Glycine is a potential biomarker for malignant transformation in brain tumors

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Target audience: Neuro-radiologists and MR spectroscopists in brain tumors.

Purpose: Precise measurement of glycine (Gly) in human brain remains challenging. Gly may be increased in brain tumors, as reported in several prior studies. However, how Gly can be used for improving patient management is largely unknown. The purpose of the study was to develop a new ^{1}H MRS scheme for Gly detection at 3T and to investigate potential alterations in Gly levels with tumor malignancy and progression.

Methods: ^{1}H MRS data were acquired from five patients with gliomas, of which a patient was scanned at four time points for studying potential changes in metabolite levels with tumor progression. The MR scan protocol included T_2w-FLAIR and single-voxel localized MRS at 3T (Philips Medical Systems). Water suppressed spectra were acquired using PRESS (TE_1, TE_2) = (32, 65) ms. The voxel size was 4 - 8 mL, depending on the tumor volume identified by T_2w-FLAIR. Data acquisition parameters included TR = 2 s, NEX = 128 - 512, sweep width = 2500 Hz, and number of samples = 2048. Following LCModel fitting, metabolite levels were estimated with reference to water at 42 M.

Results: The PRESS sequence used included optimized 180° pulses, whose refocusing profile was quite rectangular without noticeable lobes outside the bandwidth, as shown in **Fig. 1A**. Numerical simulations indicated that, at PRESS TE = 97 ms, the mIns multiplet at ~3.55 ppm was substantially reduced and consequently the signal strength at 3.55 ppm was comparable to the Gly signal for a Gly-to-mIns concentration ratio of 1/6 (**Fig. 1B**). As the Gly-to-mIns concentration ratio increased from 0/6 to 3/6, the Gly+mIns composite signal pattern changed noticeably (**Fig. 1C**), suggesting that the Gly and mIns signals can be well separated *in vivo*. The MRS method was tested in a patient with WHO grade-3 oligodendroglioma (**Fig. 2**). The spectral pattern between 3.5 and 3.7 ppm was clearly different between the tumor and contralateral normal-appearing brain, indicating Gly elevation in the tumor. The Gly estimate from the tumor was 2.4 mM while Gly was not measurable in the white-matter (WM) dominant contralateral brain, in which Gly was reported to be markedly low compared to gray-matter (GM) rich regions [1]. It is noteworthy that the C4-proton resonance of 2-hydroxyglutarate (2HG) at 2.25 ppm was clearly discernible in this IDH-mutated glioma. In the data from three subjects with glioblastomas, the signals between 3.5 and 3.7 ppm were dominated by the Gly singlet (**Fig. 3**), showing substantial reduction of myo-inositol in the grade-4 gliomas. The Gly estimate was 4-5 mM in two brainstem tumors (**Fig. 3A,B**) and as high as 9 mM in a multi-focal glioblastoma (**Fig. 3C**). An oligoastrocytoma patient was scanned at 4 time points over a 9 month period (**Fig. 4**). The tumor mass, identified by T_2w-FLAIR, became larger by ~2 fold for 9 months (**Fig. 4A**), during which the clinical symptoms got worse. The Gly estimate, which was ~0.3 mM at the first time point, was increased to 1.6 mM with the tumor progression (**Fig. 4B**). 2HG was also increased. The total choline and N-acetyl aspartate levels were about the same over the study period.

Discussion & Conclusion: The present study shows that PRESS TE = 97 ms at 3T can separate the Gly and mIns signals well and provides a noninvasive tool for evaluating the Gly status in brain tumors *in vivo*. Our data indicate Gly elevation in brain tumors. Given that brainstem is dominated by WM, the Gly estimates in glioblastomas are ~10 times (or more) higher than the normal Gly levels, which may be ~1 and ~0.3 mM in GM and WN rich regions respectively [1]. The current paper reports Gly increase with tumor progression for the first time. In conclusion, Gly may be a useful biomarker for evaluating the tumor malignancy and for monitoring the malignant transformation.

References: 1. Banerjee et al. Magn Reson Med 2012;68:325-331.

