A Case of Late-Onset MELAS

Kevin G. Kimata, MD; Lucio Gordan, MD; E. Todd Ajax, MD; Patricia H. Davis, MD; Thomas Grabowski, MD

We describe a 60-year-old man with MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes) and discuss the mitochondrial DNA point mutation 3243. A diagnosis of MELAS should be considered in the appropriate clinical setting at any age.

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Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) characterize a rare disorder that usually presents before the age of 40 years.\textsuperscript{1-4} Strokelike episodes often present with hemianopsia and hemiplegia. Since MELAS is a condition that primarily affects the young, it may not be considered in the differential diagnosis of a stroke syndrome in an older adult. We describe a 60-year-old man who presented with strokelike episodes and encephalopathy. Further investigation revealed an elevation of the cerebrospinal fluid lactate level. A muscle biopsy specimen showed ragged red fibers, and mitochondrial DNA analysis revealed a point mutation at nucleotide 3243.

**REPORT OF A CASE**

A 60-year-old right-handed man presented with a 1-year history of behavioral changes and stuttering speech. His family first noted inappropriate fear of a minor surgical procedure. Three months later, a diagnosis of depression was made, and he was treated with paroxetine hydrochloride (Paxil) and then fluoxetine hydrochloride (Prozac), with little improvement. One month later, his family noted emotional lability, slowed speech, cognitive decline, and short-term memory loss. He experienced spells of confusion and became lost while driving on familiar roads.

He became involved in several automobile accidents, yet seemed unconcerned. Over the next month, he worsened to the point that he could not remember how to start his car. His word-finding skills diminished, and family members found his speech difficult to interpret. He experienced a generalized tonic-clonic seizure and was admitted to a local hospital. His only medication was fluoxetine. A computed tomographic (CT) scan of the brain revealed no abnormalities. A magnetic resonance imaging (MRI) scan of the brain with gadolinium contrast revealed a left temporal lesion with little enhancement and diffuse cortical atrophy (Figure 1). The results of cerebral angiography were unremarkable. An electroencephalogram showed focal slowing and paroxysmal sharp waves in the left frontotemporal region. The patient was treated with phenytoin sodium (Dilantin) and aspirin. He underwent speech therapy and improved. One month later, an MRI scan showed complete resolution of the lesion.

Three months later, the patient experienced the sudden onset of a right-lateralized headache and a left visual field disturbance and was readmitted to a local hospital. A left homonymous hemianopia and left upper extremity pronator drift were found on examination. A CT scan revealed a new region of low attenuation in the right temporopolar and right inferior medial occipital lobes and periventricular white matter.
changes. These lesions did not enhance with gadolinium contrast (Figure 2). A transesophageal echocardiogram revealed no abnormalities. An electroencephalogram showed right postero temporal slowing but no epileptiform activity. Cerebrospinal fluid analysis revealed 35 erythrocytes; 4 lymphocytes; protein, 0.79 g/L (79 mg/dL); and glucose, 31.1 mmol/L (56 mg/dL). The cytologic findings, bacterial and fungal cultures, cryptococcal antigen titer, and VDRL test result were unremarkable. Electrophoresis of cerebrospinal fluid revealed an elevation of the IgG level. Serum angiotensin-converting enzyme, antinuclear antibody, and anticardiolipin antibody titers were normal. The findings of serial serum glucose determinations were normal. A second cerebral angiogram revealed no abnormalities. A CT scan obtained 9 days later showed improvement in the right temporo-occipital lesion. The patient was treated with phenytoin, ticlopidine hydrochloride, and fluoxetine.

Several weeks later, the patient’s mental status again began to deteriorate, and he had visual and auditory hallucinations. He became excessively compulsive about body cleanliness and manifested an increased sexual drive. He was then seen for the first time at the Department of Neurology, University of Iowa, Iowa City. During that visit, he complained of headaches, exercise intolerance, general fatigue, and auditory hallucinations. His birth and developmental history were unremarkable. He had no significant prior medical problems. His son had died of a brain tumor. There was no history of any other neurologic disorder in the family. His mother and 3 of his 5 siblings have diabetes mellitus but have not experienced similar problems. He was graduated from high school and, for financial reasons, was unable to attend college. He later obtained a private pilot’s license.

