Case Report

Auditory Symptoms: A Critical Clue for Diagnosis of MELAS

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Mitochondrial encephalopathy, lactic acidosis with stroke-like episodes (MELAS) is a rare mitochondrial disorder that affects adults. MELAS syndrome can mimic cerebrovascular disease, encephalitis or toxic-metabolic encephalopathy. The authors reported two patients who presented with auditory symptoms before the onset of encephalopathy and stroke-like episodes. The first patient was a 28 year-old man, who presented with acute sensorineural hearing loss (SNHL) followed by headache, left hemiparesis and generalized tonic-clonic seizure. CT scan of the brain showed hypodensity lesion at the tip of right temporooccipital region. Audiogram and brainstem auditory evoked potential (BAEP) showed abnormal conduction of left brainstem auditory pathway. MRI of the brain showed a lesion involving gray and white matters of the right occipital, parietal and temporal lobes. The distribution of the lesions was not compatible with distribution of arterial supply. MRA was normal. The second patient was a 56 year-old woman with a one-year history of hearing loss. The audiogram revealed bilateral SNHL. A few days before admission, her hearing was acutely deteriorated. She could not understand a conversation while she could communicate by writing. CT scan of the brain showed hypodensity in both temporal lobes and MRI revealed lesions in the same area. Pure tone audiogram showed moderate SNHL but BAEP was normal. One week later, she developed global dysphasia and generalized tonic-clonic seizure. Both patients had elevated cerebrospinal fluid and serum lactate:pyruvate ratio. Polymerase chain reaction-restriction fragment length polymorphism disclosed A3243G mtDNA mutation in the blood in the first patient and in muscle biopsy in the second patient. Ubiquinone supplement was prescribed. The auditory symptoms in combination with stroke-like episode in supratentorium are important clues to diagnose MELAS syndrome.

Keywords: *MELAS, Hearing loss, Stroke-like episode*

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Mitochondrial cytopathies are a group of disorders defined by biochemical, morphological and genetic abnormalities that are difficult to classify on clinical grounds alone. They present in a heterogenous group of diseases with multisystem manifestations. Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, form a clinical syndrome entitled "MELAS"[1]. Other associated features in MELAS syndrome include short stature, diabetes, migraine-like headache, seizure and deafness[1]. Due to these diverse and usually unrelated multisystem presentations, MELAS syndrome is difficult to diagnose, especially in the early clinical course of the syndrome. Although hearing impairment is common in MELAS syndrome, it is often neglected and not recognized as an important clinical clue for the diagnosis of this syndrome. The authors report two patients who presented with auditory symptoms before the onset of MELAS syndrome. Medline search from 1984 to 2004 was carried out using the key words "MELAS, hearing impairment" resulting in 25 documents were reported. The relevant data are discussed in this document.

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Case Report

Case 1

A 28-year-old Thai male, presented with hearing impairment 5 days before developing left sided weakness. His auditory symptoms consisted of tinnitus, ear pain and hearing loss in the left ear. He also had throbbing headache on the right. One day before admission, he developed an episode of generalized tonic-clonic seizure followed by left sided weakness. His past medical history was unremarkable. Physical examination revealed an afebrile, short young man with normal pulsation, respiration and blood pressure. He was alert and his mental state examination was normal. Left spastic hemiparesis grade III (MRC), left facial weakness of upper motor neuron type and left hemianopsia were observed. The rest of the neurological examinations were normal. Both external ears were intact and bilateral sensorineural hearing loss (SNHL) were detected. Audiogram disclosed hearing loss in high tone frequency. Brainstem auditory evoked potential (BAEP) revealed abnormal conduction of the left brainstem auditory pathway beyond the brainstem level. Tympanogram and acoustic reflex were normal. No other systemic abnormality was detected.

