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^{1}H magnetic resonance spectroscopy in the diagnosis of paediatric low grade brain tumours

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ABSTRACT

Introduction: Low grade gliomas are the commonest brain tumours in children but present in a myriad of ways, each with its own treatment challenges. Conventional MRI scans play an important role in their management but have limited ability to identify likely clinical behaviour. The aim of this study is to investigate ^{1}H magnetic resonance spectroscopy (MRS) as a method for detecting differences between the various low grade gliomas and related tumours in children.
Patients and methods: Short echo time single voxel ^{1}H MRS at 1.5 or 3.0 T was performed prior to treatment on children with low grade brain tumours at two centres and five MR scanners, 69 cases had data which passed quality control. MRS data was processed using LCModel to give mean spectra and metabolite concentrations which were compared using *T*-tests, ANOVA, Receiver Operator Characteristic curves and logistic regression in SPSS.
Results: Significant differences were found in concentrations of key metabolites between glioneuronal and glial tumours (*T*-test $p < 0.05$) and between most of the individual histological subtypes of low grade gliomas. The discriminatory metabolites identified, such as choline and myoinositol, are known tumour biomarkers. In the set of pilocytic astrocytomas and unbiopsied optic pathway gliomas, significant differences ($p < 0.05$, ANOVA) were found in metabolite profiles of tumours depending on location and patient neurofibromatosis type 1 status. Logistic regression analyses yielded equations which could be used to assess the probability of a tumour being of a specific type.
Conclusions: MRS can detect subtle differences between low grade brain tumours in children and should form part of the clinical assessment of these tumours.

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1. Introduction

Collectively, low grade gliomas are the most common brain tumours in children and present considerable management challenges [1]. Although commonly grouped together for treatment, low grade gliomas are a diverse group in terms of histopathology, age at occurrence and anatomical location. There is increasing evidence that histological type is an important prognostic marker [2]. Most low grade gliomas in children are grade 1 pilocytic astrocytomas (PA) but some are grade 2 diffuse astrocytomas and many other rarer tumour types are seen. Furthermore, low grade glioneuronal tumours such as gangliogliomas are often grouped with the 'pure gliomas' in treatment protocols. Low grade gliomas may occur throughout the brain and prognosis depends greatly on the site, age and presence of disseminated disease [3]. Cerebellar PAs have an excellent prognosis with virtually all being cured following complete resection [2]. Conversely, optic pathway tumours are much more challenging to treat. Although overall survival (OS) rates are generally high at 5 years for low grade gliomas in children, progression-free survival (PFS) is much lower [3]. A significant number of children progress after incomplete tumour resection or biopsy, and patients who have not had a complete surgical resection at diagnosis often receive adjuvant treatment with chemotherapy and/or radiotherapy [4]. Response to adjuvant treatment is variable and differs between tumour types, accurate diagnosis and improved tumour characterization are therefore important.

Many low grade gliomas are not biopsied or have a limited biopsy with its inherent risks of sampling error. Currently, clinical findings together with conventional magnetic resonance imaging (MRI) appearances are used for non-invasive diagnosis, which provides information on the position, size, shape and structure of tumours. Advanced magnetic resonance techniques can give information on tumour properties and provide insight into the biology of these lesions [5]. One such technique, ^{1}H magnetic resonance spectroscopy (MRS) can easily be combined with current MR imaging protocols [5] to determine chemical composition and is a valuable tool for aiding diagnosis of brain tumours both in adults and children [6].

The aim of this study is to investigate with MRS, a sufficiently large cohort of low grade brain tumours to allow differences between the subgroups of tumours to be established. Data is collected from several scanners from more than one centre following common acquisition protocols, thereby establishing the technique in a multi-scanner clinical environment.

