Cerebral Blood Flow in Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Strokelike Episodes

Y. Ooiwa, MD; Y. Uematsu, MD; T. Terada, MD; K. Nakai, MD; T. Itakura, MD; N. Komai, MD; and H. Moriwaki, MD

Background and Purpose: The precise mechanism of neurological symptoms with mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) is still controversial. We investigated the correlation between strokelike episodes and cerebral blood flow in two patients with MELAS and discuss the pathogenesis of strokelike episodes with MELAS.

Summary of Report: Cerebral dynamic computed tomography and cerebral angiography were used to measure cerebral circulation in the first case, that of a 20-year-old woman with MELAS. The second subject was a 13-year-old female who was studied with xenon-enhanced computed tomography. The cerebral blood flow studies were performed 3–72 hours after the onset of strokelike episodes. Serial cerebral angiography, dynamic computed tomography, and xenon-enhanced computed tomography showed vasodilation localized in the affected cerebral cortices during strokelike episodes, without any reduction in regional cerebral blood flow.

Conclusions: Our study suggests that the strokelike episodes associated with MELAS are different in origin from ischemic stroke. (Stroke 1993;24:304–309)

Key Words: • cerebral blood flow • MELAS • mitochondrial encephalomyopathy • tomography, x-ray computed • xenon

The constellation of mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) is a mitochondrial encephalomyopathy characterized by the presence of “ragged” red fibers on muscle biopsy, normal early development, short stature, seizures, and hemiparesis, hemianopia, or cortical blindness.1,2 The underlying dysfunction relates to a defect in substrate utilization in the respiratory chain or of oxidation–phosphorylation coupling in the mitochondrion.3–5 Although the syndrome strongly resembles cerebrovascular thrombotic and embolic disease, the exact mechanism by which symptoms are produced remains unknown. We investigated the correlation between clinical symptoms and cerebral blood flow in two patients with MELAS.

Case Reports

Case 1

A 20-year-old woman with an unremarkable medical history developed scintillating scotoma followed by a severe throbbing headache and nausea lasting several days. On admission, a right homonymous hemianopsia was identified. Computed tomographic (CT) scan showed an irregular low-density area in the left occipital lobe interlaced with contrast-enhanced lesions (Figure 1A). Cerebral angiography revealed dilation of the cortical arteries, capillary blush, and early venous filling in the left occipital lobe (Figure 1B). The hemianopsia and the occipital radiolucency demonstrated on CT scan disappeared over 2 weeks.

One year later, the patient developed generalized clonic seizures that progressed to status epilepticus with generalized delta burst discharges on electroencephalography. The seizures were resistant to anticonvulsant therapy and lasted 5 days. Six months later, the patient developed anorexia and fatigability. Neurological examination showed a left hemiparesis and hemihypesthesia, and homonymous hemianopsia. CT scan revealed a large low-density area over the right parieto-occipital region in which the cortical surface was enhanced with contrast medium. Capillary blush and early venous filling were noted in this region by cerebral angiography. Magnetic resonance imaging (MRI) revealed prolongation of the T1 and T2 relaxation times in the affected cerebral cortex (Figures 2A and 2B).

The patient’s height was 140 cm, short stature for a 20-year-old woman. Lactic acidemia (38.8 mg/dl; normal value, 3.3–14.9 mg/dl) and pyruvic acidemia (1.21 mg/dl; normal, 0.30–0.94 mg/dl) were present. The cerebrospinal fluid (CSF) concentration of lactate and pyruvate also were elevated (51.2 mg/dl and 1.86 mg/dl, respectively). A biopsy specimen from the biceps brachii muscle showed scattered ragged red fibers by modified Gomori trichrome staining. Respiratory enzyme assay revealed that cytochrome c oxidase activity was abnor-
FIGURE 1. Radiological findings at time of hospital admission in a 20-year-old woman with MELAS syndrome (case 1). Panel A: Contrast-enhanced computed tomography shows a low-density lesion with irregular cortical enhancement in left occipital lobe. Panel B: Left internal carotid angiography, late arterial phase, shows dilated cortical arteries, capillary blush, and early venous filling in left occipital lobe. Panel C: Time–density curves of dynamic computed tomography (DCT) at 72 hours after onset show increased peak height in left compared with right occipital lobe. Panel D: Time–density curves of DCT at 2 weeks after onset show no difference between right and left occipital lobes.

mally low (60 nmol/min per milligram of mitochondrial protein; normal, 144.7–355.8 nmol/min per milligram).

Dynamic computed tomography (DCT) was performed according to the method of Terada et al.6,7 Time–density curves in the regions of interest were obtained from serial 24 rapid-sequence CT images during the first 50 seconds after an intravenous bolus injection of amidotrizoate sodium meglumine (Urografin). On the patient’s first admission, 72 hours after the onset of neurological symptoms, DCT demonstrated that the peak height of the time–density curve was abnormally elevated in the lucent area seen on CT scan (Figure 1C). The peak time (the time to peak height from the beginning of DCT) and the transit time (the time between the first and second inflection points of the time–density curve) were not prolonged...
in the area of the lesion compared with the contralateral side. Two weeks later, no difference was noted between the right and left occipital lobes (Figure 1D). On the patient's second admission, when she exhibited left-sided sensory and motor deficits for 6 hours, DCT showed identical findings in the right parietal cortex (Figure 2C). Three weeks later, the time-density curves were normal in the region.

