APT-CEST in post-therapeutic gliomas imaging

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Louis Deprez: Nothing to disclose
Gautier Kempinaire: Nothing to disclose

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Purpose or Learning Objective:

-- To understand the physical basis of amide proton transfer (APT) chemical exchange saturation transfer (CEST) imaging

-- To understand the applications and utility of APT-CEST in brain tumor imaging and in the follow-up of high-grade gliomas (HGG), to help differentiating between tumor progression (TP) and post-therapeutic effects (PTE).

Methods or Background:

High grade gliomas (HGG) are aggressive and invasive malignant brain tumors, of poor prognostic and survival. In this poster, the term “high grade glioma” will refer to the entities described as “glioblastoma, isocitrate dehydrogenase (IDH) wild-type” and “grade 4 astrocytoma, IDH-mutated) by the World Health Association (WHO) 2021 classification of tumors of the central nervous system(1). The treatment of those lesions revolves around surgery, looking for maximally safe tumor resection, followed by radiation therapy and chemotherapy (Temozolomide)(2).

Tumor recurrence (more accurately qualified as “progression” (TP), given the infiltrative and by definition non-completely resectable nature of HGG) is the norm, with a median progression free survival of a bit less than 7 months(2). Thus, regular follow-up imaging is mandatory to precociously identify TP and evaluate re-treatment possibilities, such a new surgery or second-line systemic treatment (Bevacizumab).

Follow-up imaging of post-therapeutic HGG can be challenging, as post-therapeutic effects (PTE), such as radionecrosis or pseudoprogression(3), can mimic tumor progression on conventional magnetic resonance imaging (MRI)(4).

Both tumor progression and PTE share a common radiologic semiology, showing extensive contrast enhancement and FLAIR hyper-signal progression. Post-contrast T1 weighted (T1W) imaging has a low specificity to differentiate between both phenomena(5).

Even with advanced MRI techniques, such as perfusion weighted imaging (PWI) or magnetic resonance spectroscopy (MRS), correct diagnostic assessment can prove difficult.

Dynamic susceptivity contrast (DSC) of arterial spin labelling (ASL) perfusion weighted imaging (PWI) showed an increased specificity compared to contrast-enhanced T1W(6), but suffer from some technical pitfalls (proximity of vascular structures, of the normally hyperperfused cerebral cortex) that limits is specificity, and is subjects to artefacts in post-therapeutic tissue due to the magnetic susceptibility of necrotic products

The clinical relevance in distinguishing TR versus PTE is high, as while TR often requires new surgery and additional chemotherapy, PTE care is mostly supportive and based on symptoms control, and morbidity is vastly different between those to treatment options.

In this context, APT-CEST has emerged as a promising MRI technique to accurately differentiate tumor progression/recurrence from post-therapeutic effects.

Results or Findings:

APT CEST is a metabolic MRI technique which allows the measurements of usually undetectable endogenous molecules in the brain tissue, such as amide or amine groups, which are found in peptides and mobile protein-rich areas of the brain(7). Those molecules concentrations are known to be elevated in malignant tumors, as shown in magnetic resonance spectroscopy studies(4). Those concentrations are lower in treatment-related brain tissue reaction, such as radionecrosis or pseudoprogression, which are histopathological phenomena characterized by necrosis and inflammatory processes, with oedema and increase in the permeability of the blood-brain barrier (BBB), and with fewer mobile cytosolic proteins and peptides than in recurrent tumoral tissue. APT-CEST signal is thus supposed to be lower in treatment-related lesions than in true tumoral tissue.

From a technical point of view, CEST is an MRI method to obtain molecular information by applying RF pulses at the resonance frequency of solute protons, which differs from bulk water protons, engaged in chemical exchange. After being saturated by this selective RF pulse, the chemical exchange phenomenon transfers the saturation from solute protons to bulk water resulting in a minuscule signal loss per transfer (Fig 1.a).

