

# Acute Hearing Loss in a Patient with Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke-like Episodes (MELAS)

Jui-Cheng Chen<sup>1</sup>, Tzung-Chang Tsai<sup>1</sup>, Chin-San Liu<sup>2</sup>, and Chung-Ta Lu<sup>1</sup>

**Abstract-** The mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is a rare congenital disorder of mitochondrial DNA. Patients with this syndrome may present acute onset of sensorineural hearing loss, which is genetic in origin. An impression of the MELAS syndrome is favored because hearing loss is part of the syndrome for some patients with epilepsy.

We report a 20-year-old man who suffered from acute onset of bilateral hearing loss with epilepsy and two stroke-like events which recovered without any sequela. Epilepsy with complex partial seizures was controlled by antiepileptic drugs. Brain magnetic resonance images showed high signal lesions in bilateral temporal lobes. Serum levels of pyruvate and lactate were elevated. Muscle biopsy showed ragged-red fibers and molecular genetic study showed a point mutation of the mitochondrial A3243G gene. Mitochondrial disease with the MELAS syndrome was diagnosed and then he was treated with Co-enzyme Q10 and carnitine. The symptoms recovered gradually.

**Key Words:** Acute deafness, MELAS, Epilepsy, DM, Mitochondrial disease, RRF

*Acta Neurol Taiwan 2007;16:168-172*

## INTRODUCTION

The syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like syndrome (MELAS) is a kind of mitochondrial disease. The syndrome usually develops at the age of 5 to 15 and has a relapsing and remitting course with stroke-like episodes and might result in a progressive neurological dysfunction and dementia<sup>(1)</sup>. Several other characteristics

such as short stature, a family history of diabetes and sensorineural deafness have been reported as part of this disorder. A point mutation of mtDNA A3243G had been found in 80 % of the MELAS patients<sup>(1)</sup>.

Here we report on a patient with histories of two stroke-like events and epilepsy, who visited our OPD with the symptom of bilateral hearing loss and then was diagnosed as MELAS.

From the Departments of <sup>1</sup>Neurology, China Medical University Hospital, Taichung; <sup>2</sup>Changhua Christian Hospital, Taiwan.

Received February 5, 2007. Revised April 9, 2007.

Accepted May 30, 2007.

Reprint requests and correspondence to: Chung-Ta Lu, MD, Department of Neurology, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung, Taiwan.  
E-mail: td.leu@msa.hinet.net

## CASE REPORT

A 20-year-old male student with histories of epilepsy and 2 stroke-like events came to our OPD due to acute hearing loss and mentality declined in recent days prior to this visit.

He had been normal of average in development until a short stature was noted at the age of 14. He came to our pediatric OPD for evaluation, but there was no specific abnormality including endocrine function. At the age of 16, he developed cough and low grade fever (BT 37.4 °C), followed by acute onset of headache, vomiting, and blurred vision. Meningoencephalitis was suspected but right homonymous hemianopia was noted, and brain MRI showed a high signal area over the left occipital lobe in diffusion weighted images (DWI) and fluid attenuated inversion recovery (FLAIR) images (Fig. 1). A routine cerebrospinal fluid (CSF) study was normal. He was treated with dexamethasone. Seven days later, the visual defect was improving and the high signal in brain MRI disappeared 1 month later.

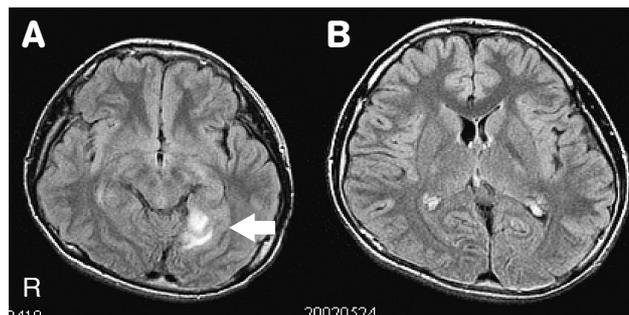
At the age of 19, another episode of left homonymous hemianopia occurred with intermittent headache, nausea, and dizziness. Sometimes few episodes of transient unresponsiveness which lasted for 1-2 minutes were noted. He was admitted to pediatric ward again and treated with dexamethasone under the impression of viral encephalitis. This visual field defect improved 10 days later, without any sequela. Brain MRI showed a high signal lesion over the right occipital lobe in DWI. Visual evoked potentials and brain-stem auditory evoked potentials (BAEP), erythrocyte sedimentation rate, anti-nuclear antibody test showed no significant abnormal findings. Electroencephalography (EEG) showed epileptiform discharges and he was treated with carbamazepine.

