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Diagnostic Modalities (Pathology, Radiology, Sono-Imaging, etc,..)

LETTER to the EDITOR

Serial MRI Scan of Posterior Fossa Tumours Predict Patients at Risk of Developing Neurocognitive Impairment

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Abstract

Background: Brain tumours are the most common solid tumours in children. More than 50% of these tumours develop in the posterior cranial fossa. Long term survivors of posterior fossa tumours (PFT) suffer from neurocognitive and memory issues. We hypothesized that serial MRI scanning of brain would show differences in hippocampal and ACC volume change in PFT patients treated with and without chemo-radiotherapy. **Material and Methods:** Twelve patients (8 females and 4 males) underwent 76 serial MR imaging examinations before and during treatment for posterior fossa tumours. Seven patients (4 medulloblastoma, 2 as ependymoma and 1 high grade glioma) were treated with maximum surgical resection followed by adjuvant radiotherapy and chemotherapy (Group 1). The other five patients were diagnosed as pilocytic astrocytoma who were treated only with surgery (Group 2). Hippocampal volumes were obtained manually on high-resolution 3Tesla T1-weighted images and normalised to intracranial volume, while ACC thickness and volume were obtained automatically using FreeSurfer software. **Results:** After the treatment period, the change in normalised hippocampal volume from baseline was significantly lower in group 1 patients compared to group 2 (mean change -0.0001470 ± 8.981e-005; Mean ± SEM vs 0.0002765 ± 9.151e-005; Mean ± SEM, respectively, P=0.004). Displayed graphically, the negative hippocampal growth trajectory in group 1 gradually returned to a positive growth pattern. There were no statistically significant changes in ACC volume and thickness. Both groups had similar rates of pre-operative hydrocephalus. **Conclusion:** Compared to PFT patients treated with surgery alone, PFT patients treated with chemo-radiotherapy showed lower hippocampal volumes and altered hippocampal growth trajectory. Serial quantitative MRI measures of brain may provide a neuroanatomical substrate for assessing functional impact on normal brain function following treatment of posterior fossa tumours.

Keywords: Brain tumour- hippocampus- MRI- chemo-radiotherapy

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Introduction

Standard therapy for posterior fossa tumour (PFT) includes maximal surgical resection of the tumour +/- craniospinal irradiation (CSI) and adjuvant chemotherapy depending on size, grade of tumour and age of patients. However, the treatment of PFT in young age children with chemotherapy and radiotherapy remains a challenge because of vulnerability of the developing brain in this age group.

Due to advances in neurosurgical approaches, neuroimaging techniques and current treatment modalities, long term survival of cancer patients has increased, and hence the neuropsychological complications are more frequently observed nowadays than before in these patients (Wefel et al., 2004; Dietrich, 2010). Moreover, reports have shown that simultaneous treatment with chemotherapy and radiotherapy elevate the risk of neurocognitive (what) outcomes compared to giving radiotherapy only (Cha, 2009)

New neuroimaging techniques have enabled researchers to identify a number of post-treatment brain changes in patients treated with PFT, such as decreases in white matter thickness (Reddick et al., 1998; Mulhern et al., 1999) and declines in corpus callosum volume (Palmer et al., 2002). While most of these white matter abnormalities have been correlated with impairments in overall intellectual functioning in these patients (Mulhern et al., 2001), none of these brain changes have been found to be specifically related to memory performance (Reddick et al., 2003). Therefore, there is no definitive understanding of the neuropathology underlying memory deficits in children with PFT.

In 2006, in a study recruited 40 children with MB, Nagel and colleagues found that patients treated with chemotherapy and radiotherapy had impairment in both recall and recognition memory. Although the mechanism of impairment was not known but they suggested that hippocampus and/or white matter abnormalities played critical roles in mediating these children's mixed memory impairment (Nagel et al., 2006). It was also found treatment with concurrent radiotherapy and chemotherapy

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have more neurobiobahavioural impact compared to treatment with radiotherapy alone (Baron Nelson et al., 2013).

In another study recruiting 25 patients who underwent 159 serial MR imaging examinations, a decrease in hippocampal volume was found after treatment that continued until approximately 2–3 years after diagnosis (Nagel et al., 2004). However, that study had some weaknesses as they did not includ a control group for comparison to specifically identify volume changes of hippocampus throughout development. Furthermore, Photoshop was used to measure the volume of the hippocampus.

