Magnetic resonance spectroscopy at 3 T for *in vivo* detection of 2-hydroxyglutarate in lower grade gliomas (LGG)

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Introduction

Lower grade gliomas (LGG) are rare brain tumor, characterized by isocitrate dehydrogenase 1/2 (IDH1/2) mutations that induce 2-hydroxyglutarate (2HG) production [1]. Hydrogen magnetic-resonance spectroscopy (1H-MRS) can be used to detect 2HG [2-4], although such metabolite overlaps with N-acetylaspartate (NAA), glutamate (Glu), glutamine (Gln) and GABA spectra at 3 Tesla spectral resolution. We tested in a previous work that the concentration of 2HG would be partially but significantly confounded by the concentration of NAA and Glu molecules on phantoms (Fig.1) [5]. We move on investigating the feasibility of 2HG detection *in vivo* LGG patients by 1H-MRS, associated to the opportune sequence configuration. We will detect 2HG in *ex vivo* tumoral samples by liquid chromatography tandem mass spectrometry (LC-MS/MS) to support our data. Such approach will be useful to identify IDH1/2 mutant LGG by non-invasive means, helping early diagnosis and furnishing a dynamic tool, also considering the incoming IDH1mut targeted therapy [6].

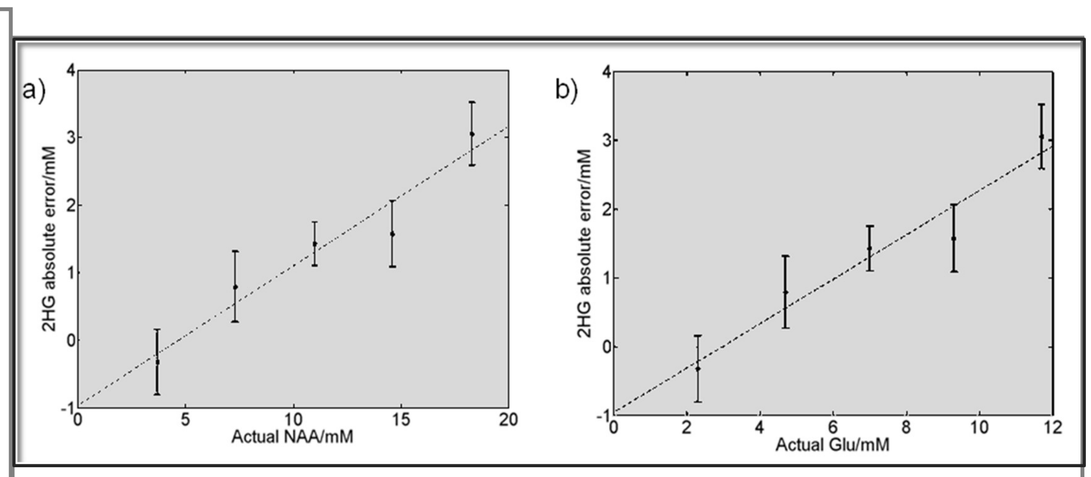

Fig. 1
Effect of NAA and Glu concentration on 2HG measurements. The charts represent absolute 2HG concentration error with respect to the concentration of NAA (a) and Glu (b); bars represent SD

Methods Spectra from LGG patients were respectively acquired with a 1H-MRS single-voxel PRESS sequence with TE=30 ms (group 1) and a tailored PRESS sequence with TE=97 ms (group 2). The MR protocol included two MRS acquisition for each subject: a voxel within the tumor and one contralateral. The voxel size was 2x1.5x1.5 cm^3 for group 1 and group 2A (n=14 total) and 2x2x2 cm^3 for group 2B (n=19 total). Group 1 counts 12 patients, group 2 (2A+2B) 33 patients. MR 3T scanner with a 32 channel head coil was used. Metabolite concentrations were estimated by linear combination analysis and a simulated basis set using LCModel software. IDH1/2 analysis were performed by immunochemistry and/or PCR.

