comparison of previously published studies on POLG mutation with SANDO phenotype

Gene	Variation	Zygosity	Inheritance	Clinical significance
POLG	chr15:89872286A>C c.911T>G p.Leu304Arg	Heterozygous	Recessive	Pathogenic
POLG	chr15:89866657C>G c.2243G>C p.Trp748Ser	Heterozygous	Recessive	Pathogenic

Figure 1: Clinical exome sequencing result showing pathogenic POLG mutations

Discussion

The POLG gene encodes for the mitochondrial DNA polymerase gamma. Mutations in POLG can result in various syndromes. The phenotypes include myocerebrohepatopathy spectrum disorder (MCHS) and Alpers-Huttenlocher syndrome (AHS), presenting in the neonatal/infantile period and chronic progressive external ophthalmoplegia (CPEO), spinocerebellar ataxia with epilepsy (SCAE), mitochondrial recessive ataxia syndrome(MIRAS), myoclonic epilepsy myopathy sensory ataxia (MEMSA), and sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO), presenting later in life. [1, 2] Our patient fulfilled the clinical triad for SANDO. This phenotype was first demonstrated by Fadic et al in 1997, associated with multiple mtDNA deletions. [3] POLG mutation has been reported only in few cases of SANDO.2-6 (Table 1). Our patient had two heterozygous missense mutations, c.911T>G and c.2243G>C in exon 4 and exon 13 of POLG gene, with autosomal recessive pattern of inheritance. (Figure 1).

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