Amide Proton Transfer MRI in Patients with High-Grade and Low-Grade Gliomas

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Introduction

The grading of gliomas has clinical significance in determining a treatment strategy and evaluating prognosis. Despite the accumulated knowledge in clinical practice, differentiating high-grade and low-grade gliomas has persistently posed a dilemma for radiologists in many cases, because of the overlapping imaging findings on conventional MR imaging. One of the differences between solid tumors and normal tissue is the acidic micro-environment around the tumor caused by hydrolysis of Amide Proton Transfer (APT) and an upregulated anaerobic metabolism. As a consequence of the increased intracellular generation of acidic values, the transport of acidic compounds to the extracellular space is upregulated correspondingly to prevent the cellular metabolism from breaking down, which, in turn, can result in slightly increased intracellular pH values [1]. APT is a new MRI technique which detects endogenous mobile proteins and peptides in biotissues, such as tumors [2]. Previous studies have showed that APT MRI is sensitive to changes in cellular pH and protein concentration [3]. Here we used APT MRI, which does not require exogenous contrast agents, as a tool to distinguish high-grade and low-grade gliomas.

Theory

Chemical exchange-dependent saturation transfer (CEST) imaging, which was introduced by Balaban in the early 1990s, is a type of magnetization transfer (MT) imaging to measure exchangeable protons in proteins. As shown in figure 1, the low-concentration proteins are labeled by saturating their exchangeable protons (e.g., hydroxyl, amine, and amide) via selective radio-frequency (RF) irradiation at their specific resonance frequency, and then the labeled protons are transferred to the bulk water via chemical exchange at an exchange rate. The

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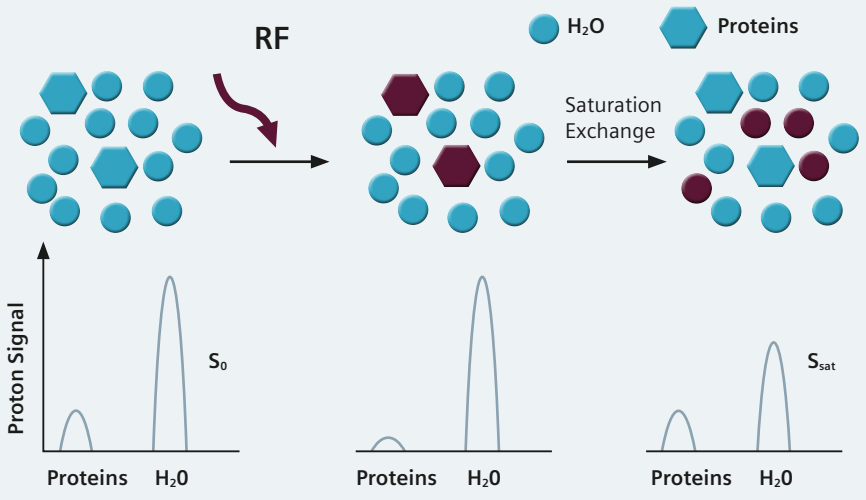


