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Mitochondrial Mimicry of Multiple System Atrophy of the Cerebellar Subtype

Arpan R. Mehta, B.A., B.M., B.Ch.,1

Susan H. Fox, M.R.C.P., Ph.D.,1

Mark Tarnopolsky, M.D., Ph.D., F.R.C.P.,2

and Grace Yoon, M.D., F.R.C.P., F.C.C.M.G.3\*

*1Movement Disorder Clinic, Toronto Western Hospital, University of Toronto, Toronto, Canada; 2Division of Neuromuscular and Neurometabolic Disease, McMaster University Medical Center, Hamilton, Canada; 3Divisions of Clinical/Metabolic Genetics and Neurology, The Hospital for Sick Children, University of Toronto, Toronto, Canada*

patients with diverse clinical presentations that include parkinsonism and cerebellar ataxia.2

Here, for the ﬁrst time, we describe a patient who presented with clinical and radiological ﬁndings sugges- tive of multiple system atrophy (MSA) of the cerebellar subtype (MSA-C), but was shown to have mutations of *POLG1*. This case highlights the importance of consid- ering primary mitochondrial disorders in the differential diagnosis of parkinsonian syndromes.3,4

# Case Report

Written informed consent was obtained from the patient to publish both video and brain imaging results for this case report. This 58-year-old woman had a pro- gressive cerebellar syndrome. Her symptoms had started

9 years prior, with imbalance when getting out of a canoe or when walking up and down stairs. She also noted poor handwriting and mild incoordination of the hands. Her speech had become slurred. Her symptoms worsened toward the end of the day or when she was fatigued. In addition, the symptoms partially improved after excluding dietary gluten and she had lost 18 kg over the previous year. She had mild urinary inconti- nence when coughing. She has type II diabetes mellitus, treated with Pioglitazone. There is no history of epi- lepsy, cognitive problems, visual problems, stroke-like episodes, hearing problems, or menstrual disturbances. Her family history revealed that she had a sister who died at 2 years of age. This child, who was blind, was never able to roll, sit, or walk independently, and she also had intractable seizures. No diagnosis was ever established. The proband’s brother has sensorineural hearing loss, glaucoma, and adult-onset diabetes melli- tus requiring treatment with insulin.



ABSTRACT

Background: We describe a patient with clinical and ra- diological ﬁndings suggestive of multiple system atro- phy of the cerebellar subtype (MSA-C). Methods/ Results: Sequencing of the polymerase-c 1 (*POLG1*) gene revealed the patient had compound heterozygous mutations of the *POLG1* gene. Muscle biopsy revealed the presence of multiple mitochondrial DNA deletions and depletion, conﬁrming the pathogenic nature of the *POLG1* mutations. Discussion: This case expands the spectrum of phenotypes associated with *POLG1* muta- tions to include multiple system atrophy and prompts further consideration regarding whether routine screen- ing for *POLG1* mutations is indicated in this patient population. VC 2011 Movement Disorder Society

Key Words: mitochondrial disease; multiple system atrophy; polymerase gamma gene; parkinsonism; ataxia

On initial examination, 4 years after the onset of her symptoms, she had slight slowing of vertical saccades but a full range of eye movements and normal fundi. She had dysarthria, mild limb dysmetria that was worse on the left, mild slowing of foot taps bilaterally, and a mildly impaired tandem gait; tone and reﬂexes were normal with ﬂexor plantar responses (see Sup- porting Information video). Investigations for coeliac

Mitochondrial disorders can result from either pri- mary defects in the mitochondrial DNA (mtDNA) or defects in nuclear encoded proteins that affect mtDNA structure or function. The maintenance of mtDNA rep- lication is critically dependent upon mtDNA polymer- ase-c,1 encoded by the nuclear genes *POLG1* and *POLG2*. Mutations in *POLG1* have been described in

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Additional Supporting Information may be found in the online version of this article.

\*Correspondence to: Dr. Grace Yoon, Divisions of Clinical/Metabolic Genetics and Neurology, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; [grace.yoon@utoronto.ca.](mailto:grace.yoon@utoronto.ca)

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M E H T A E T A L .