On examination, his temperature was 35.6°C, his heart rate was 80/min, his respirations were 18/min, and his blood pressure was 117/65 mm Hg. He was alert, but not oriented to person, place, or time. He did not follow directions. He appeared unusually anxious and confused. His speech was stuttering and dysarthric and contained paraphasic errors and perseverative thoughts. He was poorly cooperative during the interview, in part because of a hearing deficit. His pupils were normal, as were the findings of the funduscopic examination. His extraocular movements were full and smooth. He would not fully cooperate with visual field testing, but exhibited decreased blink response to visual threat from the left in both eyes. He exhibited no sign of facial weakness or asymmetry. There was no loss of facial sensation or corneal reflexes, and there was no abnormality of movement of the sternocleidomastoid, trapezius, or tongue muscles. On motor examination, he demonstrated normal strength, but had mildly increased muscle tone throughout all 4 limbs. The results of the sensory examination were unreliable, but he withdrew to pinprick in all 4 extremities. He could not cooperate enough to do coordination testing. The muscle stretch reflexes were 2+ and symmetrical throughout, and the plantar responses were flexor, bilaterally. His gait was slow, wide based, and shuffling. His neck was supple and he had full range of motion. There were no carotid bruits. The findings of the general physical examination were unremarkable.
The next day, the patient experienced 2 generalized seizures. He was admitted to a hospital, and carbamazepine (Tegretol) was added to his regimen. The MRI revealed a new left anterotemporal lesion and signal changes attributable to his previous right temporoparietal brain lesion (Figure 3).

Two weeks later, the patient was admitted to the University of Iowa Hospitals for evaluation. On examination, his vital signs were normal. He had auditory and visual hallucinations, paraphasic speech, and impaired verbatim word repetition, comprehension, confrontation naming, calculation, reading, and writing. The findings of cranial nerve examination were remarkable for decreased blinking to threat from the left side. He would not cooperate with confrontation visual field testing. Motor examination revealed mildly increased muscle tone. His strength and coordination appeared to be normal, although he was poorly cooperative. He withdrew to pinprick consistently in all extremities. He demonstrated a wide-based, shuffling gait. The results of Romberg testing were negative. He exhibited 2+ reflexes in the upper extremities, 3+ in the lower extremities, and downgoing plantar responses. There was no startle response. The findings of his general physical examination were unremarkable.

The results of a complete blood cell count, thyroid function studies, and serum electrolyte panel were normal, as were the erythrocyte sedimentation rate and the serum vitamin B12 and C-reactive protein levels. Serologic tests were negative for human immunodeficiency virus, and the antineuronal and anti-Purkinje cell antibody titers were normal. An abdominal CT scan revealed calcified granulomas in the spleen and a left renal cyst. There was no retroperitoneal adenopathy or other intra-abdominal mass. Cerebrospinal fluid analysis revealed the following values: protein, 0.78 g/L (78 mg/dL); glucose, 31.6 mmol/L (57 mg/dL); lactate, 4.3 mmol/L (reference range, 0-3.0 mmol/L); no erythrocytes; and 1 lymphocyte. Formal neuropsychological testing confirmed the presence of a Wernicke aphasia. Another MRI scan showed improvement of the left anterotemporal lesion.

The complete resolution of brain lesions on MRI, as well as their lack of conformity to vascular territory, made the diagnosis of ischemic stroke unlikely and suggested the possibility of MELAS. A quadriceps muscle biopsy specimen was obtained, and ragged red fibers were seen on Gomori trichrome staining. Genetic analysis of this tissue by polymerase chain reaction analysis identified an adenine to guanine mitochondrial DNA point mutation at nucleotide 3243 coding for the transfer ribonucleic acid gene (Leu). Two thirds of the mitochondrial DNA contained the mutation in the muscle biopsy sample. Peripheral blood samples to determine the degree of heteroplasmy were not obtained. The analysis was performed using the Hae III restriction endonuclease according to standard protocol.

