

Polg Mutation–Related Mitochondrial Disease Presenting With Progressive Cerebellar Ataxia: A Case Report and Review of The Literature

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ABSTRACT

Background

POLG-related mitochondrial disorders are a heterogeneous group of inherited diseases caused by pathogenic variants in the POLG gene, which encodes the catalytic subunit of mitochondrial DNA polymerase gamma. Neurological manifestations range from developmental regression and epilepsy to cerebellar ataxia, peripheral neuropathy, cognitive impairment, and progressive neurological decline.

Case Presentation

A 28-year-old woman presented with approximately 9 years of progressive giddiness, recurrent falls, gait imbalance, sensory symptoms involving both lower limbs, headache, behavioral abnormalities, and developmental regression. She was born to second-degree consanguineous parents and had a history of delayed speech followed by poor scholastic performance and cognitive decline. Neurological examination revealed an MMSE score of 13/30, scanning speech, impaired multiple sensory modalities in both lower limbs, limb incoordination, positive Romberg sign, stance and gait ataxia, and reeling gait. Brain MRI demonstrated symmetrical T2/FLAIR hyperintensities involving the bilateral thalami, midbrain tegmentum, pons, and cerebellar hemispheres, with sparing of the dentate nuclei and basal ganglia. There was no significant enhancement or definite spinal cord involvement. Whole-exome sequencing identified a homozygous POLG p.Trp748Ser (W748S) missense variant.

Conclusion

This case highlights the clinical and radiological heterogeneity of POLG-related mitochondrial disease. Progressive cerebellar ataxia associated with sensory dysfunction, cognitive/developmental regression, characteristic bilateral MRI abnormalities, consanguinity, and a biallelic pathogenic POLG variant should prompt consideration of a POLG-related disorder. Molecular genetic testing is particularly useful when clinical and radiological findings overlap with other inherited metabolic and neurodegenerative disorders.

Keywords: POLG; mitochondrial disease; W748S; cerebellar ataxia; sensory neuropathy; mitochondrial DNA polymerase gamma; whole-exome sequencing; neuroimaging.

INTRODUCTION

Mitochondrial disorders are inherited metabolic diseases resulting from abnormalities of oxidative phosphorylation, mitochondrial DNA maintenance, or related mitochondrial functions. The nervous system is particularly vulnerable because of its high energy requirements, resulting in diverse neurological manifestations including developmental regression, neuropathy, seizures, dysarthria, cognitive impairment, and cerebellar ataxia. [1-3]

The POLG gene encodes the catalytic subunit of mitochondrial DNA polymerase gamma, which is essential for mitochondrial DNA replication and repair. Pathogenic POLG variants cause a broad spectrum of autosomal-recessive and autosomal-dominant disorders, including ataxia-neuropathy syndromes, progressive external ophthalmoplegia, epilepsy, and other neurological phenotypes. [4,11]

The p.Trp748Ser (W748S) variant is an established pathogenic POLG variant associated particularly with autosomal-recessive ataxia and neuropathy. Functional studies have demonstrated impaired polymerase activity associated with this variant. [5,6]

We report a young woman with progressive cerebellar ataxia, sensory impairment, cognitive/developmental regression, and unusual bilateral cerebellar, brainstem, and thalamic MRI abnormalities in whom whole-exome sequencing identified a homozygous POLG p.Trp748Ser variant.

REVIEW OF LITERATURE

POLG-related disorders comprise a clinically heterogeneous group of mitochondrial diseases caused by pathogenic variants in the POLG gene. POLG is essential for mitochondrial DNA replication and maintenance;

pathogenic variants may result in mitochondrial DNA depletion, multiple mitochondrial DNA deletions, or impaired mitochondrial DNA replication. The nervous system and skeletal muscle are particularly vulnerable. [4,11]

The clinical spectrum includes epilepsy, cerebellar ataxia, peripheral neuropathy, ophthalmoplegia, myopathy, cognitive impairment, and progressive neurological decline. Recognized phenotypes include Alpers-Huttenlocher syndrome, mitochondrial recessive ataxia, SANDO, progressive external ophthalmoplegia, and overlapping ataxia-neuropathy phenotypes. [4,11]

The W748S variant is an important cause of autosomal-recessive neurological disease, particularly progressive ataxia. Hakonen et al. identified W748S as a recurrent cause of autosomal-recessive ataxia, while subsequent functional studies demonstrated impaired polymerase function. [5,6]

Neuroimaging findings in POLG-related disease are variable and may include cerebellar atrophy, white-matter abnormalities, and involvement of the brainstem, thalami, or other deep grey-matter structures. MRI findings are supportive rather than pathognomonic and should be interpreted together with the clinical phenotype and molecular findings. [3,4,11]

The present case is notable for progressive cerebellar ataxia, sensory dysfunction, cognitive/developmental regression, consanguinity, and bilateral cerebellar, brainstem, and thalamic abnormalities associated with a homozygous POLG W748S variant.

