Adult-Onset MELAS Presenting as Herpes Encephalitis

Sophia R. Sharfstein, MD; Mark Forrest Gordon, MD; Richard B. Libman, MD; Elfrida S. Malkin, MD, MPH

Objective: To report an unusual presentation of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) manifested in late life with a clinical picture of herpes simplex encephalitis.

Design: Case report.

Setting: Clinical neurology department in a tertiary care hospital.

Case Description: A 55-year-old woman developed aphasia and delirium during ophthalmic herpes zoster infection treated with oral prednisone and ophthalmic steroids, which was followed by progressive cognitive decline without acute neurologic events for 5 years. At age 60, the patient presented with new onset of seizures, hemiparesis, and hemianopsia. Subsequently she developed cortical blindness, multiple tramautic soft tissue injuries from falls, acute psychosis, and severe dementia with periods of agitation. She died in a nursing home in March 1997, 6 years after initial presentation.

Results: Magnetic resonance imaging scan of the brain showed hyperintensity on T₂-weighted images involv-

ing temporal, parietal, and occipital lobes bilaterally as well as mild atrophy of brainstem and cerebellum. Single photon emission computed tomographic imaging showed hypoperfusion of temporal, parietal, and occipital lobes. Results of video electroencephalographic monitoring showed periodic lateralizing epileptiform discharges in temporal and occipital areas. The serum lactate level was normal in May 1996 and elevated in October 1996. The creatine kinase level was elevated with a 100% MM fraction in August 1991 and normal in March 1996. Results of repeated cerebrospinal fluid analyses indicated elevated protein levels. Analysis of DNA was diagnostic of MELAS by mitochondrial DNA point mutation at position 3243. The results of autopsy showed moderate cerebral, cerebellar, and brainstem atrophy with signs of infarction in temporal and parietal lobes bilaterally.

Conclusions: The clinical presentation as well as age at onset of MELAS are highly variable. Onset of mitochondrial disorders can be provoked by febrile illness when there is mismatch between energy requirements and availability. In the differential diagnosis of herpes encephalitides, MELAS syndrome should be considered.

Arch Neurol. 1999;56:241-243

From the Departments of Neurology, Long Island Jewish Medical Center, Long Island Campus for the Albert Einstein College of Medicine, New Hyde Park (Drs Sharfstein, Gordon, and Libman) and Columbia Presbyterian Medical Center, New York (Dr Malkin), NY. ITOCHONDRIAL encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is one of the mitochondrial cytopathy syn-

dromes that may present with migrainelike headache, vomiting, seizures, homonymous hemianopsia, cortical blindness, and hemiparesis.¹⁻⁴ It belongs to a group of mitochondrial diseases characterized by point mutation of mitochondrial DNA (mtDNA).¹⁻⁴ Besides MELAS syndrome, this group consists of myoclonic epilepsy with ragged red fibers; neuropathy, ataxia, and retinitis pigmentosa; and Leber hereditary optic neuroretinopathy. Another group of mitochondrial disorders characterized by deletions of mtDNA is represented by Kearns-Sayre syndrome, sporadic progressive external ophthalmoplegia with ragged red fibers, and Pearson marrowpancreas syndrome.1 Pavlakis et al2 first described MELAS syndrome in 1984, reporting 2 cases and finding 9 other similar cases in the literature. The disorder is due to a point mutation of mtDNA at the transition at nucleotide (nt)3243 and less frequently at nt3271 in the transfer RNA gene.^{1,3-8} There may be variable clinical presentations of MELAS, but to our knowledge, there are few cases resembling viral encephalitis. Johns et al⁹ reported 3 cases of MELAS syndrome mimicking herpes simplex encephalitis. We report a case of late-onset MELAS that developed after an episode of herpes zoster ophthalmicus and mimicked herpes encephalitis.

REPORT OF A CASE

A 55-year-old woman was brought to the emergency department in July 1991 by her daughter, who stated that her mother was

ARCH NEUROL/VOL 56, FEB 1999 241

©1999 American Medical Association. All rights reserved.

sleepy and unable to express herself or understand spoken language. She had had right V1 (ophthalmic branch of the transgeminal nerve) herpes zoster during the previous 3 weeks and was treated with oral prednisone 60 mg/d and topical ophthalmic steroids. On day 5 of steroid treatment she developed delusions and hallucinations, generalized weakness, lethargy, blunted affect, and inability to ambulate without support. These symptoms were initially attributed to prednisone, but in spite of a rapid steroid taper, she developed global aphasia on day 8 of steroid treatment. The prednisone regimen was stopped on day 9 and her generalized weakness improved, but aphasia persisted. Computed tomographic scan of her brain at that time showed no abnormalities.

The patient had a history of frequent headache, the characteristics of which could not be adequately ascertained. She also had a history of hearing loss, hypercholesterolemia, and hypertension. Her mother had a history of recurrent strokes and was, according to the family, very ill and cognitively impaired at that time.