The damage of hippocampus due to chemotherapy and or radiotherapy is complex and multifactorial. Chemotherapy might cause damage to or loss of healthy neurons as well as a decrease in the number of hippocampus progenitor cells. In the past, it was believed that radiotherapy result in neurocognitive decline through microvascular changes and neuroglial loss. However, there is increasing evidence of cognitive changes after radiotherapy that appears to be mediated through the neurogenic zones including the hippocampus. Preclinical and clinical evidence support the role of hippocampus in early changes of cognitive function after radiotherapy, most notably in memory-related domains of neurocognition (Gondi et al., 2014) .

Cerebral cortex plays an important role in higher order cognition, therefore extensive neurocognitive deficit observed after intensive treatment of PFT could be caused by changes in the cerebral cortex. Anterior cingulate cortex (ACC) is the frontal part of cingulate cortex. It plays important role in regulating autonomic functions like heart rate and blood pressure, as well as cognitive functions (Decety and Jackson, 2004; Jackson et al., 2006). Previous researchers found important changes in grey matter, where they have used a single axial slice and they have the whole cerebral cortex as target of their study. However, surprisingly they found cerebral cortical changes mainly observed in the posterior portion of the brain (Liu et al., 2007) .

We hypothesised that treatment with chemotherapy and radiotherapy would result in abnormal hippocampal and anterior cingulate cortical thickness and volume development. The purpose of our study was to include a proper control group and use of a better parameter for volume measurement of the hippocampus. Furthermore to use a more sensitive technique with automated anterior cingulate cortex segmentation from high resolution MR images, to compare changes in these two important structure in patient treated with postsurgical radiotherapy and chemotherapy compared to a control group of patients treated with surgery alone.

Materials and Methods

Patients

All patients' carer participating in this study signed informed consent to have their data collected and used for research. This study was approved by a UK National Health Service (NHS) Research Ethics Committee. In this retrospective analysis, 12 children with PFT were included. Eight were females and 4 were males. Four were medulloblastoma, 2 Ependymoma, 5 pilocytic astrocytoma and one high grade glioma (Table 1).

All patients received treatment at Nottingham University Hospital from September 2006–to September 2011. Patients were divided into 2 basic groups in terms of treatment type that they had been given. The first group consisted of MB, ependymoma and high grade glioma who had been treated with total surgical resection of the primary tumour (except for two patients, one had MB where only debulking of the tumour mass was performed for him and the second one was a high grade glioma case in whom incomplete resection was performed). All patients had the diagnosis confirmed by histology as reviewed by 2 neuro-pathologists. After the diagnosis was established, they received radiotherapy and chemotherapy accordingly. In the first group, 4 children were treated with concurrent radiotherapy and chemotherapy, 2 had radiotherapy later after the course of chemotherapy has finished and only one patient who was a case of ependymoma, had received radiotherapy prior to the start of chemotherapy. The second group included Patients with PA were used as controls, and had been undergone surgery solely for removal of the tumour.

MRI

Each patient went through serial MR imaging and almost all patients (apart from one M.B patient whose first scan was at 17 days post-operation), had one baseline MR scan taken shortly before the operation (ranging from 0-6 days pre-operatively) and at least another 2 scans in the post-operative period. The total number of images that were collected from all patients was 76 . The duration between subsequent scans during the follow up period varied across patients.. All scans were gained in 3D sequence, axial plane, apart from 2 scans that were obtained in sagittal plane and had been reformatted and realigned to the rest of the scans. All scan reviewed by experienced neuroradiologists. All patients received standard clinical treatment (Table 1).

Manual Tracing of Hippocampus

Pre- and post-surgery left and right hippocampus volume were manually drawn by MRIcro software (The University of Nottingham, UK; http://www.nottingham.ac.uk/ scs/divisions/clinicalneurology/software/MRIco.aspx) and then these volumes were calculated by using 3D-Slicer software.

The protocol that we have used in our analysis for definition of the hippocampal boundaries has been extracted from the most commonly used protocols and been compiled and tested at Division of Radiological and Imaging Sciences, University of Nottingham, Supplement and supporting data.

The intra class correlation coefficient was 0.94 for both right and left hippocampi ($P<0.0001$).

In addition to intra-observer reliability, an inter-observer reliability test also was done with a trained person in the department who has enough experience in hippocampal volume measurement. The reliability was 0.96 ($P<0.0001$)

The severity of hydrocephalus was also assessed in these patients using the Evan's index (Merchant et al., 2004) .

Cortical Measurement

Measurement of the cortical thickness was accomplished by using FreeSurfer, sophisticated software that provides an objective and straight forward measure of the cortical morphology.

