Case Report/Case Series

Early-onset Ataxia With Progressive External Ophthalmoplegia Associated With POLG Mutation

*Autosomal Recessive Mitochondrial Ataxic Syndrome or SANDO?*

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**Abstract:** Autosomal recessive ataxias caused by mutations of the polymerase g (*POLG*) gene make an important group of progressive ataxias accompanied by a diverse spectrum of neurological disorders. Because the clinical picture can be quite miscellaneous, it is chal- lenging to assort patients to any of the currently described syndromes; therefore, to provide such a patient with a conclusive diagnosis can be challenging for the neurologist. A typical magnetic resonance imaging finding is probably the most useful landmark in the diagnostic process, which will steer the clinician toward *POLG* gene testing. To illustrate this, we present a case of progressive ataxia caused by A467T and W748S mutations of *POLG* gene, who presented with overlapping symptoms of autosomal recessive mitochondrial ataxic syndrome and SANDO, as well as choreoathetotic movements and dysphonia. After lengthy investigations, magnetic resonance imaging showed T2 and FLAIR hyperintensities in the thalamus, inferior olives, and cer- ebellum, which led us to the analysis of POLG mutations.

**Key Words:** ataxia, autosomal recessive, MRI, POLG, choreoathetotic movements, dysphonia

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rogressive loss of balance followed by other heterogenous neurological symptoms is usually challenging for physi- cians due to the spectrum of hereditary and acquired disorders that should be taken into consideration. Depending on the mode of inheritance, hereditary ataxia can be divided into autosomal dominant, autosomal recessive, X-linked, and mitochondrial

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ataxias.

Many patients with autosomal recessive disorders have negative family history, but the presence of additional char- acteristic phenotypic features makes it obligatory to include these disorders into differentials. These include the onset of symptoms before the age of 20, peripheral sensorimotor

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neuropathy with loss of proprioception and vibration sense as prominent signs, absence of deep tendon reflexes, and involve- ment of other systems besides the nervous system.[1](#_bookmark1) It is clinically useful to divide autosomal recessive ataxias into 2 groups. In one group, there are disorders in which the phe- notype resembles Friedreich ataxia [including polymerase g (POLG) mutations phenotype], whereas the other group includes early-onset ataxias with cerebellar atrophy. This emphasizes magnetic resonance imaging (MRI) of the brain as an important diagnostic tool.[1](#_bookmark1)

Defects in mitochondrial DNA (mtDNA) may be a product of mutations of mitochondrial or nuclear genome involved in mtDNA homeostasis.[2](#_bookmark2) Mutations of nuclear genes such as mtDNA polymerase (POLG),[3](#_bookmark3) adenine nucleotide transporter,[4](#_bookmark4) and Twinkle, a mitochondrial helicase[5](#_bookmark5) cause mtDNA deletions or a quantitative loss called mtDNA depletion. Although most common phenotypic presentation of these nuclear genome defects is progressive external ophthalmoplegia (PEO),[3](#_bookmark3) other manifestations have been described, particularly in patients with mutations affecting POLG. Many mitochondrial disorders may include ataxia as an additional sign, but only disorders asso- ciated with POLG mutation and infantile-onset spinocerebellar ataxia caused by mutation of the C10orf2 gene that encodes for Twinkle proteins, a mitochondrial helicase, have ataxia as a defining feature.[1](#_bookmark1)

We report on a patient with POLG mutations presenting with ataxia, ophthalmoparesis, and some additional features, who was diagnosed on the basis of MRI findings.

# CASE REPORT

A 32-year-old woman was referred to our center for evaluation of ataxia. Symptoms started at the age of 13 years with difficulties in balancing with closed eyes. At the age of 24, during pregnancy, she developed broad-based gait and paresthesias in the feet. During the next 2 years, she started to develop dysarthria and dysphonia. In an out- patient clinic, she underwent electroneurography, which showed mild slowing of nerve conduction velocities and absent sensory potentials in hands and feet. Brain MRI showed increased signal intensity in both thalami and cerebellar hemispheres. Extensive genetic workup for spinocerebellar ataxias 1, 2, 3, 6, 7, 12, 17, DPRLA, and mitochondrial transfer RNA leucine was negative. Studies for ceruloplasmin, vitamin E, a-fetoprotein, ammonium, lactate, pyruvate, carnitine, fatty acids, organic acids, phytanic acid, very long fatty acids, b-hexosaminidase A, galactocerebrosidase, congenital disorders of glycosylation, neuronal lipofuscinosis, oligosaccharides, and mucopolysaccharides in urine were negative.

Neurological examination performed on the patient’s initial pre- sentation revealed almost complete horizontal gaze palsy (only minimal adduction of the right eye was possible). She had severe ataxia of all 4 limbs and gait, reflexes were absent, and choreoathetotic movements of the hands were noted. Complete absence of proprioceptive sensation of the legs was present. Cognitive examination was normal.

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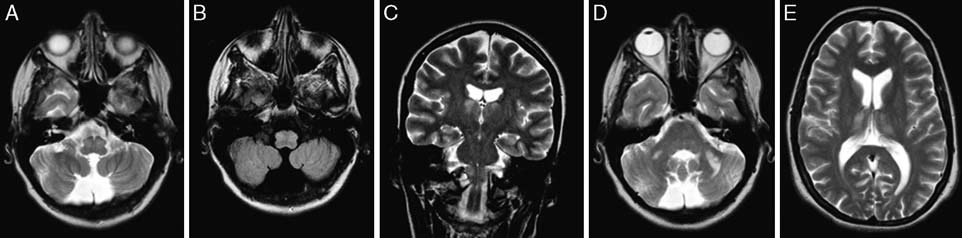


FIGURE 1. Magnetic resonance imaging of the brain showing T2 and FLAIR hyperintensities in the thalamus (C, E), inferior olives (A–C), and cerebellum (D).

