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Chemoradiation impairs normal developmental cortical thinning in medulloblastoma

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Abstract

Medulloblastoma patients are treated with surgery, radiation and chemotherapy. Radiation dose to the temporal lobe may be associated with neurocognitive sequelae. Longitudinal changes of temporal lobe cortical thickness may result from neurodevelopmental processes such as synaptic pruning. This study applies longitudinal image analysis to compare developmental change in cortical thickness in medulloblastoma (MB) patients who were treated by combined modality therapy to that of cerebellar juvenile pilocytic astrocytoma (JPA) patients who were treated by surgery alone. We hypothesized that the rates of developmental change in cortical thickness would differ between these two groups. This retrospective cohort study assessed changes in cortical thickness over time between MB and JPA patients. High-resolution magnetic resonance (MR) images of 14 MB and 7 JPA subjects were processed to measure cortical thickness of bilateral temporal lobe substructures. A linear mixed effects model was used to identify differences in substructure longitudinal changes in cortical thickness. The left temporal lobe exhibited overall increased cortical thickness in MB patients relative to JPA patients who showed overall cortical thinning (mean annual cortical thickness change: MB 0.14 mm/year versus JPA -0.018 mm/year across all substructures), particularly in the inferior temporal lobe substructures ($p < 0.0001$). The cortical thickness change of the right temporal lobe substructures exhibited similar, though attenuated trends ($p = 0.002$). MB patients exhibit overall increased cortical thickness rather than cortical thinning as seen in JPA patients and as expected in normal cortical development. These observations are possibly due to chemoradiation induced-disruption of normal neuronal mechanisms. Longitudinal image analysis may identify early biomarkers for neurocognitive function with routine imaging.

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Compliance with ethical standards

Conflict of interest No conflict of interest to disclose.

Keywords

Medulloblastoma; Chemoradiation; Neurocognitive; Cortical thinning

Introduction

Medulloblastoma (MB) is treated with a combination of surgery, radiation and chemotherapy. These treatment modalities often lead to neurocognitive sequelae with associated neuroanatomical changes. Dosimetric-epidemiological analysis from the childhood cancer survivorship study reveals radiation to the temporal lobe to be particularly associated with neuropsychological late effects in a dose-dependent manner, and in complementary domains not limited to memory impairment, such as social functioning, emotional well-being and task efficiency [1]. While thinner temporal lobe gray matter in MB patients has been identified in a previous, cross-sectional study comparing absolute differences from healthy controls, rates of longitudinal cortical thickness change over time are more robustly correlated with neurocognitive development and have not been studied in patients receiving chemoradiation [2, 3]. Following initial cortical growth during infancy through early childhood, cortical thinning during late childhood through adolescence is a normal developmental process associated with synaptic pruning, the consolidation of neuronal synapses that is essential for learning, and for which the effects of chemoradiation are unknown yet may be amenable to medical interventions with agents already in clinical trials [3]. Longitudinal image analysis can capture the rate of cortical thickness change over time with better statistical power compared to cross-sectional analysis—a desired feature given the low prevalence of pediatric brain tumors [4, 5]. To better highlight longitudinal changes in cortical thickness of substructures of the temporal lobe due to chemoradiation, we applied longitudinal image analysis to compare developmental change in cortical thickness in medulloblastoma patients who were treated by combined modality therapy to that of cerebellar juvenile pilocytic astrocytoma (JPA) patients who were treated by surgery alone. Thus, we hypothesized that the rates of developmental change in cortical thickness would differ between these two groups.

Methods and materials

Patients

This institutional review-board approved, retrospective study included MB patients treated with concurrent vincristine-based, craniospinal chemoradiation and JPA patients managed only with surgery at Lucile Packard Children's Hospital between 2005 and 2015.

MRI studies

All patients underwent brain MR imaging at 3 T (Signa or Discovery 750; GE Healthcare, Milwaukee, Wisconsin). Image analysis was done on the axial precontrast and contrast-enhanced T1 spoiled gradient-recalled (SPGR) echo image sequences (TR/TE, 8/3 ms; 1-mm section thickness, 0 skip).

Longitudinal imaging analysis

All MR images were anonymized prior to image processing, and thus all post-processing analysis was blind to both primary diagnosis and prior therapy. Cortical thickness for bilateral temporal lobe substructures was measured with the open-access *FreeSurfer* longitudinal image analysis software. Longitudinal image segmentation greatly reduces measurement noise and requires smaller sample sizes with shorter follow-up times than cross-sectional studies for sufficient statistical power, and was thus appropriate for our dataset [4]. Individual images were processed to create an average template image, which was then used to refine the initial cortical segmentations according to the Desikan–Killiany atlas (Fig. 1). Each time point was treated the same for temporally unbiased segmentations. The template images were reviewed for errors and appropriately corrected, and all final segmentations were verified.