Cortical surface reconstruction

The reconstruction of the cortical surface is a composite procedure that has been previously described in detail (Dale et al., 1999; O'Donnell et al., 2005). The quality of the cortical surface reconstruction (particularly in the anterior cingulate cortex region) was carefully inspected prior to extraction of the region-of-interest (ROI) values. Using Excel, normalized total anterior cingulate volume was gained by adding right to the left anterior cingulate together then divided by the TICV. Assessment of any decline in the cortical thickness or volume was observed over time using GraphPad Prism and SPSS software.

Statistical Analysis

The changes in the hippocampal and ACC volumes over time before, during and after treatment were analysed in both groups 1 and 2. For group 1, volume differences were calculated as changes in the normalised volumes that were observed on the preoperative and the 1st scan following completion of the chemo-radiotherapy. The median number of days between pre-operative and post-treatment scan was obtained for group 1 (Median 529 days). For group 2, who didn't receive post-surgical chemo-radiotherapy, the scan closest to this median group 1 interval was chosen for inclusion in the group comparison.

Statistical analysis was performed using PASW Statistics 18, release version 18.0.0 (SPSS, Inc.). The data were normally distributed and were reported as the mean ± SEM and were analysed using Independent t-test between both groups. The significance level was defined as $P < 0.5$.

Results

Patient characteristics

The first group consisted of 7 patients with high grade posterior fossa tumour while the second group consisted of 5 patients with low grade pilocytic astrocytoma. The mean age for group 1 at time of diagnosis was 8.71±4.24 years, while the mean age for group 2 was 11.76±3.52 years. All of the patients and controls have been treated with shunt placement. Table 1 provides additional patient and control characteristics.

Hippocampal volume measurement The total hippocampal volume was measured on coronal sections of MRI scans in Group 1 patients who were treated with postsurgical chemo-radiotherapy and Group 2 control patients who were treated with surgery alone. The hippocampal volume was normalized as mentioned in materials and methods. The growth pattern of hippocampus was compared in both groups during treatment and follow up after treatment. The pre-surgical/pre-treatment mean nHV for group 1 (0.002566 cm^3 ± 0.0001507; mean±SEM) was higher than the mean nHV of control (0.002117 cm^3 ± 0.0001354; mean ± SEM) (P=0.07). Hippocampal volume was reduced in Group 1 patients at the start of treatment while in Group 2 the volume showed gradual increase pattern over the time. This abnormal volumetric pattern in Group 1 was followed by a gradual return to normal positive growth pattern (Figure 1).

The mean of hippocampal volume differences (Δ volume; the differences in the volume between the first preoperative scan to the first scan after the end of the treatment in each patients) in Group 1 patients was compared to that of Group 2 control patients. For the group 1 patients Δ volume were negative in 5 out of 7 patients (-0.0001470 ± 8.981e-005; Mean ± SEM) where all the group 2 control patients were positive (0.0002765 ± 9.151e-005; Mean ± SEM). The nTHV of both groups

Table 1. Patients and Control Clinicopathological Characteristics

Characteristics	Group 1	Group 2
Gender		
M	3	1
F	4	4
Age		
<3	1	0
>3	6	5
Resection status		
complete	5	5
incomplete	2	0
Radiation received		
Yes	7	-
No	-	5
Chemotherapy received		
Yes	7	-
No	-	5
Tumour location		
midline	6	1
Cerebellar hemisphere	1	4
Evan's Index		
>0.3	5	4
<0.3	2	1
Tumour type		
MB	4	-
Ependymoma	2	-
PA	-	5
HGG	1	-

Group 1 are patients treated with chemotherapy and radiotherapy after surgery while Group 2 are patients treated with surgery only. M, Male; F, female; MB, medulloblastoma; PA, pilocytic astrocytoma; HGG, high grade gliomaa