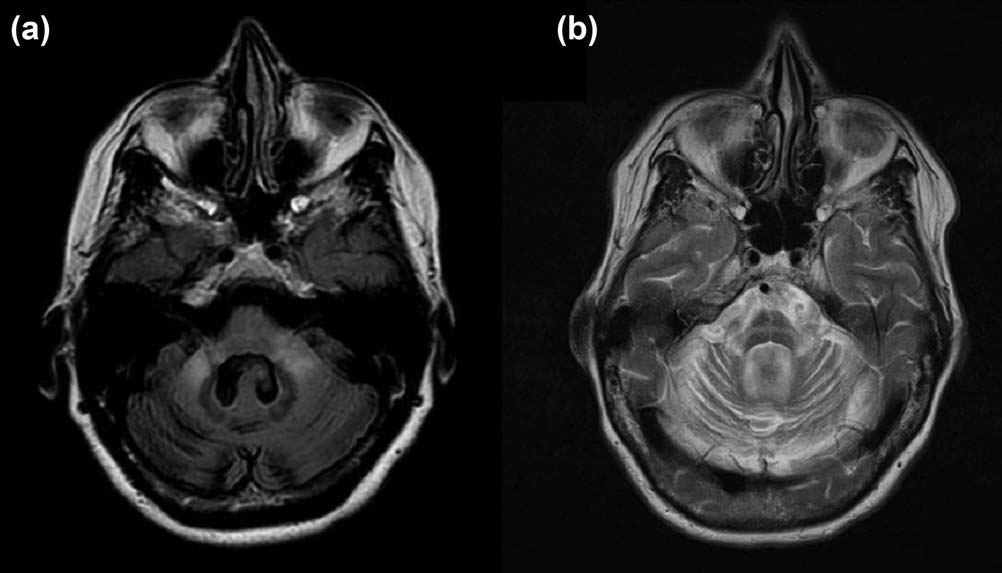


FIG. 1. a: MRI FLAIR brain scan showing an enlarged fourth ventricle because of pontine and cerebellar atrophy, in association with hyperintensities in the middle cerebellar peduncles bilaterally. b: MRI T2-weighted brain scan demonstrating the ‘‘hot-cross bun’’ sign, classically associated with MSA.

disease, including a small bowel biopsy, were negative. Sensory testing was normal and nerve conduction stud- ies were normal. In view of the signiﬁcant weight loss, investigations for a paraneoplastic process were per- formed and the anti-Purkinje cell antibody was nega- tive. Computed tomography of thorax and mammogram were normal. Her Vitamin B12 and E levels were normal. Metabolic studies, including plasma amino acids, urine organic acids, carnitine pro- ﬁle, lactate, ammonia, and leukocyte hexosaminidase A activity, were all normal. Spinocerebellar ataxia (SCA) types 1, 2, 3, 6, and 7 testing were negative. She was found to have an intermediate-range expansion of the CTG repeat of the SCA type 8 (*SCA-8*) gene, with al- lele sizes of 75 and 26 CTG repeats, which were not felt to be clinically signiﬁcant. Her magnetic resonance imaging (MRI) brain scan showed pontine and cerebel- lar atrophy with some T2 hyperintensities in the mid- dle cerebellar peduncles (Fig.1).

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Her symptoms continued to progress and 7 years af- ter symptom onset her dysarthria and cerebellar ataxia had signiﬁcantly worsened. Despite using a walker, she fell and sustained a right hip fracture. She developed postural dizziness owing to orthostatic hypotension. Moreover, her urinary urgency worsened and she developed nocturia. She had drooling of saliva and intermittent dysphagia for liquids. Examination revealed a supine blood pressure of 110/60 and 90/40 mm Hg after standing for 3 minutes, with no corre- sponding change in pulse rate. She had polyminimyo- clonus of her outstretched hands, a positive glabellar tap and brisk deep tendon reﬂexes with ﬂexor plantar responses. She was unable to walk unaided and required a wheelchair. On recent examination (9 years after onset), she had jerky saccades, marked dysarthria,

limb dysmetria, rigidity in the legs worse than in the arms, brisk reﬂexes, and mild bilateral bradykinesia in association with dystonic posturing of the left hand (see Supporting Information video).