On examination, patient's weight was 49.5 kg, and her height was 1.6 m, which was similar to other members of her family. The patient had healing vesicular lesions on the right side of her scalp and forehead. She was alert but unable to follow any commands. There was diminished spontaneous speech output as well as verbal perseveration. She was periodically agitated. Findings from cranial, motor, and sensory nerve examinations were difficult to obtain because of poor cooperation, but they appeared to be normal.

Results of a lumbar puncture showed a protein level of 63 mg/dL, a glucose value of 53mg/dL, a white blood cell count of 3×10^{6} /L, a red blood cell count of 14×10^{6} /L, bacterial, viral, and fungal cultures negative for organisms as well as normal serological test results. A repeated lumbar puncture was performed 2 weeks later and showed a protein level of 101 mg/dL, a glucose value of 78 mg/dL, a white blood cell count of 2×10^{6} /L, and a red blood cell count of 20×10^{6} /L. Creatine kinase levels were normal (60 U/L) on admission and in a range of 224 to 514 U/L with a 100% MM fraction 2 weeks after admission (normal range, 38-173 U/L).

Intravenous acyclovir sodium treatment was begun for presumed herpes zoster encephalitis. On day 14 of hospitalization she developed complex partial seizures and treatment with phenytoin sodium was initiated. This prompted a consideration of herpes simplex encephalitis. Video electroencephalographic monitoring showed periodic lateralizing epileptiform discharges in the left hemisphere, maximal in the posterior temporal and occipital areas. Magnetic resonance imaging (MRI) scans demonstrated edema in the left temporal and parietal lobe consistent with focal cerebritis (Figure 1). A repeated MRI 10 days later showed the same lesion in the left parietooccipital region. Cerebral angiography results were normal. The results of a stereotactic brain biopsy were negative for viral inclusions and showed a nonspecific lymphocytic reaction. In particular, there was no evidence of the presence of herpes simplex or herpes zoster.

The patient was treated with intravenous acyclovir for 14 days with moderate improvement in her mental status and aphasia. She was discharged home with speech therapy and showed gradual improvement in receptive and expres-

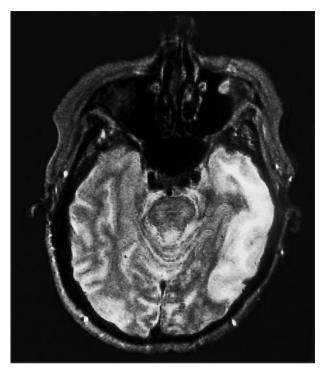


Figure 1. *T*₂-weighted magnetic resonance image showing edema in the left temporal and parietal lobes consistent with focal cerebritis.

sive language over the next few years, although her general cognitive function gradually declined. She was unable to take care of her finances, and she needed supervision with activities of daily living. However, she did not have further acute neurologic events until March 1996, when she presented with worsening aphasia, global confusion, and agitation. She was hospitalized with a presumptive diagnosis of recurrent herpes simplex encephalitis. She remained stuporous for several weeks with periods of complex partial status epilepticus. There were no clinical signs of myopathy, retinopathy, endocrinopathy, or cerebellar dysfunction; however, neurologic examination was limited because of the patient's condition. Her creatine kinase level was 105 U/L. Spinal fluid analyses showed a protein level of 56 mg/dL, a glucose level of 68 mg/dL, bacterial, viral, and fungal cultures negative for organisms as well as normal serological test results. Persisting high signal appeared on MRI in the left temporoparietal area as well as a new area of increased signal in the right temporal region (Figure 2). The patient was treated with intravenous acyclovir without notable improvement. At that time, a diagnosis of MELAS was considered, and this was confirmed in May 1996 by a blood analysis that showed an mtDNA point mutation at position nt3243. Her serum lactate level was 1.8 mmol/L (normal range, 0.7-2.1 mmol/L) in May 1996 and 3.1 mmol/L in October 1996. Her serum pyruvate level was 45 µmol/L (normal range, 34-102 µmol/L) in May 1996. She was treated with coenzyme Q10, riboflavin, carnitine, phenytoin, clonazepam, and aspirin and discharged to a rehabilitation facility.

In September 1996, she presented with complaints of inability to see for 1 week prior to admission. She "bumped into things" and had multiple falls. She also developed right-sided weakness, with subsequent partial im-

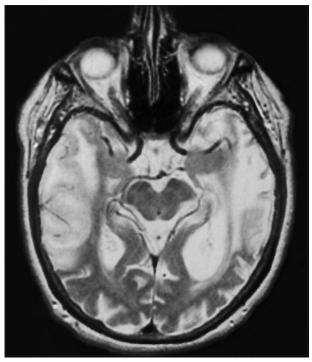


Figure 2. *T₂-weighted magnetic resonance image showing persisting high signal in the left temporoparietal area and a new area of increased signal in the right temporal lobe interpreted initially as a new manifestation of herpes simplex encephalitis.*

provement. She had mixed aphasia, cortical blindness, a fluctuating level of consciousness, and right arm paresis. Results of MRI showed bilateral temporal encephalomalacia and a new left calcarine and medial parietooccipital area of hyperintensity on T₂-weighted image as well as mild atrophy of the cerebellum and brainstem. Single photon emission computed tomography showed hypoperfusion of parietal, temporal, and occipital lobes bilaterally. Transcranial Doppler study results were normal. Transthoracic echocardiographic results were inconclusive with regard to the potential cardiac source of embolism. Transeophageal echocardiographic tests could not be performed because of lack of cooperation.