Repeat brain MRI is shown in [Figure](#_bookmark0) 1. On the basis of MRI findings, we performed analysis for POLG mutations, which revealed 2 mutations in the *POLG* gene (1399G > A, A467T and 2243G > C, W748S), both in *trans* position. The patient was prescribed vitamin C 1 g qid, coenzyme Q10 100 mg tid, L-carnitine 500 mg qid, and lamotrigine 25 mg bid.

# DISCUSSION

Differential diagnosis of autosomal recessive ataxias is wide. Broadly, they can be divided into 3 groups: (1) Friedreich ataxia-like, (2) Friedreich ataxia-like with cerebellar atrophy, and (3) early-onset ataxia with cerebellar atrophy.[1](#_bookmark1) The second group of ataxias includes 4 diseases: late-onset Tay-Sachs disease, cerebrotendinous xanthomatosis, spinocerebellar ataxia with axonal neuropathy, and DNA POLG disorders (mito- chondrial recessive ataxia syndrome).

The human mtDNA polymerase, a crucial enzyme for mtDNA replication and repair, is a heterotrimer consisting of a catalytic subunit (POLG) containing the polymerase and exo- nuclease activities, and 2 accessory subunits (POLG2),[6](#_bookmark6) and is encoded by nuclear *POLG* gene located on chromosome 15q25.[7](#_bookmark7) The consequence of POLG mutation is the accumu- lation of multiple mtDNA deletions in postmitotic tissues such as muscle and brain. A great majority of the mutated alleles are missense mutations, whereas frameshift and nonsense muta- tions account for a smaller portion.[8](#_bookmark8) Numerous mutations of *POLG* gene have been identified to cause a broad spectrum of disorders inherited in autosomal dominant or autosomal recessive manner, including the autosomal dominant and recessive forms of PEO,[3,9,10](#_bookmark3) the autosomal recessive lethal Alpers syndrome,[11,12](#_bookmark10) the mitochondrial recessive ataxia syn- drome with[13](#_bookmark12) and without ophthalmoplegia,[14](#_bookmark13) ataxic neuro- pathy with dysarthria and ophthalmoparesis (SANDO),[15](#_bookmark14) par- kinsonism,[16](#_bookmark15) and male infertility.[17](#_bookmark16) As reported by Wong et al,[8](#_bookmark8) in a cohort of 350 patients, the most common POLG mutation in patients with autosomal recessive inheritance (Alpers disease, ataxia, sensory neuropathy, and PEO syn- dromes) was A467T, followed by G848S and T251I + P587L (in *cis*), W748S and T914P. Our patient was found to be compound heterozygous (A467T and W748S mutations).

Clinical presentation of recessive POLG mutations is expanded by ataxia and the neuropathy spectrum,[8](#_bookmark8) combined with variable features of involvement of central nervous sys- tem and other organs. Our patient presented with ataxic syn- drome, which includes an overlapping spectrum of disorders organized around the finding of ataxia demonstrating recessive inheritance, primarily due to its onset before the age of 20 and presence of peripheral sensory neuropathy. Most patients have

additional symptoms, which may include PEO, neuropathy, and dysarthria. MRI is very helpful in deciding when to order genetic testing for POLG mutations as MRI shows character- istic lesions that are hyperintense relative to gray matter. Typically, these are seen centrally in the posterior part of the thalamus, dentate nuclei, and inferior olives, and probably are caused by neuronal loss with secondary gliosis.[12,18](#_bookmark11) These MRI findings after lengthy investigations revealed the true etiology of symptoms in our patient. The involvement of these particular brain areas can be explained not just with high- energy demands of the brain region involved but also with secondary vascular effects due to pH changes.[12](#_bookmark11)

Taking into account the genetic, clinical, and neuro- radiologic findings, SANDO or autosomal recessive mito- chondrial ataxic syndrome due to mitochondrial POLG muta- tions were the 2 syndromes considered in our patient. SANDO comprises of a triad of sensory ataxic neuropathy, dysarthria, and ophthalmoparesis.[19](#_bookmark17) Palatal tremor and memory loss have been reported as additional symptoms.[13](#_bookmark12) Besides POLG mutations, other gene mutations can cause this syndrome as it is a genetically heterogenous disease.[20](#_bookmark18) POLG mutations that are reported to be the cause of SANDO include A467T, R627W, H932Y, and G1051R.[10,21–23](#_bookmark9)

Autosomal recessive mitochondrial ataxic syndrome is characterized by gait and limb ataxia, dysarthria, polyneur- opathy, hyporeflexia, nystagmus, cognitive impairment, epi- lepsy, and in some cases ophthalmoparesis. POLG mutations have been found in A467T and T748S.[1,14](#_bookmark1)

We present a case exhibiting features of both SANDO and autosomal recessive mitochondrial ataxic syndrome. Recently, some authors were inclined to include these 2 syndromes as well as spinocerebellar ataxia with epilepsy into the ataxia neuropathy spectrum or syndrome.[23,24](#_bookmark19) In addition, our patient presented with choreoathetotic movements and dysphonia. As there is a huge inconsistency in muscle biopsy and biochemical findings in patients with POLG mutations,[13](#_bookmark12) brain MRI is the diagnostic procedure of choice that can lead to molecular analysis of *POLG* gene, thus yielding definitive diagnosis. Because there is no clear correlation between genotype and phenotype in patients with POLG mutations, we believe it to be clinically more useful to consider POLG mutation-related phenotype as a clinical entity with a diverse symptomatic presentation.

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