Amide Proton Transfer Imaging of Diffuse Gliomas: Correlation with Histopathological Grades

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Target audience: Researchers and clinicians interested in brain tumor imaging, particularly with regard to amid proton transfer (APT) imaging.

Purpose: Amide proton transfer imaging[1] employs the exchange between protons of free tissue water and the amide groups (-NH) of endogenous mobile proteins and peptides, imaged by a chemical exchange saturation transfer technique. Previous preliminary reports demonstrated that APT signal intensity (SI) was found to increase by 3 – 4 % in tumor compared with normal brain tissue in an experimental rat gliosarcoma model at 4.7 T[2] and human brain gliomas at 3T[3]. In the latter study in patients, the APT SIs in 6 high-grade gliomas were higher than those in 3 low-grade gliomas. These results suggested the potential of APT imaging in grading of gliomas based on this novel contrast mechanism in clinical settings. Since APT is a newly developed technique in neuroradiology, a further verification and a larger statistical basis is required to determine whether APT imaging accurately reflects pathological condition of diffuse glioma. Therefore, the purpose of our study is to prospectively assess the ability of APT imaging for grading of diffuse gliomas in a large cohort of patients compared with histopathological evaluations.

Methods: *Subjects:* Consecutive 28 patients with diffuse glioma (47.7±13.8 year-old, 10 males and 18 females) who underwent subsequent surgical resection (n=24) or biopsy (n=4) were included in the prospective study. Histological types of gliomas are as follows; 1 astrocytoma; 4 oligodendrogliomas; 3 anaplastic astrocytomas; 6 anaplastic oligodendrogliomas; 14 glioblastoma multiforme (GBMs). Recurrent gliomas after previous treatments (n=8) were included. Twenty-six patients had supratentorial lesions and 2 patients had infratentorial lesions. The interval between the MRI and the surgery was shorter than 2 weeks in all patients.

MRI: MRI was conducted in a 3T clinical scanner (Achieva TX 3.0T, Philips Healthcare, NL) using an 8-channel head coil for signal reception and 2-channel parallel transmission via the body coil. Acquisition software was modified to alternate the operation of the two transmission channels during the RF saturation pulse[4] and to allow a special RF shimming for the saturation homogeneity of the alternated pulse (identical mean B1 level per channel). Saturation pulse-trains: 50ms sinc-gaussian elements, $B_{1,rms}$=2.0μT. 2D fast spin-echo sequences with driven equilibrium[5,6] refocusing were used. The imaging parameters were as follows: T_{sat}=2.0s, TR/TE=5s/6ms, FOV (230 mm)^2, matrix 168^2, resolution 1.8×1.8×5 mm^3, 25 saturation frequency offsets S[ω], ω=-6 to 6ppm (step 0.5ppm) and S_0 (ω=-160ppm), affording 2 minutes scan time. δB_0 maps for off-resonance correction were acquired separately (identical geometry, 2D GRE, ΔTE=1ms, TR/TE=15ms/8ms, 16 averages, 33 sec). Maps of the MT asymmetry MTR_{asym}=(S[-3.5ppm]-S[+3.5ppm])/S0 were calculated with a point-by-point δB0 correction [5,6]. Region-of-interests (ROIs) were carefully placed by 2 neuroradiologists independently to measure APT SI in the solid component of brain tumors. For histological analysis, Ki-67 labeling index (LI) was measured to assess cell proliferative activity of the diffuse gliomas.

Results and Discussion: The measured APT SIs by two observers showed excellent agreement. Mean APT SI was 2.1 ± 0.5 %, 3.3 ± 0.8 %, 4.1 ± 0.9 % in grade II, III, IV gliomas, respectively (**Figure 1**). Significant differences in APT intensity were observed between grade II and III ($P < .05$) as well as between grade II and IV ($P < .001$). The low-grade (grade II) and the high-grade (grade III and IV) groups were separated by the cutoff value of APT SI of 2.5% with a sensitivity of 95% and a specificity of 100%. There was a significant positive correlation between APT SI and Ki-67 LI ($P < 0.01$, $R^2 = 0.25$, **Figure 2**). **Figure 3** shows representative cases of the 3 different grades of diffuse glioma. The increase in APT signal in high-grade glioma might result from elevated proteins/peptides level due to abundant cytoplasm and high cell density. The long saturation pulse of 2 sec enabled by the parallel transmission technique increased a sensitivity of the APT signal for grading diffuse glioma [6]. Given that APT imaging reflected cell proliferative activities of diffuse glioma, APT imaging can be a method to monitor therapeutic response or tumor activity, as shown in the animal experiment[7].

Conclusion: APT imaging can predict histopathological grades of diffuse gliomas.

References: 1. Zhou J et al., Nat Med (2003), 2. Salhotra et al. NMR biomed (2008)

3. Zhou J et al., MRM (2008), 4. Keupp J et al., ISMRM (2011)

5. Keupp J et al., ISMRM (2012), 6. Togao et al., ISMRM (2012)

7. Sagiyama et al. ISMRM (2012)

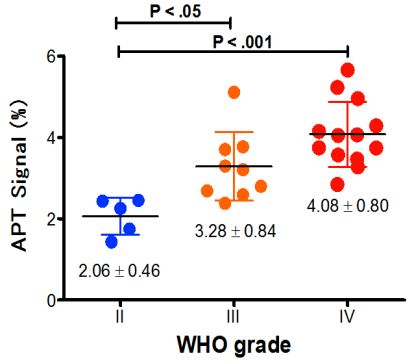

Figure 1. APT SI and WHO grade of diffuse glioma. APT SI increases with the grade of glioma.

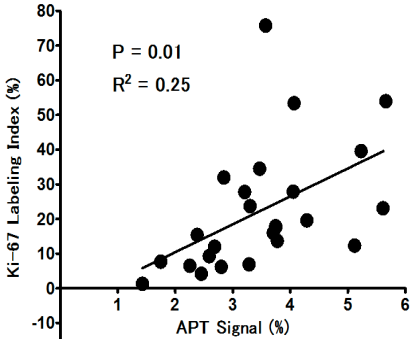

Figure 2. APT SI and Ki-67 LI. A moderate positive correlation is observed, which indicates that high APT SI is related to active proliferation of tumor cells.

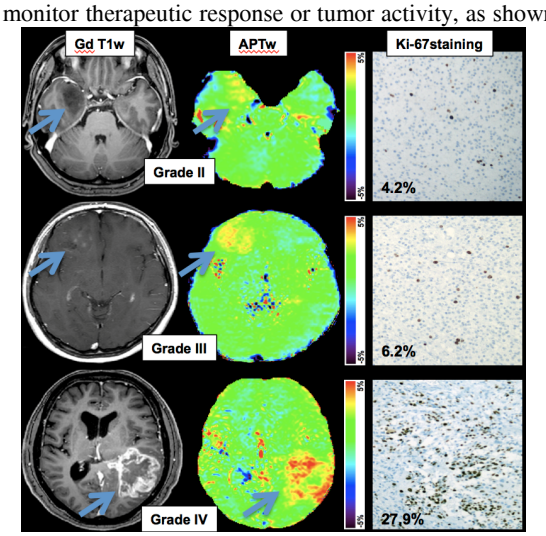

Figure 3. Top , middle, bottom row shows grade II astrocytoma, grade III anaplastic oligodendroglioma, grade IV glioblastoma, respectively. Note that APT SI and KI-67 LI increase with the grade of glioma.