MEDICAL UNIVERSITY OF VIENNA

Metabolic mapping in gliomas using 7T-CRT-FID-MRSI

Cornelius Cadrien[a,b], Sukrit Sharma[a], Philipp Lazen[a], Julia Furtner[c], Alexandra Lipka[a,d], Eva Hečková[a], Lukas Hingerl[a], Stanislav Motyka[a], Stephan Gruber[a], Bernhard Strasser[a], Barbara Kiesel[b], Mario Mischkulnig[b], Matthias Preusser[e], Thomas Roetzer[f], Adelheid Wöhrer[f], Georg Widhalm[b], Karl Rössler[b], Siegfried Trattnig[a,d] and Wolfgang Bogner[a], Gilbert Hangel[a,b]

a) High-field MR Center, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria
b) Department of Neurosurgery, Medical University of Vienna, Vienna, Austria
c) Division of Neuroradiology and Musculoskeletal Radiology, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria
d) Christian Doppler Laboratory for Clinical Molecular MR Imaging, Vienna
e) Division of Oncology, Department of Inner Medicine I, Medical University of Vienna, Vienna, Austria
f) Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University of Vienna, Vienna, Austria

Introduction

Glioblastomas are one of the most challenging tumor entities for both healthcare providers and patients. With the goal in mind of overcoming some of the challenges – p.e. the need for a highly invasive biopsy to obtain tumor mutation status for a targeted therapy, we conducted a preliminary evaluation of metabolic mapping results. We saw different alterations of biochemical microenvironments in these tumors, both within lesions and between different types. These first results point towards a deeper understanding of tumor metabolism, especially with respect to tumor grade and IDH mutation status. Now, we tried to better map and quantify these preliminary findings.

Patients and Methods

The pilot study included patients diagnosed with WHO Grade I-IV, who were in treatment at the department of neurosurgery. We obtained the magnetic resonance spectroscopic imaging measurements using a high-resolution whole-brain 3D-MRSI sequence (15 min, 3.4 mm isotropic resolution) at High Field MR Centre's 7T. The processing of the obtained data was performed using an in-house software pipeline with LCModel quantification. A neuroradiologist provided segmentation of different tumor regions (contrast enhancing, non-contrast enhancing, necrosis and edema). Metabolic images were evaluated for regions of increased metabolic activity ("hotspots"), using tools like RStudio and MincToolkit. Differences within the tumor segmentation were compared between grades and mutation types.

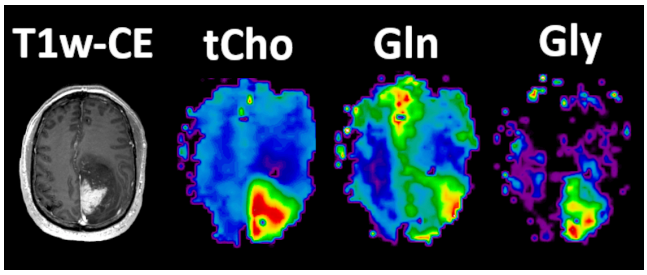

Figure 1 – **T1-contrast enhancing (T1ce) vs. total Choline (tCho), Glutamine (Gln) and Glycine (Gly) hotspot in a patient with IDH1 mutation**

Results

The provisionary results of the preliminary evaluation yielded 10 usable metabolites, including NAA, tCho, tCr, Glu, Gln, Ins, Gly, GABA and GSH. Tumor regions showed distinct differences compared to the surrounding tissue: Especially in HGGs, Gln, Gly, and tCho signals were increased, whereas NAA and tCr were decreased. Gly, which is difficult so separate from Ins at lower fields, was mapped consistently. The comparison of 3T-CE images and 7T metabolic mappings yielded consistency in contrast-enhancing and metabolic hotspots (Fig 1). We saw the ratio of Glutamine to Creatine elevated in the region of the contrast enhancing lesions in gliomas with IDH1 mutation. Our provisional ROI analysis showed distinct differences in myo-Inositol levels between HGG vs. LGG (Fig 3). Glutamate levels in IDH1 mutated gliomas differed from IDH-wt (Fig 4)

Discussion

The obtained results contributed to better visualize high-grade glioma metabolism. The consistent increase or decrease of certain metabolites in actively proliferating tumor regions could enable us to delineate tumors very precisely according to metabolic profiles. Certain metabolites can be related to either tumor metabolism (Gln and tCho) or proliferation (Gly) concordant with the literature. We observed a high level of metabolic heterogeneity within tumor tissue and also in between different patients. Other state-of the art MRS techniques lack the spatial resolution for such delineations. These preliminary results might be related to altered tumor metabolism in higher grade tumors. mIns is considered a marker of astrocytosis.

Conclusion

We successfully demonstrated metabolic mapping in WHO Grade I-IV gliomas. The first results for 3D MRSI yielded promising images. Our first analysis of metabolic differences in IDH1-mutated vs IDH1-WT gliomas and HGG vs. LGG yielded provisional results, which we plan to further investigate in greater detail. The use of 7T-CRT-FID-MRSI could potentially provide powerful insights into high-grade glioma microenvironments, pending more research.