2. Patients and methods

Multicentre ethical approval was given for the study and parental consent obtained. Single voxel MRS was performed routinely in children with brain tumours as part of the clinical imaging, at 1.5 T (Siemens Symphony, 2 GE Signa Excite, Philips Intera) or 3.0 T (Philips Intera Achieva), prior to any treatment (except stereotactic biopsy) at the Birmingham Children's Hospital (BCH) and Queen's Medical Centre (QMC), from 1st September 2003 to 31st March 2009. Children with low grade brain tumours have been included in this study. Diffuse intrinsic pontine gliomas are excluded as they are widely accepted to be high grade tumours. The acquisition protocol was point-resolved spectroscopy (PRESS) localization with an echo time of 23–41 ms and a repetition time of 1500–2000 ms. A cubic voxel was selected to fit entirely within the tumour avoiding cysts where possible with a side length 2 cm or 1.5 cm and 128 or 256 repetitions used respectively. A water unsuppressed MRS was acquired for eddy current correction and as a concentration reference (assuming a water concentration of white matter).

As this is a bi-centre study involving 5 scanners, protocols for quality control (QC) of multicentre ^{1}H MRS have been implemented. These protocols utilize phantoms of two different designs (flood phantom and localization phantom) to assess basic localization efficiency, signal-to-noise ratio (SNR), water linewidth for shimming efficiency, water line-shape for eddy current distortions, effectiveness of eddy current (B_0) correction and scalp lipid suppression. The localization phantom information is used to calibrate the "true" voxel sizes indicated by the "nominal" voxel size for each scanner. The flood phantom results show variations of less than 10% in metabolite concentration measurements between scanners.

Raw MRS signal data and voxel position images were transferred to a dedicated computer and processed using LCModel (version 6.2.0) [12] which determines metabolite concentrations by fitting the data to a linear combination of individual metabolite spectra collected at 1.5 T or 3.0 T as appropriate. Experimental basis sets provided with LCModel software was used at 1.5 and 3.0 T. Crammer-Rao Lower Bounds (CRLBs), determined by LCModel, estimate the accuracy of the metabolite concentrations.

The spectra were reviewed against the following quality control criteria: signal-to-noise ratio (S/N) $\geq$ 4; full-width half-maximum (FWHM) $\leq$ 0.15 ppm; stable baseline; good phasing, adequate water suppression and absence of artefacts. The voxel positioning was also reviewed to ensure the voxel was positioned over tumour and did not include significant amounts of normal appearing brain or cyst and was at least 3 mm away from lipid-containing bone and scalp. All metabolites where at least 2 patients had a CRLB < 30 were included (aspartate (Asp) and GABA were excluded from all analyses).

Statistical analysis was carried out using SPSS statistics software (version 17.0) and p-values of <0.05 were considered statistically significant. The metabolite values were overall normally distributed. Univariate analysis used two-tailed independent

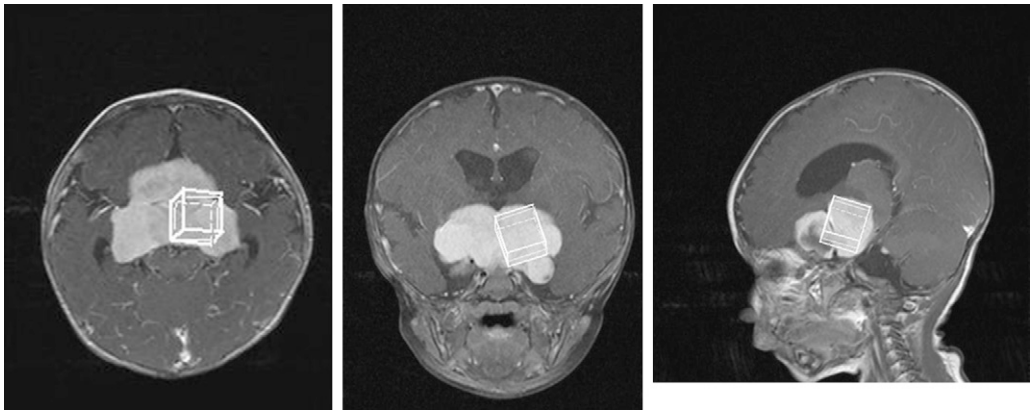

Fig. 1. Voxel placement over an optic pathway tumour.