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■ CASE REPORT ■

Recurrent Stroke-Like Episodes in a Patient with Elderly Onset Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS)

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Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) uncommonly develops after the age of 40. We describe a patient with MELAS whose first stroke-like episode presented at age 65, followed by two more episodes. The brain MR imaging for each stroke-like episode demonstrated hyperintense lesion in diffusion weighted image (DWI), and variable signal intensities in apparent diffusion coefficient (ADC) maps in temporo-parietal and occipital regions. We diagnosed the patient as MELAS with 3243A>G point mutation.

Key Words: *MELAS, Elderly, Stroke, MR imaging*

INTRODUCTION

In 1984, Pavlaki *et al.* first described the mitochondrial encephalomyopathy, lactic acidosis, and recurrent stroke-like episodes (MELAS) [1]. MELAS is a mitochondrial cytopathy associated with a mitochondrial DNA mutation at nucleotide position 3243 [2-4]. The clinical features include headaches, stroke-like episodes, seizures, cognitive dysfunction progressing to dementia, short stature, hemiparesis, hemianopsia, sensorineural hearing loss, and exercise intolerance [5, 6].

The onset of stroke-like episodes in MELAS usually occurs before the age of 40; however there are reported cases on late onset of stroke-like episodes [7, 8]. To the best of our knowledge, elderly onset stroke-like episodes in MELAS have not been reported in Korean patients [9-11]. We report the first case of elderly onset MELAS with recurrent stroke-like episodes in Korean patients.

CASE REPORT

A 65-yr-old right-handed woman complained of noises that she believed were coming from a nearby construction site, even though there were no construction sites and no noises.

She also complained of hearing unpleasant sounds in a quiet chapel. She uttered incomprehensible sentences during conversation. Her family members noticed the symptoms progressed rapidly over two weeks. She became aggressive, spoke incoherently, had difficulty recognizing family members, stared vacantly, and developed convulsive seizures. She was admitted to a local university hospital for evaluation. Cerebrospinal fluid (CSF) analysis revealed no abnormalities except for mild elevation of the CSF protein levels (52 mg/dL). Bacterial, viral, and fungal cultures of her serum and CSF were negative. Brain MRI taken 10 days after the symptom onset revealed hyper-intensity in diffusion weighted image (DWI, *b*-1,000 s/mm^2), and iso-intensity in apparent diffusion coefficient (ADC) maps in the left temporal lobe, but there was no stenosis of the intracranial vessels (Fig. 1A). Follow-up image taken 3 weeks later showed expansion of the initial hyper-intensity in DWI to the left temporo-parietal areas, and iso- or hyper-intensity in ADC maps of the corresponding areas (Fig. 1B). The patient's past medical history was remarkable for an upper respiratory infection one month prior to symptom onset. The patient presented with bilateral hearing loss beginning in her 50s, hyperthyroidism, and type II diabetes mellitus. Caregivers said she frequently complained of headaches and general weakness. Her mother had no remarkable medical history, but one brother and one sister out of her four siblings died at their 30s without an identified cause of death (Fig. 2). After the admission to the local university hospital, the patient was prescribed anti-epileptic drugs: levetiracetam (1,000 mg/day) and carbamazepine (600 mg/day).