CASE PRESENTATION

Patient Information

A 28-year-old woman presented with progressive giddiness and recurrent falls beginning in September 2015. The symptoms gradually progressed over approximately 9 years, with marked worsening during the preceding 4 months.

She also reported bilateral mild throbbing headache for approximately 3 months without aura, nausea, or vomiting. Additional symptoms included numbness and a foreign-body sensation involving both feet, excessive anger, episodes of self-talking, and progressive cognitive and developmental regression.

There was no history of fever, vomiting, visual blurring, bowel or bladder dysfunction, or other acute infective symptoms.

Developmental and Family History

The patient was the first child of a second-degree consanguineous marriage. She was delivered by normal vaginal delivery with an immediate cry, and the antenatal and early postnatal periods were reportedly uneventful.

Speech development was delayed but improved by approximately 3 years of age. Developmental regression became apparent from approximately 11 years of age, followed by poor scholastic performance, particularly from the ninth grade. She completed the tenth standard after multiple attempts.

Menarche occurred at approximately 15 years of age, followed by irregular menstrual cycles. She married at 25 years of age and experienced two spontaneous first-trimester abortions by 27 years of age. She subsequently separated from her husband for personal reasons.

No similar neurological illness was reported among other family members.

Clinical Examination

The patient was conscious, alert, and cooperative. MMSE was 13/30, indicating significant cognitive impairment. Speech examination revealed scanning speech. Cranial nerve examination did not demonstrate a definite abnormality. There was no significant focal weakness, and muscle tone and power were relatively preserved. Sensory examination revealed impaired touch, pain, vibration, temperature, and joint-position sense, predominantly involving the lower limbs. Cerebellar examination demonstrated impaired limb coordination. She had stance ataxia, a positive Romberg sign, ataxic gait, and reeling towards the right. The overall phenotype suggested involvement of cerebellar, sensory, and cognitive functions.

Investigations

Routine hematological and biochemical investigations were within normal limits. Nerve-conduction studies did not demonstrate significant abnormalities. Given the combination of developmental regression, progressive cerebellar ataxia, sensory abnormalities, consanguinity, and unusual MRI findings, an inherited metabolic or mitochondrial disorder was suspected.

Magnetic Resonance Imaging

Brain MRI demonstrated symmetrical T2/FLAIR hyperintensities involving:

- Bilateral thalami
- Bilateral midbrain tegmentum
- Bilateral pons
- Bilateral cerebellar hemispheres

The dentate nuclei and basal ganglia were spared. There was no significant post-contrast enhancement, definite spinal cord lesion, or conventional territorial infarction. The combination of bilateral cerebellar, brainstem, and thalamic involvement prompted consideration of a mitochondrial or inherited metabolic disorder.

Genetic Analysis

Whole-exome sequencing was performed because of the consanguinity, developmental regression, progressive ataxia, and characteristic neuroimaging findings.

A homozygous missense variant in POLG was identified.

Molecular Findings

Parameter	Finding
Gene	POLG
Variant	p.Trp748Ser (W748S)
Coding HGVS	c.2243G>C
Zygosity	Homozygous
Exon	13
Chromosome	15
Sequencing depth	168x

The W748S variant has been reported as a pathogenic POLG variant associated with autosomal-recessive ataxia and impaired DNA polymerase function. [4-6,11]

Variant Interpretation

The identified homozygous POLG p.Trp748Ser variant was interpreted as pathogenic based on previously reported clinical and functional evidence. Functional studies have demonstrated impaired polymerase activity and abnormal DNA-binding properties associated with W748S. [5,6]. The homozygous state in a patient born to consanguineous parents further supports an autosomal-recessive POLG-related disorder. [4,6,11]

Although the phenotype overlaps with the POLG ataxia-neuropathy spectrum, the patient had no documented ophthalmoparesis or ophthalmoplegia. Therefore, she should not be definitively classified as having classic SANDO.

The most appropriate clinical description is:

POLG-related mitochondrial disease presenting predominantly with progressive cerebellar ataxia, sensory dysfunction, cognitive/developmental regression, and characteristic cerebellar-brainstem MRI abnormalities.