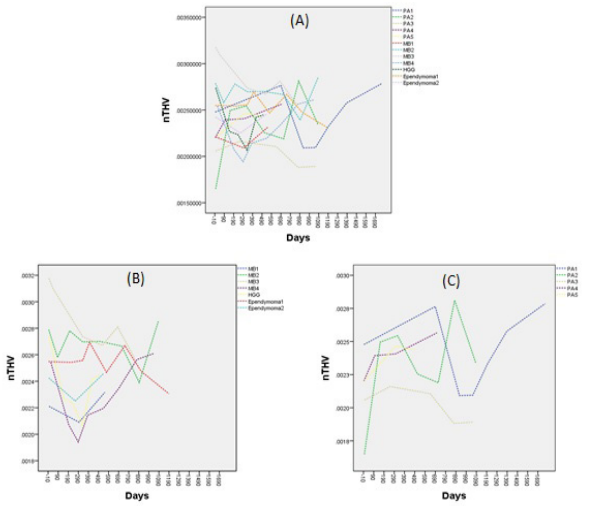

Figure 1. Growth Pattern of Each Individual Patient Over Time. A) Individual patient's and predicted nTHV over time since diagnosis in both group. B) Individual patient's and predicted nTHV over time since diagnosis in group 1. C) Individual patient's and predicted nTHV over time since diagnosis in group 2

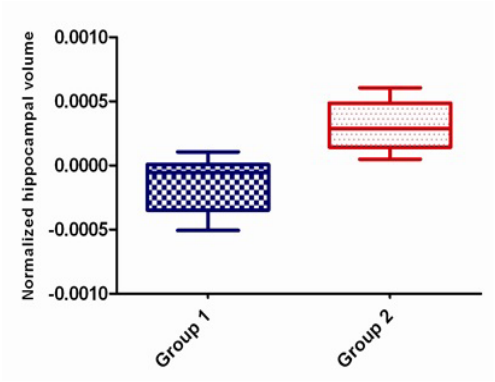

Figure 2. Treatment Related Volume Changes in Group 1 Treated Patients with Chemo-Radiotherapy after Surgery and Group 2 Treated with Surgery Alone. Significant reduction of Δ volume was observed in group1 compared to control group (P=0.004).

showed significant differences in the mean (P=0.004) (Figure 2).

Anterior Cingulate Cortex measurement

The ACC thickness and volume were measured automatically in T1-weighted MRI scans in Group 1 and Group. The changes in the Left and Right ACC thickness between both groups were statistically non-significant as shown in Figure 3 and Figure 4.

The ACC volume was normalized with the total intracranial volume similar to hippocampus. Although nACC volume was not changed in both groups at the start of treatment (Figure 5), but there was statistically non-significant reduction in the nACC volume in Group 1 patients (-0.0008883 ± 0.0004893; Mean ± SEM) compared to control group 2 (0.0008403 ± 0.001417; Mean ± SEM) patients at the first scan after completion of the treatment (Figure 6). This abnormal volumetric

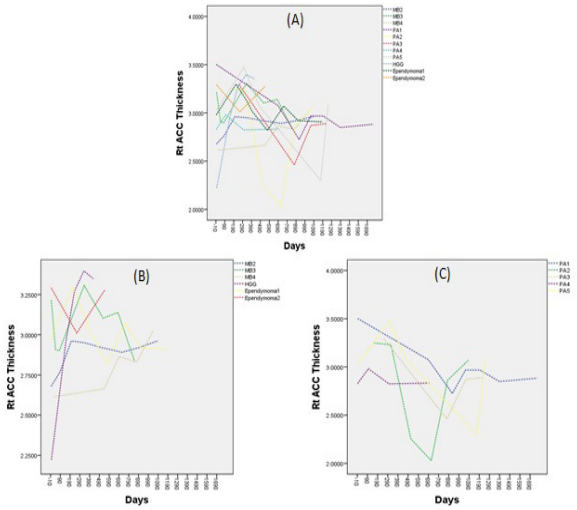

Figure 3. The Changes in Rt ACC Thickness in Each Individual Patient Over Time. A) Individual patient's and predicted RT ACC thickness alteration over time since diagnosis in both group. B) Individual patient's and predicted Rt ACC thickness variation over time since diagnosis in group 1. C) Individual patient's and predicted Rt ACC thickness changes over time since diagnosis in group 2.

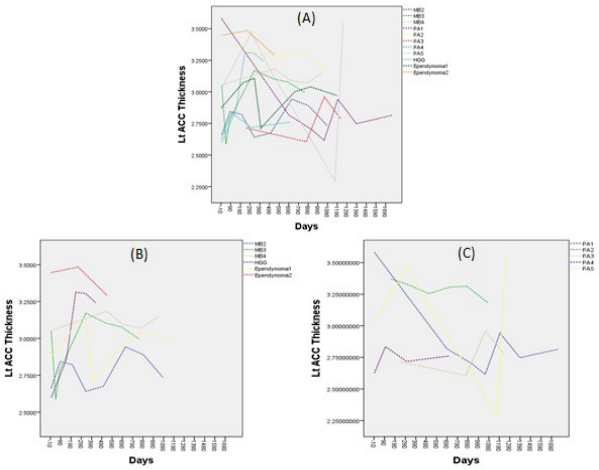

Figure 4. The Changes in Lt ACC Thickness in Each Individual Patient Over Time. A) Individual patient's and predicted Lt ACC thickness alteration over time since diagnosis in both group. B) Individual patient's and predicted Lt ACC thickness variation over time since diagnosis in group 1. C) Individual patient's and predicted Lt ACC thickness changes over time since diagnosis in group 2.