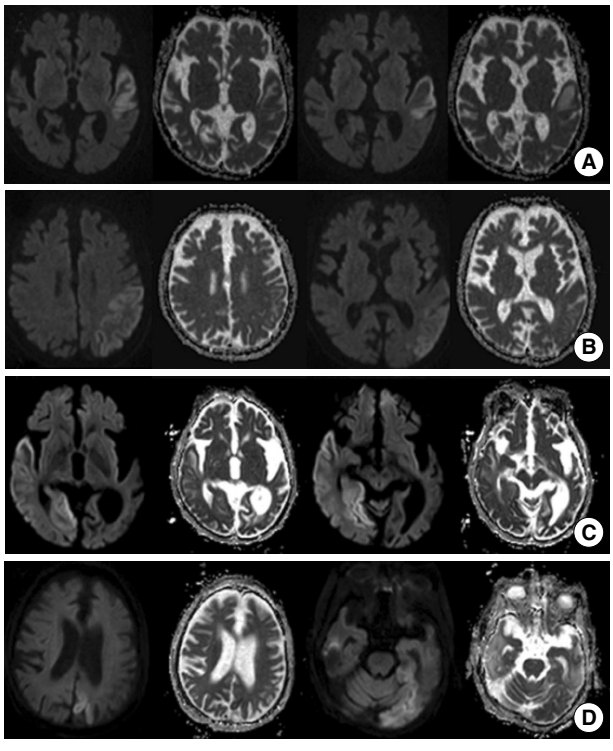

Fig. 1. Brain MR imagings that depicts hyperintensity in diffusion weighted image (DWI) and variable intensity apparent diffusion coefficient (ADC) maps. (A) Brain MRI taken 10 days after the symptom onset reveals hyper-intensity in diffusion weighted image (DWI), and iso-intensity in apparent diffusion coefficient (ADC) maps in the left temporal lobe. (B) Follow-up image taken 3 weeks later shows expansion of the initial hyper-intensity in DWI to the left temporo-parietal areas, and iso- or hyper-intensity in ADC maps of the corresponding areas. (C) Brain image taken 3 weeks after the symptom onset reveals newly developed hyper-intensity on DWI and hypo-intensity on ADC maps in the right occipito-temporal areas. (D) Brain image taken 3 weeks after the third episode reveals hyper-intensity on DWI and hypo-intensity on ADC maps in the left occipito-temporal areas.

The patient visited our hospital two months after the initial symptom onset with no significant neurological improvements. Her vital signs were stable, but she had emaciated feature (body weight, 33 kg; height, 152 cm; and body mass index [BMI], 14.3 kg/m^2). She was alert, but disoriented. The patient repetitively replied "no" or "I do not know" to questions and her speech was often meaningless and incomprehensible. The Korean version of the Western Aphasia Battery (K-WAB) [12] revealed profound Wernicke type aphasia. The patient scored no points in the Korean version of the Mini Mental Status Examination [13]. Cranial nerve,

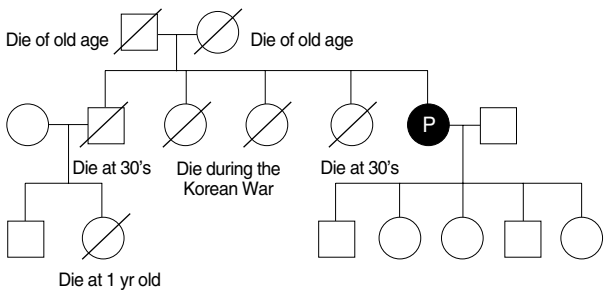

Fig. 2. The family pedigree. The patient had four siblings; two die during the Korean War, two died in their 30's without definite diagnosis. The five children are in their 40-50's and none have history of stroke like episode, seizure, diabetes mellitus, hearing loss, or short stature, but have exercise intolerance (P, patient).

motor and sensory system examinations revealed no abnormalities except for mild unsteady gait. The results of the laboratory tests were unremarkable; complete blood count, electrolyte levels, liver function tests, thyroid function tests, blood urea nitrogen and creatinin levels. An electroencephalography revealed spike waves in the left parietal area and intermittent slow waves in the left hemisphere. Brain fluid attenuated inversion recovery (FLAIR) MRI taken upon arrival revealed encephalomalacic changes of the previous lesions in the left temporal areas. The patient's insidious onset aphasia, behavioral changes, auditory hallucinations, and seizures after upper respiratory tract infection, along with brain MRI lesions involving the unilateral temporal lobe led us to a tentative diagnosis of herpes simplex encephalitis. We excluded stroke as a possible etiology, because of the clinical course, the MRI lesions which did not occur along vascular territory and expansion to adjacent area in follow up study, and normal electrocardiography finding. After two weeks of intravenous antiviral therapy, the patient had no further deterioration. The anti-epileptic drugs were maintained. The patient gradually improved to the point where she could speak short sentences and understand half of conversations.

Eleven months after the initial onset, she experienced a second episode. The second episode was much like the first, but more severe. Over the course of one week, she became incommunicable, and spoke meaningless words to herself. She manifested akinetic mutism and lay still in bed. A follow-up K-WAB revealed Wernicke type aphasia, similar to the previous study, but severe. Brain image taken 3 weeks after the symptom onset revealed newly developed hyperintensity on DWI and hypo-intensity on ADC maps in the right occipito-temporal areas with gyral enhancement (Fig. 1C). The patient's hearing loss, seizures, and short stature, along with recurrent stroke-like episodes suggested a diagnosis of mitochondrial disease. The patient's serum lactate level was mildly elevated at 2.82 mmol/L (normal: 0.5-2.2). A gene study for point mutations characteristic of MELAS syndrome was positive at the nucleotide pair 3243A>G in blood sample. After the diagnosis of MELAS syndrome, the patient was treated with coenzyme Q-10, thiamine, folic acid, and acetyl L-carnitine. She gradually improved over several months and was able to understand and speak simple conversation.

