Enhanced detection of glutamine (Gln) and glutamate (Glu) with 1H MRS using single voxel STEAM: their potential to stage brain tumors

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Introduction: It has been demonstrated that glutamine (Gln) and glutamate (Glu) levels are both directly and indirectly (via reactive oxygen species signaling) involved in tumor proliferation and apoptosis (1), and thus could provide useful information for tumor diagnosis and treatment. Consistently, *in vivo* 1H MRS studies of human brain tumors illustrate tumor-induced changes in Glx (Gln + Glu), and even suggest Glx/Cr index to be a good predictor of tumor grading (2). However, Glx cannot be used to evaluate the individual changes in Gln and Glu. This poses an obstacle to full utilization of Gln and Glu information, particularly since there is a strong biochemical coupling between the two. Indeed, *in vitro* 1H MRS studies have suggested that Gln/Glu ratio is useful in detecting an early stage of malignant transformation (3). Due in part to the technical difficulty, *in vivo* detection of well-separated Gln and Glu of human tumors has not been reported. A recent study proposed that a standard STEAM sequence with optimized TE/TM (80/50 ms) can be used to simultaneously detect Gln and Glu peaks around 2.4 ppm with virtually no spectral overlap at 4T (4). In this study, we report preliminary results of the application of this technique for brain tumors.

Materials and Methods: 1H MRS of eight patients with brain tumors were acquired with a quadrature head coil in a 4T system. Four patients had biopsies within two weeks of their respective MRS study, and the remainder had biopsies prior to their scans. A standard STEAM sequence was used with TE=80ms, TM=50 ms, TR = 2 –3 seconds, spatial resolution = 4 - 12 cm^3, and acquisition time =15-30 minutes. All data sets were processed using LCMode.

Results: In addition to providing "typical" characteristics of NAA, Cho, and Cr for brain tumors, one of the striking observations is a consistent and remarkable increase in both Gln concentration (using water as a reference) and Gln/Cr ratio for all cases studied. Another observation is a decrease in Glu concentration (using water as a reference) but wide variability in Glu/Cr ratio (from virtually zero to three times the corresponding contralateral control). Figure 1A and 1B show typical spectra of a contralateral control tissue and gliobastoma (confirmed by biopsy 5 days later), respectively. In addition to remarkable changes in the "traditional" MRS marks (NAA/Cho/Cr), the Gln signal also dramatically increases in tumor from a virtually unobservable peak in the control to clearly visible. Figure 1C illustrates an example of a brain mass with different spectral characteristics. It has only small-to-moderate changes in NAA, Cho, and Cr, but a remarkable increase in Gln. Biopsy 11 days later for this patient indicated that it was recurrent glioblastoma multiforme. Similar spectral characteristics to figure 1C are also shown in another patient with previously diagnosed recurrent persistent astrocytoma.

Discussion: All 1H MRS experiments have been performed successfully without incurring additional technical difficulty beyond a typical STEAM 1H MRS study of brain tumors. The results illustrate "extra" Gln and Glu information can be obtained without sacrificing standard biochemical information, such as NAA, Cho, or Cr, in contrast to many editing techniques. The results also demonstrate occurrences of opposite changes between Gln and Glu content for brain tumors, illustrating the importance of simultaneously detecting Gln and Glu for the study of tumor metabolism. The consistent and remarkable increases in Gln content suggest direct Gln involvement in tumor metabolism, in agreement with previous biochemical analysis. Moreover, the remarkable changes in Glu and Gln with only small-to-moderate changes in "traditional" MRS markers suggest Gln/Glu could be an early indicator of malignant transformation. Although it is too early to draw any conclusion, the preliminary results demonstrate the easiness of obtaining "extra" Gln and Glu information, and their potential in tumor diagnosis and treatment.

References: 1. Mates JM, *etc*. International Journal of Biochemistry & Cell Biology; 34:439-458 (2002); 2. Calvar JA, *etc*, J Neuooncol., 72:273-80(2005); 3. Lehnhardt FG, *etc*, NMR in Biomedicine,18:371-382(2005); 4. Hu, J, *etc*. the 13th ISMRM annual meeting, 2528(2005).

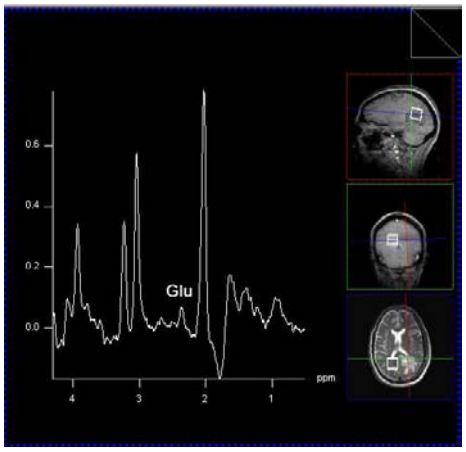

Figure 1.A

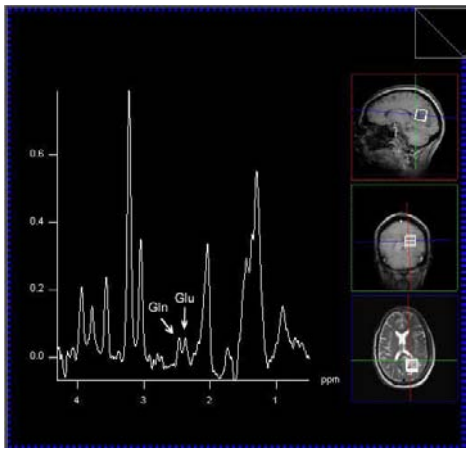

Figure 1.B

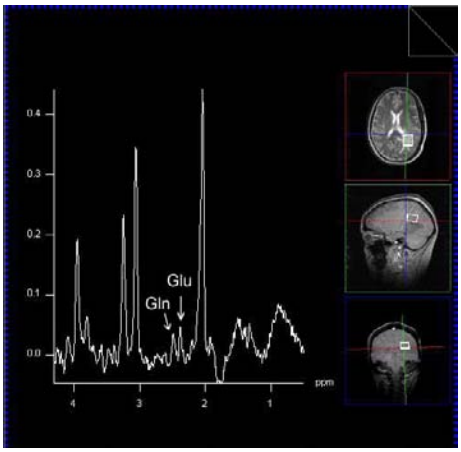

Figure 1.C