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MELAS ASSOCIATED WITH MUTATIONS IN THE *POLG1* GENE

MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes) syndrome is a characteristic mitochondrial disorder caused by point mutations in the mitochondrial genome (mtDNA).[1] In addition to primary mtDNA defects, mutations in nuclear genes essential for mtDNA maintenance are emerging as important causes of mitochondrial disease leading to secondary mtDNA changes including mtDNA depletion and multiple mtDNA deletions. Of particular interest are mutations in the mtDNA polymerase γ (*POLG1*) gene, which are associated with a phenotypic spectrum ranging from Alpers syndrome to recessive ataxia and late-onset progressive external ophthalmoplegia (PEO).[2-5] We describe a patient with strokelike episodes typical of MELAS due to mutation of *POLG1*.

Case history. A 28-year-old man was admitted to hospital at age 23 years because of acute onset of head jerking to the left side and vomiting, preceded by several days of visual scintillations and right-sided headache. He had been well until 2 years previously when it was noted that he had problems with coordination and concentration. Neurologic examination revealed left homonymous hemianopia, areflexia, and sensory ataxia. A few hours after admission, he developed left-sided focal seizures with secondary generalization leading to status epilepticus, which was successfully treated with clonazepam and valproate. Cognitive deficits in memory and attention were noted, and there was a degree of motor apraxia. Over the past 5 years, there have been no further strokelike-episodes or seizures. Neurologic examination reveals left-sided homonymous hemianopia, a mild cognitive deficit, areflexia, and sensory ataxia but no ophthalmoplegia. There is no family history of note.

Laboratory investigations, including measurements of blood lactate, liver enzymes, and creatine kinase, were unremarkable. Examination of CSF showed a mild increase in protein (62.1 mg/dL, normal <50 mg/dL) and elevated lactate (3.4 mmol/L, normal <2.1 mmol/L). Brain MRI revealed a right-sided occipital lesion (figure, A). EEG showed focal sharp waves in the right occipital region. Neurophysiology and sural nerve biopsy revealed a sensory axonal peripheral neuropathy. Examination of a muscle biopsy specimen demonstrated subsarcolemmal accumulation of mitochondria in some fibers, with enzyme histochemistry revealing 5% cytochrome *c* oxidase (COX)–deficient fibers but no strongly succinate dehydrogenase (SDH)–positive vessels (figure, B). Respiratory chain complex activities were normal in muscle.

The 3243A>G, 3271T>C and 8344A>G mtDNA mutations were not detected in muscle, and Southern blot analysis did not reveal evidence of mtDNA rearrangements. Long-range PCR, however, amplified several smaller bands compatible with multiple mtDNA deletions, which was confirmed by real-time PCR analysis of clonally expanded mtDNA deletions in individual cells (figure, C).[6]

Sequencing of the *ANT1* and *PEO1* genes revealed no mutations, but analysis of *POLG1* revealed two reported heterozygous missense mutations in compound c.1880G>A in exon 10 predicting R627Q and c.2542G>A in exon 16 predicting G848S. Sequencing of parental samples confirmed recessive inheritance of the mutated alleles (figure E-1 on the *Neurology* Web site at www.neurology.org).

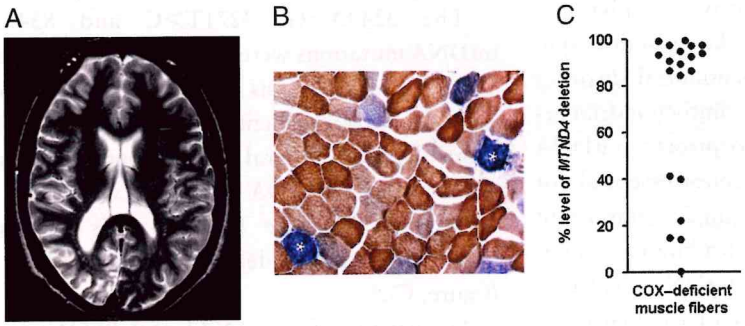
Discussion. Our patient's clinical presentation (strokelike episode with occipital localization, headache, and seizures) and laboratory investigations (elevated CSF lactate, ragged-red fibers) fulfill the diagnostic criteria for MELAS.[1] The presence of COX-deficient fibers (although unusual in MELAS) and the absence of typical mtDNA point mutations prompted further investigations. Both long-range PCR and real-time PCR analyses detected multiple mtDNA deletions, confirming that low levels of multiple mtDNA deletions may sometimes remain undetected by Southern blot analysis[3,4]

