

Brain Single Photon Emission Computed Tomography in Patients with A3243G Mutation in Mitochondrial DNA tRNA

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ABSTRACT: Brain single photon emission computed tomography (SPECT) studies were conducted in three patients with A3243G mutation of the mitochondrial (mt) DNA tRNA. All were born to mothers suffering from chronic progressive external ophthalmoplegia (CPEO) with the same A3243G point mutation of the mtDNA tRNA. The first case manifested clinically with MELAS, the second case manifested with CPEO, and third case was characterized by recurrent migraine-like headache, tremor, and epilepsy. Brain SPECT of all patients, regardless of whether they had or had not suffered from stroke-like episodes, showed multiple areas of asymmetrical decreased perfusion, particularly in the posterior and lateral head regions, especially the temporal lobes. Crossed-cerebellar diaschisis may occur. Conventional brain magnetic resonance images failed to show some of the lesions. Decreased regional cerebral blood flow, rather than previously proposed hyperemia, is likely to be the cause. We conclude that mitochondrial vasculopathy with regional cerebral hypoperfusion may be seen on brain SPECT in patients with mitochondrial disorders and A3243G mutations, regardless of whether they have or have not suffered from stroke-like episodes.

KEYWORDS: mitochondrial disease; A3243G mutation; MELAS; brain SPECT; CPEO; diaschisis; hypoperfusion; migraine

INTRODUCTION

Mitochondrial (mt) diseases are notorious for their heterogeneous genotypes and phenotypic expressions. Dozen of clinical syndromes have been recognized, such as chronic progressive external ophthalmoplegia (CPEO), mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke-like episode (MELAS), Kearn-Sayre syndrome (KSS), mitochondrial myopathy with myoclonic epilepsy and

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Ann. N.Y. Acad. Sci. 1042: 48–54 (2005). © 2005 New York Academy of Sciences.
doi: 10.1196/annals.1338.005

TABLE 1. Demographic characteristic of three patients with various phenotypes of mitochondrial disorders and A3243G mutation in the mtDNA tRNA Leu(UUR) gene

Case/ Age (yr)/ Sex	Phenotype	Maternal phenotype	Genotype	Lactate/ Pyruvate (mg/dL)	T2WI and PDI of brain MRI	Brain SPECT
1/32/M	MELAS	CPEO	A3243G	53.5/1.9	Infarctions/ ischemia	Hypoperfusion
2/18/M	CPEO	CPEO	A3243G	22.5/1.0	Negative	Hypoperfusion
3/15/M	Migraine, tremor, epilepsy	CPEO	A3243G	20.2/0.8	Negative	Hypoperfusion

ragged-red fiber (MERRF), Leber hereditary optic neuropathy (LHON), overlap syndrome, Leigh's disease, and so forth.¹⁻⁴ Even in a single family with the same genotype, the affected siblings and mother may have different clinical features (phenotypes).^{5,6} The most common mt DNA mutation found in Taiwanese/Chinese patients with these disorders is an A-to-G substitution at nucleotide position 3243 (A3243G) of the mtDNA tRNA Leu(UUR).⁶⁻¹² Other single-point mutations or double mutations have also been reported in Taiwanese patients.¹³ As a consequence of the alterations of the mitochondrial machinery, oxidative phosphorylation uncouples and cellular energy deficit ensues, and that deficit is reflected in the brain of patients with MELAS. However, brain perfusion studies of patients with mitochondrial diseases other than MELAS are rarely reported.¹⁴⁻¹⁷ We herein report the brain single photon emission computed tomography (SPECT) of three different phenotypes of mitochondrial disease with the same A3243G mutation.

PATIENTS AND METHODS

The diagnosis of mitochondrial diseases is based on the clinical manifestations with positive family history (maternal relative with CPEO), the A3243G genotyping performed in the peripheral white blood cells and/or muscles, and electron microscopic examinations of the muscle biopsy. Demographic characteristics of the three patients are shown in TABLE 1. Conventional magnetic resonance imaging (MRI) of the brain, and technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) SPECT of the brain were performed in all patients within 7 days of onset. Brief case history are described in case reports.

