^{1}H MRS detection of glutamate predicts survival in pediatric medulloblastoma

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Introduction

Medulloblastoma is the most common malignant brain tumour occurring in childhood and a significant cause of morbidity and mortality in paediatric oncology[1]. More intense treatment strategies are recommended for patients displaying high-risk factors, however considerable variation in outcome remains, indicating a need for improved predictive markers. In this study, ^{1}H single voxel magnetic resonance spectroscopy (MRS) was used to investigate non-invasive molecular biomarkers of survival in medulloblastoma.

Methods

Short echo-time (30ms) single voxel MRS using PRESS localisation was performed on a series of 35 biopsy confirmed medulloblastoma cases. The typical voxel size was 8ml and was placed entirely within the tumour region encompassing as much of the solid component of the lesion as possible. MRI and MRS were carried out, prior to the patient receiving treatment, on 1.5T Siemens and 1.5T GE scanners. Standard imaging included T1 and T2 weighted images followed by gadolinium contrast administration and T1 weighted images of the head and spine where appropriate. MRS metabolite quantitation was performed using the TARQUIN algorithm[2] and one case was excluded due to poor quality MRS. The prognostic value of MRS detectable biomarkers was investigated using Cox-Regression retrospectively (N=15). A prospective analysis (N=19) was also performed to reduce the chance of type I errors. Where available, high-resolution *ex-vivo* MRS of biopsy tissue was used to confirm biomarker assignments.

Results

The retrospective analysis revealed that creatine, glycerophosphocholine, glutamate (Fig 1a) and glycine were significant markers of survival ($p<0.01$). The subsequent prospective analysis showed that glutamate was the most robust marker, with a hazard ratio of 8.0 for the full dataset ($p=0.0003$, N=34) (Fig 1b,c). A good correlation between in-vivo and ex-vivo MRS glutamate levels was found ($p=0.001$), validating the in-vivo assignment. The Glu/TCho ratio from the *ex-vivo* samples was also found to predict survival (N=15, $p<0.01$). Figure 2 shows average spectra for the cases with high and low glutamate, good SNR and spectral resolution was seen in the majority of cases.

Discussion

The role of glutamate metabolism in medulloblastoma is underexplored, however in recent years there has been particular interest in glutamate metabolism in adult gliomas. Studies of cell line and rodent glioma models have demonstrated an elevation in glutamate secretion promoting neural degeneration in the tumor vicinity and disease spread[3]. Parallels between medulloblastoma and adult glioma glutamate metabolism may highlight common therapeutic targets suitable for future study.

Conclusion

The identification of glutamate as a predictive biomarker of survival in medulloblastoma provides a clinically viable risk factor, highlighting the importance of detailed studies into metabolism of this disease. Non-invasive biomarker detection using MRS may offer improved disease monitoring and potential for widespread use following multi-centre validation.

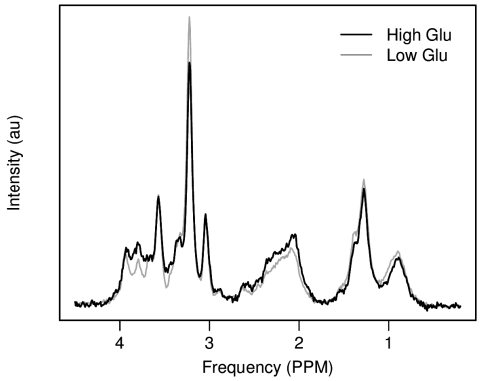

Figure 2. Average spectra for cases with high and low levels of glutamate.

References

1. Northcott et al. JCO 2011 29(11):1408-14. 2. Wilson et al. MRM 2011 65:1-12. 3. Takano et al. Nat Med 2001 7:1010-5.

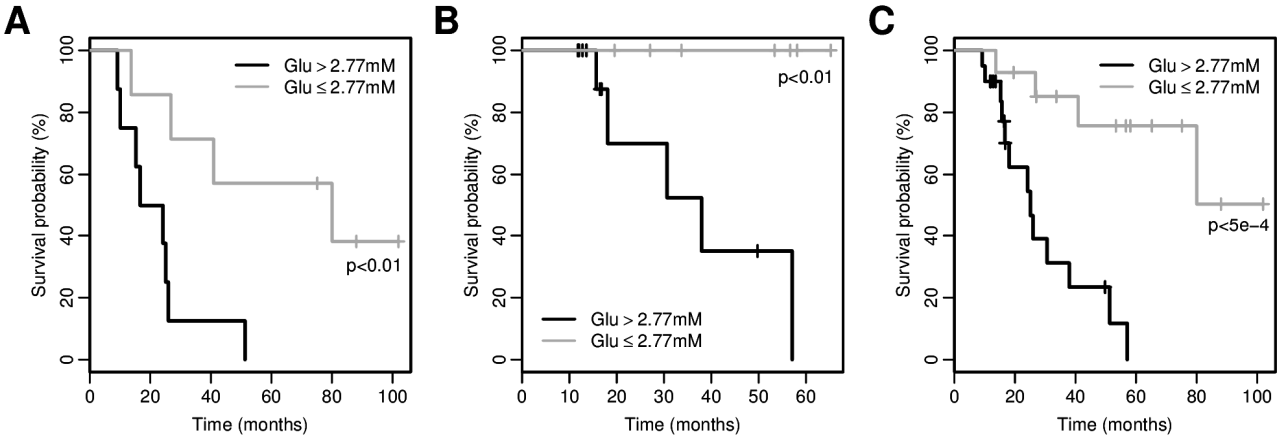

Figure 1. Kaplan-Meier survival plots for A) retrospective cohort; B) prospective cohort and C) full cohort. Significance values represent the chisquare test for equality.