pattern was followed by a gradual return to normal positive growth pattern (Figure 5)

Discussion

To the best of our knowledge, this study is the first to evaluate patterns of hippocampal volume development among children with resected PF tumours and comparing those who did and did not receive radiation therapy and chemotherapy. The study confirms that the analysis of serial brain MRI scans can identify differences in

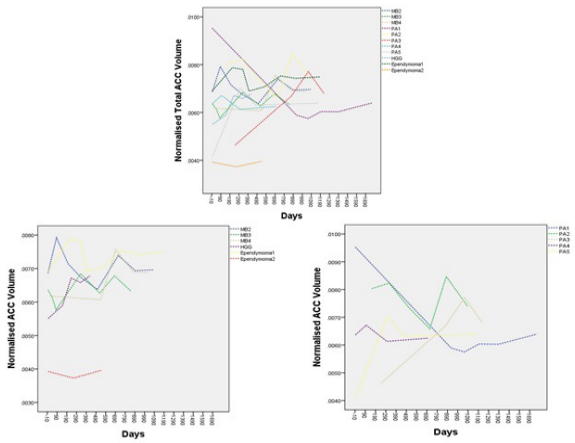

Figure 5. The ACC Volume was Normalized with the Total Intracranial Volume Similar to Hippocampus. Although nACC volume was not changed in both groups at the start of treatment (Figure 5), but there was statistically non-significant reduction in the nACC volume in group 1 patients (-0.0008883 ± 0.0004893; Mean ± SEM) compared to control group 2 (0.0008403 ± 0.001417; Mean ± SEM) patients at the first scan after completion of the treatment (Figure 6). This abnormal volumetric pattern was followed by a gradual return to normal positive growth pattern (Figure 5).

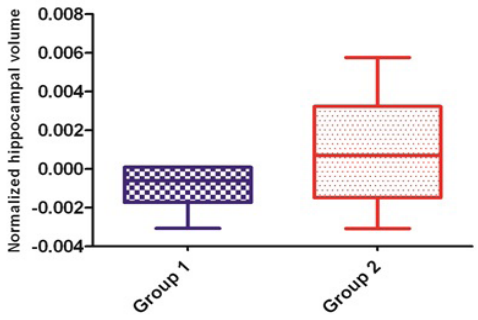

Figure 6. ACC Volume Changes after Treatment in Group 1 Treated Patients with Chemo-Radiotherapy after Surgery and Group 2 Treated with Surgery Alone. Non-Significant reduction of Δ volume was observed in group1 compared to control group (P=0.2).

hippocampal volume changes over the time. Specifically, longitudinal analysis of 76 MR imaging studies in these populations revealed that hippocampal volumes significantly declined shortly after the beginning of the treatment and then gradually returned toward a positive growth curve in patients with PF tumour treated with postsurgical intensive chemo-radiotherapy compared to control patients diagnosed with PF PAs treated with surgery alone. However, no significant changes were found in ACC volume and thickness in both groups.

By using the PA group as a 'control' group, the study attempted to control for the potential direct impact of both hydrocephalus and posterior fossa surgery on hippocampal development, as these features are common to both groups. Results of the current study suggest that that the effect on hippocampal volume demonstrated is related to the chemo-radiotherapy. Furthermore, the pre-treatment/pre-surgical nHV of controls was smaller than that of Group 1 which is against any suggestion that tumour biology is a factor that drives down the hippocampal volume. Therefore, this supports that our findings are not related to tumour type but they are rather due to the effect of chemo-radiotherapy.

In previous studies on normal human hippocampus, a decline in hippocampal volume had been shown over time with increasing age (Durston et al., 2001). Also, reduction of hippocampal volume is observed in some neurological diseases like Alzheimer disease (Apostolova et al., 2006). Previous literature on paediatric MB has shown decline in hippocampal volume that recovered after 2-3 years of treatment (Nagel et al., 2004). The findings of the current study were consistent with those of previous work, which showed reduction of hippocampal volume with the initiation of therapy that gradually recovered after the completion of treatment.