Two weeks after discharge she was readmitted to a psychiatric institution with acute psychosis. In December 1996, she showed improvement in her aphasia and partial resolution of right-arm weakness. In March 1997, she was treated in the emergency department of our hospital for multiple soft tissue ecchymoses on the head, body, and extremities due to multiple falls. Because of her progressive cognitive deterioration, she was sent to a nursing home where she died several weeks later.

On autopsy, gross examination of the brain showed moderate cerebral and cerebellar atrophy and chronic degeneration of the left superior and middle frontal cortex. Microscopic examination of the brain showed moderate astrocytosis in the superficial layers of the frontal cortex, patchy loss of cerebellar Purkinje cells and Bergmann cell astrocytosis, and changes consistent with infarction in the cortex and subcortical white matter of the temporal and parietal lobes bilaterally. No changes were found in the leptomeningeal and parenchymal vessels in the affected areas of the brain. No pathological findings suggestive of viral encephalitis and herpes simplex encephalitis in particular were identified.

COMMENT

The clinical presentation of MELAS syndrome is extremely variable and can mimic viral encephalitides, especially herpes simplex encephalitis.^{2,9} Our case is unique because the patient, in spite of the presence of persistent headache, did not exhibit other signs of MELAS until age 55. The MELAS syndrome usually presents in adolescence or early adult life.^{4,5,10} We speculate that ophthalmic zoster and possibly steroid treatment provoked manifestations of MELAS in a previously compensated older patient, possibly because of the low distribution of mutant mtDNA. Hirano and Pavlakis¹⁰ state that mitochondrial diseases manifest when there is a mismatch between energy requirements and availability. Affected mitochondria try to meet energy demands of the cell during febrile illnesses, when energy demands are especially high. Relative deficiency of cellular adenosine triphosphatase results in "metabolic strokes."10

The patient's mother had a history of "multiple strokes" in late adulthood. No further information is available regarding the nature of her "strokes," but the possibility of MELAS in her case cannot be excluded. Two of the patient's daughters were diagnosed with MELAS by DNA analyses. They are in their late 30s and are asymptomatic.

More observations are needed with regard to clinical presentation and predisposing factors to clinical manifestation of MELAS. The MELAS syndrome should be included in differential diagnoses of herpes encephalitides. The mtDNA mutation can be easily detected in blood and urine without need for invasive procedures such as muscle biopsy.

Accepted for publication July 2, 1998.

Corresponding author: Mark Forrest Gordon, MD, Department of Neurology, Long Island Jewish Medical Center, Long Island Campus for the Albert Einstein College of Medicine, New Hyde Park, NY 11042.

REFERENCES

- DiMauro S, Moraes CT. Mitochondrial encephalomyopathies. Ann Neurol. 1993; 50:1197-1208.
- Pavlakis SG, Phillips PC, DiMauro S, DeVivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: a distinctive clinical syndrome. *Ann Neurol.* 1984;16:481-488.
- Gilchrist JM, Sikirica M, Stopa E, Shanske S. Adult onset MELAS: evidence for involvement of neurons as well as cerebral vasculature in strokelike episodes. *Stroke*. 1996;27:1420-1423.
- Koo B, Becker LE, Chuang S, Merante F, Robinson BH. Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS): clinical, radiological, pathological, and genetic observations. *Ann Neurol.* 1993;34:25-32.
- Ciafaloni E, Ricci E, Shanske S, Moraes CT, Silvestri G, Hirano M. MELAS: clinical features, biochemistry, and molecular genetics. *Ann Neurol.* 1992;31:391-398.
- Goto Y, Horai S. A mutation in the tRNA leu(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature*. 1990;348:651-653.
- Goto Y, Nonaka I, Horai S. A new mtDNA mutation associated with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). *Biochim Biophys Acta*. 1991;1097:238-240.
- Goto Y, Horai S, Matsuoko T, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): a correlation study of the clinical features and mitochondrial DNA mutation. *Neurology*. 1992;42:545-550.
- Johns DR, Stein AG, Wityk R. MELAS syndrome masquerading as herpes simplex encephalitis. *Neurology*. 1993;43:2471-2473.
- Hirano M, Pavlakis SG. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS): current concepts. J Child Neurol. 1993;4-12.

ARCH NEUROL/VOL 56, FEB 1999 243