Case Reports

Patient 1

A 32-year-old man presented with MELAS since the age of 26 years. Six years after initial presentation he was demented. He was born to a mother with CPEO. Biopsy of left biceps muscle showed typical paracrystalline inclusions with "parking lot" appearance of the mitochondria on electron microscopic examinations. Se-

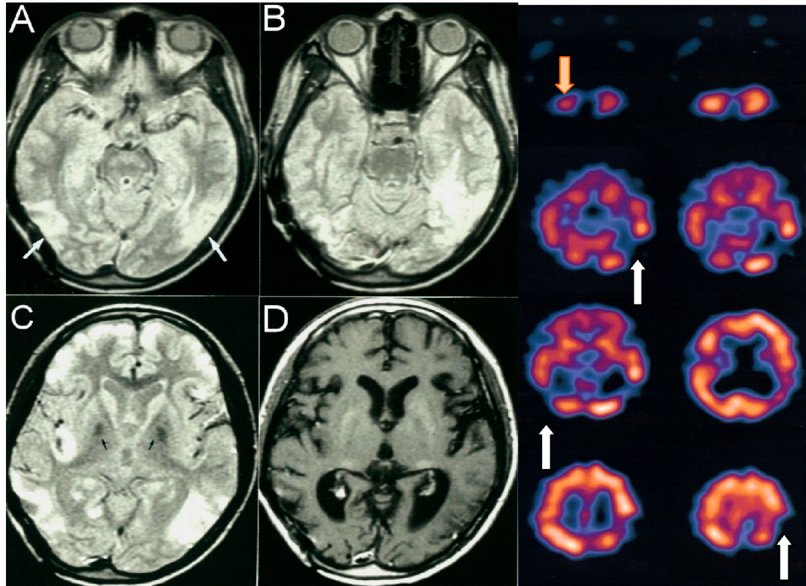


FIGURE 1. Brain MRI shows areas of increase signal intensity at bilateral posterior temporal lobes (*white arrows*) (A–C) proton density images (PDI). Symmetrical low signals on PDI (C) and high signals on T1WI (D) at bilateral basal ganglia suggest calcification. Brain SPECT (*right panel*) shows multiple regions of hypoperfusion at bilateral posterior temporal lobes (*white arrows*), left parietal lobe, and right frontal lobe. Crossed-cerebellar diaschisis is striking (*short arrow*).

quencing of the whole mitochondrial genomic DNA of the patient's white blood cells and muscles showed heteroplasmic A3243G. Brain MRI (FIG. 1) showed multiple areas of increased signal intensities in the cortical areas crossing the vascular territories on proton density images (PDI) and T2-weighted images (T2WI). The cerebellum appeared normal on MRI. Brain SPECT showed asymmetric regions of multifocal hypoperfusion in bilateral temporal lobes, left parietal lobe, and, to a lesser degree, the frontal lobes. The most prominent region of decreased perfusion was at the left posterior temporal lobe. Crossed-cerebellar diaschisis (CCD) was noted (FIG. 1). Transcranial doppler ultrasonographic examinations showed high resistance flow profile of the middle (MCA) and posterior cerebral arteries (PCA) with elevated pulsatility index, especially in the left PCA (FIG. 2). MR angiography showed segmental narrowing of bilateral PCAs and MCAs (FIG. 2). Patient was put on co-enzyme Q therapy, and he remained stable in the past 3 years of follow-up.

Patient 2

An 18-year-old man who manifested with slowly progressive external ophthalmoplegia without stroke-like episode, which began at 11 years of age. Complete external ophthalmoplegia with fixed eyes and ptosis were striking. Elevated plasma lactate/pyruvate (L/P) ratio, molecular diagnosis of A3243G, and electron micro-

