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*Neurol Genet*  
2016;2:e121; doi: 10.1212/  
NXG.000000000000121

## MITOCHONDRIAL CYTOPATHY WITH COMMON MELAS MUTATION PRESENTING AS MULTIPLE SYSTEM ATROPHY MIMIC

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome<sup>1</sup> is one of the most frequently inherited mitochondrial disorders. MELAS syndrome is a systemic disease with multiple organ involvement.<sup>2</sup> The most common mutation in MELAS is the m.3243A>G mutation in the *MT-TL1* gene.<sup>2</sup>

We describe a patient with the m.3243A>G mutation who presented with only partial clinical manifestation of MELAS. In addition, our patient had a multiple system atrophy (MSA) phenotype due to mitochondrial cytopathy. He was treated with levodopa, which led to clinical improvement of his extrapyramidal syndrome.

**Case report.** In 2012, a 60-year-old white man was referred for progressive gait abnormalities over the preceding 10 years. He reported deteriorating unsteady gait and abnormal fatigue of the lower extremities. Personal history revealed diabetes (onset at age 31), sensorineural hearing loss (dependent on hearing aids), and longstanding generalized fatigue. Family history was remarkable for tetraparesis of unknown origin in his deceased mother.

Examination showed mild cerebellar dysarthria, left-sided hyperreflexia, atrophic proximal tetraparesis (shoulder girdle, gluteal muscles, and posterior thighs), slight ataxia of the left upper limb, and distally reduced vibration sense of the lower extremities with positive Romberg test. The combination of atrophic paresis, diabetes, sensorineural hearing loss, signs of multisystemic affection of the CNS, and potential maternal inheritance led to the clinical suspicion of mitochondrial cytopathy. Biopsy of the left deltoid muscle displayed findings compatible with mitochondrial myopathy (figure, B–D). MRI of the brain and the spinal cord showed bilateral calcifications of the basal ganglia, thalami, nuclei dentati, and the pons (figure, E and F) as well as infratentorial atrophy (figure, G). Endocrine dysfunction was ruled out as an underlying cause of calcifications. Sequencing of the mitochondrial genome revealed the common

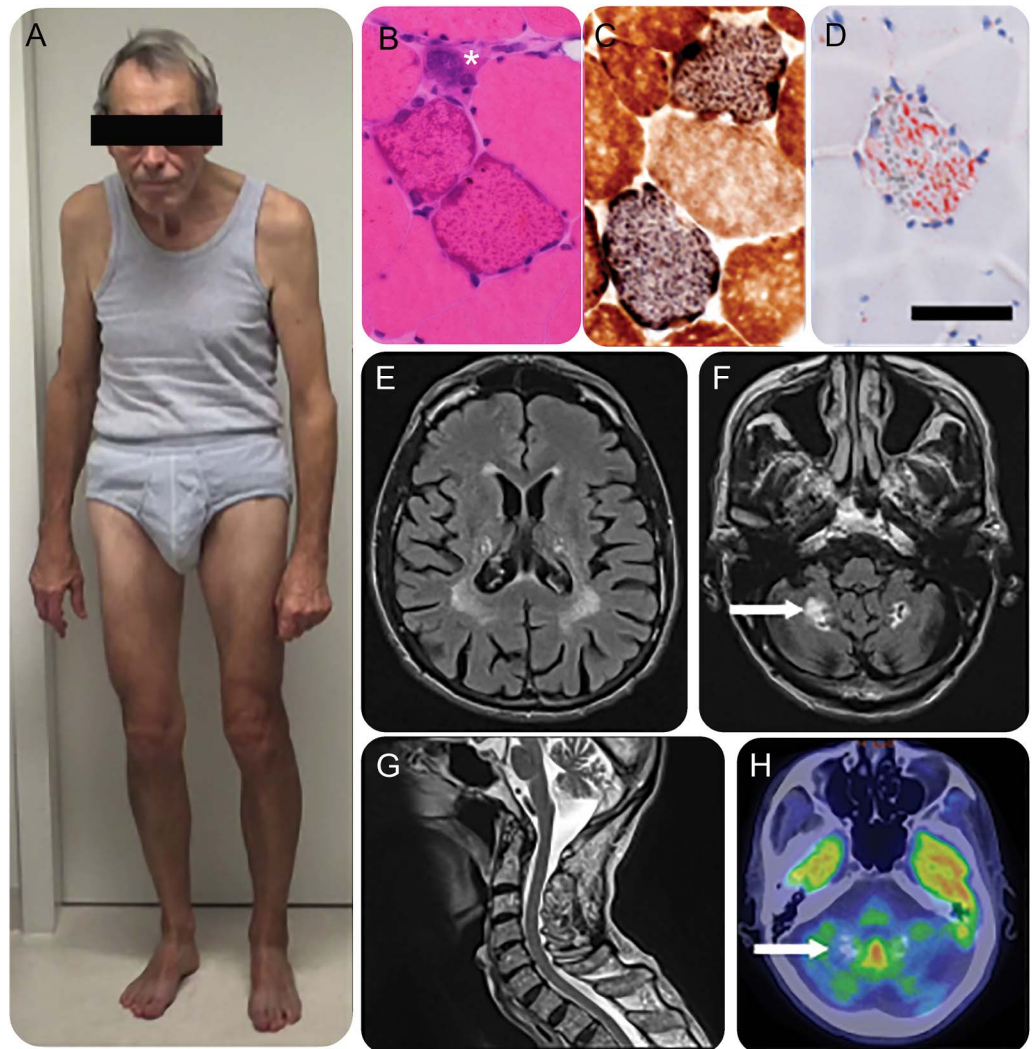
MELAS mutation m.3243A>G in the *MT-TL1* gene (55% heteroplasmy in skeletal muscle and 2% in blood).