Statistical analysis

Statistical analyses were completed in SAS (Cary, North Carolina). A linear mixed effects age model, which can rigorously account for varying imaging follow-up and schedules across patients, was used to compare longitudinal temporal cortical thickness changes during late childhood through adolescence (6–18 years) between MB patients at least 1 month after completion of radiation treatment and JPA patients 2 month post-surgery. The model compared bilateral temporal lobe substructure thicknesses with age at MRI scan as a random and fixed effect, age at treatment as a random and fixed effect, and interactions of these terms with the effect of receiving versus not receiving chemoradiation treatment. The interaction between age at scan and chemoradiation treatment was the main effect of interest as this reflected differences in rates of longitudinal cortical thickness changes between treatment groups.

Results

At our institution, 40 MB patients (age 1.6–21.1 years, mean 8.4 years; 9 female) and 36 JPA patients (age 0.9–19.7 years, mean 7.8 years; 17 female) were diagnosed between 2005 and 2015. Cases were then selected based on availability of high-resolution SPGR scans, which limited total number of JPA patients and subsequent matching. The retrospective review yielded 14 MB patients (3.3–17.9 years, mean 9.7 years; 5 Female; 3 high risk 36 Gy, 4 18 Gy, 7 23.4 Gy) and 7 cerebellar JPA (3.1–16.2 years, mean 8.8 years; 4 Female) with characteristics reported in Table 1. Mean follow-up time and mean observations were 379 days and four scans per patient respectively. All patients were right-handed.

Left temporal lobe cortical thickness changes

MB patients exhibited left temporal lobe increased cortical thickness over time that averaged 0.14 mm/year across all substructures (Fig. 2a). JPA patients demonstrated cortical thinning at a mean rate of -0.018 mm/year. The difference in rates between MB and JPA groups was most significant in the left fusiform and left inferior temporal lobe substructures, 0.18 mm/year ($p < 0.0001$) and 0.19 mm/year ($p < 0.0001$) respectively.

Right temporal lobe cortical thickness changes

MB patients exhibited right temporal lobe increased cortical thickness over time that averaged 0.062 mm/year across all substructures (Fig. 2b). JPA patients demonstrated cortical thinning at a mean rate of -0.033 mm/year. The difference in rates between MB and JPA groups was most significant in the right fusiform and right inferior temporal lobe substructures, 0.11 mm/year ($p = 0.003$) and 0.12 mm/year ($p = 0.002$) respectively.

Discussion

Cortical thinning is a normal process during late childhood that may be correlated with normal neurocognitive development. In fact, longitudinal studies in healthy children reveal that vigorous thinning by early adolescence to be dynamically associated with intelligence [3]. The inferior temporal lobe substructures in particular are associated with facial recognition, interpretation of emotional expression, visual perception, IQ, language and semantic memory, which may account for the neuropsychological late effects seen with radiation dose to these areas [6–9].

We report overall cortical growth over time instead of cortical thinning in MB patients receiving chemoradiation compared to the control group of posterior fossa tumor JPA patients receiving surgery alone. Thus we conclude that chemoradiation may disrupt or delay the normal process of cortical thinning and potentially impair optimal cognitive development. It is of interest that a previous, cross-sectional study that compared cortical thickness of MB patients to healthy controls showed decreased cortical thickness in MB patients [2]. To reconcile these observations, we postulate that the use of absolute cortical thickness as done in the cross-sectional study, without a temporal reference lacks definitive value. For this reason, longitudinal changes in cortical thickness within each patient are of better value. Our longitudinal cortical thickness study more specifically highlights the effects of chemoradiation, suggesting that changes in cortical thickness over time may be an indicator of cortical plasticity. Although three different dose levels of craniospinal irradiation were employed, correlations of cortical changes relative to dose level were not made due to the small sample size. An additional control group receiving only chemotherapy would be informative to even further distill the effects of radiation, however our study focused on posterior fossa tumors given the comparable localized disease site and availability of routine follow-up imaging. Increased left temporal lobe thinning, which was attenuated in MB patients in our study, has been associated with improved vocabulary performance and IQ in healthy children [3, 10]. Schnack et al. [11] reported differences in longitudinal cortical thickness changes from ages 10–20 between the left and right hemispheres such that dynamic changes in the left hemisphere lagged approximately 3 years behind the changes on the right. This phenomenon may explain why the cortical changes in the current study were more pronounced in the left compared to the right [11].

Unfortunately as is the case for many studies in pediatric cancer patients, longitudinal neurocognitive data was incomplete and could not be correlated with the imaging findings, and therefore our study focused on objective neuroimaging findings, which have been previously correlated with neurocognitive data in healthy patients [3]. With the advent of routine neurocognitive testing in pediatric brain tumor patients, future studies may further

verify the correlation of cortical thinning rates with neurocognitive outcomes specifically in patients receiving chemoradiation.