At the age of 20, he had acute onset of bilateral hearing loss in the morning after sleep deprivation. No structure defect in the external ear was noted.

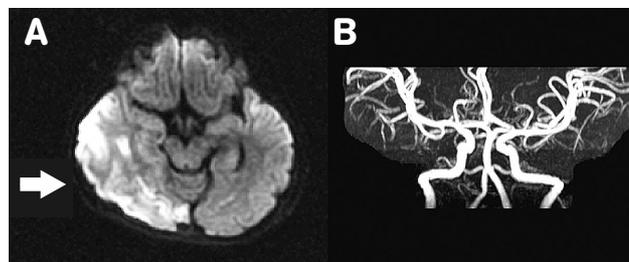
His family history was unremarkable. On physical examination, the patient was 140 cm in height and 50 kg in weight. His skin was smooth and his retina was normal. On neurological examination, he was alert, and ori-

ented. He had fluent speech but couldn't hear any voice. Visual acuity was 20/20 in the both eyes. The visual fields were normal without afferent defect. Weber and Rinne's tests were failed on both sides. The remaining cranial-nerve functions were intact. The left arm was pronated. Sensation was intact. The tendon reflexes showed brisk bilaterally. Rapid alternating movements and fine finger movements were slower in the left hand. The Romberg test, finger-to-nose test, heel-to-shin test and tandem walking were normal.

BAEP was done and a peripheral sensorineural lesion of the acoustic nerve was noted. EEG revealed diffuse cortical dysfunction with a predominance on the right hemisphere. Serum levels of pyruvate and lactate were elevated. Urine organic acid analysis showed mild



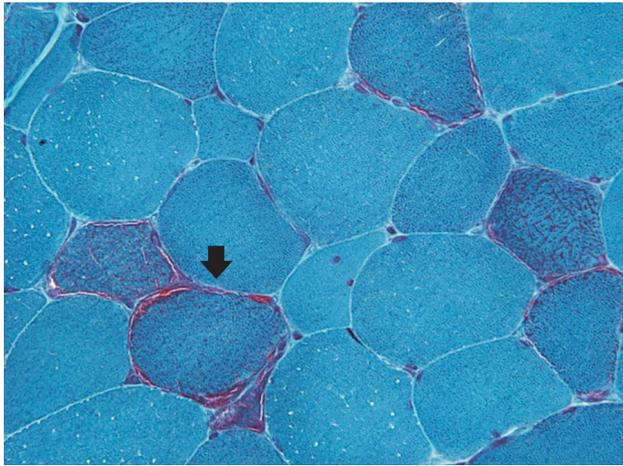
**Figure 1.** (A) In the first attack, right homonymous hemianopia was noted while examining, and the brain MRI showed a high signal area over the left occipital lobe in FLAIR sequence (arrow). (B) A follow-up brain MR image one month later showed disappearance of high signal lesion. R: right.



