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Original article

Pathophysiologic evaluation of MELAS strokes by serially quantified MRS and CASL perfusion images

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Abstract

Purpose: To clarify the roles of serial MR spectroscopy (MRS) and continuous arterial spin labeling (CASL) perfusion images for evaluating cerebral lesions in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). *Materials and methods:* Two cases of MELAS followed up serially using MRS and CASL images in addition to routine MR imaging were enrolled. *Results:* Newly appeared lesions assessed by MRS revealed increased lactate doublets which correlated well with CSF lactate level, and these showed a decreasing trend after treatment, although conventional T2 weighted images revealed hyper-intensity in both phases. Spectra from normally appearing white matter depicted slight lactate peaks during clinical exacerbation periods with marked elevation of CSF lactate and showed a decreasing NAA concentration during the prolonged course. In CASL images, acute lesions of the disease were clearly visible as hyper-perfusion foci, and chronic lesions were demonstrated as hypo- or iso-perfusion regions. *Conclusion:* The detection of lactate peaks in the MR spectrum from normally appearing white matter may be considered as systemic lactic acidosis or an exacerbation of MELAS, and active lesions can be distinguished from chronic inactive lesions by the increase of lactate peaks in MRS or the state of hyper-perfusion in CASL images.

Keywords: MELAS; MR spectroscopy (MRS); Lactate; Continuous arterial spin labeling (CASL); Perfusion

1. Introduction

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is one of the most common multisystem mitochondrial disorders. It is characterized by abnormalities of mitochondrial function due to enzymatic malfunction or deficiency, which result in impaired adenosine triphosphate (ATP) production [1,2]. Although MELAS induces repeated stroke-like episodes and the accumulation of lactate in brain tissue or systemic lactic acidemia in some clinical phenotypes, the precise pathophysiology remains controversial based on a lack of appropriate measures to assess the lesions over time.

MR spectroscopy (MRS) has been used as a non-invasive tool for evaluating brain metabolites *in vivo*. Previous reports concerning mitochondrial encephalopathy were able to demonstrate abnormally high lactate peaks in brain lesions or even in uninvolved areas of the brain [3–5]. However, the diagnostic value of MRS

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alone for this disease has not been established, since an elevated level of lactate is not specific for this disease.

Continuous arterial spin labeling (CASL) method is one of the arterial spin labeling methods which have potential to quantify local perfusion [6,7]. Since contrast media are not needed in this method, CASL is suitable for use in serial studies especially in pediatric cases. The clinical application of CASL has been mainly reported in common ischemic stroke cases [8,9], while no attempt using CASL techniques has been reported for MELAS.

The purpose of this study was to clarify the usefulness of serial MRS and CASL techniques quantitatively-measured in patients with MELAS and to try to discuss the pathophysiological aspects of the brain lesions present in this disease.

2. Materials and methods

Two cases of MELAS were retrospectively reviewed. The diagnosis was confirmed based on the finding of mutation of an A-to-G transition at nucleotide position 3243 (A3243G) in the mitochondrial DNA (mtDNA) by blood examination in both cases. In Case 1, MR examinations were performed at 3, 9, 17, 37, 56, and 119 days after the initial onset of symptoms in a stroke-like episode. Lactate and pyruvate levels in the cerebrospinal fluid (CSF) were also examined at 3, 10, 28, and 56 days. Case 1 had a second stroke-like attack at 56 days after the initial onset. Also in Case 2, a second attack occurred at 8 days after initial onset and MR examinations were performed at 2, 9, 16, and 24 days after the initial onset and at 14 days before the onset (day 0). Lactate and pyruvate levels in CSF were examined 1 day after the initial onset. In case 2, they were followed by longitudinal MR examinations even after the episodes. Biochemical, neurological, clinical symptoms are summarized.

2.1. Case 1

A 42-year-old female was apparently normal until the age of 23, when hearing reduction and muscle weakness were noticed. She developed dyspnea and hypotonic upper extremities at the age of 39 and was diagnosed as having hypertrophic cardiomyopathy and diabetes. Around the same time, she developed a reduction in intelligence and her leukocyte DNA examination confirmed the diagnosis of MELAS. At the age of 42, she suddenly experienced speech disturbance and was referred to our hospital. Neurological examinations on admission showed abduction disturbance of the left eye, saccadic eye movement, nystagmus, left hearing loss, and hypotonia. The concentrations of lactate in the CSF were 41.8, 24.0, and 9.5 mg/dl (normal range: 9.0–25.0 mg/dl), and those of pyruvate in the CSF were 2.58, 1.65, and 0.85 mg/dl (normal range: 0.6–1.2 mg/dl) at 3, 10, and 28 days after initial onset, respectively. She gradually recovered and left the hospital one and a half months later. However, she had a second stroke-like attack (dysphasia) after discharge. The concentrations of lactate and pyruvate in the CSF after the second admission, at 56 days after initial onset, were 23.3 and 1.53 mg/dl, respectively. Although her dysphasia improved, she died of generalized convulsions and heart failure despite all possible treatment at 127 days after the initial onset.

2.2. Case 2

This 10-year-old male with a normal prenatal and perinatal history is the same patient who was described in our previous report [10]. He had repeated symptoms of strokes, migraine headache, vomiting, and visual disturbance since 9 years of age, and was diagnosed with MELAS based on the finding of mutation of mtDNA A3243G by blood examination. He experienced a sudden onset of a migraine headache with scintillating scotoma in the left visual field and was referred to our hospital at the age of 10. Neurological examinations on admission showed mild truncal ataxia, left homonymous hemianopsia, and myoclonic jerks affecting the arms and legs. The concentrations of lactate and pyruvate in the CSF at 1 day after onset were 41.4 and 1.98 mg/dl (normal range: 9.0–25.0 and 0.6–1.2 mg/dl), respectively. He underwent treatment with intramuscular administration of dexamethasone for a week, and his migraines and hemianopsia markedly improved. At 8 days after onset, he experienced a mild headache and began taking medication again at 10 days. His symptoms disappeared in a few days.

2.3. MR spectroscopy

Proton spectra were acquired from $1.5 \times 1.5 \times 1.5$ to $2.0 \times 2.0 \times 2.0$ cm^3 voxels placed in hyper-intense region or normally appearing white matter on T2 weighted images. The point resolved spectroscopy (PRESS) localization method was used with the parameters of TE/TR = 28, 136/2000 ms, NEX = 64 and 128 for TE = 28 and 136 ms, respectively. Water suppression was achieved using three chemically selective pulses (CHESS) before the localization scheme. In order to evaluate the absolute concentration of metabolites, we placed a sample of pure water near the subjects to be examined. We calculated the relative intensity of the voxel region to the water phantom on the proton density image. Assuming the water content of the phantom is 55 mol/l, the mean water concentration in the voxel was estimated. Metabolite peak area ratios to water peak obtained without water suppression from the same voxel of interest (VOI) were converted to absolute concentrations expressed in mmol/l using the following formula [11]: