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

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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 cortexes 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, hemianopsia, 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 hemihypesthesias, 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-
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.\textsuperscript{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
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, respec-
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 [13C]pyruvate 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 ischemic stroke.

**References**

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