Water chemical shift in childhood brain tumours at low echo times: what are we measuring?

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Purpose: To investigate the chemical shift measure in MRS thermometry of childhood brain tumours at low echo times.

Introduction: The rate of improvement in survival, among children with brain tumours, has decreased in recent years. Novel prognostic markers that may contribute to associated treatment stratification and improved outcomes are required. Non-invasive measures of tumour microenvironment, which may provide such markers, have been relatively unexplored. In addition to metabolite levels, Magnetic Resonance Spectroscopy (MRS) can provide measures that are sensitive to temperature and micro-environmental factors; such measures could be useful for the characterisation of childhood brain tumours. A previous preliminary study showed differences between two broad categories of childhood brain tumours [1]. In the presented study, water Proton Resonance Frequency (PRF) measurements, relative to reference metabolite peaks, were compared between the same tumour groups, with increased cohort numbers, and a control group containing MRS from white and grey matter regions in children with apparently normal brains. In addition, the water PRF measure was compared to metabolite tumour marker concentrations, which has yet to be reported in the literature, to understand the PRF measure further.

Methods: Single-voxel MRS data, acquired using a 1.5T Siemens system (PRESS, TR 1500ms, TE 30ms) in 38 childhood brain tumour patients (19 Primitive Neuroectodermal Tumour (PNET) and 21 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 [2]) and TARQUIN [3]; 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. Amplitude weighting of the water PRF was utilised to increase measurement precision [1,4,5]. The mean (standard error) of the water PRF was compared between the groups (PNET, Gliomas, BG,WM) using pair-wise two-tailed student t-tests. Metabolite concentrations were calculated through TARQUIN; metabolites with low concentrations were excluded from the analysis. The water PRF value, within each tumour type cohort, was then correlated with individual metabolite concentrations within the spectra, between 0.2–4 ppm. Statistical significance for tests was deemed $p<0.05$, trends $0.05>p<0.10$, and all correlation values, r, given were significant.

Results & Discussion: A comparison of the mean (standard error) of the Cho based, Cr based and weighted average absolute water PRF for each group. The PNET group had a significantly higher water PRF compared to Gliomas. A lower temperature/ionic strength and/or higher protein content in PNETs compared with Gliomas may explain the difference [1, 6]. The PNET PRF value significantly correlated to Glycine and lipid metabolite concentrations for the Cho reference measure , 0.62 and 0.455, Figure 1. Lipid concentration has been shown to be a marker of necrosis/apoptosis and Glycine a marker of malignancy [8, 9]. Temperature may be reduced by increased vasculature within high grade tumours, which may significantly increase thermal transport away from the tumour, and increased necrosis. Necrosis would however decrease the chemical exchange affects, which would reduce the PRF. The effect of temperature has the larger contribution to the PNET results. 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 may be attributed to the range of tumour grades within the Glioma cohort. The water PRF correlated with NAA (total) and PCh (-0.485 & -0.507), which may also relate to the variation in Glioma tumour grade/aggressiveness as changes in NAA and Pch are malignancy markers [8]. Trends were also seen with lipids, suggesting variation of necrosis within the glioma cohort. Reduced necrosis would produce a relatively higher temperature, ie decreased PRF, compared to the PNET cohort. The water PRFs for white and grey matter (BG) were not significantly different. The healthy cohort PRF values also did not correlate significantly with metabolite concentrations. Interestingly the Cho based shift provided significantly different correlation values with metabolite concentrations, also providing a larger number of significant correlations, than Cr based shift in the PNET cohort. However in the Glioma this occurred to a lesser extent and within the healthy cohorts correlation values were similar. This may shed light on how the Cho and Cr references maybe affected by fast exchange processes. Hence may also provide discrimination between temperature and chemical exchange effects on the PRF.

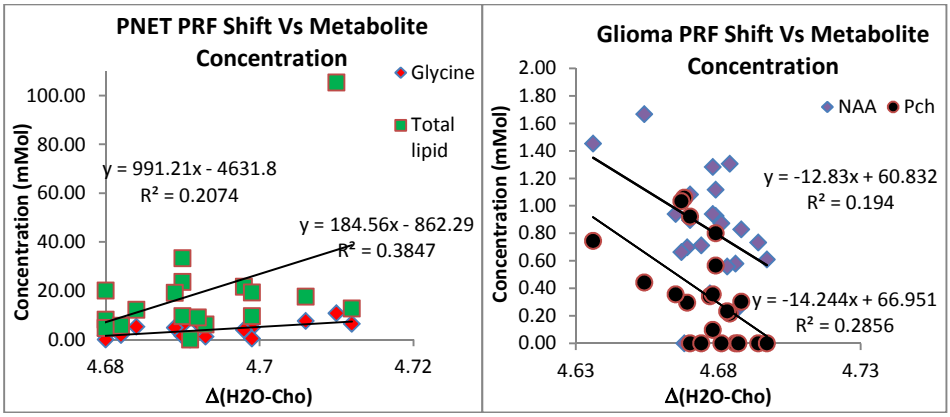

Figure 1: Metabolite concentrations vs water PRF for PNETs (left) and gliomas(right)

Conclusion: A chemical shift difference was seen between tumour types and within a tumour type cohort the PRF measure is sensitive enough to distinguish more aggressive tumours. The shift is predominantly temperature driven but significant contributions are made from micro-environment changes.

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