Complete blood count (hemoglobin 12.5g/dL, hematocrit 35.9%, white blood cell 9,850 /mm^3 neutrophil 75%, lymphocyte 20% monocyte 5% platelet 221,000/mm^3) and other blood chemistry including plasma glucose(87 mg/dL), blood urea nitrogen (19 mg/dL), creatinine(1.0mg/dL), electrolytes (sodium 136 mEq/L, potassium 4.0 mEq/L, chloride 100 mEq/L, carbon dioxide 20 mEq/L), calcium level (9.9 mg/dL) were normal. No coagulopathy was detected (international normalized ratio 1.1). Electrocardiogram and echocardiogram revealed normal findings. Plain cranial computerized tomography showed an abnormal hypodensity lesion at the tip of the right temporal lobe with loss of cortical sulci at right temporooccipital region. Magnetic resonance imaging of the brain revealed evidence of an infarction-like lesion involving the cortical grey matter at the right parietotemporal (Fig. 1) and occipital lobes but magnetic resonance angiography was normal. Blood lactate:pyruvate was high (5.94; normal 0.5 to 2.2). Cerebrospinal fluid(CSF) analysis revealed a normal CSF profile with high lactate:pyruvate ratio (3.12; normal 0.5 to 2.2). The evidence of lactic acidosis in blood and CSF was suggestive for the diagnosis of mitochondrial disease. Mitochondrial DNA study was analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) technique (Fig. 2) and A3243G mtDNA mutation was detected.

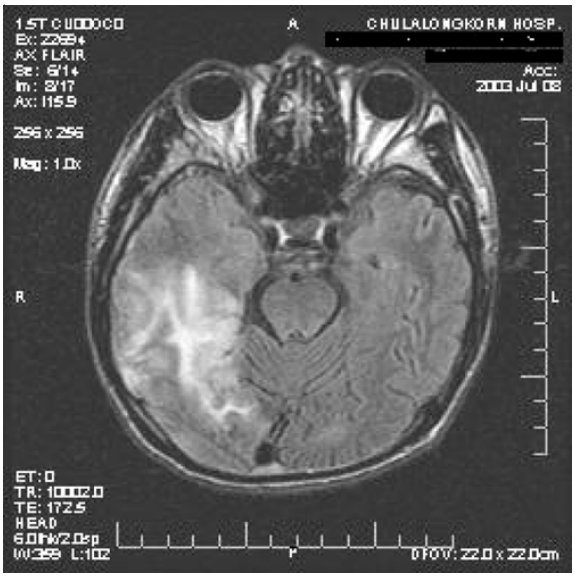

Fig. 1 Axial FLAIR imaging of case 1, high signal intensity lesion was detected in right parietotemporal region

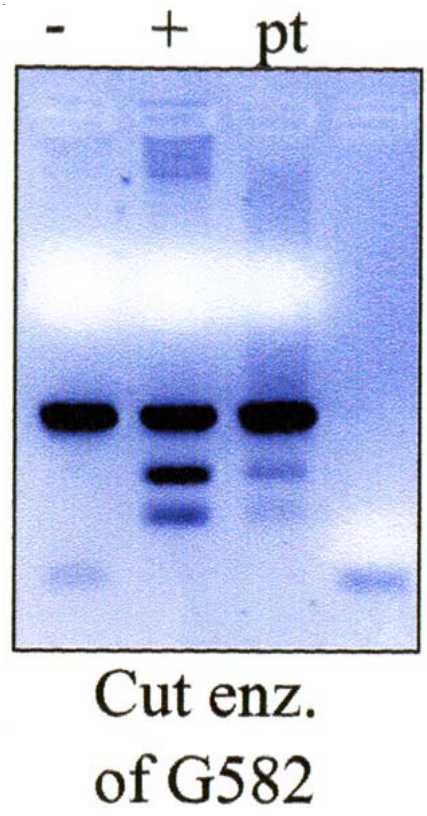

Fig. 2 Restriction enzyme digestion for A3243G

MELAS syndrome was diagnosed based on clinical features of short stature, hearing loss, stroke-like episodes, seizure, lactic acidosis and was confirmed by mutation of A3243G mtDNA. Treatment with ubiquinone, nutritional supports and phenytoin were prescribed. The patient gradually improved. No convulsion occurred and left hemiparesis, left facial weakness and visual field defect could not be detected after 2 months. His hearing also became normal within 2 months. He has a younger sister who also has mutation of A3243G mtDNA but is currently asymptomatic. His mother has normal mtDNA.

