Diffusion-Weighted Image and MR Spectroscopic Analysis of a Case of MELAS with Repeated Attacks

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We report the clinical and MR manifestations of an 18 year-old girl with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. Recurrent status epilepticus caused reversible cytotoxic edema on diffusion-weighted images (DWI). Initial and one month follow-up MR spectroscopy, after seizure control, showed some discrepancies in the ratio of metabolites. N-acetylaspartate (NAA) partially recovered (NAA/creatinine (Cr) ratio: 1.27→1.84). This was because of a normalization of decreased NAA due to cellular dysfunction as a result of status epilepticus. A low ratio of NAA/Cr due to abnormal mitochondria remained in the decreased state. Reversible NAA/Cr ratios in the acute lesion suggested that NAA reflects the neuronal function as well as the level of neuronal structural damage. The altered NAA/Cr ratio better correlated with the abnormal signal intensity area of T2-weighted images (T2WI) and DWI than the lactate (Lac)/Cr ratio. With conservative treatment with anti-epileptics not accompanied by coenzyme Q or sodium dichloroacetate, lactate persistently increased (Lac/Cr ratio: 1.01→1.21) because of the continued production of lactate in cells with respiratory deficiency, which is the main pathology of MELAS.

Key Words: Magnetic resonance imaging, diffusion study, spectroscopy, MELAS, brain metabolism

INTRODUCTION

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome are a group of inherited mitochondrial abnormalities characterized by strokes, stroke-like events, nausea, vomiting, encephalopathy, seizures, short stature, headaches, muscle weakness, exercise intolerance, neurosensory hearing loss, and myopathy. Although the findings of single photon emission computed tomography (SPECT), magnetic resonance (MR) imaging and MR spectroscopy of MELAS have been reported, the role of diffusion weighted images (DWI) and the follow up data of MR spectroscopy have not been described. We report the detailed findings of MR images including DWI and MR spectroscopy in a patient with MELAS, presenting with recurrent status epilepticus.

CASE REPORT

An 18 year-old girl presented to the emergency department with status epilepticus, consisting of recurrent focal motor seizures of the right upper extremity and generalized tonic-clonic seizures (GTCs). She had her first GTCs at 15 years of age and was evaluated by a pediatrician. At that time, the level of lactate in her cerebrospinal fluid (CSF) was normal and MR imaging of the brain revealed a large area of high signal intensity and swelling in the right temporal lobe on T2-weighted images (T2WI). Her seizure was controlled with phenobarbital 60 mg and carbamazepine 300 mg.

Two years later, she developed another episode of seizure clustering, which consisted of recurrent leftward deviation of the eyes and head. Follow-up MR imaging showed a newly developed high
intensity area in the right parietal lobe. The previous lesion in the right temporal lobe showed mild volume loss with normal signal intensity. Conventional cerebral angiography and CSF lactate examination were normal. She was managed with carbamazepine monotherapy (600mg/day) without any seizure recurrence until the most recent admission.

At this occasion, her status epilepticus consisted of a jerking movement of the right upper extremity, which was easily terminated by the intravenous administration of lorazepam (4mg) and phenytoin (18mg/kg). Her height was 146cm (less than 2 percentile) and her body weight was 37kg (less than 10 percentile). Visual field test and the fundoscopic examination were normal. Motor examination revealed G4/5 strength of the right extremities. Sensory function, cerebellar function and deep tendon reflex were normal. IQ score was 45 on the Weschler Adult Intelligence test. The CSF and serum lactate levels were significantly elevated to 5.9 mmol/L (normal: 0.7-2.1 mmol/L) and 3.5 mmol/L (normal: 0.6-1.7 mmol/L) respectively. Electroencephalography showed slightly decreased amplitude of background activities on the left side and an episode of electrical ictal rhythms consisted of evolving patterns of rhythmic delta waves to theta waves. The electromyography of the biceps brachii muscle showed slightly increased insertional activity. Biopsy of the biceps brachii muscle showed “ragged red fiber” on modified Gomori-trichrome staining. The diagnosis of MELAS was confirmed by molecular genetic analysis, which showed the 3,243 mtDNA point mutation (Fig. 1).

