대한임상신경생리학회지 8(1):84~87, 2006 ISSN 1229-6414

# 가역적인 뇌기능장애를 보인 MELAS 증후군

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정진성 · 이학승 · 박현영 · 장 혁 · 김요식 · 조광호

# Reversible Brain Dysfunction in MELAS Syndrome

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The MELAS (Mitochondrial Encephalomyopathy with Lactic Acidosis, and Stroke-like episodes) syndrome is one of the inherited mitochondrial disorder. We have experienced a 16-year-old girl with headaches and left hemianopsia. Diagnosis of MELAS syndrome with multiple brain parenchymal lesions was confirmed by gene study. The stroke-like lesion of MELAS syndrome showed significant improvement in radiological follow up study. Therefore, MRI findings in MELAS could be interpreted as metabolic cellular dysfunction rather than ischemic vasculopathy

**Key Words**: MELAS syndrome, Stroke-like lesion

MELAS syndrome is characterized by mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.[1-7] The stroke-like episodes associated with infarcts may appear on head computed tomography (CT) or magnetic resonance imaging (MRI). But the precise pathogenic mechanism of MELAS is still controversial. There are two hypothesis for pathophysiologic mechanism. One is nonvascular, transient oxidative phosphorylation dysfunction within the brain parenchyme. The other is ischemic angiopathy. In recent study, the former are more acceptable for mechanism than the later.[2,3]

We report a patient of MEALS syndrome with clinical and radiological improvement in follow-up study, and we tried to figure out the relation between clinical symptom, diffusion MRI and pathophysiologic mechanism of stroke-like lesions of MELAS syndrome.

## CASE

A 16 year-old girl (Ⅲ-3, Fig. 1) was transferred to our hospital for headaches and left sided hemianopsia. She was normal at birth and had normal development.

Since the age of 13, she complained about lasting unilateral headache. Headache occurred intermittently and was exacerbated by physical activity or fatigue. But, 7th days before first admission, right-sided headache was steady in duration, pulsatile in nature, and accompanied by nausea or vomiting. Two days later, left sided hemianopsia occurred. Her mother has been diagnosed as having sensorineural hearing loss and migraine headache, and the second elder sister

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* This study was supported by the Wonkwang University Reserch Grant 2005.

(Ⅲ-2, Fig. 1) also suffered migraine headache.

At the time of admission, blood pressure was 120/80 mmHg, pulse rate was 68 beats per minute with a regular rhythm and respiratory rate was 22 beats per minute. Body temperature was 36.8℃. The patient had a normal physique without diabetes or any other history except for headache. The neurological examination reveled that mental status was slightly drowsy with slurred speech. Left homonymous hemianopsia was detected in a visual field test. No other neurological deficits and, signs of meningeal irritation were found. Laboratory results showed a white blood cell count of 11.800/$mm^3$ and an ESR was normal. Test for hepatitis surface antigen, antibodies to human immunodeficiency virus (HIV), anti-nuclear antibody, rheumatoid factor, anti-DNA antibody and VDRL were all negative. Blood chemical studies were normal except that lactates was increased to 32.6 mg/dl (normal 4.5 to 19.8 mg/dl). Chest radiograph and echocardiogram revealed no abnormal findings. The brain MRI showed high signal intensity on T2 weighted image and diffusion weighted image in right temporo-occipital and left temporal cortices, and scattered enhancement on contrast enhanced MR images (Figure 2-A). A transfemoral cerebral angiogram showed no abnormality in the arterial or venous phase of the studies. Electroencephalography showed generalized intermittent slowing with multiregional epileptiform discharges with out conwmitant clinical seizure. Muscle biopsy from the medial gastrocnemius processed for histochemistry (Hematoxylin-Eosin, modifided Gomori's trichrome stains), showed mild increased variation in fiber size, suggesting myopathy, but no ragged red fibers. Mitochondral DNA analysis for the patient, mother and second elder sister were performed, and revealed an A→G point mutation in the transfer RNALeu gene at base pair 3243 of the patient and second elder sister, thereby confirming the clinical diagnosis of MELAS. But, we could not find abnormal finding in mother's mitochondrial DNA.

She was treated with multi-vitamin and nicotinamide. The patient was discharged from the hospital without headache, but left homonymous hemianopsia remained. A follow up brain MRI was performed two months later from the initial study and showed significant improvement in right temoporo-occipital lesion and cerebral edema (Figure 2-B).

## DISCUSSION

The MELAS (Mitochondrial Encephalomyopathy with Lactic Acidosis, and Stroke-like episodes) syndrome is one of inherited mitochondrial disorders.[1-7] The stroke like episodes associated with infarcts may appear on head CT or MRI, and occur in more than 90% of patients with MELAS syndrome.[3]

The focal neurological deficits of abrupt onset landmarking the evolution of MELAS are clinically indistinguishable from stroke events and the precise mechanism of neurological symptoms is

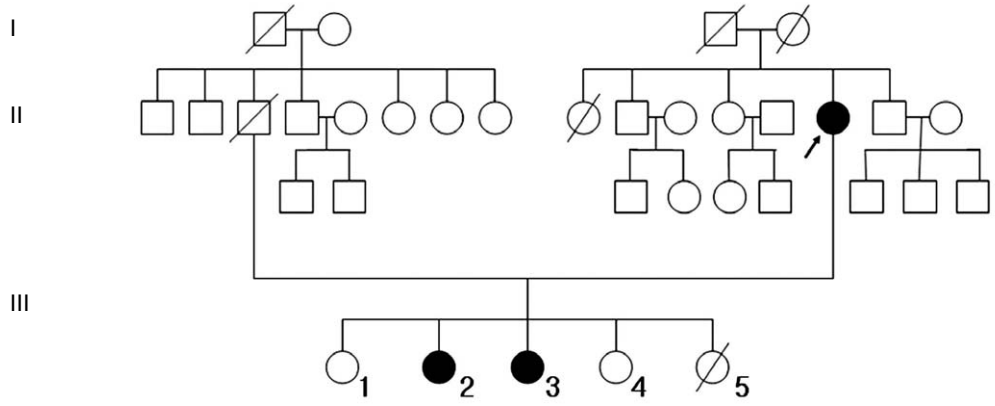


**Figure 1.** Pedigrees of family. The black symbols indicate affected individuals; diagonal lines across symbols, deceased individuals; and arrows, proband.

