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Case study

Comparison of magnetic resonance spectroscopy (MRS) with arterial spin labeling (ASL) in the differentiation between mitochondrial encephalomyopathy, lactic Acidosis, plus stroke-like episodes (MELAS) and acute ischemic stroke (AIS)

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ABSTRACT

To compare the utility and limitation of magnetic resonance spectroscopy (MRS) and arterial spin labeling (ASL) in the differentiation between mitochondrial encephalomyopathy, lactic acidosis, plus stroke-like episodes (MELAS) and acute ischemic stroke (AIS), a retrospective review of 17 MELAS and 26 AIS patients were performed. In all patients both MRS and ASL scans were performed within 1 week after admission. Demographic, clinical, laboratory and MR imaging data were reviewed and compared between the two groups. Compared with AIS, MELAS patients had a younger age of onset, a longer disease duration, a higher occurrence of epilepsy attack, occipital and parietal lesions, and dilated cerebral arteries ($P < 0.05$). In all MELAS patients lactate peak and hyperperfusion of the lesion was revealed. However in AIS lactate peak was observed in only 69.2% and hyperperfusion was observed in only 34.6% ischemic lesions ($P < 0.05$). Choline/Creatine ratios and Lactate/Creatine ratios were higher in AIS, while in MELAS cerebral blood flow and lesion-normal perfusion ratio was much higher ($P < 0.05$). No correlations was found between metabolite ratios and perfusion parameters in either group ($P > 0.05$). Area under curve (AUC) of perfusion for the differentiation between MELAS and AIS was 0.958 ($P < 0.001$). The cut-off value was 2.075, with a sensitivity of 88.2% and a specificity of 96.2%. AUC of Lactate/Creatine ratio was 0.469 ($P = 0.737$). Utility of MRS is limited in the differentiation between MELAS and AIS, while MR perfusion profiles are much more sensitive and specific.

1. Introduction

Mitochondrial encephalomyopathy, lactic acidosis, plus stroke-like episodes (MELAS) is a neurodegenerative disorder caused by mitochondrial DNA point mutations. It is characterized by mitochondrial dysfunction, diminished respiratory enzymes and ATP levels, and elevated lactate production [1]. Both MELAS and acute ischemic stroke (AIS) can present as acute neurological deficits. Differential diagnosis at disease onset could be very difficult. Elevated lactate peak on magnetic resonance spectroscopy (MRS) is a consistent finding of MELAS [2] and is helpful in predicting disease onset and monitoring treatment effect [3]. But it could also be detected in AIS [4]. Recent studies indicate that MR perfusion profiles, revealed by arterial spin labeling (ASL), may be distinct in these two disease entities [5]. In the present study we compared the utility and limitation of these two MR techniques in the differential diagnosis between MELAS and AIS.

2. Methods and patients

A retrospective review of all MELAS and AIS patients was performed from July 2011 to December 2016. Any patients who underwent both MRS and ASL scans during hospitalization were included. The diagnosis of acute ischemic stroke was made when the history and examination were considered to be completely typical of a vascular brain event, and there was supportive or

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noncontradictory brain imaging [6]. The diagnosis of definite MELAS was based on positive genetic test. According to the diagnostic criteria [7], in all patients with a diagnosis of probable or possible MELAS, detection of the most common mutations of *MT-TL1* gene (including m.3243A > G, m.3271 T > C and m.3252A > G) was performed by sequencing the hotspot mutations region of mt.3150_3403. Twenty one patients with A3243G point mutation was found in a total of 155 candidates. Four patients were excluded from further analysis because MRS and/or ASL scans were not performed, leaving 17 MELAS patients into final statistical analysis. All MR examinations were performed on a 3.0 T MR scanner (HDx Signa, GE Healthcare, Milwaukee, WI) with a 8-channel head coil. Conventional clinical imaging included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences. T2 weighted imaging was used for 1H MRS voxel localization. Short (35 ms) TE Probe-SV (time point-resolved spectroscopy, single-voxel, size = 6.25 cm^3 or 8 cm^3 as appropriate) sequence was used to obtain lactate (Lac), N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr) levels from acute lesions. In some cases intermediate TE (144 ms) MRS was also performed to confirm the existence of lactate peak. Off-line spectral post-processing was carried out using semi-automated software (Functool, Version 9.4.05, GE Medical Systems) on an AW Volume Share workstation. All spectra were reviewed with two neuroradiologists who were blind to the diagnosis. Metabolite ratios from short TE spectra were used for statistics.

The cerebral blood flow (CBF) images were acquired with a 3-dimensional pseudo-continuous arterial spin labeling (3D pCASL) technique, using a background-suppressed 3D spiral FSE sequence [8]. The parameters were as follows: 8 arms were used with 512 sampling points for each arm, effective resolution 3.39 mm, bandwidth 62.5 Hz, TR 4521 msec, TE 9.8 msec, post labeling delay (PLD) 1525 msec, slice thickness 4.0 mm, number of slices 36, FOV 24 × 24 cm, matrix 512 × 512, NEX 3. The scan extended from the vertex to the base of the skull. Isotropic whole-brain T1-BRAVO imaging, an IR-prepared, 3D, high-resolution gradient echo technique, was performed for anatomic segmentation and Region of interest (ROI) selection, with the following parameters: TR/TE = 7.8/3.0 msec, flip angle = 12°, voxel size = 1 × 1 × 1 mm^3. Quantitative CBF maps derived from 3D pCASL were generated using semi-automated software (Functool, Version 9.4.05, GE Medical Systems). Generally, darker colors and lower CBF values indicated hypoperfusion regions, and lighter colors and higher CBF values indicated hyperperfusion regions. ROI was placed in the central part of the lesion, irrespective of the perfusion state. Structures like ventricles and cerebral fissures were carefully avoided. To reduce individual variance to the minimum, contralateral regions that located symmetrically to the lesions was used as reference for the calculation of lesion-to-normal CBF ratio (relative CBF, rCBF).

