

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)-like phenotype in a patient with a novel heterozygous *POLG* mutation

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Dear Sirs,

POLG-related disease can present with varying degree of severity and timing of onset with multiple organ involvement [1]. In adulthood, *POLG* mutations usually present with progressive external ophthalmoplegia (PEO). PEO can be due to dominant or recessive mutations in *POLG*. Autosomal dominant PEO is associated with generalized progressive myopathy. Affected individuals may also have sensorineural deafness, ataxia, axonal neuropathy, depression, parkinsonism, cataract, and hypogonadism. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)-like presentations have been reported previously with autosomal recessive *POLG* mutations [2, 3]. Here, we describe a 38-year-old male with a novel heterozygous mutation in *POLG* presenting as MNGIE.

The patient had bilateral cataracts removed in early childhood. He developed chronic diarrhea and weight loss in his 20s, which were associated with a rash that on biopsy showed features of dermatitis herpetiformis. Hence, he was diagnosed with celiac disease. Gluten-restricted diet led to resolution of rash, but diarrhea persisted. At the age of 35 years, the patient presented with weakness of upper extremities and bilateral ptosis. A muscle biopsy revealed ragged-red fibers and cytochrome c oxidase (COX) negative fibers. Mitochondrial genome sequencing from peripheral blood was normal. His weakness continued to progress and involved lower extremities, accompanied by impaired upgaze. He developed cachexia associated with chronic persistent diarrhea. Electromyography and nerve

conduction study showed chronic myopathy and severe sensory neuropathy, respectively. MNGIE was suspected due to progressive gastrointestinal dysmotility and cachexia, but sequencing of *TYMP* gene was normal. *POLG* sequencing and deletion/duplication analysis from peripheral blood DNA showed a heterozygous novel variant, c.2669C>A (p.D890A). Mitochondrial genome next-generation sequencing on skeletal muscle revealed multiple deletions confirming pathogenicity of this variant. Magnetic resonance imaging (MRI) of the brain was normal (Fig. 1). On further evaluation, the patient was found to have hypogonadism, hypothyroidism, and osteopenia. The patient has gained weight after starting testosterone.

MNGIE is characterized by progressive gastrointestinal dysmotility, cachexia, PEO and peripheral neuropathy [4]. It is caused by autosomal recessive mutations in *TYMP* gene. A MNGIE-like phenotype has also been reported in a patient with recessive mutations in *RRM2B* [5]. Autosomal recessive mutations in *POLG* presenting as MNGIE was first reported by Van Goethem et al. [2] in two sisters. Tang et al. [3] reported clinical features consistent with MNGIE in 3 of 92 patients with two pathogenic mutations in *POLG*. We are reporting the first patient with heterozygous *POLG* mutation presenting as MNGIE. This is a novel and likely to be pathogenic mutation due to characteristic clinical presentation, muscle histology, and associated multiple deletions in mitochondrial DNA in muscle biopsy. Aspartate at 890 position is evolutionally conserved from yeast to human and resides at the critical site for catalysis. Mutations at this position (D890N) in cultured human cells resulted in mitochondrial DNA depletion [6, 7]. Moreover, expression in cultured human cells suggested that this mutation may be pathogenic in heterozygous state [7]. In the absence of affected relatives, this mutation is likely a de novo dominant mutation in our patient. Like the previous

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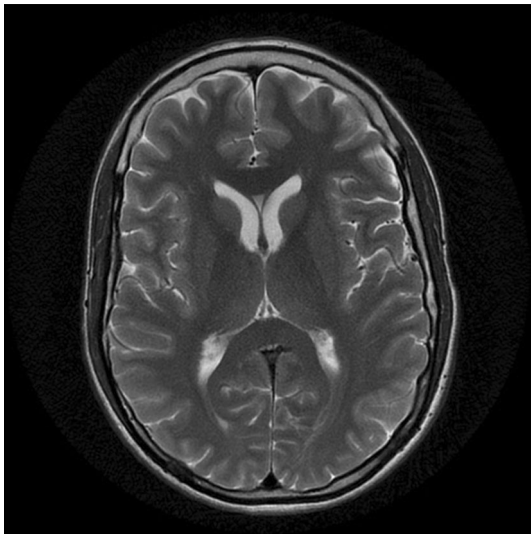


Fig. 1 Brain MRI at diagnosis of POLG-related condition revealed no leukodystrophy

patients with *POLG* mutations and MNGIE phenotype, our patient too had absence of leukodystrophy on brain MRI [2, 3]. Leukodystrophy is hallmark of MNGIE [8]. Although gastrointestinal dysmotility is commonly seen in mitochondrial disorders [9], the combination of severe dysmotility, cachexia, peripheral neuropathy, ophthalmoplegia, and asymptomatic leukodystrophy is suggestive of MNGIE. As many of these features are also seen in POLG-related disorders, clinical presentation may overlap. Brain MRI revealing diffuse leukodystrophy is suggestive of MNGIE. In the absence of asymptomatic diffuse leukodystrophy, other possible etiologies, particularly POLG-related conditions should be considered [10]. Thus, this case expands the spectrum of phenotypes linked to AD *POLG* mutations to include MNGIE-like presentations.

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