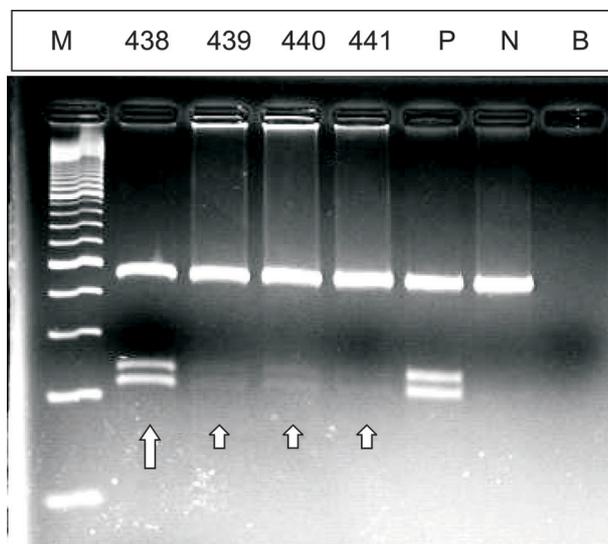
**Figure 2.** (A) Brain MRI showed high signal lesions in the cortical and subcortical areas of the right temporo-occipital lobes in DWI (arrow). (B) Brain MRA showed normal cerebral arteries.

elevation of lactic and pyruvic acid. Brain MRI showed high signal lesions in the cortical and subcortical areas of the right fronto-temporo- parieto- occipital lobes and left temporal lobes (Fig. 2). The MR angiogram showed normal cerebral arteries.

Ragged-red fibers were found from his biceps muscle biopsy in H&E stain (Fig. 3), and a molecular genetic



**Figure 3.** Muscle biopsy from the biceps showed a ragged red fiber (arrow)(Modified Gomori-trichrome stain  $\times 200$ ).



**Figure 4.** The patient had a A3243G mutation (long arrow) and her family members also had a faint band for A3243G mutation(short arrows).(by PCR-RFLP)  
M: Marker; P: Positive control; N: Negative control; 438: the patient; 439&441: two sisters; 440: the patient's mother.

study showed a mitochondrial A3243G mutation (Fig. 4). The diagnosis of MELAS was confirmed genetically.

## DISCUSSION

We present the patient who had histories of epilepsy and transient neurological deficits and manifested acute onset of bilateral hearing impairment. This patient had a short stature and epilepsy with antiepileptic drug treatment. He also had two stroke-like events. Unlike most embolic infarcts, these lesions, as observed on the Brain CT and MRI scans, tend to cross the boundaries of the major arterial territories and involve the gyral area. Vasculitis and some metabolic diseases such as Fabry's disease, homocystinuria, organic acid disorder and the MELAS syndrome should be considered.

MELAS, a kind of mitochondrial disease, stands for mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. Patients with this syndrome might have symptoms of onset at the age of 4 to 15 with a poor growth, seizures, and recurrent stroke-like episodes. The stroke-like episodes hemianopia, hemiparesis, and cortical blindness often recovered, but might lead to permanent focal neurological deficits or progressive encephalopathy. Laboratory abnormalities included elevated serum and CSF levels of lactate and pyruvate. Brain MRI changes, usually involving the cerebral cortex, are not related to the distribution of usual vascular territory. Occipital lobes are usually involved. These infarcts, caused by transient oxidative phosphorylation dysfunction within the brain parenchyma and a mitochondrial angiopathy of small vessels, are documented by contrast enhancement of the affected regions<sup>(2)</sup>.

Magnetic resonance spectroscopy (MRS) can detect lactate in specific area of the brain<sup>(3)</sup>. Ragged-red fibers can be recognized in mitochondrial diseases by the use of Gomori trichrome stain on muscle biopsy. Subsarcolemmal and intermyofibrillar accumulation of mitochondria appear as bright red masses against the background of the blue myofibrils. These abnormal accumulations represent for a compensation for poor function of mitochondria. In about 80% of patients, the molecular defect is a A-to-G point mutation in the tRNA

gene of mtDNA at base pair of 3243. Another point mutation of 3271 of the tRNA responsible for 10% of MELAS<sup>(4,5)</sup>. Maternal inheritance is common, but sporadic cases exist. In patients' leukocytes, alteration in the copy number of mtDNA is related to the proportion of mtDNA with a point mutation or large-scale deletion, which may serve as a biomarker in the pathogenesis and disease progression of MELAS<sup>(6)</sup>. Unexplained deafness as this patient in our report or diabetes in family members might raise the suspicion. Approximately 30 to 70% of MELAS patients have a sensorineural hearing loss<sup>(7-9)</sup>. One major cause of SNHL in patients with MELAS is in the auditory periphery, involving function of the stria vascularis and spiral ganglion cells. This is consistent with clinical and audiologic observations reporting benefit of both hearing aids and cochlear implantation in patients with MELAS<sup>(10)</sup>.