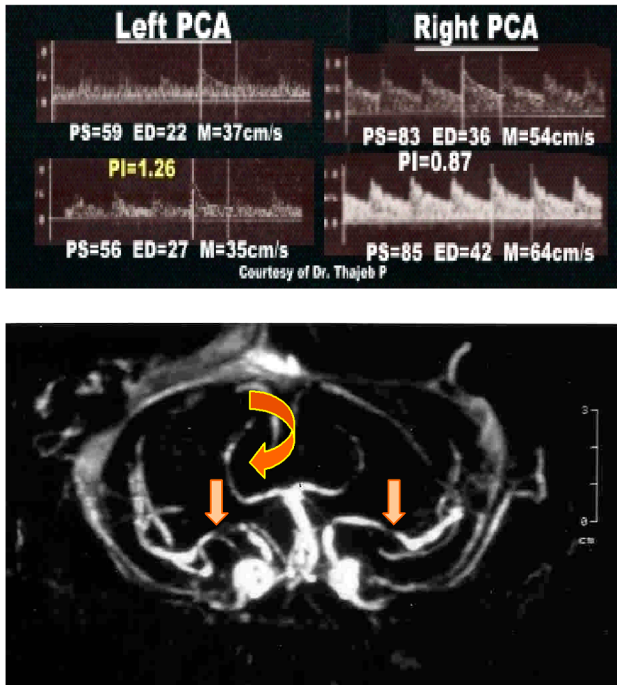


FIGURE 2. Transcranial doppler ultrasonography (*upper panel*) shows increased in pulsatility index of left posterior cerebral artery (PCA) suggesting increased downstream flow resistance, and elevated mean flow velocity of the contralateral PCA. Brain MR angiography [TR54/TI0/TE9/TOF 250] (*lower panel*) shows multiple segmental stenosis of bilateral PCAs (*curved arrow*) and MCAs (*short arrows*) suggestive of the mitochondrial vasculopathy.

scopic examinations of muscle biopsy confirmed the diagnosis of mitochondrial disease. The mother of this patient, who had undergone eye surgery twice for drooping eyelids, had CPEO. Conventional brain MRI was unrevealing. However, brain SPECT showed asymmetric areas of hypoperfusion in the posterior head regions, especially the temporal lobes, and to a greater extent than the frontal region (FIG. 3). He was placed on co-enzyme Q therapy and his CPEO did not improved.

Patient 3

The third patient was a 15-year-old boy with one-year history of recurrent migraine-like headache and limb tremors. He has had epilepsy since 13 years of age and has continued on carbamazepine therapy. Brain MRI was unrevealing. Transient homonymous hemianopsia was recorded within 24 h of onset of the migraine-like headache attacks. The interictal brain SPECT showed asymmetric areas of reduced perfusion, most remarkable in the left temporal lobe (FIG. 3). There was no CCD. He was born to a mother with CPEO. He himself did not have ophthalmoplegia. How-

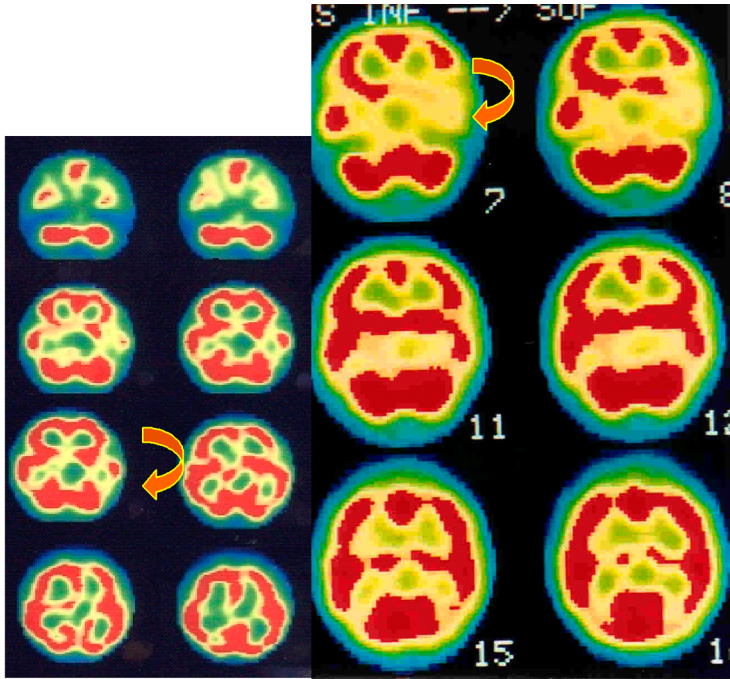


FIGURE 3. Brain SPECT of Patient 2 (*left*) and Patient 3 (*right*) show most remarkable decreased radiotracer uptake at left temporal lobe (*curved arrow*). Decreased perfusions are also seen in the right temporal lobe, bilateral parietal lobe, and the frontal lobes. The left temporal lobe hypoperfusion in Patient 3 corresponded to the clinical sign of transient homonymous right hemianopsia after the migraine-like attack.