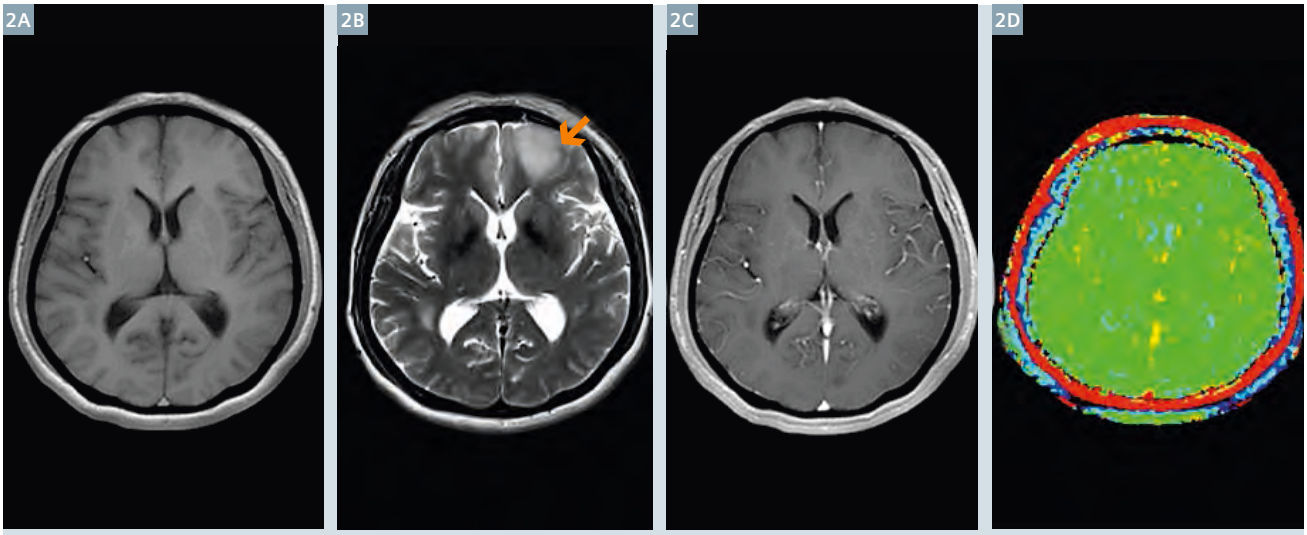
1 A schematic of chemical exchange saturation transfer (CEST). Water and proteins are two pools of protons and have distinct chemical shifts. Protons of proteins are saturated at their specific resonance frequency via RF irradiation. This saturation is transferred to water and decreases the water signal.

solute protons are always at a very low concentration and hard to detect directly using standard MR protocols. However, after a certain time of continuous transfer, this effect decreases the MRI signal and the protons are detected indirectly through the attenuation of the water signal. This effect is measured by using the ratio of water signals with (S_{sat}) and without saturation (S_0).

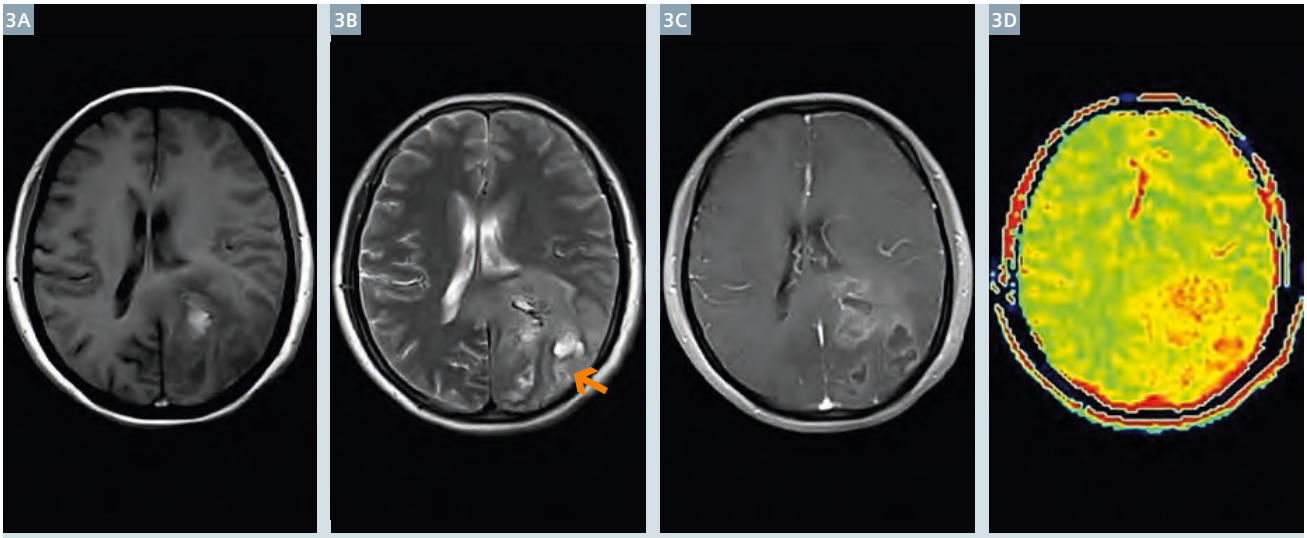
For the CEST analysis, the most common metric used is the magnetization transfer asymmetry (MTR_{asym}) analysis by subtracting the right and left MT ratio ($MTR=1-S_{sat}/S_0$) to reduce the interference of the coexisting conventional MR and direct saturation effects:

$$MTR_{asym} = S_{sat}(-\Delta\omega)/S_0 - S_{sat}(+\Delta\omega)/S_0 \quad (1)$$

in which $\Delta\omega$ is the frequency difference with water. Plotting MTR with the saturation frequency gives a Z-spectrum (also called CEST spectrum). The amide protons resonate at 8.3 ppm of the proton MR spectrum (3.5 ppm to water signal) and are used for amide proton transfer (APT) imaging.



2 51-year-old female patient with astrocytomas (WHO grade II) in the left frontal lobe. **(2A)** T1-weighted image; **(2B)** T2-weighted image; **(2C)** Post-gadolinium T1-weighted image; **(2D)** APT map.



3 47-year-old male patient with glioblastoma (WHO grade IV) in the left occipital lobe. **(3A)** T1-weighted image; **(3B)** T2-weighted image; **(3C)** Post-gadolinium T1-weighted image; **(3D)** APT map.

Patient history

Case 1 is a 51-year-old female patient with astrocytomas (WHO grade II) in the left frontal lobe (Fig. 2). She had neurologic complaints including dizziness, nausea and vomiting for 5 hours before the MRI examination.

Case 2 is a 47-year-old male patient with glioblastoma (WHO grade IV) in the left occipital lobe (Fig. 3). He had a two months history of insomnia and a five hours history of complaints including dizziness, nausea and vomiting before the MRI examination.

Sequence details

The patients were examined at a 3T MR system (MAGNETOM Trio a Tim System, Siemens AG, Erlangen, Germany). The APT images were acquired using a GRE-based CEST* WIP sequence with the following parameters: TR 3200 ms, TE 2.87 ms, FA 10 degrees, slice thickness 5 mm. The saturation module was applied before the imaging readout. Four RF pulses were repeated for 21 different offset frequencies from +5 to -5 ppm (interval is 0.5 ppm) with respect to the water frequency. MTR asymmetry analysis at the offset around 3.5 ppm is calculated to obtain APT images.

*WIP, the product is currently under development and is not for sale in the US and other countries. Its future availability cannot be ensured.

Imaging findings

In Case 1, the low-grade glioma in the left frontal lobe is not very apparent on the T1-weighted image (Fig. 2A), but shows hyperintensity on the T2-weighted image (Fig. 2B). No enhancement is revealed on the contrast-enhanced T1-weighted image (Fig. 2C). The APT map demonstrates the tumor's isointensity (Fig. 2D).

In Case 2 the solid part of the high grade glioma shows hypointensity on the T1-weighted image (Fig. 3A) and heterogeneous hyperintensity on the T2-weighted image (Fig. 3B). The hemorrhage area in the tumor shows isointensity to hyperintensity on the T1-weighted image (Fig. 3A) and hyperintensity on the T2-weighted image (Fig. 3B). Irregular enhancement is revealed on contrast-enhanced T1-weighted image (Fig. 3C). The APT map demonstrates that the tumor, including the solid and hemorrhage components, is hyperintense (Fig. 3D).

Conclusion

Our preliminary results demonstrate that this GRE-based CEST sequence can provide APT images with good quality. It has been shown that intracellular pH is almost the same in tumor and in normal tissue. High APT signal in high-grade cerebral gliomas is usually due to high protein concentration [2, 3]. The non-invasive technique of APT may be a useful tool to detect the mobile cellular proteins and an upward pH shift *in vivo*. It has the potential to be an alternative imaging modality to improve the diagnostic accuracy in grading gliomas.

References

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