Sequencing of the *POLG1* gene identified compound heterozygous mutations, consistent with the negative family history and indicative of autosomal recessive inheritance. Both mutations have been reported previously as recessive mutations, although not together; the R627Q mutation has been documented in patients with PEO and sensory ataxia, and Alpers syndrome, whereas the G848S mutation has been reported in patients with either PEO or Alpers syndrome (http://dir-apps.niehs.nih.gov/polg/).

Although *POLG1* mutations are widely described in patients with encephalopathy, typical strokelike episodes are unusual, although there is a report of an ataxic patient with the A467T mutation whose 17-year-old sister had acute encephalopathy and seizures followed by cortical blindness and stupor, Cheyne-Stokes respiration, and sudden death.[3] In other patients with *POLG1* mutations, cerebral lesions in the occipital lobes similar to MELAS were observed, but strokelike-episodes were not reported.[4,5] Many of these patients presented with epilepsy and headache typically observed during strokelike

Supplemental data at www.neurology.org

Figure MRI, histochemistry, and PCR of the brain



(A) T2-weighted MRI of the brain demonstrating a right-sided occipital hyperintense cortical lesion that spares deeper white matter and does not conform to a large arterial territory as typically seen in MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes). (B) Histochemical demonstration of combined cytochrome c oxidase (COX) and succinate dehydrogenase activities in the patient's muscle biopsy specimen, revealing COX-deficient ragged-red fibers (shown by asterisk). (C) Single-fiber real-time PCR showing that the majority of fibers contain high levels of *MTND4* gene deletion, which confirms a diagnosis of multiple mtDNA deletions.

episodes, but their lesions were small compared with the occipital hyperintensity seen in our patient. The majority of patients presenting with liver failure did so following valproate treatment of status epilepticus, and even though our patient was treated successfully with valproate without precipitating liver failure, valproate administration should be avoided in patients with *POLG1* mutations.

In addition to the strokelike episode, our patient had a sensory neuropathy but no evidence of ptosis or PEO. Neuropathy with sensory ataxia is typically observed in patients with *POLG1* mutations[3-5] and, although not a characteristic feature of MELAS, a significant proportion of patients with the 3243A>G mutation have clinical signs of neuropathy.[7]

In conclusion, our case highlights the complexity of the relationship between genotype and phenotype in mitochondrial disorders and broadens the striking phenotypic variability of *POLG1* mutations that now must also include MELAS, a classic mitochondrial syndrome.

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THE TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME, THE BRAIN, AND TUMOR NECROSIS FACTOR-α ANTAGONISTS

Case report. The tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS) is an autosomally dominant inherited disorder resulting from mutations within the TNF receptor super family 1A gene (*TNFRSF1A*), which impair cleavage of p55 TNF receptors (TNFR1), decrease soluble TNFR1 serum levels, and affect intracellular trafficking of mutant proteins.[1] The associated unopposed TNFα signaling confers self-limited autoinflammation and may promote amyloidosis. Here, we provide clinical and histologic evidence that TRAPS may affect the CNS and has to be included in the spectrum of autoimmune inflammatory CNS disorders.

Our patient was diagnosed with a C55A mutation in exon 3 of the *TNFRSF1A* gene and had experienced recurrent attacks of fever, myalgias, arthralgias, and painful migratory rashes since childhood. At age 38 he developed brainstem and cerebellar symptoms from an extensively contrast-enhancing lesion in the left cerebellar peduncle; acute disseminated encephalomyelitis (ADEM) or lymphoma was considered.[2] However, brain biopsy revealed a T-cell-predominated inflammatory infiltrate without evidence of demyelination (figure, A through D). Moreover, treatment with several courses of methylprednisolone was only transiently effective, and cranial MRI revealed striking persistence of contrast enhancement in the left infratentorial lesion 1 year after disease onset (figure, E and F). CSF analysis showed a mild lymphocytic pleocytosis of 7 cells/μL and repeatedly negative oligo-