Seven months after the second episode, the patient experienced a third episode. Along with the previous manifestations, she exhibited prominent behavior changes. She became aggressive and violent to others. She also experienced generalized clonic seizures. Brain image taken 3 weeks after the third episode showed hyper-intensity on DWI and hypo-intensity on ADC maps in the left occipito-temporal areas (Fig. 1D). EEG revealed periodic lateralizing epileptiform discharges in the left occipital areas. Additional antiepileptics and antipsychotics were prescribed. After the repeated episodes, the patient was left with extensive neurologic deficits, especially cognitive dysfunction, and severe akinetic mutism.

DISCUSSION

Overall, our patient met the diagnostic criteria for MELAS, which include; 1) stroke-like episodes; 2) encephalopathy characterized by seizures, dementia, or both; and 3) lactic acidosis, ragged-red fibers, or both, along with at least two of the following: normal early development, recurrent headache, or recurrent vomiting [14]. One feature of our patient was her emaciation. Caregivers of the patient reported that she had a poor appetite since her youth, and remained emaciated even after the nutritional support. Her BMI was 16.2 kg/m^2 at the time of her third hospital discharge. Though it was not described overtly, a previously reported case also seems to have exhibited emaciation as one of the features of the mitochondrial disorder [15]. And we misdiagnosed the patient initially as herpes simplex encephalitis, and such as have occurred in previous reports [16, 17].

Other symptoms that were consistent with MELAS in our patient were short stature, hearing loss, and diabetes mellitus. The diagnosis were finally confirmed when the gene study revealed a point mutation associated with MELAS.

However, our patient's presentation was not entirely compatible with the definition of MELAS, because MELAS criteria specify that stroke onset occurs before age 40 [14]. Con-

sidering the fact that the first attack of stroke-like episodes usually occur between the ages of 5 and 15 yr in 80% of MELAS patients [5, 6, 18], it can be a diagnostic challenge to identify MELAS in patients demonstrating elderly onset of first stroke-like episodes.

To our knowledge, there have been reports of MELAS patient who experienced the first stroke-like episode after age 60 in different countries, but this is the first case of elderly onset MELAS in Korean population. One detailed case report described a patient with three episodes of a relapsing and remitting course of neurologic syndrome that began with a seizure, followed by residual aphasia and right visual field loss, resulting in a state in which she could not answer questions or follow verbal commands [8]. Our patient, who had an initial stroke-like episode at age 65, also had a relapsing and remitting course of neurologic syndrome. After 17 months, she became wheelchair bound and unable to communicate, similar to the previous case.

The first stroke-like episodes in elderly, unlike usual presentation time of 40 yr or younger have not been well explained. However, since the mitochondria mutation load varies among given organs of any person whether the mutation will reach a threshold for clinical expression cannot be predicted [8]. This might explain variable onset time of first stroke-like episodes.

The pathophysiologic mechanisms of stroke-like episode in MELAS have not been fully discovered, but there are theories proposed for explanation. First, mitochondrial angiopathy described as the impairment of autoregulation by alteration in nitric oxide (NO) homeostasis can create a region of hypoxia surrounding the affected blood vessels, which results in microvascular stroke like pattern [18, 19]. Second, mitochondrial cytopathy described as oxidative phosphorylation defect in the brain tissue can produce sufficient amount of ATP under normal conditions, but are unable to respond to increased energy demand [19, 20]. Third, the neurovascular cellular mechanism proposed that both neuronal and vascular mechanisms underlie in the pathogenesis and this is characterized by neuronal hyper-excitability, neuronal vulnerability, increased capillary permeability, and hyperemia [19, 21].

Several authors have reported that the vasogenic edema was associated with the mitochondrial angiopathy, which is shown in MRI as high signal intensity in DWI, and ADC in the affected area and this was a clue to distinguish stroke like lesions of MELAS from typical ischemia [19, 22]. However not only the vasogenic edema, but also the cytotoxic edema can coexist. The cytotoxic edema caused by neuronal ischemia and neurovascular mechanism, manifestate as high signal intensity in DWI and low signal intensity in ADC. The reason why ADC findings vary can be explained by the time interval between stroke like episode onset and MRI study [23]. This explains the variable (hyper, hypo, or iso) ADC signal intensity of our patient (Fig. 1). Given that MELAS is a rare genetic disorder, clinical diagnosis may often be challenging, especially when presentation is atypical. Our patient revealed her first neurologic symptoms at the age of 65 with auditory hallucinations, seizure, and prior history of respiratory infection, which mimicked temporal lobe epilepsy followed by herpes simplex encephalitis. Since the stroke-like episodes in MELAS are diagnostic challenge, high clinical suspicion for MELAS in patients exhibiting relapsing and remitting stroke-like episodes even in elderly patients.

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