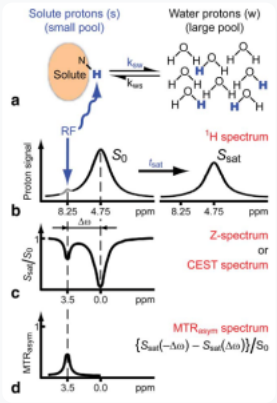

Fig 1: "Chemical exchange saturation transfer (CEST): principles and measurement approach for pure exchange effects. a, b: Solute protons (blue) are saturated at their specific resonance frequency in the proton spectrum (here 8.25 ppm for amide protons). This saturation is transferred to water (4.75 ppm) at exchange rate ksw and nonsaturated protons (black) return. After a period (tsat), this effect becomes visible on the water signal (b, right). c: Measurement of normalized water saturation (Ssat/S0) as a function of irradiation frequency, generating a so-called Z-spectrum (or CEST spectrum or MT spectrum). When irradiating the water protons at 4.75 ppm, the signal disappears due to direct (water) saturation (DS). This frequency is assigned to 0 ppm in Z-spectra. At short saturation times, only this direct saturation is apparent. At longer tsat the CEST effect becomes visible at the frequency of the low-concentration exchangeable solute protons, now assigned to 8.25 4.75 1⁄4 3.5 ppm in the Z-spectrum. d: result of magnetization transfer ratio (MTR 1⁄4 1 – Ssat/S0) asymmetry analysis of the Z-spectrum with respect to the water frequency to remove the effect of direct saturation. In the remainder of this article we will use the standard NMR chemical shift assignment for water at 4.75 ppm in 1H spectra, while the 0 ppm assignment will be used in Z- spectra." Reproduced with permission from the author(9)

Since the solute concentration is very low relative to free water, exchanged saturated protons are replaced by unsaturated water protons which can be saturated again. If the exchange rate is fast enough and the saturation time long enough, repeating the labelling enhances the saturation effect thus becoming visible on the water signal(9). An unsaturated water image is also acquired allowing us to quantify the signal decrease(Fig 1.b)(10).

By repeating the saturation at different frequencies, a plot of normalized water intensity as function of saturation frequency can be generated, called the Z-Spectrum (Fig 1.c). In the Z-Spectrum, frequencies are considered relative to water, which is assigned as 0. This spectrum contains signal from different saturation mechanisms, such as Direct Saturation (DS), CEST, relayed Nuclear Overhauser Effect (rNOE) and semisolid Magnetization Transfer Contrast (MTC)(9,11).

The APT-CEST method targets intracellular proteins and their exchangeable amide protons. To best assess the APT effect alone, the Magnetic Transfer Ratio (MTR) asymmetry is employed, which is defined by subtraction of left and right signal intensity ratios (Fig 1.d).

The range of APT is from 1 to 6 ppm from water with a maximum effect at 3.5 ppm(8,12). Additionally, inhomogeneities in both the static field (b0) and the RF field (b1) lead to distortions in the signal and need to be compensated. Methods of corrections, such as WAter Shift And B1 (WASABI)(13,14), have been proposed to address this issue. After applying b0 and b1 correction, pixel by pixel subtraction allows us to measure the APT-CEST effect.

Multiples studies have shown an increase in APT signal in tumor progression areas compared to proven pseudo-progression or radionecrosis.

In a paper published in 2011, Zhou et al.(15) showed a clear difference between tumoral tissue and radiation necrosis on rat brain tumor models with APT CEST imaging, paving the way to its study in the neuro-oncologic field.

In 2016, Ma et al.(16) analyzed the utility of APT in 32 patients with suspected tumor progression in the first 3 months after chemotherapy and radiotherapy. In their results, APT signal intensity was significantly higher in the TP group than in the PTE group ($p<0,001$), as TP was associated with APTW hyperintensity (APTWmean = 2.75% ± 0.42%), while pseudoprogression was associated with APTW isointensity to mild hyperintensity (APTWmean = 1.56% ± 0.42). They determined a cutoff APTWmean and APTWmax intensity values of 2,42%/2,54% for the distinction between TP and PTE (the first having the highest specificity of 100% and the second the highest sensitivity of 95%).

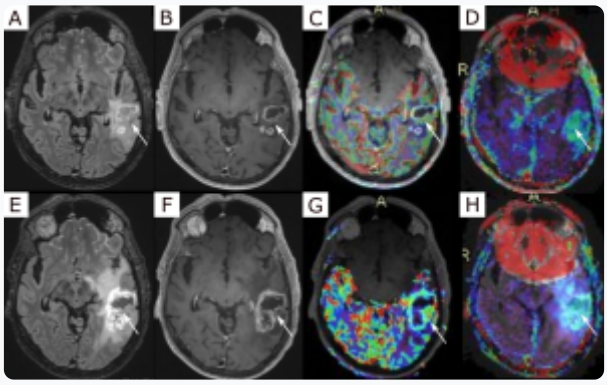

Fig 2: Top row: first MRI examination after temozolomide and radiation therapy. Bottom row: follow-up MRI after 3 months. Contrast-enhanced Fluid Attenuated Inversion Recovery (FLAIR) (A, E). Contrast-enhanced T1W (B, F). DSC PWI relative Cerebral Blood Volume (rCBV) (C, G). APT map (D, H). We can see tumor progression between the top and bottom row on conventional (FLAIR, T1W) images and on perfusion and APT imaging. Based on literature(17), APT signal was over the suggested thresholds for TP (>2,795%).

