Metabolite profile analysis of childhood brain tumours using quantitative in vivo ^{1}H Magnetic Resonance Spectroscopy

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Introduction: Quantitative ^{1}H MRS offers a means of improving non-invasive diagnostic accuracy and furthering our understanding of the biology of childhood brain tumours (1-3). Pattern recognition analysis has been shown to provide a useful diagnostic aid in adults with brain tumours and small studies in children have shown that average metabolite profiles differ between major tumour classes. Larger numbers of cases allow metabolite profile variability to be explored and pattern recognition techniques to be used.

Method: Short TE single voxel ^{1}H MRS was performed on 84 children prior to treatment at 1.5 T in a single centre study. Cubic voxels were placed within the tumour visualised on post contrast T_1-weighted images, with side 1.5 or 2.0 cm according to tumour size. A PRESS sequence was used (TE, TR 30, 1500 ms) with 128 or 256 averages depending on voxel size. A water signal was acquired for use in post processing and quantitation. Cases accrued as follows: 28 astrocytomas (21, 3, 1, 3 grade I, II, III, IV), 5 optic pathway gliomas (OPG), 2 tectal plate gliomas (TPG), 6 diffuse pontine gliomas (DPG), 19 medulloblastomas, 9 ependymomas, 5 germinomas, 4 supratentorial primitive neuroectodermal tumours (sPNET), 1 atypical teratoid / rhabdoid tumour, 1 lymphoma, 1 Langerhans cell histiocytosis (LCH), 2 dysembryoplastic neuroepithelial tumours (DNET) and 1 undiagnosed. In 66 cases where biopsy was performed diagnosis was confirmed by histology. The rest were diagnosed on clinical and imaging criteria. MRS data were processed using LCModel™ to determine metabolite concentrations, signal to noise ratio (SNR) and full-width-at-half maximum (FWHM). Cases were only included if the voxel was correctly located, the SNR was greater than 5 and the FWHM was less than 0.15ppm. The metabolite concentrations were compared between the groups using analysis of variance (ANOVA). Further analysis to investigate metabolite profile patterns was performed by principal components analysis (PCA) and multivariate analysis of variance (MANOVA). The MANOVA reveals the linear combinations of variables that produce the largest separation between the groups.

Results: Out of the 84 cases, 72 satisfied the QC criteria. These were allocated to 7 main groups, incorporating OPG and TPG with astrocytoma grades I and II into a single low grade glioma (LGG) group, and including astrocytoma grades III and IV into a high grade glioma (HGG) group. The remaining groups were DPG, ependymoma, medulloblastoma, germinoma and sPNET. Individual cases of other tumour types were analysed separately. Of the metabolites that were reliably determined, all showed a significant difference between the groups in the ANOVA test ($P < 0.05$) apart from glucose (Glc) and lactate (Lac). Highly significant differences ($P<0.01$) were found for alanine (Ala), creatine (Cr), glutamate (Glu), glutamine (Gln), myo-inositol (Ins), N-acetyl aspartate (NAA), scyllo-inositol (Scyllo), taurine (Tau), glycerophosphocholine (GPC) and phosphocholine (PCh). Total choline (PCh + GPC) was highest in medulloblastoma and lowest in DPG, however significant levels of PCh were apparently only present in medulloblastoma, sPNET and germinoma. Tau concentration was highest in medulloblastoma, but was also present in sPNET, germinoma and ependymoma. NAA was high in DPG and LGG and lowest medulloblastoma and HGG. Cr and Ins were highest in ependymoma and low in LGG, HGG and sPNET. Glu was high in sPNET and germinoma and low in HGG and DPG, with nearly the reverse pattern for Gln. Ala was highest in sPNET, high in medulloblastoma and LGG, and low in ependymoma and DPG.

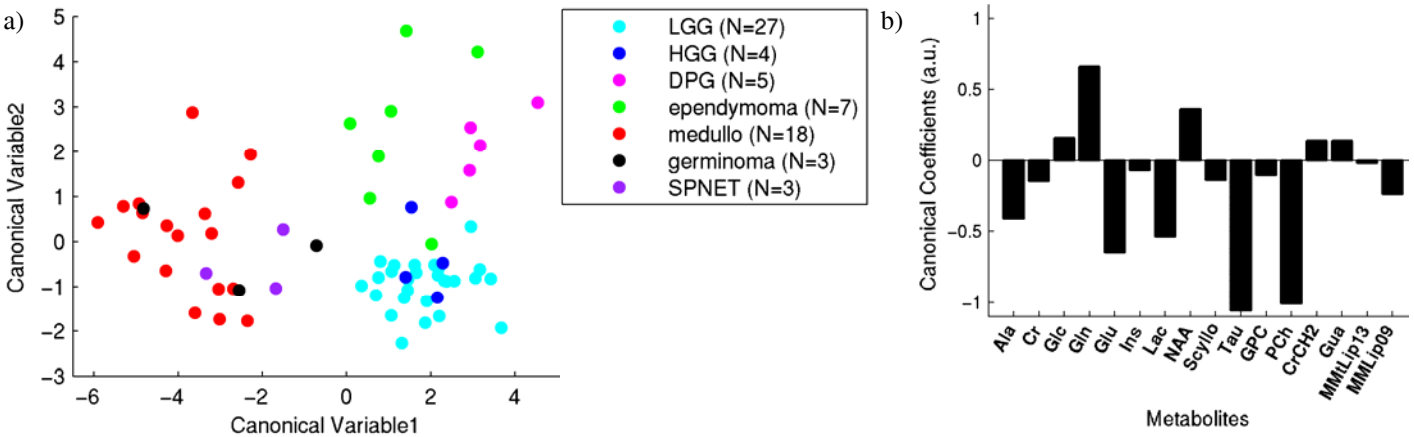

Figure 1 a) MANOVA scatter plot of canonical variable scores colour coded by tumour type and b) metabolite coefficients for canonical variable 1.

The metabolite profile analysis (Fig. 1) revealed that medulloblastoma, germinoma and sPNET had similarly low scores in canonical variable 1, and thus were characterised by a combination of high taurine, PC and glutamate and low glutamine and NAA. The reverse was true for the remaining groups. Ependymoma and DPG were somewhat separated from HGG and LGG by canonical variable 2, analysis of which (not shown) shows the former characterised by a combination of high Ins, Cr and Scyllo and low Ala.

Conclusions: The results of this study show that metabolite profile analysis using MRS can be useful both to differentiate and reveal similarities between tumour types seen in the brain. MRS provides a non-invasive method for aiding the diagnosis of brain tumours in children and also provides an insight into their biological diversity and similarities.

REFERENCES: 1. Negendank WG et al, J Neurosurgery 1996; **84**, 449. 2. Wang Z et al, AJNR 1995; **16**, 1821. 3. Panigraphy A et al AJNR 2006; **27**, 560.