Case 2

A 13-year-old female with an uneventful prenatal and perinatal history and normal development experienced...
FIGURE 3. Magnetic resonance imaging (MRI) and xenon-enhanced computed tomography (CT) in a 13-year-old female with MELAS syndrome (case 2). Panel A: T2-weighted axial MRI shows increased signal intensity in left occipital lobe. Panel B: On T1-weighted MRI, lesion is not enhanced with gadolinium diethylenetriamine pentaacetic acid. Panel C: Functional image of regional cerebral blood flow (rCBF) as determined by xenon-enhanced CT reveals increased rCBF within lesion.

a generalized seizure and repeated right-sided motor seizures. Four months later, the patient developed a throbbing headache, vomiting, and left-sided motor seizures. The patient’s height was 147 cm, normal for a 13-year-old female. Mild muscular atrophy of the hands and feet was noted. A CT scan showed multiple lucencies in the putamen bilaterally, the left caudate nucleus, and the left lower parietal cortex. Two weeks later, clusters of left-sided, migraine-like headaches and right-sided motor seizures developed. Neurological examination showed right homonymous hemianopsia, dyslexia without dysgraphia, and right–left disorientation, associated with left parieto-occipital lucencies on CT scan and MRI (Figure 3A). The lucent areas seen on MRI were not enhanced with gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) (Figure 3B).

The serum lactic acid concentration (29.2 mg/dl) and the pyruvic acid concentration (2.01 mg/dl) were elevated. The CSF lactate and pyruvate concentrations were also elevated (25.1 mg/dl and 1.27 mg/dl, resep-
tively). Biopsy specimens of the biceps brachii muscle revealed ragged red fibers by modified Gomori tri-chrome staining.

Three hours after development of headache and right-sided homonymous hemianopsia, regional cerebral blood flow (rCBF) was evaluated by the xenon-enhanced CT technique.\(^8,9\) The rCBF was 54.0 ml/100 g per minute in the lucent area of the left occipital cortex and 31.5 ml/100 g per minute in the corresponding contralateral region (normal value, 34.4±6.7 ml/100 g per minute). Functional rCBF mapping demonstrated increased rCBF in the left occipital cortex and hypoperfusion in the lucent areas of the basal ganglia (Figure 3C).

**Discussion**

The pathogenesis of strokelike episodes in patients with MELAS has not been determined. Some authors have suggested a nonvascular etiology for the neurological deficits because the cortical lesions usually do not correspond to anatomic vascular distributions and eventually disappear.\(^10,11\) Recent pathological studies, however, have demonstrated a vascular abnormality, termed "mitochondrial angiopathy," in patients with MELAS.\(^12-14\) Mitochondrial accumulation in the smooth muscle and endothelial cells of cerebral arteries has been postulated as a possible cause of the ischemic lesions in the brain.\(^12,13\)

Both patients in this study had the radiological signs of MELAS, as described recently.\(^15-18\) The CT and MRI findings revealed that the shape and size of the infarct-like lesions in the cerebral cortex changed during the patients’ clinical course. On CT scan, low-density areas showing cortical enhancement corresponded to regions of capillary blush on cerebral angiography.\(^16\) Despite strong enhancement on CT scan, the lucent areas seen on MRI were not enhanced with intravenous Gd-DTPA in case 2, which suggested that the blood–brain barrier was intact.

We examined cerebral circulation of our patients by DCT and xenon-enhanced CT scan within 72 hours after the onset of stroke-like episodes. The affected cortical area in case 2 showed an increase in rCBF by xenon-enhanced CT during the strokelike episodes. In case 1, the peak height on DCT was elevated without changing in the transit time. Because rCBF is a function of cerebral blood volume and transit time, increased rCBF in the affected area was most likely caused by an increase in cerebral blood volume.\(^6,7,19\) We also think that the increase in rCBF with MELAS is different from the luxury perfusion seen in the subacute phase of an ischemic stroke because serial cerebral blood flow studies failed to show an ischemic area throughout the patients’ clinical course. We therefore assume that the transient increase in rCBF was caused by vasodilation due to metabolic acidosis localized in the affected cerebral cortex.

Recently some reports on the cerebral circulation in patients with MELAS have been published. In a single photon emission-computed tomographic (SPECT) study, \(^123\)Iodobenzamide (IMP) accumulated locally several days before the appearance of low-density areas on CT, suggesting increased rCBF with metabolic acidosis.\(^20\) However, defects on \(^123\)IIMP SPECT were observed in the lucent areas seen on CT scan.\(^21\) The authors interpreted this as dysfunction of the capillary endothelium. Unlike the finding on SPECT studies, positron emission tomography (PET) studies have shown clearly metabolic dysfunction in brain tissue and thus support our hypothesis. Luxury perfusion of the cerebral cortex, appearing as increased cerebral blood flow, reduced cerebral metabolic rate of oxygen (CMRO\(_2\)), and a lower oxygen extraction fraction (OEF), has been reported in a PET study on two patients with MELAS.\(^22\) Another PET study using \(^13\)Cpyruvate has shown an increase in the glycolytic metabolism of pyruvate in the brains of patients with mitochondrial encephalomyopathy having neurological deficits, in whom CMRO\(_2\) and OEF were decreased markedly.\(^23\) Based on these studies and our data, we propose that central nervous system dysfunction in MELAS is a result of metabolic dysfunction in the neural tissues rather than of ischemic stroke.

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