Demographic, clinical, laboratory and MR imaging data were reviewed and compared between the two groups. The Statistical Package for the Social Sciences version 18.0 software was used to perform all statistical comparisons (IBM, Armonk, NY, USA). Categorical variables were compared with Fisher's exact test. For continuous variables Shapiro–Wilk test was used to assess the normality of data. For comparison of demographic and clinical data between two groups, independent samples *t*-test or Mann–Whitney *U* test was used as appropriate. For comparison of the group level difference in metabolite ratios and perfusion parameters, two independent samples *t*-tests were used. Correlations with perfusion parameters (CBF of lesions and the lesion-normal perfiusion ratio) were tested with NAA/Cr ratio, Cho/Cr ratio and Lac/Cr ratios from the same lesions. Receiver operator characteristic (ROC) curves were generated for the lesion-perfusion ratios and Lac/Cr ratios to determine and compare their individual test characteristics in distinguishing MELAS from AIS patients, including area under curve, sensitivity and specificity. Differences with a p value of <0.05 were considered statistically significant.

3. Results

3.1. Demographic and clinical features

A total of 26 AIS patients and 17 MELAS patients were recruited in this study. In all patients MRS and ASL scans were carried out within 1 week after admission. In 15 AIS patients and 11 MELAS patients diffusion weighted imaging (DWI) scans were also performed. The demographical and clinical features of the study subjects were shown in Table 1. Clinical symptoms of the two groups included headache, dizziness, limb weakness, aphasia and dysarthria, blurred vision, hearing loss and mental disturbance. None of their distributions had a statistical difference between the two groups (P > 0.05). Compared with AIS, patients with MELAS had a younger age of onset a longer disease duration and were more prone to epilepsy attack (P < 0.05) (Table 1).

3.2. Radiological findings

The radiological features of the two groups are shown in Table 2. In MELAS group occipital (P = 0.002) and parietal lobe (P = 0.019) were more prone to be affected. Centrum semiovale and corona radiata was not affected in any MELAS patient, but the difference between the two groups did not reach statistical significance (P > 0.05). Stenosis of internal carotid arteries and/or intracranial arteries was much more frequent in AIS (P < 0.001). Vasculitis of cerebral arteries, confirmed by digital subtraction angiography and laboratory findings, were revealed in 6 AIS patients but not in any MELAS patients (P = 0.092). Moyamoya disease was highly suspected in two AIS patients but in none of MELAS patients (P = 0.667). Abnormally dilated cerebral arteries were confirmed by angiography in 2 AIS (posterior cerebral artery) and 6 MELAS patients (middle cerebral arteries) (P = 0.035).

Metabolite and perfusion profiles of the two groups were also shown in Table 2. Lactate peak was observed in all MELAS patients and in 69.2% AIS patients (P = 0.033). NAA/Cr ratios were comparable between two groups (P = 0.944). Both Cho/Cr ratios and Lac/Cr ratios were higher in AIS patients (P < 0.001 and P = 0.01 respectively). Hyperperfusion of the ischemic lesions was found in 34.6% AIS patients (9 cases). Among them petechial hemorrhage within the infarction was found in 5 cases (3 cases with cerebral vasculitis and 2 cases with sufficient collateral circulation). A CBF range of 8.85 to 119.82 (mean 37.99 ± 34.67) mL/100 g per minute was observed in the ischemic lesions and a CBF range of 22.97–87.68 (mean 45.10 ± 13.65) mL/100 g per minute was observed in the contralateral normal internal reference brain tissues. The lesion-to-normal CBF ratio ranged between 0.12 and 2.74, with a mean of 0.86 ± 0.70. Compared with AIS, a much higher percentage (100%) of patients were found with hyperperfusion lesions in MELAS group (P < 0.001). A CBF range of 55.98–234.85 (mean 151.07 ± 48.11) mL/100 g per minute was observed in the lesions and a CBF range of 21.89–87.08 (mean 53.69 ± 16.10) mL/100 g per minute was observed in the contralateral normal parenchyma. The lesion-to-normal CBF ratio ranged between 1.09 and 5.01, with a mean of 2.93 ± 0.98. Compared with AIS, MELAS patients have much higher cerebral blood flow (P < 0.001) and much higher lesion-normal perfusion ratios (P < 0.001).

Illustration of multimode MR scans in an AIS patient and a MELAS patient were shown in Figs. 1 and 2, respectively. In both patients characteristic lactate peak were revealed by both intermediate TE and short TE MRS scans. In AIS (Fig. 1) ADC value of MELAS 0.341 × 10^{-3} mm^2/s, which was comparable with

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