T2 weighted MR showed a high signal intensity area in left parietal lobe. The previous high signal intensity of the right parietal lobe had disappeared. DWI also showed high signal intensity in the left parietal lobe, suggesting a cytotoxic edema (Fig. 2). The ⁹⁹mTc-ethyl cysteinate dimer (ECD) SPECT showed global reduction of cerebral blood flow (CBF) in the bilateral temporal and parietal lobes, which was more severe in the left parietal lobe (Fig. 3). MR spectroscopy was performed on a GE 1.5T SIGNA MRI/MRS system (Milwaukee, WI, USA); MR spectra were obtained using the PRESS sequence (TR/TE = 1,500 ms/272 ms, 48 AVG, 2 NEX). ¹H-spectroscopy with single (8 ml/voxel) and multi voxels showed diffusely increased lactate levels even in the normal signal intensity area on the T2WI. The affected left parietal lobe showed lower NAA/Cr ratio and higher Lac/Cr ratio than the contralateral side (Table 1, Fig. 4).

Follow-up T2WI and DWI taken one month

![Fig. 1. Molecular genetic analysis of mitochondrial DNA.](image)

Restriction enzyme (Apa I & Hae III) digestion of PCR products from patient and the patient’s mother reveal point mutation of A-to-G on 3,243 site of mitochondrial DNA. The pattern of fragmented DNA is much more prominent in the patient. M, marker; *, patient; #, mother of patient; N, normal.

![Fig. 2. Diffusion weighted image taken three days after control of the third and most recent status epilepticus attack shows high signal intensity in the left parietal lobe.](image)
later were normal without any evidence of high signal intensity foci. $^{3}$H-spectroscopy with single voxel showed a partially recovered NAA/Cr ratio and a persistently high Lac/Cr ratio in the left parietal lobe (Table 1, Fig. 5).

**DISCUSSION**

Although the pathogenesis of newly developing lesions in MELAS is unclear, mismatches of metabolism and CBF may initiate the event, which progresses to the development of seizures. Further deterioration of metabolism/CBF mismatches results in the obvious cytotoxic edema that can be sensitively detected on DWI. Although this patient had the history of seizures over a period of 3 years, it is unlikely that the seizures themselves initiated the brain lesions because the semiology of seizures on each occasion was quite different and her seizures had been under excellent control between attacks. If seizure was the initiating

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<th>Status epilepticus</th>
<th>One month later</th>
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<tr>
<td></td>
<td>Cho/Cr</td>
<td>NAA/Cr</td>
</tr>
<tr>
<td>Right</td>
<td>1.23</td>
<td>2.05</td>
</tr>
<tr>
<td>Left</td>
<td>1.13</td>
<td>1.27</td>
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* Four days after the control of the third status epilepticus.

Normal value (11.19 yrs, n=8): Cho/Cr: 1.48 ± 0.12, NAA/Cr: 2.79 ± 0.29.

Lactate: not detectable.

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**Fig. 4.** $^{3}$H-spectroscopy with single and multi voxels taken four days after control of the recent status epilepticus. (A) $^{3}$H-spectroscopy with multi voxels shows diffusely increased parenchymal lactate level even in the normal signal intensity area on the T2-weighted image. (B) $^{3}$H-spectroscopy with single voxel shows decreased NAA in the left parietal lobe of a recent attack. The left parietal lobe has a higher lactate level than the right parietal lobe.

event, we might also expect that the recurrent attacks should have involved the same region as the previous attack.

Diffuse elevation of the parenchymal lactate level by $^1$H-spectroscopy taken four days after the control of the third status epilepticus, suggests that the possibility of respiratory deficiency from mitochondrial dysfunction in MELAS, and general lactic acidosis may play a partial role in this phenomenon. Persistently higher Lac/Cr ratio in the recent lesion of the left parietal lobe as compared to the contralateral side is an interesting observation not previously described, and suggests regional variation of respiratory deficiency according to the level of metabolism/CBF mismatch. Hypometabolic zone as a result of severe mitochondrial dysfunction and secondary hypoperfusion (Fig. 3) shows persistently increased lactate level as in the right temporal old lesion (Table 2, Fig. 6) and in the left parietal recent lesion. There are two possibilities for the persistently higher lactate level of the attacked brain parenchyma in MELAS.