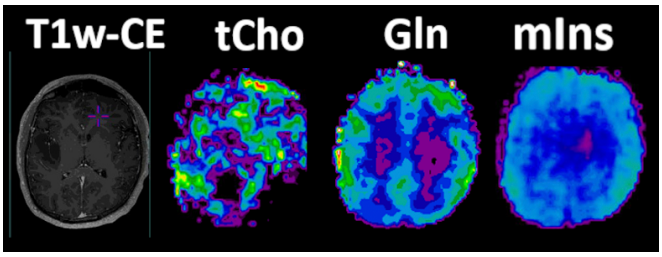

Figure 2 – **T1-contrast enhancing (T1CE) vs. total Choline Glutamine hotspot in a patient LGG and IDH-wt**

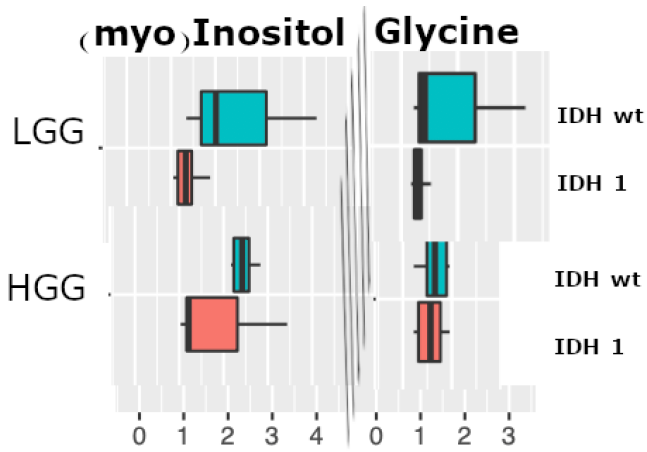

Figure 3 – **Preoperative Glioma Grading?** Our results showed different ratios of show Inositol/Creatine in low-grade gliomas (LGG) compared to high-grade gliomas (HGG). Also the ranges differed slightly in IDH1-mutated gliomas vs. IDH1-wt.

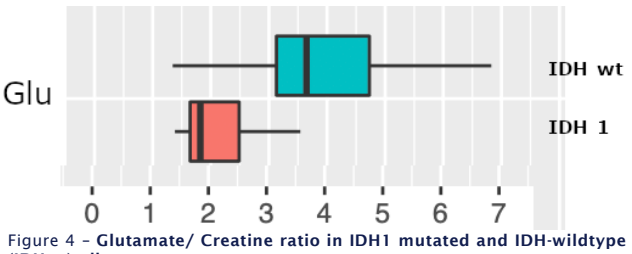

Figure 4 – **Glutamate/ Creatine ratio in IDH1 mutated and IDH-wildtype (IDHwt) gliomas**

The patients show markedly different ratio levels of Glu in IDH1 mutated vs. IDHwt gliomas. This finding might be related to the metabolic shift of the cells towards anaerobic glzcolzsis and glutaminolysis.

References

Hangel, G., et al. (2020). "High-resolution metabolic imaging of high-grade gliomas using 7T-CRT-FID-MRSI." NeuroImage: Clinical 28: 102433.
Hangel, G., et al. (2019). "High-resolution metabolic mapping of gliomas via patch-based super-resolution magnetic resonance spectroscopic imaging at 7T." NeuroImage 191: 587-595.
Hangel, G., et al. (2018). "Ultra-high resolution brain metabolite mapping at 7 T by short-TR Hadamard-encoded FID-MRSI." NeuroImage 168: 199-210.
Hingerl, L., et al. (2020). "Clinical High-Resolution 3D-MR Spectroscopic Imaging of the Human Brain at 7 T." Investigative Radiology 55(4): 239-248.
Kim, M. M., et al. (2016). "Non-invasive metabolic imaging of brain tumours in the era of precision medicine." Nature Reviews Clinical Oncology 13(12): 725-739.
Stadlbauer, A., et al. (2020). "Intratumoral heterogeneity of oxygen metabolism and neovascularization uncovers 2 survival-relevant subgroups of IDH1 wild-type glioblastoma." Neuro-Oncology 20(11): 1536-1546.
Wang, J. H., et al. (2013). "Prognostic significance of 2-hydroxyglutarate levels in acute myeloid leukemia in China." Proceedings of the National Academy of Sciences 110(42): 17017-17022.
Yan, H., et al. (2009). "IDH1 and IDH2 Mutations in Gliomas." http://dx.doi.org/10.1056/NEJMoa0808710.
Zhou, W. and D. R. Wahl (2019). "Metabolic Abnormalities in Glioblastoma and Metabolic Strategies to Overcome Treatment Resistance." Cancers 11(9): 1231.