Case 2

A 53 year-old Thai female secretary presented with deterioration of previous hearing impairment. Her past history revealed eight years of well controlled diabetes mellitus and one year of bilateral sensorineural hearing loss which was rather static. There was deterioration of auditory symptom characterized by word deafness which gradually progressed within 3 weeks. Physical examination showed an afebrile, middle aged woman with normal pulsation, respiration and blood pressure. No systemic abnormality was detected. She was alert, could not communicate by conversation but was able to read all messages. Her mental status was normal. Her speech was fluent. Pure tone audiogram showed moderate bilateral SNHL but speech audiogram could not be performed due to incorporation. BAEP was normal. One week after hospitalization, she developed acute global dysphasia and an episode of generalized tonic-clonic convulsion. Laboratory findings revealed normal complete blood count (Hb 13.8 g/dL, Hct 41% WBC 8,100 /mm^3 N 66%, L 25%, Mo 9%, Platelet 325,000/mm^3), blood chemistry which included plasma glucose (77mg/dL), blood urea nitrogen (10 mg/dL), creatinine (1.0mg/dL), electrolytes (Na^+ 140 mEq/L, K^+ 4.0 mEq/L, Cl^- 102 mEq/L, $HCO3^-$ 22 mEq/L), calcium level (8.7 mg/dL). Serum lactate:pyruvate ratio was high(5.13). Electrocardiogram was within normal limit. Cranial CT scan demonstrated hypodensity lesions in bilateral superior temporal cortices. MRI of the brain showed low signal intensity along cortical gyri in bilateral temporooccipital regions in T1 weighted image, high signal intensity in T2 weighted image, FLAIR (Fig. 3) and DWI weighted image. MR angiography was normal. CSF analysis revealed normal profile with high lactate: pyruvate ratio (4.13).

Mitochondrial DNA analysis by PCR-RFLP technique detected a weakly positive A3243G mtDNA in the blood sample. Muscle biopsy was performed

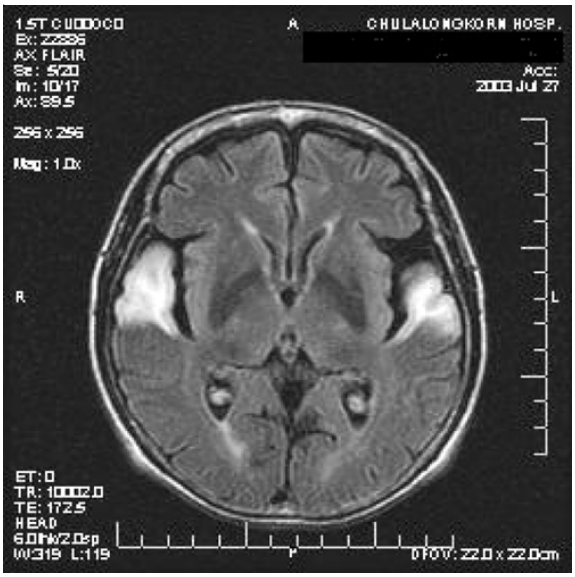

Fig. 3 FLAIR imaging of case 2 demonstrated high signal lesions involving bilateral temporal regions

and was analyzed by modified Gomori trichrome and cytochrome oxidase stains. Histopathology of the muscle revealed no ragged red fiber but disclosed several COX-negative muscle fibers. A3243G mtDNA mutation was strongly positive in the muscle tissue by PCR-RFLP technique. MELAS syndrome was diagnosed based on clinical profiles, serum and CSF lactate/pyruvate, as well as the genetic study. Treatment with ubiquinone was started. Seizure was controlled and her hearing was improved within five months. However, dysphasia persisted. Seven months later, she developed gastrointestinal bleeding and then expired due to a ruptured hepatoma.

Discussion

Human mtDNA is a 16,569 nucleotide base pair, circular molecule that encodes 13 messenger RNAs, 22 organelle-specific transfer RNAs, and 2 mitochondrial ribosomal RNAs. These RNAs are required to generate mitochondrial-specific proteins that interact with nuclear encoded proteins to form the four complexes (I to IV) of the mitochondrial respiratory chain used to generate ATP. The mutation in mitochondrial gene will cause mitochondrial cytopathies which affect many organs[2].

MELAS caused by point mutation in the $tRNA^{leu(UUR)}$ gene[1]. The A3243G mtDNA transition is the most common mutation(80%)[3]. Tissue studies showed 80% mtDNA with mutation at A3243G in muscle tissue, over 80% in brain tissue, over 90% in both liver

and kidney samples, but less than 20% in blood[4]. Major manifestations of MELAS syndrome include an acute stroke-like episode, status epilepticus, severe headache, vomiting[5]. Minor manifestations are deafness, diabetes mellitus, intractable constipation, myopathy, familial peptic ulcer[5]. The onset of symptoms usually occur before 15 years-old in 62% of cases[6]. Of the 110 cases of MELAS, 70% had sensorineural hearing loss (SNHL)[7]. Hearing loss appeared significantly earlier in the patient with full-blown clinical syndrome of MELAS with stroke-like episode. The association of hearing loss with stroke-like episode in MELAS is prominent during the age of 14-44 years old. The groups of patient who have incomplete MELAS without stroke-like episode are in the older age group between 42-52 years old[6,8]. Hearing impairment is often the first clinical symptom preceding neurological deficit in patients who have MELAS[9]. The simultaneous presentation of hearing impairment or rapidly deterioration of hearing and stroke-like episode which observed in the presented case has not been well documented in the literature.

