CLINICAL FEATURES, MANAGEMENT AND OUTCOMES OF PAEDIATRIC CENTRAL NERVOUS SYSTEM TUMOURS DISSEMINATED AND NONDISSEMINATED AT PRESENTATION: A FOURTEEN-YEAR EXPERIENCE

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BACKGROUND: It is unusual for paediatric central nervous system (CNS) tumours to be disseminated at presentation, and literature on the clinical features, management and outcomes of this specific group is scarce. Surgical management decisions can be challenging, particularly in the presence of hydrocephalus. We present our experience in managing paediatric CNS tumours disseminated and nondisseminated at presentation over fourteen years. METHODS: Retrospective review of prospectively-collected data on children presenting to our tertiary centre between 2003 and 2016 inclusive. RESULTS: We identified 53 patients with CNS tumour dissemination at presentation (M:F=34:19, median age=3.8 years, range=7 days-15.6 years) and 308 without dissemination (M:F=161:147, median age=5.8 years, range=1 day-16.9 years). Five tumour groups were studied: medulloblastoma (disseminated n=29/nondisseminated n=74), other primitive neuroectodermal tumour (n=8/n=17), atypical teratoid rhabdoid tumour (n=8/n=22), pilocytic astrocytoma (n=6/n=138), and ependymoma (n=2/n=57). Median follow-up in survivors was not significantly different between those with (64.0 months, range=5.2–152.0 months) and those without disease dissemination at presentation (74.5 months, range=4.7–170.1 months; P>0.05). Dissemination status at presentation significantly impacted survival, risk of recurrence, rates of complete resection of the operated lesion, chance of proceeding to palliative care as an early management strategy, surgical complication rate, and risk of requiring CSF diversion (all Ps<0.05). Differences between the five tumour groups were evident. No factors to predict the need for permanent CSF diversion following temporary external ventricular drainage were identified on multivariate analysis, and there was no clear superiority of either ventriculoperitoneal shunt or endoscopic third ventriculostomy as a permanent CSF diversion procedure. CONCLUSIONS: Tumour type and dissemination status at initial presentation significantly affect outcomes across a range of measures. The management of hydrocephalus in patients with CNS tumours is challenging, and further prospective studies are required to identify the optimal CSF diversion strategy or strategies in this population.

DISCONNECTION VS EXCISION? A TEN YEAR REVIEW OF HYPOTHALAMIC HAMARTOMAS

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OBJECTIVE: Hypothalamic hamartomas (HH) are rare tumors of childhood. They are usually associated with gelastic seizures. The optimal management of these tumors lacks a consensus. We present our experience with hypothalamic hamartomas over a ten year period. METHODS: This study presents a retrospective review of 16 patients with HH's treated between 2002 and 2012 at the All India Institute of Medical Sciences (AIIMS), New Delhi, India, a tertiary care neurosurgical centre. RESULTS: There were 16 patients with an age ranging from 1.5 years to 20 years and included 9 males and 7 females. The most common symptom was seizures (81%; gelastic seizures-62.5%) followed by precocious puberty (56.2%). The median tumor volume was 5.9 cc (range 1.3 to 108 cc). Fourteen patients underwent surgery while two were managed conservatively. Three patients received secondary Gamma Knife therapy. A good seizure outcome (Engel class I and II) post surgery was seen in 8 (50%) patients. The median follow up period was 39 months (range 1 to 114 months). The odds ratio for a better seizure outcome was 2.5 times more in disconnection than for excision. The symptoms of precocious puberty had resolved in 7 of the 9 affected patients (78%). Transient diabetes insipidus was seen in one (6.2%) patient postoperatively while hyperphagia was noted in four (25%) patients. Hyperphagia persisted in all four patients until last follow up. CONCLUSIONS: HHs present with gelastic seizures or precocious puberty. Disconnection of the HH is more effective and a safer procedure vis-a-vis excision for controlling seizures.

