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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[1] is one of the most frequently inherited mitochondrial disorders. MELAS syndrome is a systemic disease with multiple organ involvement.[2] The most common mutation in MELAS is the m.3243A>G mutation in the *MT-TL1* gene.[2]

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).

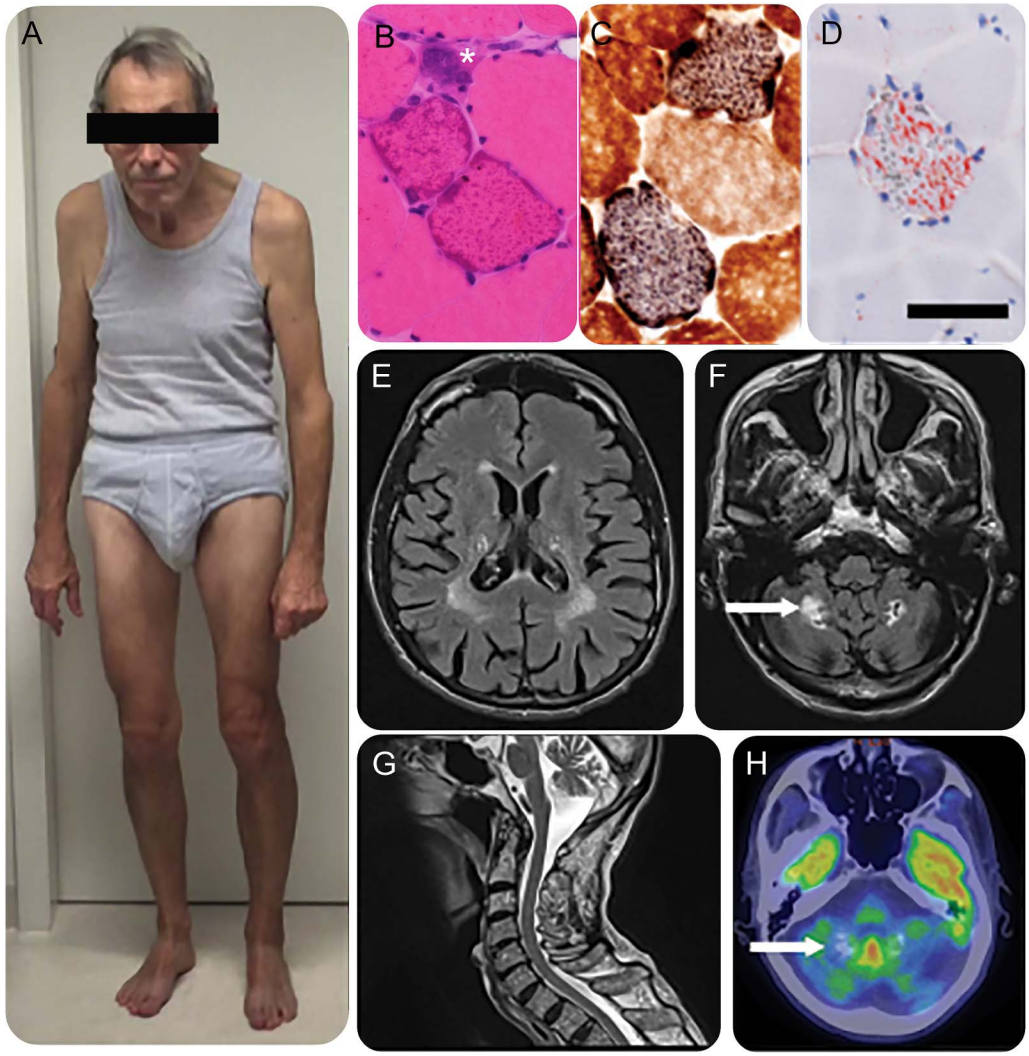
After 3 years of clinical stability, he presented with deterioration of gait. Examination affirmed disease progression with a marked cerebellar syndrome (progressive dysarthria, saccadic dysmetria, bilateral cerebellar ataxia left > right, and bilateral dysdiadochokinesia left > right), a pyramidal syndrome (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 β-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 $tRNA^{Leu(UUR)}$ 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.[3–5] The neuropathologic correlate is a widespread CNS α-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.[6] In addition, another case with mitochondrial polymerase-γ 1 mutation[7] 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

Figure **Case presentation**



(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, camptocormia, 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 μm). 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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Mitochondrial cytopathy with common MELAS mutation presenting as multiple system atrophy mimic

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