Effects of age on brain tumour metabolite levels measured by in-vivo ^{1}H MRS in children and young people are tumour type specific

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Purpose: To investigate associations between age and metabolite levels measured by ^{1}H magnetic resonance spectroscopy (MRS) in paediatric brain tumours, accounting for differences in histopathological and clinical features.

Introduction: MRS provides non-invasive measurements of metabolite profiles which are useful for the diagnosis, prognosis and management of brain tumours. It is known that clinical, histopathological and molecular genetic features of brain tumours vary with age in children and adults, even within the same histopathological tumour type. However, in most cases it is not known whether these characteristics manifest as differences in metabolite levels. Moreover, potential variations with age in the metabolite profile of brain tumours measured by in-vivo MRS have not been investigated.

Methods: MRS data were acquired from 243 children (age mean±SD 7.5±4.7 years, male/female 141/102) subsequently diagnosed with a primary brain tumour using one of three 1.5 Tesla MRI scanners at a single centre between March 2003 and March 2012. Diagnoses were made using histopathology (N=188) or clinical and radiological criteria (N=55). Short-TE PRESS was used (TR/TE 1500/30ms, spectral resolution 1Hz, 128-256 signal averages) with a single cubic volume of side 1.5-2cm placed within the contrast-enhancing or solid part of the tumour on standard structural MRI. Retrospective data retrieval and analysis was successful in 221/243 cases. LCModel™ (v.6.2-0) [1] was used to estimate metabolite levels relative to water using a basis set of 17 metabolites and 9 macromolecular and lipid (MMLip) components. Quality control criteria (SNR>4, FWHM of water peak < 10Hz) were applied giving 175 cases for further analysis (age range 2 months to 16.5 years, mean±SD 7.4±4.7 years, male/female 111/64). The effect of age at diagnosis on metabolite and MMLip levels was investigated using Pearson's correlation analysis for the whole cohort and for the two most common histopathological types: medulloblastomas (MB) (N=42) and pilocytic astrocytomas (PA) (N=42). Statistical metabolite comparisons between three age groups (0-3, 4-11 and 12-17 years) were also computed using the non-parametric Kruskal-Wallis test. To account for differences in the age distributions of histopathological sub-types, comparisons were also made between the classic (N=35, age mean±sd 6.7±3.5 years), desmoplastic (N=5, age mean±sd 5.7±5.6 years) and large cell (N=2) variants of MB. The Bonferroni correction for multiple comparisons was applied to all P-values.

Results: No significant correlations with age or differences between age groups were found for the whole cohort or for PA. In MB, total choline (tCho) was significantly correlated with age (Fig. 1,) and was significantly higher in the old group compared with the young group ($P<0.05$). No significant difference was found in tCho when comparing classic with desmoplastic MB, but taurine, glycine+myo-inositol and levels of MMLip at 0.9ppm were significantly ($P<0.05$) lower in desmoplastic MB. There was no difference in metastatic status among MB between the age groups, although there was a relative preponderance of male patients in the adolescent group.

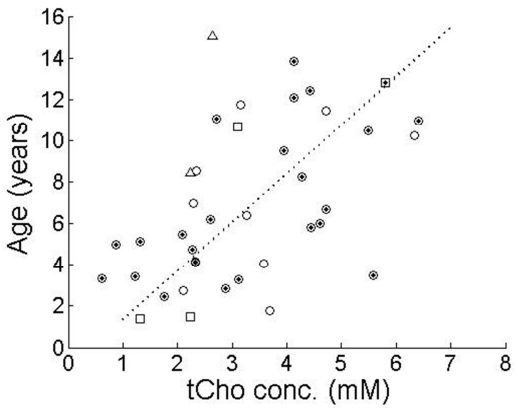

Fig. 1 Correlation of tCho with age (R=0.5, P<0.05) in childhood MB (desmoplastic: squares, large cell: triangles, males: filled).

Discussion: tCho is a known biomarker of aggressiveness in adult brain tumours, but its role in childhood brain tumours is less clear. The results show a significant correlation of tCho with age in childhood MB (the most common malignant brain tumour type in children) that cannot be explained by maturation of the paediatric brain or differences in gender, metastatic status or histopathological subtypes. Interestingly, the difference in taurine levels found between desmoplastic (better prognosis) and classic MB is consistent with a previous report [2]. It has been shown that there are four genetic subtypes of MB each with a specific age distribution [3] and potentially a different metabolite profile. While the genetic subtypes show some correspondence to histopathological subtypes, there is considerable overlap. A formal analysis of the tumour molecular genetics compared with MRS is required and this may reveal the apparently biological source of the variation in tCho with age in MB found in this study.

Conclusion: To our knowledge, this is the first reported investigation into the variation of brain tumour metabolite levels with age. The specific correlation of tCho with age in MB, independent of histopathological subtype and other clinical features, suggests a relationship with tumour molecular genetics and detailed exploration of this link is warranted. Furthermore, confirmation in larger studies of the prognostic relevance of metabolite differences found between desmoplastic and classic MB, may define a role for MRS in non-invasive treatment stratification of childhood MB.

References: [1] Provencher SW et al Magn. Reson. Med. (1993) 30:672-679. [2] Panigrahy A et al, 12th Annual Meeting Soc. for Neuro-Oncology 2007, RA-10. [3] Huse JT et al, Nat. Reviews Cancer (2010) 10:319-331.