There is high prevalence of hearing loss in MELAS patients and hearing loss often occurs before 35 years old[10]. In about two thirds, the hearing loss was gradual and symmetrical[10]. The age of onset of hearing loss in the presented patients paralleled with the cases in the literature and one of the presented patients had an acute onset of unilateral hearing loss (Case 1), while the other one had rapid deterioration of bilateral hearing deficit (Case 2). The severity of hearing loss varied from transient reversible hearing loss to profound deafness (34%), severe hearing impairment (30%), moderate hearing impairment (30%) and mild hearing impairment (6%)[4]. Hearing impairment is permanent in 78%[11]. The presented patients had a severe but reversible hearing impairment (Case 1) and moderate with partial hearing improvement (Case 2).

In MELAS, audiogram showed loss to air-conducted sounds suggesting sensorineural hearing loss involving high tone frequency with intact central nervous system auditory pathway from BAEP study in some patients[12]. From this physiologic study, the lesion of auditory impairment in MELAS should be in cochlear rather than a central nervous system lesion. However in one study, cochlear lesions occurred in patients who suffered from a mild degree of hearing loss, whereas patients with more severely affected hearing, retrocochlear involvement suggested [12].

Otopathology study in two cases of MELAS depicted diffuse and severe loss of the stria vascularis as well as spiral ganglion cell loss[13]. The present study also showed a marked loss of neurons and severe gliosis in the ventral nuclei in one but intact auditory pathway in another patient. The amount of mutant-to-total mtDNA in various auditory tissuses in one patient was: organ of Corti 85%, stria vascularis 78%, lateral semicircular canal 89%[13].

Stroke-like episodes manifest in an abrupt onset of neurological deficits[3,14] but this sometimes can progress in a few weeks[15]. Hemiparesis and hemianopsia are most common symptoms[3]. The first presented case had hemiparesis and hemianopsia while acute word deafness was observed in the second case. Bilateral temporal lesions detected in case 2 have never been reported in the literature. The authors believe that the temporal lobe lesions in the presented patient accounted for the hearing problem manifested as pure word deafness. The mechanism leading to the stroke-like episodes in MELAS syndrome might result from a focal, transient impairment of oxidative metabolism in the brain parenchyma[14,16], reduction in blood supply[17] or from large vessel occlusion[1,16].

Myopathy in MELAS has a wide spectrum of manifestations ranging from fatigability, myalgia, hypotonia to weakness[18]. The muscle morphological study may demonstrate ragged-red fibers and cytochrome oxidase (COX) deficit[18]. Both of the presented cases had no clinical myopathy. Muscle biopsy was performed in case 2 and showed several COX negative fibers but no ragged red fibers.

CT scan abnormalities were detected in 85% of cases[3]. Basal ganglia calcification was demonstrated in 53%, and affected the globus pallidus in 46%. Enlargement of the fourth ventricle and cerebellar atrophy were observed in 34%, and usually observed in patients under the age of 60 years(88%). Focal hypodense lesions was demonstrated in 34% of cases, and 88% of the focal lesions involved the parietal and occipital lobes. Lesions predominantly affected the grey matter[14]. Cerebral angiography is usually normal. MRIs depicted increased signal intensity in T2 weighted images, mainly within the grey matter [14] and cerebral atrophy, usually detected in younger patient (less than 40 years old), was presented in 23%[14].

The differential diagnosis of MELAS syndrome in patients who presented with hearing loss and stroke-like episode and/or encephalopathy include brainstem stroke[19], otologic and neurosyphilis[20], bacterial meningitis especially *Streptococcus suis* infection[21] and Susac syndrome[22]. Clinical profiles, natural history, neuroimaging and other appropriate

investigations are needed to rule out these conditions and the confirmatory tests such as mitochondrial DNA study, blood/CSF lactate/pyruvate ratio, muscle biopsy are necessary for diagnosis of MELAS syndrome.

