Diffusion Weighted Magnetic Resonance Spectroscopy in different stages of MELAS patient

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Target audience MRI researchers who are interested in diffusion weighted spectroscopy and the mechanisms of MELAS.

Introduction MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome is one of the most common multisystem mitochondrial disorders, mainly affecting both the skeletal muscle and the central nervous system. It is characterized by disorders in mitochondrial function due to point mutations of mitochondrial DNA, which impairs adenosine triphosphate production [1]. However, the underlying mechanism of MELAS has not been fully elucidated. Diffusion weighted MRI (DWI) and MR spectroscopy (MRS) has respectively been demonstrated to be viable tools to study the physiopathology of the stroke-like events in MELAS patients [2]. Hence diffusion weighted magnetic resonance spectroscopy (DW-MRS), which takes MRS measurement under the influence of diffusion gradients, permits the evaluation of the intrinsic diffusion properties of the metabolites that may provide valuable information understanding of pathphysiological process [3]. In this study, the DWMRS is used to probe the mechanisms underlying the pathogenesis of MELAS.

Method Eight patients with MELAS (5 males and 3 females, mean age 20.3±4.2 years) in the acute stage (within one month), twenty-six patients (13 males and 13 females, mean age 24.1±3.6 years) in the interictal phase of MELAS and eleven age matched healthy controls (7 males and 4 females, mean age 18.6±2.9 years) were recruited for this study. Written consent forms were obtained prior to the study. Diagnoses of MELAS syndrome were based on the clinical symptoms (seizures, dementia, and recur- rent headache) and the finding of a mutation at the nucleotide position 3243 in the mitochondrial DNA by blood examination. The DW-MRS sequence used is based on point resolved spectroscopy (PRESS) sequence technique with a pair of single polar diffusion gradients. The MR scanner used was a 3.0T clinical whole-body system (Signa EXCITE HD, GE). Parameters for the proton DW PRESS are as follows: TR = 2000 ms, TE = 288 ms, voxel size = 2×2×2 cm^3 (8 mL), spectral band width = 5000 HZ and data points = 4096. MRS data without diffusion weighting and a b-factor of 1000 s/mm^2 were acquired. Post-spectral processing was performed using SAGE software (GE Medical Systems). The ROIs were selected based on the T2 Flair image or DWI image. Pure water subtraction was performed to reduce residual water from each suppressed frame. Phase corrections were performed before the summation of FIDs. Since the integral peak area was more sensitive to the random noise, peak height was used to determine the signal intensity of metabolites in this study. The apparent diffusion coefficients (ADCs) values were estimated in the conventional way and used for statistical analysis.

Results The obtained spectral with and without diffusion weightings for MELAS patients and the healthy volunteers are shown in Fig.1, along with the location of the selected ROIs. The ROIs were placed in the lesion-appearing regions for the METAS patients, and were placed in the frontal lobe region for the healthy controls. The measured ADCs of three major metabolites, including choline-containing compounds (Cho), creatine (Cr), N-acetyl-aspartate (NAA) in patients and healthy controls are listed in Table 1. As there is no Lac signal detected in MELAS patients in interictal stage and healthy volunteers, the ADC of Lac has been excluded for comparison. Comparing to the healthy volunteers, the ADC of all three metabolites obtained in acute MELAS patients reveal significant increase ($P<0.05$). Compared to the MELAS patients with acute MELAS, the ADC of NAA and Cr obtained in patients in interictal stage show a further 10% ($p<0.05$) and 18% ($p<0.05$) increase respectively.

Discussion It is seen that the NAA of acute MELAS patients decrease significantly compared to health controls [2], however only mild increase is observed in the ADC of NAA. This is due to the fact that in the acute phase of MELAS, degeneration pycnosis neurons, mitochondrial swelling and the neurons with strange shapes can be found [4]. In the interictal stage, as the ischemia-like lesions of MELAS are characterized by laminar necrosis and extensive neuronal loss, some of the metabolites may leak into the extracellular space and the neuronal loss can lead to the expansion of the extracellular space, which would lead to higher ADCs of the metabolites.

Conclusion This study has demonstrated that MELAS is a mitochondrial neuropathy and DW-MR spectroscopy can be a viable tool for probing useful intracellular pathophysiologic information that conventional MR imaging fails to supply.

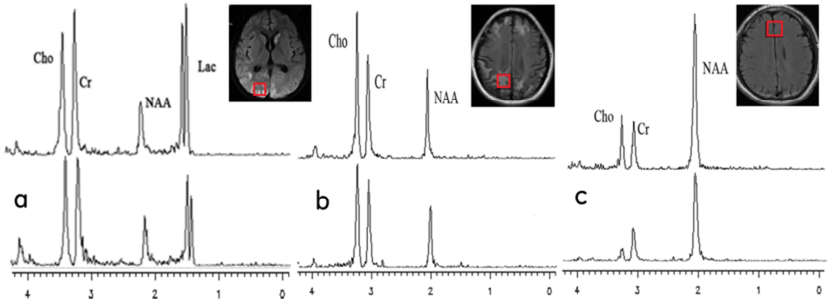

Fig.1 Spectral plots of ROIs without (top row) and with (b=1000) diffusion weighting for (a) patient with MELAS in stage (b) patient with MELAS in interictal stage (c) healthy volunteer. Positions of the ROIs are shown on the T2 weighted images or DWI image as shown on the top right corner.

Table 1 ADCs of metabolites in the MELAS patients and health volunteers

Population	Age	n	NAA	Cr	Cho
MELAS acute	12-35	8	0.26±0.02‡	0.27±0.01†‡	0.26±0.02†
MELAS interical	12-42	26	0.29±0.01†‡	0.32±0.02†‡	0.27±0.03†
Healthy control	11-38	11	0.24±0.02†	0.23±0.03†	0.20±0.04†

†P <0.05. (Two-sided, unpaired and unequal variance)
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Reference [1] DiMauro S, et al, NEngl JMed 2003
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