The hippocampal volume loss in almost all of these patients started shortly after the 1st chemotherapy course but the volume decline was specifically more evident at time points where radiotherapy was given concomitantly with chemotherapy. The serial scans that were performed during follow-up period in Group 1 patients, showed returns of normal hippocampal growth, but due to the irregular scanning periods among these patients, it was not possible to estimate the exact time for recovery of abnormal hippocampal volume toward the ordinary developmental pattern.

Although this study provides information about volume changes in the hippocampus in paediatric patients treated with PF tumour, it did not provide an insight into the pathology that might have been present in this structure. Other radiologic modalities like MR spectroscopy and PWI may provide more information about the degree of injury. Future researcher should consider these methodological advantages.

Despite methodological limitations of the current study, it provides important clinical implications for children with PFT. Firstly, the volumetric findings suggest that patients treated with chemo-radiotherapy have deviant development in hippocampal volume. Hence, there is important clinical implications for radiation oncology and conformal radiation techniques to avoid hippocampal regions during planning for radiotherapy. Secondly, cognitive functioning and academic achievement are important components of quality of life after successful treatment for paediatric brain tumour. Thus, the functional implications (memory functioning and learning abilities) of such abnormal development may have a notable effect on age-appropriate academic achievement and learning (Nagel et al., 2006, Gondi et al., 2014). This possibility may hold further importance for defining a timeline on which to expect functional improvements as well as for explaining delays in problem solving, academic achievement and independent living in PFT survivor.

This study could not find a difference in volume or thickness of the anterior cingulate cortex. The posterior parts of the cerebral cortex i.e. the parietal, posterior temporal and occipital lobes have the fastest rate of maturation during childhood and undergo age related thinning. Studies have shown that the developing brain regions are more vulnerable to the effect of treatment of

MB after surgery (Sowell et al., 2004; Liu et al., 2007). Liu et. al., showed that treatment-induced cerebral cortical thinning was mainly located in the posterior parts of cerebral cortex in both parietal and occipital lobes. Additionally, they have demonstrated in follow up of 65 normally developing children that the cortex in the posterior frontal and anterior temporal lobes did not significantly change with age; this may be due to lower growth rates in these parts of the brain. All the areas of relative cortical thinning were found in the regions of cerebral cortex that undergo normal age-related cortical thinning (Liu et al., 2007). Our data showed very small volume reduction in ACC in Group 1 patients compared to Group 2 control patients which was statistically non-significant with no changes in Rt. and Lt. ACC thickness over time and between different groups. This observation could be due to either: 1) the fact that this area has less growth development after early childhood (Liu et al., 2007); 2) it may be due small size of our sample; 3) or it may be due the position of ACC which is located in the anterior part of brain which is far from radiation fields.

Although the severity of hydrocephalus is associated with more loss of hippocampal volume (Rueckriegel et al., 2010) we could not statistically analyse this factor in our data because of the small sample sizes. However, the comparable rates of hydrocephalus in our two groups (71% and 80% with hydrocephalus with Evan index >0.3 (ISHI 2010) in Group 1 and Group 2 respectively) suggest that this is unlikely to account for the group difference in hippocampal volume change.

We could not correlate our findings to the treatment related neurocognitive outcomes in both groups, because of the absence of regular follow for the IQ, memory and cognitive parameters before and after treatment. However 6 cases had neurocognitive assessment during follow up this could not be interpreted because only one case had preoperative assessment.

Our results showed that hippocampus had significant reduction in the volume whereas the ACC did not change significantly during and after treatment. Given that the hippocampus is located closer to radiation fields for PF tumour, there may be important clinical implication for radiation oncology and conformal radiation techniques (e.g., avoiding hippocampal region during planning for radiotherapy). In addition to clinical implication for treatment planning, the current finding` in volume changes may play an important role in post-treatment learning abilities and memory functioning.

In conclusion, serial quantitative MRI measures of hippocampus may provide a neuroanatomical substrate for assessing functional impact of chemo-radiotherapy on normal brain function following treatment of malignant brain tumours. Long term survivors of PF tumours demonstrated abnormal patterns of hippocampal volume development after postsurgical chemo-radiotherapy, while ACC volume and thickness were not significantly affected. These results need to be confirmed in a larger prospective cohort study with regular frequent optimised follow-up scanning. Importantly, techniques such as those used in this study could be used to monitor novel neuroprotective treatments or strategies targeted at minimising hippocampal injury in this patient group.

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