A regimen of phytanadione, ascorbic acid, and a multivitamin was subsequently initiated. Carbamazepine therapy was continued, and phenytoin therapy was discontinued. The patient was seen in follow-up 5 months after his last seizure and reported no new strokelike episodes. He complained of headache and generalized fatigue. He was alert and oriented to person, place, and time and had improved auditory comprehension, fluency of speech, and a left homonymous hemianopia persisted. The results of the rest of his physical examination remained unchanged.

Pavlakis et al1 described MELAS in 1984. In 1994, Hirano and Pavlakis4 published a review of 110 cases of MELAS. Clinical stroke, ragged red fibers (seen on Gomori trichrome staining of muscle biopsy specimens), exercise intolerance, lactic acidosis, seizures, and onset of symptoms before 40 years of age occurred in more than 90% of the cases; normal early development and dementia occurred in 90% of the cases; and short stature, headache, hearing loss, nausea, vomiting, limb weakness, and hemianopia occurred in 75% to 89% of the cases.5

Genetic analysis of muscle biopsy specimens frequently reveals mitochondrial DNA point mutation(s) at either nucleotide 3243 or 3271.6,7 Encephalopathy may manifest itself as mental retardation or dementia. Elevations of lactate may be found in samples of serum and/or cerebrospinal fluid.2 Strokelike episodes often include symptoms and signs of hemianopia and hemiplegia. The CT and MRI brain scans that are obtained after these episodes reveal strokelike signal changes that frequently cross major cerebrovascular territories.8 Brain MRI and CT scan abnormalities in patients with strokelike episodes occur in temporal, parietal, and occipital regions without respect to the boundaries of major vascular territories.
A diagnosis of MELAS syndrome was delayed in our patient because it was not considered in the differential diagnosis. Clues to the diagnosis were the atypical distribution and resolution of signal changes on MRI scans correlating with seizure and stroke-like events, prodromal behavioral changes, headache, and elevated cerebrospinal fluid lactate levels.

Virtually all patients described with MELAS have had signs and symptoms that occurred before the age of 40 years. There are few published cases involving patients older than 50 years with mitochondrial DNA point mutations known to be associated with MELAS. In the review of 110 cases of MELAS published by Hirano and Pavlakis, there was only 1 in which the patient was older than 40 years at presentation. The patient's age and the findings of the genetic analysis were not published in that case. Mosewich et al published a study of the family of a 46-year-old woman with MELAS. In the study, the patient's 69-year-old mother and 59-year-old maternal aunt were found to have a mitochondrial DNA 3243 point mutation on muscle biopsy specimens, but neither of them had the MELAS syndrome. Castillo et al published the radiographic findings in 8 cases of MELAS. One of the patients was 80 years old, and another was 60 years old. The clinical details of these cases were not published, and it is unclear whether the patients had the entire syndrome and/or mitochondrial DNA point mutation(s). The patients did not have MRI changes correlating with their stroke-like episodes. Ciafaloni et al published a series involving 23 patients with MELAS, one of whom experienced onset at the age of 53 years. She had a mitochondrial DNA 3243 point mutation. In a series of 40 patients with MELAS described by Goto et al, 80% tested positive for the mitochondrial DNA point mutation. Thus, to our knowledge, as of this writing there are no well-documented published cases of MELAS presenting after the age of 53 years.

The MELAS syndrome is an uncommon condition. It is in its infancy, and its boundaries are not yet defined. Although it is often associated with mitochondrial DNA point mutations, its pathogenesis is not fully understood. Nevertheless, it should be considered in older patients when the appropriate clinical setting arises.

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References: