Clinical Utility of Amide Proton Transfer Imaging in Patients with Brain Tumors

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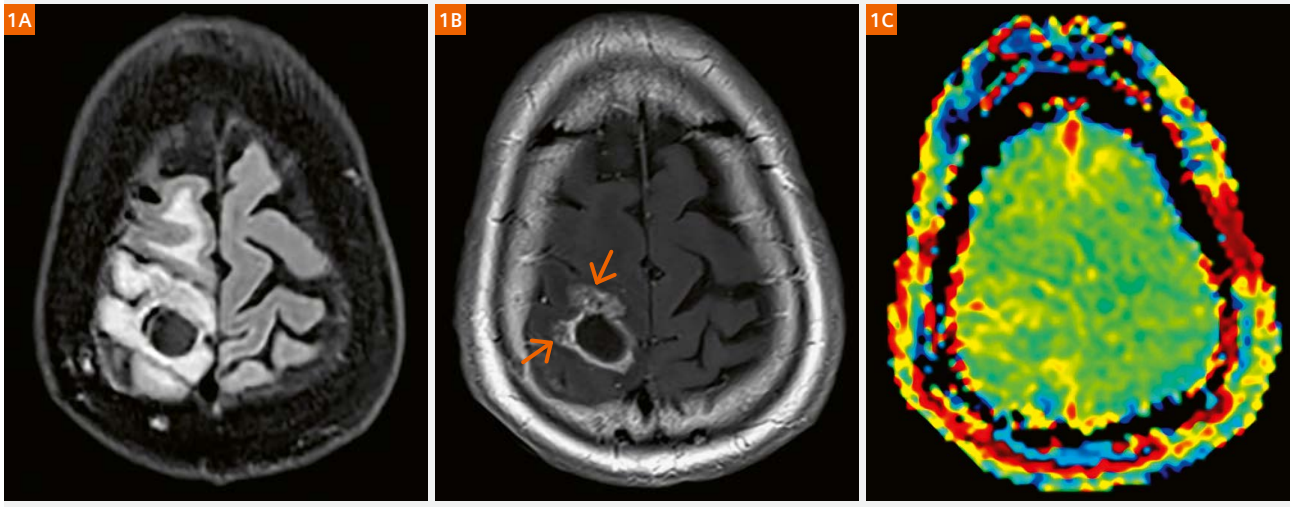
Introduction

Amide Proton Transfer-weighted (APTw) MRI is an emerging technique that does not require using gadolinium contrast. It is a promising tool for tumor grade characterization [1, 2] and for separating tumor recurrence and treatment related changes [3–5]. The concept is based on that exchangeable protons will amplify the MR imaging signal using a method called chemical exchange saturation transfer (CEST) [6]. In APTw imaging it is the amide protons of mobile proteins and peptides in the tissue that are saturated using a selective radio frequency (RF) pulse at 3.5 ppm from the water resonance. This amide proton saturation is then transferred to water protons through physical exchange and by repeating this process one can detect the MR signal of these low concentration proteins and peptides with sensitivity enhancements of a factor of about fifty or more. This allows imaging of the signal from millimolar concentration of the exchangeable amide protons with the molar sensitivity of water protons.

Case 1: Pseudo progression of a high-grade glioma



Case 1 shows post-resection MR imaging in a patient with a high-grade glioma. **(1A)** FLAIR images show heterogeneous signal changes surrounding the resection area. **(1B)** Post-Gd, T1-weighted images demonstrate ring enhancement and focal areas (arrows) of scattered enhancement indicating tumor progression. **(1C)** In contrast to FLAIR and post-GD T1-weighted imaging, APT images demonstrate no measurable tumor. The assumption of pseudo progression in FLAIR and T1-weighted imaging was confirmed on follow-up MR examinations.

A tumor has other protein characteristics than normal tissue, leading to a difference in the number of amide protons between these tissues [1]. While other signal contributions are mixed in, leading to the term APT-weighted (APTw) MRI, the contrast at 3.5 ppm is due, in main part, to the mobile proteins and peptides. Previous studies have shown that APTw MRI can separate tumor from edema [1, 7] and correctly detect non-enhancing high grade tumors as malignant and enhancing low-grade tumors as nonmalignant [2]. In addition, the technique has shown the ability to separate tumor recurrence from treatment related changes [4, 5].

Patient cases

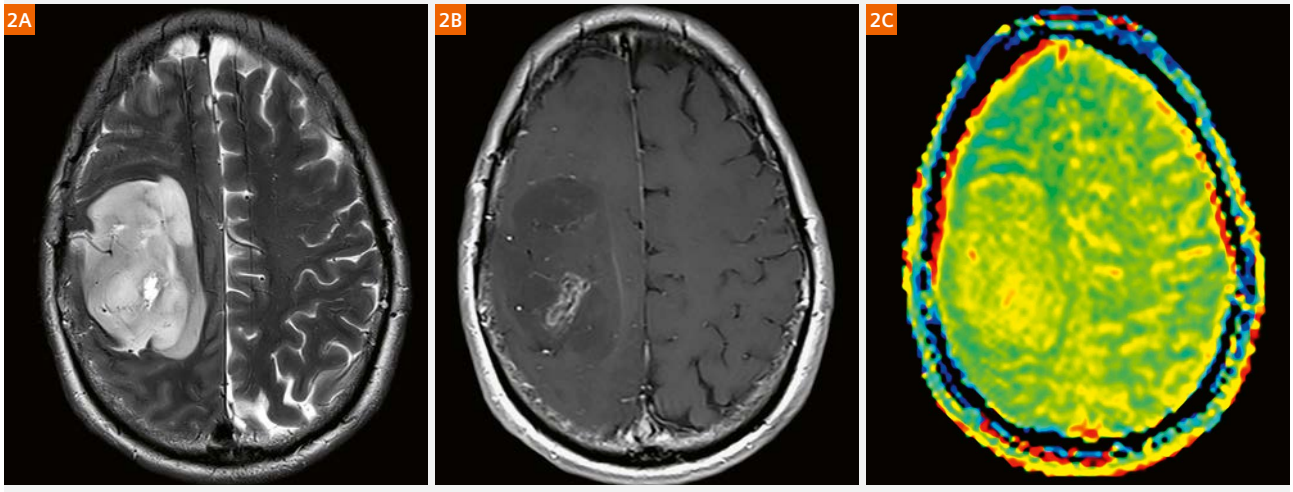
We present our first experience with the CEST[1] WIP on a 3T scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany). APTw images were generated based on 3D GRE (22 slices, 2 x 2 x 4 mm^3) acquisition of a water saturation spectrum (Z-spectrum, 21 offset points from -610 to 610 Hz, B1 = 2 µT, tsat = 600 ms, 5 HS pulses, 60 ms spacing, TA 6:50 min), followed by B_0 correction and processing optimized for APT-weighted contrast at 3.5 ppm, providing the typical green brain background and tumor signal highlighted by hyperintensity (yellow or red). Note that blood vessels have a high protein content and may also show up red. In addition, field inhomogeneity may cause enhancement at the brain edges. Figure 1 shows a post-treatment glioma case where APTw MRI could distinguish treatment necrosis from recurrent tumor; In Figure 2, APTw hyperintensity confirmed a high grade glioma, and in Figure 3, APTw MRI identified a recurrent tumor for a case where Gd-enhancement was unclear.

Conclusion

Our early results confirm the promise of APTw MRI for assessing tumor grade and distinguishing recurrent tumor from treatment necrosis. In the future, it might offer a potential surrogate for contrast-enhanced scanning in patients undergoing follow-up scans and may help to better classify the aggressiveness and infiltrative growth of tumors.