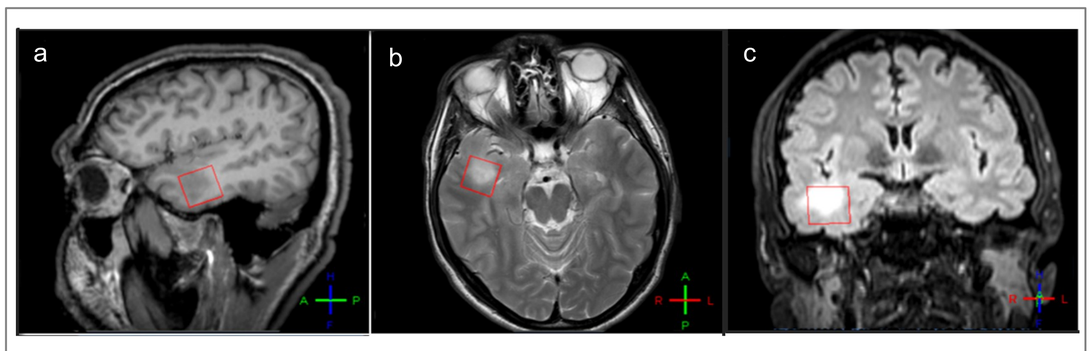

Fig. 2 An example of sagittal T1 (a), axial T2 (b) and coronal (c) FLAIR plains at TE 97 ms, with acquisition voxel = 2x2x2 cm^3.

Results

Spectra at TE=30 showed low specificity: 2 false positive (FP) and 4 false negative (FN) were identified out of the 12 LGG patients (10 IDH1mut and 2 IDH1wt). Group 2A correctly identified 4 mutated and 2 wt LGG, but also 2 FP and 6 FN out of the 14 patients (10 IDH1mut and 4 IDH1 wt). The larger voxel TE97 sequence resulted in higher specificity: no FP and 4 FN only (including two with technical issues: one suboptimal spectrum and one including 40% normal tissue) were detected (Tab.1). Besides, TE30 sequence detected 2HG in the contralateral region in 5 cases, while TE=97 sequences did not (Fig. 2, 3).

Tab. 1 Specificy and sensitivity among the groups.

TE 30	IDH1 mut	IDH1 wt	TE 97 small	IDH1 mut	IDH1 wt	TE 97 large	IDH1 mut	IDH1 wt
2HG-MRS+	6	0	2HG-MRS+	4	2	2HG-MRS+	9	0
2HG-MRS-	4	2	2HG-MRS-	6	2	2HG-MRS-	4	6
tot	10	2	tot	10	4	tot	13	6

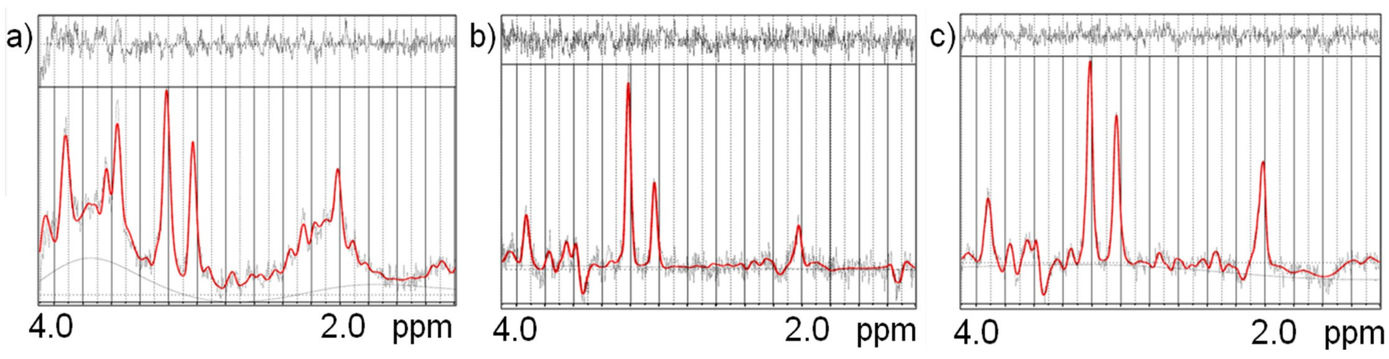

Fig. 4 Examples of spectra analysis from the three PRESS sequences configuration: short TE (30 ms) spectrum (a), longer TE (97 ms) spectrum (b) and 97msTE with larger voxel size (2x2x2 cm^3) (c). It is evident the baseline differences from short to longer TE and a decreasing noise increasing the voxel size.

Conclusions

Our data suggest that MRS TE97 is rather specific for 2HG detection and the 2x2x2 cm^3 voxel bring to highest specificity and sensitivity than a smaller one. Larger number of patients will confirm the accuracy of the technique. We will also pair the *in vivo* detection by MRS with 2HG quantification by HPLC on tumoral samples and other biological fluids. The detection of 2HG could help for a non-invasive diagnosis, clinical follow-up, and possibly patient screening for targeted anti-IDH1mut therapy.

Bibliography

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