DIFFERENTIAL DIAGNOSIS

The major differential diagnoses included other mitochondrial disorders, hereditary cerebellar ataxias, leukodystrophies, Wilson disease, FXTAS, CADASIL, multiple sclerosis, and vitamin B12 deficiency. [1-3,8,9,12-17]

Other Mitochondrial Disorders

Leigh syndrome, MELAS, MERRF, Kearns-Sayre syndrome, and mitochondrial DNA depletion disorders can produce bilateral and symmetric abnormalities involving deep grey matter, brainstem, and cerebellum. However, the clinical phenotype and molecular identification of a homozygous POLG variant favored POLG-related disease. [1-4,10,11]

Hereditary Cerebellar Ataxias

Friedreich ataxia and other autosomal-recessive ataxias can produce progressive gait disturbance, sensory impairment, and dysarthria. However, the combination of cognitive/developmental regression, characteristic MRI abnormalities, consanguinity, and the POLG variant favored a mitochondrial etiology. [12,17]

Leukodystrophic and Metabolic Disorders

Inherited leukodystrophies and peroxisomal disorders may cause progressive neurological deterioration and symmetrical MRI abnormalities. The distribution of lesions and the molecular findings in this patient were not typical of a primary leukodystrophy or peroxisomal disorder. [1]

Wilson Disease

Wilson disease may produce basal-ganglia and brainstem abnormalities, including the “face of the giant panda” appearance. However, the clinical and biochemical context was not supportive, and the POLG variant provided a more appropriate explanation. [15,16]

CADASIL

CADASIL may cause migraine, psychiatric manifestations, strokes, and cognitive decline, with characteristic anterior temporal and external-capsule white-matter abnormalities. The MRI pattern in this patient was different from the typical CADASIL distribution. [13,14]

FXTAS

FXTAS occurs predominantly in older FMR1 premutation carriers and may present with intention tremor, ataxia, cognitive decline, neuropathy, and middle cerebellar peduncle abnormalities. The patient's age, clinical presentation, and POLG molecular diagnosis did not support FXTAS. [8,9]

Multiple Sclerosis and Vitamin B12 Deficiency

The bilateral symmetric distribution, chronic progressive course, and absence of typical dissemination in time and space argued against multiple sclerosis. Vitamin B12 deficiency may cause sensory ataxia but does not explain the characteristic brain MRI abnormalities or the pathogenic POLG variant.

MRI DIFFERENTIATION AND SHRIMP-LIKE CEREBELLAR CONFIGURATION

Mitochondrial disorders may produce bilateral and relatively symmetric MRI abnormalities because of selective vulnerability of metabolically active brain structures. [1-3]. In this case, the combination of bilateral cerebellar, pontine, midbrain, and thalamic T2/FLAIR hyperintensities was unusual. The imaging findings were not considered pathognomonic for POLG disease but became diagnostically relevant when integrated with the clinical phenotype, family history, and molecular findings.

The unusual cerebellar appearance also raised consideration of the “shrimp sign.” This term has been described in cerebellar progressive multifocal leukoencephalopathy (PML). [7] However, the present case differed from typical PML because of the chronic clinical course, absence of a typical PML context, dentate-nucleus sparing, and presence of a pathogenic POLG variant. Therefore, the finding in this patient is best described as a “shrimp-like cerebellar configuration” rather than a true diagnostic shrimp sign.

GENOTYPE–PHENOTYPE CORRELATION

POLG-related disease represents a broad clinical continuum that includes ataxia-neuropathy syndromes, SANDO, mitochondrial recessive ataxia, progressive external ophthalmoplegia, epilepsy, myopathy, and Alpers-Huttenlocher syndrome. [4,11]. Early-onset disease may present with seizures, liver disease, developmental abnormalities, and encephalopathy, whereas juvenile- and adult-onset disease more commonly includes ataxia, neuropathy, seizures, cognitive abnormalities, and ophthalmoplegia. [4,11]. The present patient demonstrated a predominantly neurological phenotype consisting of progressive cerebellar ataxia, sensory impairment, cognitive/developmental regression, behavioral abnormalities, and characteristic MRI abnormalities. Although W748S has been associated with several POLG phenotypes, genotype-phenotype correlations remain complex and the clinical presentation cannot always be predicted from the genotype alone. [4-6,11]

PATHOPHYSIOLOGICAL BASIS

POLG encodes mitochondrial DNA polymerase gamma, which is essential for mitochondrial DNA replication and repair. Pathogenic variants can impair polymerase activity and mitochondrial DNA maintenance, resulting in mitochondrial DNA depletion or accumulation of mitochondrial DNA deletions and impaired oxidative phosphorylation. [4-6,10,11]

The resulting reduction in cellular energy production and increased oxidative stress particularly affects tissues with high metabolic demands, including neurons and skeletal muscle. These mechanisms provide a biological basis for the progressive neurological manifestations observed in POLG-related disease. [1,4,11]

DISCUSSION

This case demonstrates an atypical but clinically important presentation of POLG-related mitochondrial disease. The patient had progressive cerebellar ataxia, sensory impairment, cognitive dysfunction, behavioral

abnormalities, and developmental regression. The history of consanguinity suggested an autosomal-recessive inherited disorder, which was subsequently supported by identification of a homozygous POLG variant.