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

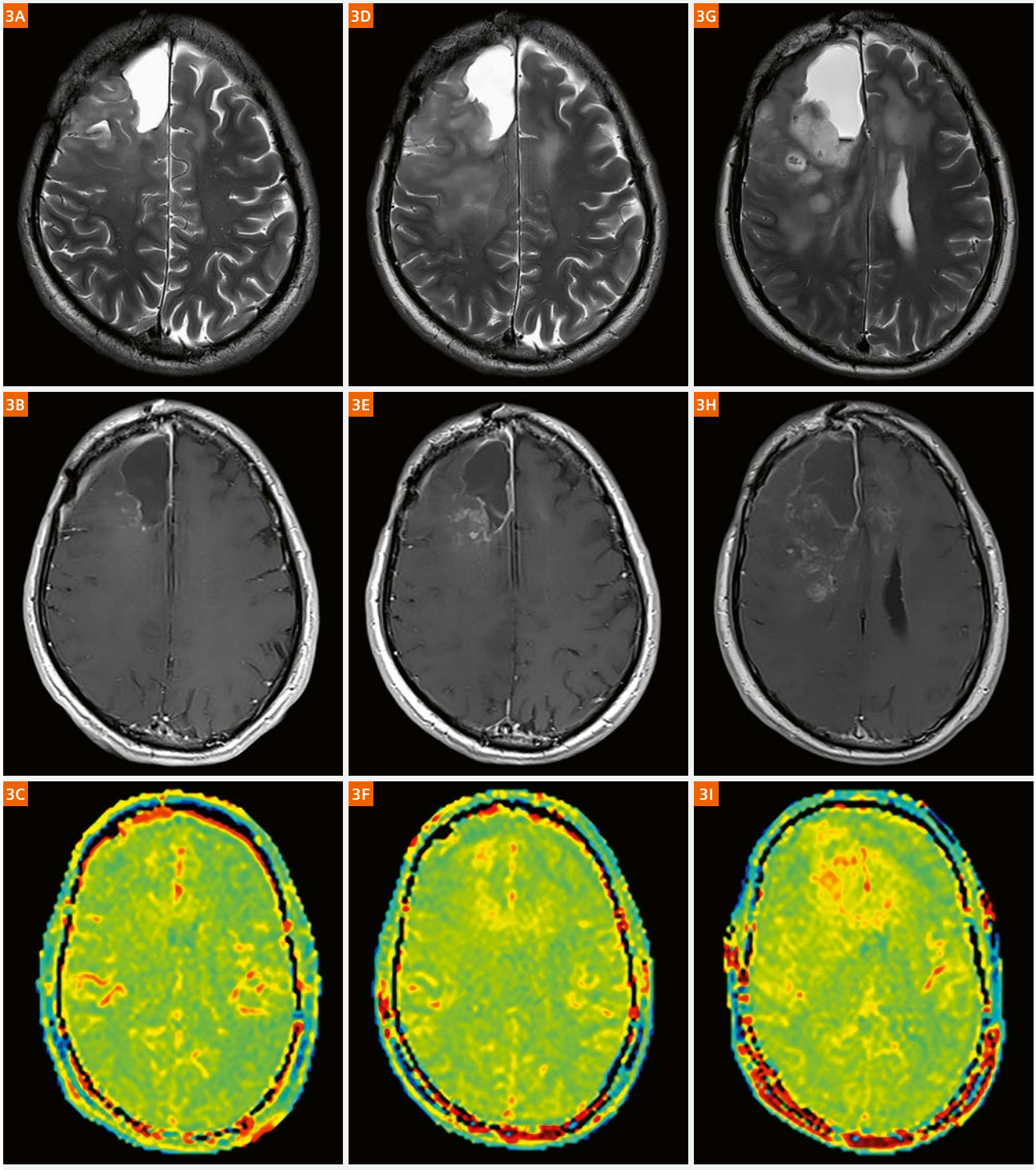
Case 2: Classification of a high-grade glioma



The patient presents with a heterogeneous, well-circumscribed lesion in the right frontoparietal region as seen on **(2A)** T2-weighted and **(2B)** T1-weighted images after GD administration. Although it is a large tumor, the mass effect is moderate. There is only a small, central region of patchy contrast uptake in the tumor, indicating high-grade cancer cells. **(2C)** APT images show a well-circumscribed lesion with moderately increased APT signal and a small central region of higher metabolic activity corresponding to the location of pronounced contrast uptake in T1-weighted images. There is a second area of high activity in the tumor that is not visible in T1-weighted images.

Histopathology after surgery confirmed a high-grade glioma with an isocitrate dehydrogenase (IDH) mutation. Location and appearance, that is a unilateral pattern of growth, sharp tumor margins, and moderate contrast enhancement on MRI, correlate well with the findings of a recent study [8] on the most common locations and prognosis of IDH-mutated gliomas. The results of that study suggest that the prolonged survival of patients with IDH-mutated gliomas is primarily due to a less aggressive biological behavior according to tumor site and MRI features. APT images in the case presented here appear to confirm these findings.

Case 3: Monitoring of a high-grade glioma under treatment presenting progression



This case illustrates true progression of a high-grade glioma located in the right frontal lobe. **(3A)** Post-surgical edema in T2-weighted images and small, focally enhancing areas in the close vicinity of the resection area in post-GD T1-weighted images **(3B)** are visible. **(3C)** Corresponding APT images show a markedly increased signal in the same region also indicating a further infiltration than visible on T1-weighted images. Follow-up exams after 3 **(3D–F)** and 6 months **(3G–I)** show fast infiltrating tumor growth with diffuse scattered contrast enhancement and progression into the left hemisphere. **(3I)** APTw MRI also shows some hyperintensity in the lateral sulci due to the presence of blood vessels.

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