ever, an elevated plasma level of creatine kinase (320 IU/dL), and lactate/pyruvate ratio (TABLE 1) suggested the presence of myopathy. Needle electromyographic examinations of left quadriceps muscles showed polyphasic potentials with mean amplitude of $291 \pm 126 \mu\text{V}$ and mean duration of $6.3 \pm 2.8 \text{ ms}$, consistent with myopathic change. Mitochondrial DNA sequencing of the white blood cells of the patient and his mother confirmed A3243G mutation. The manifestations of recurrent migraine-like headache, limb tremor, epilepsy, myopathy, and A3243G mutation suggested a mitochondrial disease. Coenzyme Q10 and carbamazepine were continued until his death 2 years later because of a status epilepticus. Autopsy was not performed.

DISCUSSION

Stroke-like lesions of MELAS are characterized by multifocal areas of increased signals on T2- and diffusion-weighted MRI, predominantly involving the cortical regions crossing the vascular territories, the occipital lobes,¹⁷ the parieto-occipital, and cerebellar regions.^{15,16} $^{99\text{m}}\text{Tc}$ -HMPAO brain SPECT was reported to show remarkably increased tracer uptake (hyperperfusion, or hyperemia) in the abnormal re-

gions revealed by MRI.¹⁵⁻¹⁷ In contrast, our observations showed that the brain lesions of the A3243G mitochondrial diseases appear to be multiple regions of decreased tracer uptake (hypoperfusion) rather than increased tracer uptake (hyperperfusion) on brain SPECT. Similar patterns of regional perfusion defects were also seen in patients with either A3243G mutation and CPEO (without stroke-like episode) or A3243G mutation and migraine-like headache (with transient homonymous hemianopsia). Transcranial doppler ultrasonographic and MR angiographic studies of Patient 1 suggested that the regional brain hypoperfusion may be related to the increased downstream flow resistance due to a vasospasm or a segmental stenosis of the intracranial arteries (mitochondrial vasculopathy) (FIG. 2).

What factors determine the regional brain perfusion defects and vulnerability in patients with mitochondrial disorders remain to be elucidated. The most common site of focal brain perfusion defects is the posterior head region. We speculate that differences in the quotient of regional oxygen requirement and cellular metabolism, the regional activity of oxidative phosphorylation, or the so-called mitochondrial vasculopathy might contribute to the pathogenesis. Likewise, regional cerebellar hypoperfusion can either be caused by these mechanisms or by a well-known phenomenon called crossed-cerebellar diaschisis (CCD). The latter has been reported to occur in patients with cerebral infarctions and herpes simplex encephalitis.

Recently, a new MR technique, apparent diffusion coefficient mapping (ADC), has been advocated to help differentiating the stroke-like episodes of MELAS from acute ischemic stroke.¹⁷ ADC is decreased in acute ischemic stroke, but is normal¹⁷ or increased¹⁴ in stroke-like episodes of MELAS. Ohshita and colleagues¹⁴ has reported the time sequence of the reversible initial high signal lesions on DWI and ADC after stroke-like episode in MELAS. These lesions may not be seen on conventional MRI. High ADC may last 30 days after the stroke-like episodes, return to normal, and lesions may disappear completely with clinical improvement. They suggested that early increases of ADC in the acute and subacute phase of stroke-like episodes of MELAS reflect vasogenic rather than cytotoxic edema. The latter is characterized by ADC decrease and decreased diffusion.¹⁸⁻²⁰

The non-neuromuscular features of A3243G mutations are common. Among 160 patients with deficiency of the respiratory chain enzyme of oxidative phosphorylation, 40% of cases manifested with neuromuscular symptoms and 60% with non-neuromuscular diseases.²¹ The non-muscular features, migraine-like headache, and tremor, of our third patient are interesting. Different mutant load and distinct expression thresholds of different tissues may contribute to this phenomenon. But this speculation has to be proven. Taken together, we conclude that A3243G mutation of the mtDNA tRNA can have different phenotypes ranging from the classic MELAS, CPEO, to recurrent migraine-like headache and tremor. In the absence of stroke-like episodes, brain SPECT may be helpful to demonstrate the subclinical hypoperfusion brain lesions.

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