After 3 years of clinical stability, he presented with deterioration of gait. Examination affirmed disease progression with a marked cerebellar syndrome (progressive dysarthria, saccadic dysmetria, bilateral cerebellar ataxia left > right, and bilateral dysdiadochokinesia left > right), a pyramidal syndrome (left-sided hyperreflexia, spasticity, and positive Babinski sign), and an extrapyramidal syndrome (hypomimia, hypophonia, bilateral rigidity left > right, camptocormia, and marked postural instability; figure, A). Gait was ataxic with a spastic component. Neuropsychological screening revealed mild cognitive deficits (Mini-Mental State Examination: 26/30). CSF showed lactic acidosis with normal levels of tau, phosphorylated tau, and  $\beta$ -amyloid 1–42. Fluorodeoxyglucose PET of the brain further supported the clinical suspicion of multiple system atrophy with cerebellar predominance (MSA-C) (figure, H). Diagnosis of an MSA mimic, most likely due to mitochondrial cytopathy, was made. Reduction of extrapyramidal motor symptoms (improved walking and faster turns) was achieved with levodopa medication.

**Discussion.** The m.3243A>G mutation in the *MT-TL1* gene encoding the mitochondrial tRNA<sup>Leu(UUR)</sup> is commonly associated with MELAS. Our patient only had partial manifestation of this syndrome, but in addition showed a clinical syndrome suggestive of MSA-C.

MSA-C is a late-onset, sporadic neurodegenerative disorder characterized by autonomic failure and cerebellar ataxia.<sup>3–5</sup> The neuropathologic correlate is a widespread CNS  $\alpha$ -synucleinopathy with neurodegenerative changes in striatonigral or olivopontocerebellar structures. Several conditions are known to mimic MSA-C including metabolic changes. Among these, a case series of mitochondrial myopathies identified a subgroup of patients (11%, 9/85) with movement disorders.<sup>6</sup> In addition, another case with mitochondrial polymerase- $\gamma$  1 mutation<sup>7</sup> is related to mitochondrial cytopathy.

The patient described here presents with an MSA mimic due to mitochondrial cytopathy harboring the common mutation associated with MELAS, although



(A) Clinical presentation: 65-year-old patient with a confirmed mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes mutation (m.3243A>G) presented with a multiple system atrophy phenotype with hypomimia, campocormia, and inner rotation of the left hand as a correlate of a left- > right-sided extrapyramidal syndrome as well as a cerebellar and pyramidal syndrome. (B-D) Histology: (B) hematoxylin and eosin: ragged red fibers and myophagia (\*); (C) cyclooxygenase/succinic dehydrogenase (COX/SDH) double enzymatic staining; COX-deficient, SDH hyperreactive fibers; and (D) Oil Red O: neutral fat accumulation (scale bar 50  $\mu$ m). Both, changes in COX/SDH as well as lipid accumulation suggest mitochondrial dysfunction. (E-G) MRI of the brain and the cervical spine: T2 fluid-attenuated inversion recovery images show bilateral signal changes in the basal ganglia, thalami (E), and dentate nuclei (F) (arrow) in the areas of calcifications, furthermore white matter changes in the periventricular zone (E) as well as cerebellar atrophy (F and G). (H) Fluorodeoxyglucose PET: transversal PET-CT shows diminished metabolism of the cerebellum as well as calcifications of the dentate nuclei (arrow).

presentation with MSA is rare in this context. The preserved cognition further argues in favor of a typical MSA presentation, although the lack of orthostatic hypotension does not. Given recent findings of decreased coenzyme Q10 levels in the serum/cerebellum of patients with MSA, it is tempting to speculate that there is a pathophysiologic link between mitochondrial dysfunction and MSA in general. The clinical course—the neurodegenerative syndrome succeeding the initial manifestation of myopathy—argues in favor of this hypothesis.