Prompted by reviewing the family history, in particu- lar the sister’s clinical history that was suggestive of Alpers’ syndrome, the patient was evaluated for muta- tions of the mitochondrial polymerase-c 1 (*POLG1*) gene using automated DNA sequencing, and was found to carry the mutations c.2554C>T (p.R852C) and c.32G>A (p.G11D). There was no associated derange- ment of her liver function tests. Long-range polymerase chain reaction (PCR) analysis of a biopsy of the right vastus lateralis muscle revealed evidence of multiple mtDNA deletions, and real-time PCR analysis of the ND1/beta-globulin DNA ratio showed mtDNA deple- tion, conﬁrming the pathological signiﬁcance of the *POLG1* mutations. As both the proband’s parents are deceased, parental genetic studies are not possible.

# Discussion

We describe a patient with adult-onset, progressive cerebellar ataxia, autonomic dysfunction, mild bradyki- nesia, and dystonia. The ataxia initially appeared to respond to gluten exclusion from her diet, although the absence of antigliadin antibodies meant that her ataxia was unlikely to be because of gluten sensitivity.5 She had an expanded CTG repeat of the SCA-8 gene, although this is of doubtful clinical signiﬁcance, as her largest allele falls within a range that is thought not to be clinically signiﬁcant.6 The constellation of symp- toms and signs, in conjunction with the MRI brain scan, are most suggestive of MSA-C.7 However, the signiﬁcant family history, presence of *POLG1*

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mutations, and deletion/depletion of mtDNA in muscle suggest a mitochondrial disorder as the predominant cause of her symptoms.

To date, an association between an MSA-C pheno- type and *POLG1* mutations has not been described. *POLG1* mutations have been described previously in association with infantile fatal encephalopathy and hepatopathy (Alpers’ syndrome),8,9 sensory ataxic neu- ropathy with ophthalmoparesis,10,11 severe axonal neuropathy,12 as well as adult-onset ataxia without progressive external ophthalmoparesis (PEO) or mus- cle involvement.13 Ataxia has been reported secondary to either dorsal column sensory loss13 or cerebellar dysfunction and has been associated with cerebellar atrophy on MRI.14 *POLG1* mutations have been reported in families with PEO, ataxia, and levodopa (L-dopa)-responsive parkinsonism; pathology revealed dopaminergic cell loss in the substantia nigra but not in Lewy bodies.15–17 Our patient has never had a trial of L-dopa. There is no link between common *POLG1* mutations and idiopathic Parkinson’s disease.18

Both the p.R582C and the p.G11D sequence variants found in our proband have been previously reported in association with known *POLG1*-associated disease phenotypes, including Alpers’ syndrome, ataxia, and neuropathy.19,20 To our knowledge, this is the ﬁrst reported case of mutations in *POLG1* causing a MSA phenotype.

Our case also illustrates the extreme clinical variabil- ity that can present within different members of the same family. The proband was a university-educated professional with no clinical symptoms until late adult- hood, whereas her sister presented in the infantile pe- riod with symptoms compatible with a diagnosis of Alpers’ syndrome. Although conﬁrmatory genetic stud- ies are not possible for the deceased sister, other cases of similar intrafamilial clinical variability have been reported.21 We expand the spectrum of phenotypes associated with *POLG1* mutations to include MSA. Clearly blood DNA screening for *POLG1* mutations is indicated in patients with a family history suggestive of a mitochondrial disorder. Whether such screening in other patients with an MSA-C phenotype can be rec- ommended remains to be determined.

# Legends to the Video

Mitochondrial mimicry of MSA-C. The ﬁrst part, recorded 4 years after onset of the disease, illustrates mild dysarthria and very mild gait ataxia. In the sec- ond part, 9 years after onset, the patient has lost weight and her speech is more dysarthric. She has limb ataxia, mild bradykinesia, and ﬁnger dystonia. She is

unable to stand or walk without assistance and has a broad-based stance. 

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