One half of the patients with MELAS may have complex I or complex I + IV deficiency in respiratory chain. Patients with MELAS received metabolites to increase the production of ATP and slow or arrest the deterioration of this condition. Treatment of MELAS includes carnitine, CoQ10, phylloquinone, menadione, ascorbate, riboflavin, nicotinamide, creatine monohydrate, idebenone, succinate, and dichloroacetate. However no controlled trial has proven the efficacy<sup>(11,12)</sup>. For patients with the A3243G mutation, the prognosis was related to status epilepticus and the number of recurrent stroke-like episodes. In addition, the prognosis was much worse in patients with A3243G mutation than patients with the A8344G mutation of mtDNA, who had stable or slowly deteriorating clinical courses<sup>(13)</sup>.

## CONCLUSION

The clinical features of seizures and stroke-like episodes might raise the suspicion of MELAS. The hallmark of this disease is the recurrence of stroke-like episodes that results in hemiparesis, hemianopia, or cortical blindness. Short stature and focal or generalized seizures, vomiting, migraine-like headache, hearing loss, and muscle weakness might accompany.

In clinical practice at OPD (out patient department),

as we met the patient with epilepsy, acute hearing loss and recurrent stroke-like episodes, particularly short stature and family history of DM, the possibility of MELAS should be considered.

## REFERENCES

1. Goto Y, Horai S, Matsuoka T, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): a correlative study of the clinical features and mitochondrial DNA mutation. *Neurology* 1992;42:545-50.
2. Ohama E, Ohara S, Ikuta F, et al. Mitochondrial angiopathy in cerebral blood vessels of mitochondrial encephalomyopathy. *Acta Neuropathol (Berl)* 1987;74:226-33.
3. Abe K, Yoshimura H, Tanaka H, et al. Comparison of conventional and diffusion-weighted MRI and proton MR spectroscopy in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like events. *Neuroradiology* 2004;46:113-7.
4. Ciafaloni E, Ricci E, Shanske S, et al. MELAS: clinical features, biochemistry, and molecular genetics. *Ann Neurol* 1992;31:391-8.
5. Tanahashi C, Nakayama A, Yoshida M, et al. MELAS with the mitochondrial DNA 3243 point mutation: a neuropathological study. *Acta Neuropathol (Berl)* 2000;99:31-8.
6. Liu CS, Cheng WL, Lee CF, et al. Alteration in the copy number of mitochondrial DNA in leukocytes of patients with mitochondrial encephalomyopathies. *Acta Neurol Scand* 2006;113:334-41.
7. Warrick PD, Wardrop P, Sim DW. Sensorineural hearing loss in MELAS syndrome. *J Laryngol Otol* 1997;111:279-81.
8. Tamagawa Y, Kitamura K, Hagiwara H, et al. Audiologic findings in patients with a point mutation at nucleotide 3,243 of mitochondrial DNA. *Ann Otol Rhinol Laryngol* 1997;106:338-42.
9. Wallace DC. Mitochondrial diseases in man and mouse. *Science* 1999;283:1482-8.
10. Rosenthal EL, Kileny PR, Boerst A, et al. Successful cochlear implantation in a patient with MELAS syndrome. *Am J Otol* 1999;20:187-90.
11. Scaglia F, Northrop JL. The mitochondrial myopathy,

- encephalopathy, lactic acidosis with stroke-like episodes (MELAS) syndrome: a review of treatment options. *CNS Drugs* 2006;20:443-64.
12. Matthews PM, Ford B, Dandurand RJ, et al. Coenzyme Q10 with multiple vitamins is generally ineffective in treatment of mitochondrial disease. *Neurology* 1993;43:884-90.
13. Huang CC, Kuo HC, Chu CC, et al. Clinical phenotype, prognosis and mitochondrial DNA mutation load in mitochondrial encephalomyopathies. *J Biomed Sci* 2002;9:527-33.