Overall, our observation widens the spectrum of phenotypes associated with mitochondrial cytopathies in general, and with MELAS in particular. Moreover, it shows partial clinical improvement to levodopa implicating residual integrity of the striatal receptors.

Thus, mitochondrial diseases should be considered as differential diagnosis in patients presenting with an MSA-C phenotype and a family history suggestive of mitochondrial disorder. Consequently, these patients should be offered testing for mutations

associated with mitochondrial dysfunction. Further studies are needed to reveal the potential link between MSA and mitochondriopathy.

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*Author contributions: A.-K.P., P.F., and M.S. cared for the patient and confirmed the diagnosis. A.-K.P. and M.S. drafted the manuscript. A.S. performed the sequencing analysis. J.L. analyzed the radiologic images. J.H. and S.F. performed the histological analysis. All authors contributed to revising the manuscript. Written consent to publication was obtained.*

*Acknowledgment: The authors thank Ioanna Athanasopoulou, Nicole Naumann, Patricia Hafner, Hanna Arends, Joachim Fladt, and Gian Marco De Marchis for clinical care of the patient.*

*Study funding: No targeted funding reported.*

*Disclosure: Dr. Pröbstel has served on the scientific advisory board of Bayer; has received research funding from the Swiss National Science Foundation, the University of Basel, and Genzyme; has received travel support from Genzyme, Baxalta, and Merck; and has received speaker honoraria from Bayer. Dr. Schaller has received research support from the Novartis Foundation. Dr. Lieb and Dr. Hench report no disclosures. Dr. Frank has received research funding from the Swiss National Science Foundation, the Novartis Foundation for Medical-Biological Research, the Desirée and Niels Yde Foundation, and the Nora van Meeuwen-Haefliger Foundation. Dr. Fuhr's institution has received and used exclusively for research support grants from Parkinson Schweiz, the Jacques and Gloria Gossweiler Foundation, the Freiwilrige Akademische Gesellschaft Basel, the Gottfried and Julia Bangert-Rhyner Foundation, the Swiss National Science Foundation, the Swiss Multiple Sclerosis Society, the Camelia Botnar Foundation, the Hedwig Widmer Foundation, the Synopsis Foundation, the Parkinson Association Switzerland, the Mach-Gaensslen Foundation, UCB Pharma AG, Roche AG, Abbvie AG, and General Electric; and has served on the advisory boards of Biogen Inc., General Electric, and UCB Pharma. Dr. Kappos has served on the editorial boards of Multiple Sclerosis Journal, Multiple Sclerosis and Related Disorders, and the Journal of Neurology; Dr. Kappos' institution has received and used exclusively for research support grants from Alkermes, Almirall, Bayer, Biogen, Excemed, GeNeuro SA, Genzyme, Merck, Mitsubishi Pharma, Novartis, REceptos, Roche, Sanofi-Aventis, Santhera, Teva, Vianex, the Swiss MS Society, the Swiss National Research Foundation, and the European Union; has received steering committee/consulting fees from Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB, and Xenoport; has received license fees for Neurostatus products (paid directly to University Hospital Basel);*

*has received speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Sanofi-Aventis, and Teva; has received support of educational activities from Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva; and has received grants from Bayer HealthCare, Biogen, the European Union, Merck, Novartis, Roche, Roche Research Foundations, the Swiss Multiple Sclerosis Society, and the Swiss National Research Foundation. Dr. Sinnreich has served on the editorial board of Acta Myologica; is coinventor on a patent application for a method evaluating a candidate compound for treating myotonic dystrophy type 1; his institution has received research support from the Swiss National Science Foundation, the Gebert-Ruef Foundation, the Uniscientia Foundation, the Neuromuscular Research Association Basel, Myosuisse, CSL Behring, and Roche; holds Novartis stock; and has received speaker honoraria for CME activities from Novartis and Mepha (used exclusively for research support). Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was paid by the authors.*

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*Received July 12, 2016. Accepted in final form October 20, 2016.*

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