Table 2. The Metabolite Ratio of Both Temporal Lobes Taken Four Days after Control of the Third Status Epilepticus

<table>
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<th></th>
<th>Cho/Cr</th>
<th>NAA/Cr</th>
<th>Lac/Cr</th>
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<tr>
<td>Right</td>
<td>1.11</td>
<td>1.63</td>
<td>1.01</td>
</tr>
<tr>
<td>Left</td>
<td>0.99</td>
<td>1.71</td>
<td>0.72</td>
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</table>

Normal value was not obtained in the temporal lobe.

Firstly, the accentuated mismatch of lactate production and the disappearance of the attacked brain tissue.

Although the volume of brain parenchyma in the measured 8 ml voxel is larger in the left temporal lobe than the atrophic right temporal lobe, the Lac/Cr ratio was higher in the atrophic right temporal lobe than the normal left temporal...
lobe. This means that brain tissues of the previously attacked right temporal lobe produced greater amounts of lactate than the normal brain parenchyma, because the attacked cells contain severely damaged and/or many abnormal mitochondria that use the anaerobic glycolysis system. The region of adaptation in the decreased metabolism will need a lower blood supply as Fig. 3 shows. These results and speculation concerning the old temporal lesion helped us understand the recent left parietal lesion.

Secondly, the slow clearance of lactate.

In the animal seizure model, cerebral lactate remains high and stable for up to 180 minutes after the beginning of the status epilepticus. Lactate can be trapped in cells, extracellular spaces and some other compartments incapable of respiration, especially in the damaged cells.30

Another interesting observation in this patient was the NAA/Cr ratio, which was lower in the high signal intensity area on T2WI and DWI and improved as the MR signal intensity normalized. These findings suggest a good correlation between the NAA/Cr ratio and MR findings. Reversible changes of NAA/Cr ratio in the follow-up studies, strongly suggest that NAA is not necessarily the marker of neuronal loss or structural neuronal damage, but that it also marks the recovery from reversible neuronal dysfunction, which is in agreement with De Stefano.31 Further investigation is certainly needed to elucidate the significance of NAA.

The present case shows a discrepancy of recovery between the NAA/Cr and Lac/Cr ratios. During status epilepticus, the extent of NAA reduction may be due to both the effect of decreased NAA from abnormal mitochondria and to the cellular dysfunction caused by status epilepticus One month after status epilepticus had been controlled, the NAA reduction due to status epilepticus had normalized and the decreased NAA level due to the abnormal mitochondria remained in a lower state. Therefore, the NAA/Cr ratio showed a gradual but incomplete recovery. On the other hand, the Lac/Cr ratio continued to increase for a substantial period after status epilepticus control had been achieved. This is probably because lactate is continuously produced in the cells with abnormal mitochondria, because the respiratory deficiency of MELAS had not changed. This patient took conservative treatment with anti-epileptics not accompanied by coenzyme Q or sodium dichlo-roacetate. If she had taken sodium dichloroacetate, the lactate level would probably have decreased, as Pavlakis et al reported.32

To summarize, we report upon the clinical and MR manifestations of a patient with MELAS. Recurrent status epilepticus caused reversible cytotoxic edema that was well visualized on DWI. In addition to MR and SPECT images, MR spectroscopy helped us to understand the pathophysiology of MELAS. Follow-up MR spectroscopy showed some discrepancy (partially recovered NAA, but persistently increased lactate) in the metabolite ratios. Abnormal signal intensity on T2WI or DWI better correlated with abnormal NAA/Cr ratio than the Lac/Cr ratio. The reversibility of the NAA/Cr ratio in the recent lesion suggests that NAA also reflects neuronal function.

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