Whole-brain Amide Proton Transfer (APT) and Nuclear Overhauser enhancement (NOE) imaging in Glioma Patients using low-power steady state pulsed CEST at 7T

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Introduction

The grading of gliomas has clinical importance in determining a treatment strategy and evaluating prognosis. Amide Proton Transfer (APT) weighted MRI has become a potentially important application of CEST-MRI due to its ability to detect gliomas, to differentiate glioma cores from peritumoral edema, and to separate recurrent tumor from treatment necrosis[1-3]. When acquiring Z-spectra using low RF power pulsed steady-state CEST acquisition with the purpose of reducing semi-solid MT contrast (MTC) and reducing and narrowing direct saturation (DS) effects, saturation-transfer effects based on slow exchange are pronounced, such as upfield relayed NOE (Nuclear Overhauser Enhancement) signals and downfield CEST/APT signals. NOEs have been highly useful in NMR spectroscopy and have recently attracted much attention in the field of CEST imaging. The NOE signal in vivo may arise from the through space dipolar coupling between the water protons and the aliphatic and olefinic components of semisolid tissue components, as well as from a relay process via intramolecular protons and exchangeable groups in mobile proteins, peptides, and lipids[4,5]. In this study, APT and NOE signals were compared among *de novo* primary gliomas with different WHO grades (I to IV) by group analysis at 7T.

Methods

Eleven patients (1 grade I, 6 grade II, 2 grade III, 2 GBM) were scanned on a 7T whole body scanner (Philips Healthcare). CEST image data were obtained using a 3D multi-shot gradient echo (TR/TE/FA =65ms/7.2ms/12°, EPI factor 7; 40 slices, 3x3x3 mm^3). The RF saturation pulse was a nominal 1μT, 25ms single-lobe sinc-gauss pulse (208°) in each TR. The saturation frequency offsets were acquired pseudo-randomly. Saturated and unsaturated volumes were acquired randomly. There were 64 saturated volumes at frequency offsets from -20 ppm to 20 ppm with a dense sampling of 0.1 ppm from -5 to 5ppm. All CEST data were registered to the first volume (unsaturated) using the rigid body registration algorithm. A smoothed B-spline function was fitted to the unsaturated data in each voxel for the signal drift correction. A Lorentzian curve was used to shift the acquired data to correct for B_0 inhomogeneity and to determine the APT and NOE effects. Three regions of the z-spectra (|f| < 1 ppm, f > 10 ppm and f < -10 ppm) were simultaneously fit to a Lorentzian function to fit out direct water saturation. A Lorentzian difference analysis (LDA) was calculated as the difference between the fitted water Lorentzian and the data. The mean LD signal was quantified at 3.5ppm for APT and -3.5ppm for NOE. The LDA approach provides a suitable alternative for quantifying downfield APT/CEST and upfield NOE signals when MTC effects are small and the direct water saturation shape is sufficiently narrow. ROI selection included only contrast-enhancing regions for grade IV tumors but included all T_2 hyperintense regions for grades I-III; mirror image ROIs were used for contralateral hemispheres.

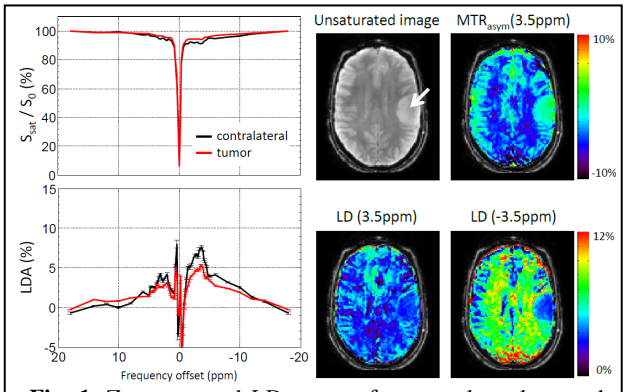

Fig. 1. Z-spectra and LD-spectra for contralateral normal tissue and tumor in a low-grade (grade II) oligodendroglioma patient, the unsaturated image, MTR$_{asym}$ at 3.5ppm, LD (3.5ppm), and LD (-3.5ppm) maps

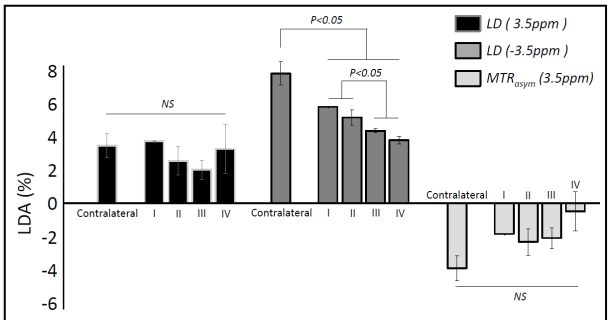

Fig. 2. LD (3.5ppm), LD (-3.5ppm), and MTR$_{asym}$ (3.5ppm) signal intensity in each WHO grade

Results and Discussion

Fig. 1 shows corrected z-spectra for tumor and contralateral regions. The LDA results are shown in the lower plot. The tumor was hyperintense on the MTR$_{asym}$ (3.5ppm) image, but hypointense on the LD (-3.5ppm) map.

Fig. 2 shows group-averaged APT, NOE, and MTR$_{asym}$ signals. The NOE signals of all grades (I-IV) of glioma were significantly lower than those of the contralateral normal brain region. When we grouped the grade I and grade II as low-grade glioma and compared them with the higher grade gliomas (grade III and grade IV), there was a significant difference in NOE signals between the groups. In addition, the NOE signal of the grade II group was significantly higher than that of the grade IV gliomas ($p<0.05$). Despite high cellular density in many tumors, water content in high-grade tumor enhancing regions (included in ROIs) is generally lower than in normal tissue due to the larger extravascular extracellular spaces. This leads to a general reduction in saturation in z-spectra and MTC and CEST effects. Such an increase in extracellular water content leads to a reduction in cell-based APT/NOE saturation effects, but this should not be interpreted as an associated decrease in the mobile cellular protein and peptide contents.

No difference was observed between contralateral normal tissue and all grades glioma in APT and MTR$_{asym}$(3.5ppm), but there was a trend towards an increase in MTR$_{asym}$(3.5ppm) of glioma relative to that of contralateral normal tissue ($p=0.07$). Previous studies showed positive APT contrast between the tumor and the normal tissue with higher RF saturation power (>2μT) and using asymmetry analysis [1,2]. However, the NOE effects become more pronounced at the lower saturation power, resulting in a reduction of MTR$_{asym}$(3.5ppm) signal in normal tissue, while the relative increase in tumor cells remains.

Conclusions

In this study, we assessed the ability of APT/NOE imaging to differentiate tumor grades of primary gliomas at 7T. Our findings suggests that NOE imaging may provide a promising biomarker for glioma grading.

References:

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