The efficacy of treatment in MELAS as well as other mitochondrial disease is inconclusive due to the lack of well established controlled clinical trials. Ubiquinone and nicotinamide has been reported to have some beneficial effects on clinical outcomes and some biochemical parameters in a variety of mitochondrial disorders[23,24]. Regarding severe auditory impairment, cochlear implantation may be beneficial in advanced cases who have no central auditory pathways involvement[11,25] demonstrated by BAEP[25].

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อาการแสดงทางระบบการได้ยินความสำคัญในการนำไปสู่การวินิจฉัยมีลาส

อิทธิพล ตะวันกาญจนโชติ, นิจศรี ชาญณรงค์ สุวรรณเวลา, กัมมันต์ พันธุมจินดา

ไมโตคอนเดรียล เอ็นเซฟาลอบพาตี, ภาวะกรดแลคติกในเลือดสูงร่วมกับภาวะคล้ายสมองขาดเลือด (มีลาส) เป็นโรคที่พบน้อยในผู้ใหญ่ มีลาสสามารถมีอาการแสดงคล้ายสมองขาดเลือด ไข้สมองอักเสบหรืออาการทางสมองที่เกิดจากสารพิษ ได้รายงานผู้ป่วยสองรายซึ่งมีอาการทางระบบการได้ยินก่อนอาการทางสมองและภาวะคล้ายสมองขาดเลือด ผู้ป่วยรายแรกเป็นชายอายุ 28 ปีมาตรวจด้วยอาการได้ยินเสียงลดลงจากระบบประสาทชนิดเฉียบพลัน อ่อนแรงแขนขาซีกซ้าย ปวดศีรษะและชักเกร็งกระตุกทั้งตัว เอกซเรย์คอมพิวเตอร์สมองพบรอยโรคที่สมองกลีบข้างและกลีบหลัง การตรวจการได้ยินและ brainstem auditory evoked potential พบความผิดปกติของการนำสัญญาณบริเวณก้านสมอง คลื่นสะท้อนในสนามแม่เหล็กพบรอยโรคในเนื้อสมองส่วนเทา และขาวของสมองกลีบหลัง, กลีบพาราอิทัล, และกลีบข้าง การกระจายตัวของรอยโรคไม่เป็นไปตามแนวที่หลอดเลือดสมองไปเลี้ยง คลื่นสะท้อนในสนามแม่เหล็กของหลอดเลือดแดงสมองพบว่าปกติ ผู้ป่วยรายที่สองเป็นหญิงอายุ 56 ปีมีประวัติได้ยินเสียงลดลงมา 1 ปี การตรวจการได้ยินพบว่าการได้ยินเสียงลดลงเป็นชนิดที่เกิดจากระบบประสาท สองวันก่อนมาโรงพยาบาลการได้ยินเสียงของผู้ป่วยลดลงอย่างเฉียบพลัน ผู้ป่วยไม่สามารถสนทนากับผู้อื่นในขณะที่สามารถสื่อสารด้วยการเขียน ภาพคอมพิวเตอร์สมองพบรอยโรคที่สมองกลีบข้างทั้งสองข้าง เช่นเดียวกับการตรวจคลื่นสะท้อนในสนามแม่เหล็กสมอง การตรวจการได้ยินด้วยเสียงพบการสูญเสียการได้ยินจากรอยโรคของเส้นประสาทในระดับความรุนแรงปานกลางแต่ brainstem auditory evoked potential ปกติ หนึ่งสัปดาห์ต่อมา ผู้ป่วยมีอาการฟังและพูดภาษาผิดปกติและชักเกร็งทั้งตัว ผู้ป่วยทั้งสองรายมีอัตราส่วนของสารแลคเตดต่อไพรูเวตสูงทั้งในน้ำไขสันหลังและในซีรัม การตรวจโพลีเมอเรสเชนรีแอคชั่น-เรสตริคชั่นแฟรคเมนท์เลนท์โพลีมอร์ฟิซึมพบว่ามีการเปลี่ยนแปลงโครงสร้างจากอะดิโนซีนเป็นกัวนิดีนของดีเอ็นเอไมโตคอนเดรียในตำแหน่ง 3243 ในตัวอย่างเลือดของผู้ป่วยรายแรกและจากตัวอย่างกล้ามเนื้อในผู้ป่วยรายที่สอง ทั้งสองรายรักษาโดยการให้ยูบิควิโนน สรุปอาการผิดปกติทางระบบการได้ยินร่วมกับภาวะคล้ายสมองขาดเลือดเป็นสิ่งบ่งที่สำคัญในการวินิจฉัยโรคมีลาส