still controversial. Thus, they are generally named "stroke-like" events.[2,4]

Brain MRI of patients with MELAS classically shows signal changes involving both gray and white matter predominantly in the occipital and parietal lobes that strongly mimic stroke lesion. But, why this region is preferentially affected remains unclear, and distribution of these infarct-like lesions on MRI does not usually follow vascular territory and pathological studies do not find lesion of the major cerebral blood vessel.[2,4] In acute ischemic infarction, intracellular diffusion of proton is restricted or reduced, corresponding to low signal on ADC map (cytotoxic edema) caused by energy failure.[2] However, in stroke like lesion of MELAS, the ADC map demonstrates a higher proton mobility, which corresponds to the high signal on ADC map (vasogenic edema) and thus not favour ischemic damage as the main mechanism explaining focal neurological deficit in MELAS.[2,4,6,8] So nonvascular, oxidative phosphorylation dysfunction within the brain parenchyma, which cause lactic acidosis and vasodilatation, is a more susceptible mechanism of stroke like episode of MELAS syndrome.[2] But, Ohama et al stated the importance of another mechanism for stroke like episodes in cases of MELAS, and described as mitochondrial angiopathy due to abnormal mitochondrial accumulation of endothelial cells and smooth muscle cells of blood vessels.[3,8] Also, the coexistence of basal ganglia calcifications and multifocal atrophy may suggest a slowly progressive degenerative process.[6]

In our case, we found the high signal intensity on T2-weighted image and diffusion weighted image in the right temporo-occipital cortices and left temporal cortices and scattered enhancement on contrast enhanced MR images. However, parenchymal lesion did not follow vascular territory and improved in follow up study. This may suggest that stroke like lesion may reflect a breakdown of the blood-brain barrier and attribute to metabolic dysfunction in cell, not angiopathy, and also related to vasogenic edema.[4,6,8] But, we experienced only one patients

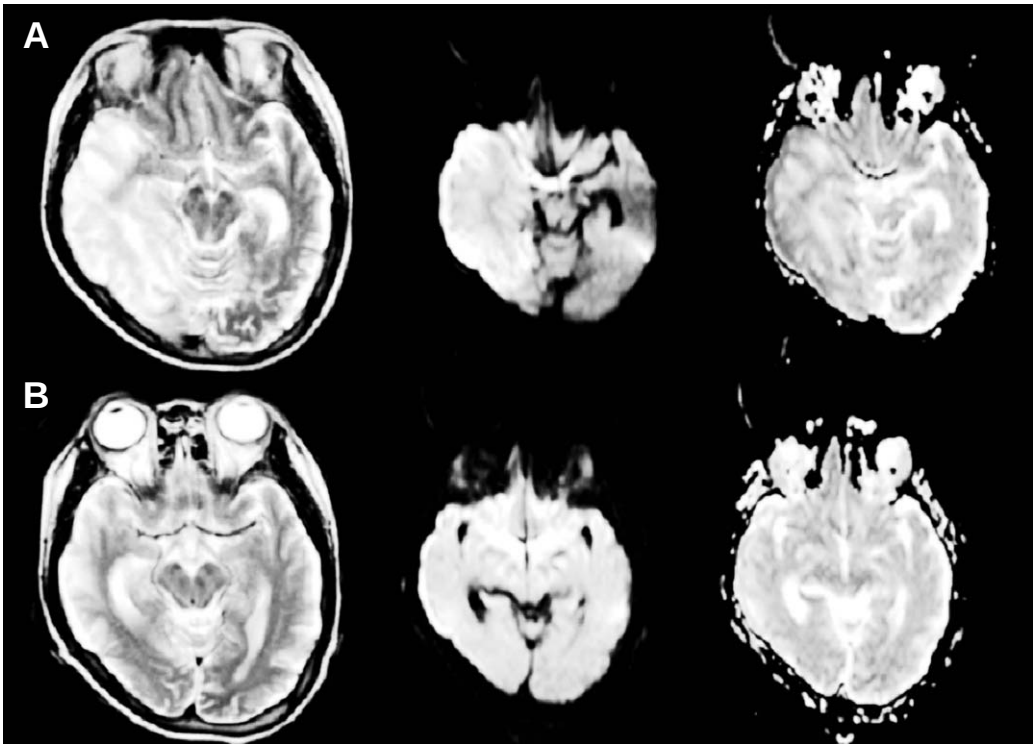


**Figure 1.** A and B Brain MRI (T2 weighted image, diffusion weighted image, ADC map, in order of figure). (**A**) Axial T2-weighted and diffusion weighted images show high signal intensity in right temporo-occipital and left temporal cortices and delayed normal signal intensity on ADC map in same lesion. (**B**) Follow-up images obtained 2 months later show resolution of the lesions.

and our study is not enough for explain the mechanism of stroke like lesion on MELAS syndrome. So, more investigations should be done for finding mechanism of stroke like lesion of MELAS syndrome.

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