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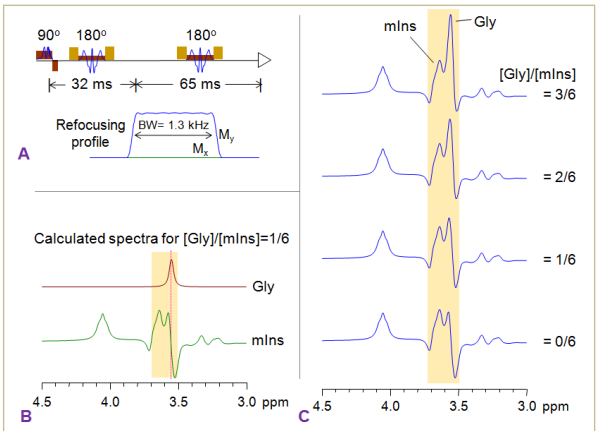

FIG 1. (A) Schematic diagram of the PRESS TE=97ms sequence used and the calculated refocusing profile of the 180° RF pulse. (B) Calculated spectra of Gly and mIns for a concentration ratio of 1/6. Spectra are broadened to singlet linewidth of 5 Hz. (C) Gly+mIns composite spectra calculated for various concentration ratios.

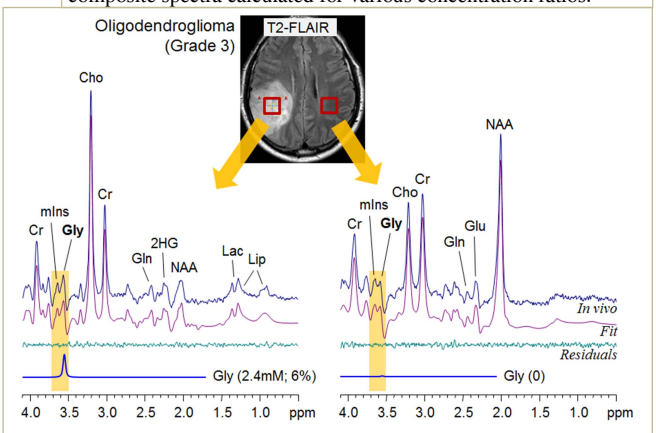

FIG 2. *In vivo* spectra, obtained with PRESS TE=97ms, from the tumor (left) and the contralateral normal-looking brain (right) in an oligodendroglioma patient are shown together with LCModel fits, residuals, and the LCModel returned signals of Gly. The Gly level was estimated to be 2.4 mM with CRLB of 6% in the tumor while Gly was not measurable in the normal brain region.

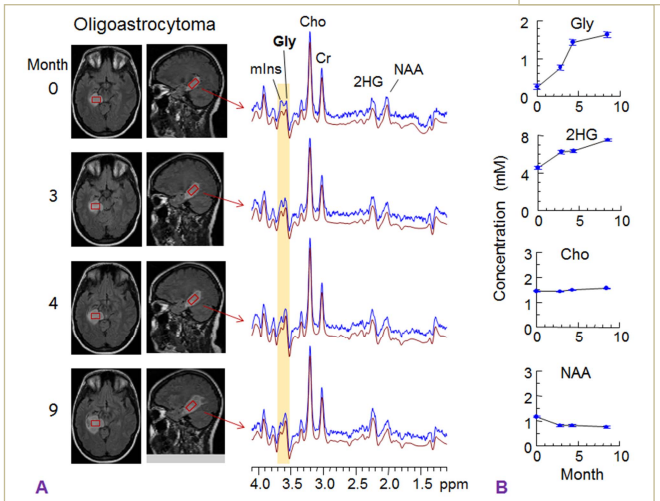

FIG 4. (A) An oligoastrocytoma patient was scanned at 4 time points over 9 months, during which the tumor volume increased. (B) The estimated levels of Gly, 2HG, Cho and NAA were plotted versus month.

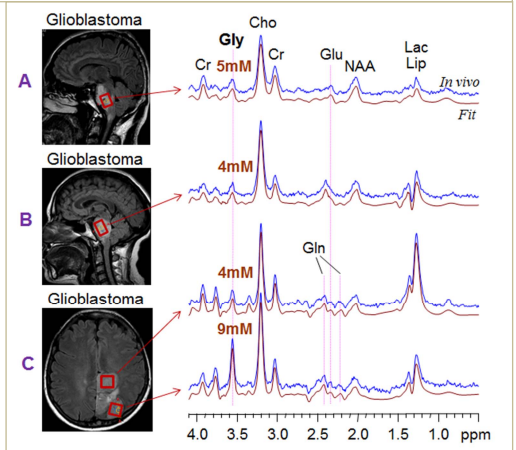

FIG 3. *In vivo* spectra, obtained with PRESS TE=97ms, from three glioblastoma patients are shown with LCModel fits. Gly was estimated to be 4-5 mM in two brainstem tumors (A and B) and to be 4-9 mM in a multi-focal glioblastoma (C).