Multiples studies were published between 2016 and 2024, whose results are summarized in a recent review and meta-analysis published early this year by Essed et al.(17), and including 12 studies and 500 patients. This study confirmed a good sensitivity (pooled 0.88 [0.82–0.92]) and specificity (pooled 0.84 [0.72–0.91]) for the differentiation between TRE and TR/TP. Interestingly, APT-CEST combined with conventional/advanced MRI (like ASL/PWI) showed an increased sensitivity 0.92 [0.86–0.96] and specificity 0.88 [0.72–0.95] compared to APT alone.

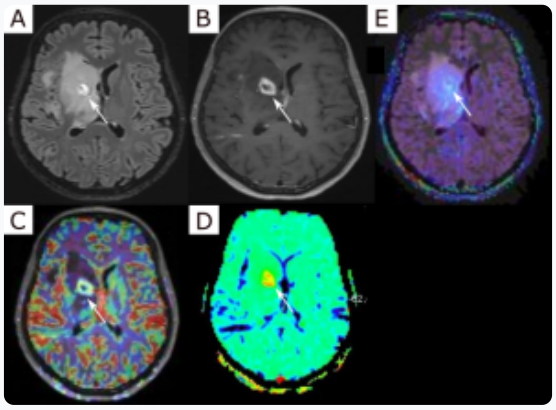

Fig 3: Contrast-enhanced Fluid Attenuated Inversion Recovery (FLAIR) (A) and contrast-enhanced T1W (B) showing central annular contrast enhancement and diffuse FLAIR hypersignal in the frontal lobe and basal ganglia. DSC PWI relative Cerebral Blood Volume (rBCV)(C) and permeability coefficient (D) showing both an elevation in their parameters, suggesting both TP and PTE, without ruling out TP. APT (E), showing mildly elevated signal, under the suggested thresholds(17), in favor of PTE.

One of the main limitations in the routine clinical use of APT-CEST in brain tumor imaging is the lack of homogeneity between studies. Both sequence parameters and results post-processing standardization are needed before APT-CEST can become a widely used technique in brain tumor imaging. Recommendations regarding APT acquisition protocol and post-processing at 3T have been published by an expert group(18), with the clear goal to allow more medical centers to use comparable techniques in brain tumor imaging, paving the way to more powerful studies and multi-center trials in large patients cohorts, the last step between routine clinical use.

Models integrating multiple advanced techniques (PWI, MRS, APT) could further increase the diagnostic accuracy of MRI in HGG follow-up(17), with the goal of reducing the number of repeated biopsies (with their associated risks) and switch therapeutic strategies earlier in the course of the disease, to maximize efficacy and limit morbidity.

Conclusion:

APT-CEST has shown increased diagnostic performance for differentiating tumor progression from post-therapeutic effects in high grade gliomas when compared to standard MRI imaging. Its combination with PWI could help achieve higher specificity than actual techniques and help reduce the need for repeated surgery and the morbidity in glioma patients.

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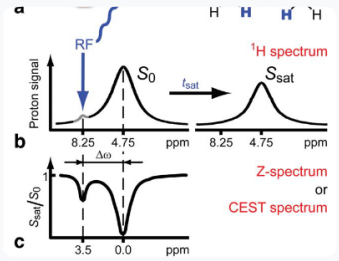

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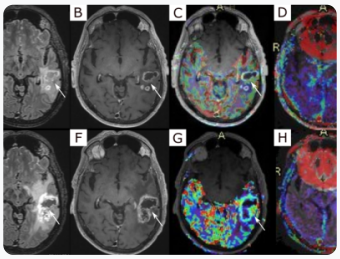

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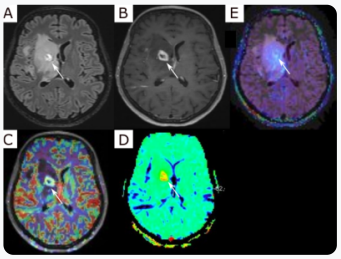

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