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Proton magnetic resonance spectroscopy differentiates tumefactive demyelinating lesions from gliomas

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ABSTRACT

Background: It is often difficult to accurately differentiate tumefactive demyelinating lesions (TDLs) from gliomas using MRI.
Objective: To investigate the utility of proton magnetic resonance spectroscopy (MRS) in differentiating TDLs from gliomas.
Methods: Cohort 1 included 6 patients with TDLs and 5 with gliomas (3 high-grade), as assessed using a 1.5T MR unit. Cohort 2 included 6 patients with TDLs and 17 patients with gliomas (8 high-grade), as assessed using a 3.0T MR unit. Single-voxel proton MRS was performed to compare the following metabolite area ratios: choline (Cho)/creatine (Cr), N-acetylaspartate (NAA)/Cr, and Cho/NAA in both cohorts. Correlations between the target-to-normal-tissue ratio (TNR) obtained using methionine-positron emission tomography (MET-PET) and each MRS metabolite ratio were examined in a subset of cohort 2 (4 patients with TDLs and 11 with gliomas).
Results: Mean Cho/NAA ratio was significantly higher in gliomas than in TDLs or MS in cohort 1 ($p < 0.05$). Mean Cho/NAA ratio was significantly higher in high-grade gliomas than in TDLs in both cohorts ($p_s < 0.05$). In the receiver operating characteristic analysis, high-grade glioma rather than TDL was indicated when the Cho/NAA ratio was >1.72 (the area under the curve was 0.958, and the maximum sensitivity and specificity were 100% and 87%, respectively). A significant positive correlation was observed between Cho/NAA ratio and the MET-PET TNR ($r^2 = 0.35$, $p < 0.05$).
Conclusion: MRS effectively differentiates TDLs from high-grade gliomas. Therefore, the clinical use of MRS is likely to enhance patient outcomes.

1. Introduction

Diagnosis of CNS inflammatory demyelinating diseases (IDDs), such as the classic form of MS, can easily be accomplished based on radiographical examination and assessment of the clinical course. However, differentiation between CNS IDDs and brain tumours is often complicated by similarities in MRI findings. In particular, differential diagnosis between tumefactive demyelinating lesions (TDLs) and brain tumours is often challenging (Lucchinetti et al., 2008; Weinshenker, 2015). It is very important to differentiate TDL from glioma, because steroid use is a poor prognostic factor in glioblastoma (steroids are often used in TDL) (Shields et al., 2015; Wong et al., 2015; Sacko et al., 2015). Therefore, more precise diagnostic tools are needed for differentiating CNS IDDs from brain tumours.

Previous studies have revealed that proton magnetic resonance spectroscopy (MRS) is useful for grading gliomas (Hollingworth et al., 2006; Chronaiou et al., 2014), and have also demonstrated that it effectively differentiates between brain tumours and CNS pseudotumours (Gajewicz et al., 2003; Al-Okaili et al., 2007). Moreover, MRS differentiates CNS demyelinating diseases from CNS lymphomas (Lu et al., 2014) or gliomas (Majos et al., 2009). In contrast, a previous study found that MRS was not useful in differentiating tumefactive autoimmune lesions from gliomas (Blasel et al., 2011). However, the sample sizes of these previous conflicting studies were small, and the comparison factors were limited (Gajewicz et al., 2003; Al-Okaili et al., 2007; Majos et al., 2009; Blasel et al., 2011). The present study aimed

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to elucidate whether MRS can differentiate TDLs from gliomas. The results have potential clinical importance, as more accurate diagnosis will improve patient outcomes.

2. Materials and methods

We conducted this retrospective study between January 2004 and May 2017, at Tokyo Women's Medical University Hospital. All participants underwent proton MRS. Patients were assigned to cohorts 1 and 2, which underwent MRS using MRI machines with different magnetic field strengths. Participants in cohort 1 had gliomas (5 total, 3 with high-grade gliomas), TDLs (6 patients), and MS as a control (24 patients), and were assessed from January 2004 to January 2011. In cohort 2, participants were 17 patients with gliomas (8 with high-grade gliomas) and 6 patients with TDLs, who were tested from January 2011 to May 2017. Gliomas were diagnosed by brain biopsy, surgical resection, or autopsy. Patients with gliomas were retrospectively classified using the 2007 World Health Organization Classification of Tumors of the Central Nervous System (Louis et al., 2007). TDLs were defined as demyelinating brain lesions that exceeded 2.0 cm in diameter on MRI, with mass effect and oedema that mimicked CNS tumours (Lucchinetti et al., 2008). TDLs were diagnosed by brain biopsy, surgical resection, or by clinical courses supported by CSF and MRI findings. Brain biopsy was performed in 6 patients with TDLs. All patients with TDLs were in relapse at the time of MRS. Patients with MS met the 2010 revisions to the McDonald criteria (Polman et al., 2011). Two patients with TDLs were administered prednisolone, and 2 patients with TDLs were administered interferon β-1b at the time of MRS. Four patients with TDLs received steroid pulses before MRS (1 patient in cohort 1 and 3 patients in cohort 2). This study was approved by the Ethics Committee of Tokyo Women's Medical University School of Medicine. Patient consent was waived, due to the retrospective nature of the study.

