

Investigating the microenvironment of childhood brain tumours using MRS

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Purpose: To investigate differences in micro-environmental factors related to temperature, water-macromolecular exchange effects and ionic strength between childhood brain tumour types, using the water proton resonant frequency (PRF) shift relative to metabolite peaks determined by MRS. Weighted averaging of the shift, based on peak amplitude, is also investigated to improve repeatability of the marker.

Introduction: Cancer is the most common cause of death in children after infancy and the brain is the most common site for solid tumours in childhood. The rate of improvement in survival, among children with brain tumours, has decreased in recent years and novel prognostic markers that may contribute to treatment stratification and improved outcomes are required. Non-invasive measures of tumour microenvironment that may provide such markers have been relatively unexplored. In addition to metabolite levels, MRS can provide measures that are sensitive to temperature and micro-environmental factors that could be useful for characterisation of childhood brain tumours. In this preliminary study, water PRF measurements relative to reference metabolite peaks have been compared between two broad categories of childhood brain tumours and a control group containing MRS from white and grey matter (GM) regions in children with apparently normal brains.

Methods: Single-voxel MRS data acquired using a 1.5T Siemens system (PRESS, TR 1500ms, TE 30ms) in 19 childhood brain tumour patients (8 Primitive Neuroectodermal Tumour (PNET) and 11 Gliomas) and 20 children with apparently normal brains were retrospectively analysed. The apparently normal control data were acquired in two consistent brain regions containing the basal ganglia (BG) and parietal white matter (WM). Spectra were analysed using jMRUI (AMARES tool [1]) and for comparison an in house program called TARQUIN[2]. Using both software tools, the water PRF relative to the reference metabolites was measured. The methyl creatine (Cr) and the total choline (tCho) peaks were chosen as references since they were prominent in all tumour and healthy spectra. The relative shifts were then added to the conventional metabolite chemical shift values of 3.03ppm and 3.22ppm respectively, giving an estimated absolute water PRF value that is comparable for different reference metabolites. Averaging of the water PRF relative to the Cr and tCho peaks, with and without peak amplitude [3] and peak amplitude-squared weighting was investigated as a means of increasing the measurement precision [4]. The mean and standard error of the water PRF was calculated for each spectrum and compared between the two tumour groups (PNET and Gliomas) and the control group of normal appearing BG and WM using pair-wise two-tailed student t-tests where $p < 0.05$ was used as the threshold for significance.

Results & Discussion: A comparison of the mean and standard error of the absolute water PRF for each group is shown in figure 1. The results show that PNETs have a significantly higher water PRF compared to Gliomas. Given the factors that are known to affect the absolute water PRF [5], this could be due to a lower temperature and/or a higher protein content and/or a lower ionic strength in PNETs compared with Gliomas. The Gliomas had a lower water PRF compared to the other groups, which was significant compared to PNETs and BG. The higher variance seen in the water PRF for the Glioma group may be attributed to the range of tumour grades within this patient cohort and the dependence on tumour grade warrants further investigation. The water PRFs for white and grey matter (BG) were not significantly different. Vescovo et al [5] predicted a difference of approximately 0.005 ppm in absolute water PRF between WM and GM due to their different protein concentrations, which is not seen in these results. However, this may be explained by a smaller difference between WM and GM protein concentrations in children than in adults and/or a small temperature difference. For the TARQUIN analysis, averaging of the water PRFs relative to Cr and tCho, with or without amplitude weighting, did not change the within group variances and did not substantially affect the between-group differences, except that it increased the significance of the difference between the water PRFs for PNET compared with basal ganglia and white matter. However, for the AMARES analysis, increased amplitude weighting decreased the water PRF difference between the tumour types and increased the standard error for the PNET group. All of this suggests that random measurement uncertainties are not the main source of the within group variances.

Figure 1: Bar charts of absolute water PRF shifts relative to Cr and tCho for PNETs, Gliomas, BG and WM, with unweighted (Met av), amplitude (A) and amplitude-squared (A²) weighted averaging using AMARES and TARQUIN

Conclusion: Metabolite referenced water PRF shifts suggest differences in the tissue microenvironment between childhood PNETs, Gliomas and healthy brain tissue. Further investigation of the clinical and biological relevance of this finding is justified.

References

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