PROBING GLIOBLASTOMA INFILTRATION INTO HEALTHY TISSUE BY MAGNETIC RESONANCE PERFUSION IMAGING: A QUANTITATIVE MRI EVALUATION

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The ability of tumour cells to invade healthy brain tissue is a major obstacle to successful treatment of Glioblastoma (GBM). This makes complete removal of the tumour by surgery impossible, leading to high recurrence rates, and reduces the accuracy of target volume delineation for radiotherapy planning. Providing with a wide range of imaging modalities, Magnetic Resonance Imaging (MRI) is an important tool for GBM diagnosis and characterisation. However, conventional MRI techniques fail to detect regions of low tumour cell density that may be responsible for subsequent tumour recurrence, while novel techniques are often not reliable due to a lack of robust evaluation protocols. Invading tumour cells often progress along blood vessels and recent results indicate that even individual cells can disrupt the normal function of the blood brain barrier (BBB), providing an opportunity to detect tumour invasion at its earliest stages. Our research focuses on the development of perfusion imaging techniques, and their quantitative assessment in detecting low tumour infiltration regions on mouse GBM models presenting highly invasive tumour margins. A high SNR multiple adiabatic boli Arterial Spin Labelling technique (mbASL) was implemented and optimised for rodent brain perfusion imaging and its ability to probe tumour invasion was evaluated by comparison with standard MRI techniques (T2 and diffusion weighted imaging) and immunohistochemistry sections. To achieve a quantitative MRI evaluation, multiple histological slices (HLA stain for human GBM) were cut in the MRI plane, registered and stacked to account for MRI slice thickness. This approach, leading to the production tumour density maps in the MRI plane, allows going beyond the standard evaluation tests to consider a voxel-to-voxel comparison between MRI and histology. Our results confirm the limitations of standard imaging modalities in probing low tumour densities and demonstrate the existence of a quantitative relation between glioblastoma invasion and brain perfusion.

REGULATION OF DNA DOUBLE STRAND BREAK REPAIR BY EGF AND VEGF SIGNALLING REVEALS AKT TO BE A CRITICAL THERAPEUTIC TARGET IN GLIOBLASTOMA

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Glioblastoma (GBM) is currently incurable. Its radioresistance has been attributed to a subpopulation of cells termed 'GBM stem-like cells' characterised by multipotentiality and tumorigenicity. The discrepancy between pre-clinical and clinical effects of molecular targeted agents on radiosensitivity indicates that 2D in vitro models of GBM do not recapitulate the clinical scenario. In a 3D model developed in our laboratory, EGFR inhibitors failed to enhance radiosensitivity recapitulating their lack of efficacy in the clinic, contrasting with their radiosensitising activity in 2D cultures. Conversely, inhibition of VEGF signalling caused significant radiosensitisation of 3D cultures but had no effect in 2D conditions. The critical role of the DNA damage response in mediating these effects is illustrated by the consistent correlation between radiosensitivity, unrepaired double-strand breaks (γH2AX foci), mitotic catastrophe and micronuclei in both 2D and 3D models. Further investigation revealed unrepaired DSB to be associated with delayed resolution of phosphorylated DNA-PKcs nuclear foci and reduced formation of Rad51 foci. Hence in 2D conditions, EGFR signalling appeared to promote efficient non-homologous end-joining (NHEJ) repair, while in 3D conditions this process was dependent on VEGF signalling. Motivated by previous reports that radiation induced EGFR signalling promotes NHEJ via Akt mediated phosphorylation of DNA-PKcs, we investigated the role of Akt signalling in 2D and 3D systems. Specific inhibition of Akt using the small molecule inhibitor MK-2206 or Akti knockdown increased radiation sensitivity in both 2D and 3D models to a similar extent as EGFR or VEGF inhibition respectively. In keeping with this, phosphorylation of Akt was EGFR dependent in 2D GSC cultures but VEGF dependent in the 3D model. MK-2206 induced radiosensitivity was correlated with increased unrepaired DSBs and extended mouse survival in an U87MGLuc2 orthotopic model compared to radiation only. Our data identify Akt as a promising therapeutic target in combination with radiation for GBM.

THE KETOGENIC DIET FOR PATIENTS WITH BRAIN TUMOURS: TWO PARALLEL RANDOMISED TRIALS

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The ketogenic diet (KD) has attracted considerable interest from the brain tumour community. There is evidence for synergy with radiotherapy in animal models, and improved seizure control in children with epilepsy due to structural abnormalities. However, there is little data on mechanism or effect in brain tumour patients, and different options for implementing the ketogenic diet.

In November 2016 we assembled multiple stakeholders, including the James Lind PSP in neuro-oncology and several charities to develop a trial outline. We addressed mechanistic, clinical and practical factors to develop a trial protocol.

Based on the meeting, we are planning two parallel open-label phase 2 randomised trials of the Modified Ketogenic Diet (MKD) in patients with high grade gliomas (HGG) receiving chemoradiotherapy, and in patients

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