2.1. MRI and MRS examination

The cohort 1 portion of the study was performed with a 1.5 Tesla MR unit (EXCELART, Canon Medical Systems Corporation, Tokyo, Japan). Single-voxel (voxel size: 20 × 20 × 20 mm^3) proton MRS was performed in the areas of abnormality, utilizing a point-resolved spectroscopy sequence (PRESS) protocol with TR/TE = 4500/100 ms. Multi-slice T1 or T2-weighted images in axial planes were obtained for MRS volume of interest (VOI) selection. The metabolites assessed were choline (Cho) at 3.20 ppm, creatine (Cr) at 3.01 ppm, and N-acetylaspartate (NAA) at 2.01 ppm.

The cohort 2 portion of the study was performed with a 3.0 Tesla MR unit (Vantage Titan, Canon Medical Systems Corporation, Tokyo, Japan). Single-voxel (voxel size: 15 × 15 × 15 mm^3) proton MRS was performed in the areas of abnormality utilizing a PRESS protocol with TR/TE = 2000/136 ms. Multi-slice T1 or T2-weighted images in axial planes were obtained for MRS VOI selection. The metabolites assessed were Cho at 3.17 ppm, Cr at 3.04 ppm, and NAA at 1.99 ppm. The peak area measurements of metabolites were used to calculate the following ratios: Cho/Cr, NAA/Cr, and Cho/NAA, in both cohorts. We did not perform MRS with short echo time in either cohort.

2.2. Positron emission tomography (PET) analysis

Methionine (MET)-PET studies were performed in 4 patients with TDLs and 11 patients with gliomas (5 with high-grade) in cohort 2. Data acquisition for MET-PET was started 20 min after administration of 6 MBq/kg MET. Since this was a retrospective study, MET-PET was conducted using 3 different machines, including an ECAT ACCEL (Siemens Medical Solutions USA, Inc., Knoxville, TN, USA), Biograph Sensation 16 (Siemens Medical Solutions), and Biograph mCT (Siemens Medical Solutions). ECAT ACCEL is a dedicated PET scanner and attenuation correction was performed by standard transmission scanning with a $^{68}Ge/^{68}Ga$ ring source. Emission data were acquired for 5 min in the 3-dimensional (3D) mode after acquisition of transmission scans for 5 min. Images were reconstructed using ordered-subset expectation maximization (OSEM) with 6 iterations and 16 subsets, a 128 × 128 matrix, and postsmoothing with a Gaussian filter (FWHM, 6 mm). Biograph Sensation 16 is an integrated PET/CT scanner and the concomitant CT data (5 mm slice thickness) were used for attenuation correction. The data were acquired for 5 min and image reconstruction was performed by 3D OSEM (iterations = 8, subsets = 16) with a 128 × 128 matrix and a 5-mm Gaussian filter. Biograph mCT is also an integrated PET/ CT scanner and attenuation was corrected by 3 mm CT slices. Emission scans were performed for 8 min and images were reconstructed by 3D OSEM (iterations = 4, subsets = 21) with a 400 × 400 matrix and a 4 mm Gaussian filter.

Regions of interest (ROIs) were indicated on the axial PET images of the target lesions, by a board-certified nuclear medicine physician. ROIs were carefully drawn based on a visual comparison of the PET/CT, contrast-enhanced MRI, and/or PET/MRI fusion images developed by syngo.via software (Siemens Healthcare, Erlangen, Germany). The examiner measured maximum standardised uptake values (SUVmax) of each patient's target lesion, as well as the mean standardised uptake values (SUVmean) of the normal contralateral frontal cortex, as references. The target-to-normal-tissue ratio (TNR) was calculated as follows:

$$TNR = \text{SUVmax of the target lesion} / \text{SUVmean of the normal contralateral frontal cortex.}$$

2.3. Statistical analysis

Statistical analyses were performed with Prism software 5 (GraphPad Software, San Diego, CA, USA) and JMP Pro 12 (SAS Institute, Cary, NC, USA). Numerical data are presented as means and standard deviations (SDs). Associations between dichotomous variables were analysed using chi-square or Fisher's exact tests, as appropriate. For statistical analysis between 2 groups, unpaired *t*-tests were used. To compare data from >2 groups, one-way analysis of variance (ANOVA) was used. Post-hoc analyses of significant differences detected by ANOVA were performed using Tukey's tests. Statistical significance was indicated by p values < 0.05. In order to assess the predictive value of metabolite ratios in MRS, ROC curve analyses were conducted using JMP Pro 12 (SAS institute); cut-off values with maximum sensitivities and specificities were then determined. Correlations between 2 variables were examined using linear regression analyses.

3. Results

3.1. Clinical manifestations

Table 1 describes the clinical characteristics of each patient group. In cohort 1, we enrolled 5 patients with gliomas. Three of the 5 cases had high-grade gliomas (2 patients with glioblastoma). Six patients with TDLs were enrolled, and 3 of the 6 were diagnosed with MS at the last follow-up. In cohort 2, we enrolled 17 patients with gliomas, and 8 of 17 patients had high-grade gliomas (6 patients with glioblastoma). In cohort 2, 6 patients with TDLs were enrolled; 1 of 6 patients was diagnosed with MS by the last follow-up, and another 2 patients were diagnosed with neuromyelitis optica spectrum disorder. The ages of onset and ages at MRS for TDLs and MS in cohort 1 were significantly lower than those for gliomas.

3.2. Cho/NAA was higher in high-grade gliomas than in TDLs

To investigate whether MRS can differentiate TDLs from gliomas,