While the observed overall cortical growth on MRI may be due to radiation-induced cortical astrogliosis or decreased lower cortical myelination, impairment of developmental synaptic pruning is a mechanism that remains to be explored. Synaptic pruning, mediated by microglia that phagocytose inefficient synaptic connections, is thought to be critical for neural remodeling and learning during late childhood. Recent research demonstrates that defective microglial-mediated synaptic pruning can be associated with social deficits and behaviors resembling neuropsychiatric disorders [12]. Radiation treatment has been shown to induce inflammatory microglia [13–17, 18], and microglia in this inflammatory state can impair synaptic pruning [17]. While prior studies have focused on the deleterious effects of radiation-induced neuroinflammation on hippocampal neurogenesis [13, 14], the impairment of normal synaptic pruning by radiation proposed here suggests that additional, novel therapeutic strategies may mitigate neurocognitive decline. Post-radiation inhibition of the microglial colony stimulating factor one receptor (CSF1R), for example, can selectively deplete inflammatory microglia with subsequent repopulation from microglial progenitor cells [19]. These inhibitors may also provide anti-tumor benefits for specific MB subtypes, are already in pediatric and adult brain tumor clinical trials (NCT02390752, NCT01790503), and may additionally offer neurocognitive benefits given the putative impaired synaptic pruning mechanism described here [20].

Our analysis applied modern imaging methods and a longitudinal study design to achieve robust segmentation with sufficient statistical power, and the mixed effects age model appropriately accounted for varying imaging follow-up across patients. However, some variables, such as gender, shunt status, chemotherapy and volume-specific radiation dose effects, could not be included. Additionally, our study examined cortical thickness change rates, which despite being previously correlated with neurocognitive outcomes in healthy children, should be specifically studied in patients receiving chemoradiation. Most patients in this study were in late childhood, during which previous studies have shown linear temporal lobe changes [3, 21], however substructure-specific cortical thickness changes over a greater age range may be more accurately generalized with different models [5]. More statistically sophisticated and high-throughput processing of larger longitudinal, high-resolution image datasets hold the potential to identify a biomarker for routine image-based neurocognitive assessment and to also guide dose-sparing of critical structures. This should be considered in the design of future clinical trial protocols.

Conclusion

Longitudinal image analysis is a powerful tool that reveals changes in the temporal lobe, a critical structure for neurocognitive late effects, specific to chemoradiation. Chemoradiation may disrupt normal cortical thinning, a process associated with neurocognitive outcomes, in medulloblastoma patients, relative to their pilocytic astrocytoma counterparts. This difference may be the result of impaired developmental synaptic pruning and could be amenable to novel therapeutic strategies.

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Fig. 1. Lateral (*left*) and medial (*right*) views of the Desikan–Killiany cortical atlas used for FreeSurfer segmentation with select temporal lobe substructures labeled. Note that the transverse temporal gyrus is buried within the lateral sulcus above the superior temporal gyrus. Reprinted from [22], with permission from Elsevier

Fig. 2.

a Left temporal lobe cortical thickness changes over time for medulloblastoma (MB) and juvenile pilocytic astrocytoma (JPA) groups with significance of interaction and absolute difference in rates (). **b** Right temporal lobe cortical thickness changes over time for medulloblastoma (MB) and juvenile pilocytic astrocytoma (JPA) groups with significance of interaction and absolute difference in rates ()

Table 1

Patient characteristics of medulloblastoma (MB) and juvenile pilocytic astrocytoma (JPA) groups

	MB (chemoradiation) N = 14	JPA (no chemoradiation) N = 7
Age	3.3–17.8 years	3.1–16.2 years
Gender	5 Female, 9 male	4 Female, 3 male
Risk	3 High (M1), 11 standard	N/A
CSI radiation dose	3 36 Gy, 7 23.4 Gy, 4 18 Gy	N/A
Chemotherapy	6 ACNS0331 (CBDCA or CDDP/CCNU/VCR, CPM/VCR) 4 CHP693 (CDDP/CCNU/VCR, CPM/ETO) 2 ACNS0332 (CDDP/CPM/VCR, ARA-C) 1 SJYC07 (CPM and TOPO) 1 CDDP/CPM/VCR	N/A
Shunt	2	1

Maintenance chemotherapy regimens shown with corresponding protocols

CBDCA carboplatin, *CDDP* cisplatin, *CCNU* lomustine, *VCR* vincristine, *CPM* cyclophosphamide, *ETO* etoposide, *ARA-C* cytarabine, *TOPO* topotecan