The W748S variant is particularly relevant because it has been repeatedly associated with autosomal-recessive POLG-related ataxia, and functional studies have demonstrated impaired polymerase activity. [5,6]

The MRI findings were unusual, with symmetrical involvement of the cerebellum, pons, midbrain, and thalami. Although mitochondrial disorders can produce symmetric abnormalities in metabolically vulnerable regions, this particular combination is not diagnostic of POLG disease. [3,4,11]

The unusual cerebellar configuration initially raises consideration of the shrimp sign described in cerebellar PML. However, the dentate nuclei were spared and the clinical context was not compatible with typical PML. [7]

The case also emphasizes the importance of distinguishing POLG-related ataxia from other inherited cerebellar disorders, including FXTAS and autosomal-recessive cerebellar ataxias. The patient's age, clinical phenotype, imaging pattern, consanguinity, and molecular findings collectively favored POLG-related mitochondrial disease. [8,9,12,17]

Importantly, the patient did not demonstrate documented ophthalmoparesis or ophthalmoplegia and therefore should not be labeled as having classic SANDO. Instead, her phenotype is best considered part of the broader POLG-related ataxia-neuropathy spectrum.

This case illustrates the value of integrating clinical examination, family history, neuroimaging, and molecular genetic testing when evaluating progressive unexplained ataxia.

CONCLUSION

POLG-related mitochondrial disease should be considered in patients with progressive cerebellar ataxia accompanied by sensory dysfunction, cognitive or developmental regression, and unusual bilateral brain MRI abnormalities, particularly in the presence of consanguinity.

The POLG p.Trp748Ser (W748S) variant is a recognized pathogenic variant associated with autosomal-recessive neurological disease. The present case demonstrates that POLG-related disease may present without the complete features of a classical named syndrome such as SANDO.

Recognition of atypical MRI patterns, together with appropriate molecular genetic testing, can facilitate diagnosis in patients with otherwise unexplained progressive neurological disease.

TABLE 1. CLINICAL FEATURES OF THE PRESENT CASE

Clinical feature	Finding
Age	28 years
Sex	Female
Consanguinity	Second-degree
Initial neurological symptoms	Approximately 19 years
Presenting symptom	Giddiness with recurrent falls
Duration of progression	Approximately 9 years
Cognitive assessment	MMSE 13/30
Speech	Scanning speech
Cerebellar findings	Limb incoordination, stance and gait ataxia
Romberg sign	Positive
Sensory findings	Impaired multiple sensory modalities, predominantly lower limbs
Nerve conduction	No significant abnormality
MRI	Bilateral cerebellar, thalamic, midbrain and pontine T2/FLAIR abnormalities
Dentate nuclei	Spared
Basal ganglia	Spared
Enhancement	Absent
Genetic diagnosis	Homozygous POLG p.Trp748Ser (W748S)

TABLE 2. DIFFERENTIAL DIAGNOSIS OF BILATERAL CEREBELLAR/DEEP-BRAIN LESIONS

Condition	Important clinical/MRI features
POLG-related disease	Progressive ataxia, sensory dysfunction, cognitive abnormalities; variable cerebellar, brainstem and deep-grey-matter involvement
Leigh syndrome	Symmetric deep-grey-matter and brainstem lesions

MELAS	Stroke-like cortical/subcortical lesions not confined to vascular territories
Hereditary cerebellar ataxia	Progressive cerebellar dysfunction with variable sensory involvement
Friedreich ataxia	Sensory ataxia, areflexia and corticospinal signs
FXTAS	Older FMR1 premutation carrier; intention tremor, ataxia and MCP sign
Wilson disease	Basal-ganglia/brainstem abnormalities with copper metabolism abnormalities
CADASIL	Anterior temporal and external-capsule white-matter lesions
Multiple sclerosis	Characteristic periventricular, juxtacortical, infratentorial or spinal lesions
PML	Usually asymmetric white-matter lesions; cerebellar shrimp sign may occur
Vitamin B12 deficiency	Sensory ataxia with posterior-column involvement

ABBREVIATIONS

POLG – DNA polymerase gamma

mtDNA – Mitochondrial DNA

MRI – Magnetic resonance imaging

WES – Whole-exome sequencing

MMSE – Mini-Mental State Examination

FXTAS – Fragile X-associated tremor/ataxia syndrome

CADASIL – Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

PML – Progressive multifocal leukoencephalopathy

MELAS – Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

MERRF – Myoclonic epilepsy with ragged red fibers

SANDO – Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis

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