Glutamate and glutamine concentrations in recurrent high-grade gliomas.

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INTRODUCTION

The glutamatergic system has a key role in the growth and invasion of glioma cells; by releasing toxic levels of glutamate, high-grade gliomas may kill the surrounding healthy neurons and invade healthy brain tissue (1). While glutamate can be detected by ¹H MRS, it has not been investigated in brain tumors, in part due to technical limitations of glutamate assessment at lower fields (mainly spectral overlap with the glutamine signal). The aim of this pilot study was to assess glutamate concentration and measurement reliability at 3T, in patients previously treated for high-grade gliomas. We hypothesized that, compared to control regions, glutamate concentration will be increased in regions suggestive of tumor recurrence.

METHODS

Ten adult patients (mean age 42.8 years, age range 22.8 – 67.3 years, 9 men) previously treated with surgery, chemotherapy, and radiation therapy for high-grade glioma (glioblastoma multiforme, N=7; anaplastic astrocytoma/oligodendroglioma, N=3) were evaluated. The patients were examined when MRI or clinical data raised suspicion of tumor progression. Clinical MRI and single voxel ¹H MRS (STEAM; TR/TE/TM=2s/20ms/10ms; NS=160-224; typical VOI=2x2x2 ml) were performed at 3T. Spectra were collected in the T_2-hyperintense lesion(s) suspect for tumor and in a contralateral control region. The ROIs included post-contrast enhancing tissue, while the central regions of necrosis were avoided. When time permitted, spectra were also collected in a region adjacent to the lesion. LCModel was applied to evaluate concentrations of detected metabolites; to account for partial volume effects, metabolite ratios were also calculated. Linear mixed effects (LME) model analyses with the Fisher's LSD method as a post-hoc test were applied for statistical evaluations. Statistical significance was set to $p<0.05$.

RESULTS

In 8 out of 10 patients, tumor progression occurred within 4 months of the MRS scan. **Figure 1** displays mean metabolite concentrations in the lesions (total 14 ROIs), adjacent regions (5 ROIs in 3 patients), and control regions (11 ROIs). Weighted means (horizontal lines) and significant differences (*) compared to control regions are shown. Total N-acetylaspartate (NAA+NAAG) and creatine (Cr+PCr) concentrations were lower in the lesions compared to the control regions while there was no difference in mean total choline (GPC+PC) concentration between the lesions and control regions. In contrast to our hypothesis, spectra collected in the lesions showed elevated concentration of glutamine (Gln) (overall LME analysis, p=0.018; lesions and adjacent regions vs. control regions, p=0.042 and 0.008, respectively) and lower concentration of glutamate (Glu) (overall LME analysis, p<0.0001, lesions and adjacent regions vs. control regions, p<0.0001 and 0.006, respectively). For individual concentrations, Cramér-Rao lower bounds were within 20% for Gln concentration in all lesions (but not in all control regions) and for Glu concentration in the control regions (but not in all lesions). The total Glu+Gln concentration (which was lower by 27% in the lesions compared to control regions, p=0.016) was determined with good reliability (all data, Cramér-Rao lower bounds ≤20%).

Figure 1: Metabolite concentrations [μmol/g] in the lesions, adjacent regions, and control white matter regions.
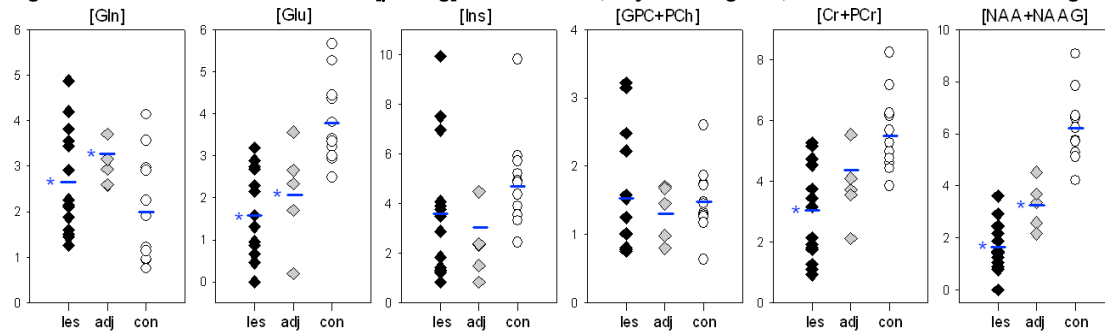
While there was an overlap in Gln and Glu concentrations between the lesions and the control regions, Gln concentrations were higher in 8 of 10 target lesions compared to control and all lesions had lower Glu concentrations compared to their respective control regions. This resulted in a lower Gln/(Gln+Glu) ratio in all lesions (p=0.007) **Figure 2** (10 lesions in 10 patients).

Figure 2: Gln/(Gln+Glu) ratio

The Gln/(Gln+Glu) ratio was not correlated with any of the ratios commonly used for evaluation of tumor progression (NAA/Cr, Cho/Cr, Ins/Cr, and Lac/Cr) (LME analyses, all p>0.1).

DISCUSSION

While the MRS findings based on Cho and NAA concentrations were non-specific for tumor progression, all patients had a low Gln/(Gln+Glu) ratio in the lesion and had tumor progression (8 patients within 4 months).

Abnormal metabolism of (Gln+Glu), low total NAA and Cr concentrations, and normal mean concentrations of total Cho and myo-inositol (Ins) were detected in regions of suspected progression in patients with previously treated high-grade gliomas. Previous ¹H MRS studies reported elevated Glu+Gln concentrations in high-grade gliomas (2, 3), meningiomas (4), and oligodendrogliomas (5). The (Glu+Gln)/Cr ratio has also been proposed as an index for tumor grading (6). Several factors may influence glutamate and glutamine levels. Glutamate regulation is affected by pharmacological interventions (7,8) and likely by irradiation (9,10), which nearly all patients with high-grade gliomas receive as part of their management. Presence of tumors results in alterations of glutamine metabolism, as glutamine is the main source of nitrogen for tumor cells (11). Increase in glutamine transport may thus have contributed to the increase in glutamine concentration detected in the lesions. However, further studies are needed to evaluate the contribution of the different factors affecting glutamine and glutamate levels in treated tumors to assess potential diagnostic utility of glutamatergic metabolism evaluation by ¹H MRS. While the resolution of the Glu and Gln resonances is improved at 3T, studies at ultra-high fields may further improve the reliability of Glu and Gln assessment (12).

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