White Matter Maturation in Healthy Children and Patients Treated with Brain Radiation: A Longitudinal DTI Study

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Introduction

New developments in treatment of childhood malignancies have contributed to significant improvements in long-term cure rate. However, with improving survival, complications of treatments become increasingly evident. In particular, radiation therapy (RT) to the brain has been associated with a spectrum of adverse acute, early-delayed, and late-delayed effects. While the acute and early-delayed effects are transient in most cases, late-delayed effects have been associated with a spectrum of brain toxicities. The dominant features of radiation injury are vascular abnormalities and white matter pathologies ranging from demyelination to necrosis [1]. The goal of our study was to apply a non-invasive technique for early detection and monitoring of brain tissue injury due to radiation treatment in children. Diffusion tensor imaging (DTI) was used to assess changes in water diffusion properties along the axons to evaluate damage to specific fiber tracts longitudinally, over a period of 27 months in a group of pediatric patients receiving RT and an age-matched group of normally developing children and adolescents.

Methods

Sixteen pediatric patients (3 girls, age range 5.5-18.6 years) who received radiation to the brain were examined. The diagnoses included medulloblastoma (posterior fossa, n=4), malignant glioneuroma (frontal lobe, n=3), germinoma (suprasellar, n=3), pilocytic astrocytoma (hypothalamic region, n=3), pharyngioma (n=1), ependymoma (n=1), and T-cell ALL (n=1). The control group was comprised of 36 healthy children (21 girls, age range 5.5-18.3 years). The patients were examined before completion of RT (first scan), 6 months (second scan), 15 months (third scan), and 27 months (fourth scan) after the end of RT. Controls were examined at baseline, 6 months, 15 months, and 27 months follow-ups. MRI was performed at 1.5 Tesla. DTI data were acquired using a single-shot spin echo planar sequence with 15 non-collinear diffusion gradient directions (b=1000 s/mm^2) and two b=0 s/mm^2 images. The following parameters were used: 24 axial slices, 96*96 acquisition matrix, FOV 240 mm^2, 5 mm slice thickness, no gap. FA and color maps were calculated from raw data using the 'DTI Studio' software. Polygonal ROIs outlining each tract were drawn on the color maps two times and the measurements were averaged after overlaying the ROIs on the FA maps. DTI data were evaluated in 15 regions in both hemispheres; detailed data are presented in 6 regions: genu and splenium of the corpus callosum, anterior and posterior limb of the internal capsule, and frontal and parietal white matter. In order to assess the dose delivered to the ROIs, the FA maps were imported into the Pinnacle Treatment Planning System (Philips Medical Systems, Madison, WI) and registered with the treatment plan using the CT simulation scan. Linear Mixed Effects (LME) models were used to determine factors associated with changes in ADC and FA. Statistical significance was set to $p<0.05$.

Results

The overall LME analysis detected significant differences in individual white matter regions between patients and controls for both FA (group x region: $p<0.0001$) and ADC (group x region: $p=0.03$). Significant FA and ADC differences among regions and over the examined age range and over time were also detected (group x region x age: $p\leq0.025$; group x region x time: $p<0.0001$). While healthy children demonstrated regional age-related increases in FA and decreases in ADC, FA tended to decrease and ADC to increase in patients. The decrease in FA in the patient group was due to increased radial diffusivities rather than decrease in the axial diffusivity (Fig.1).

At the last follow-up, the most pronounced abnormalities were observed in the genu of the corpus callosum, with a 10.4% lower mean FA ($p=0.019$) and a 18.6% higher mean ADC ($p=0.033$) in patients. At the last follow-up, a tendency to FA decrease, proportional to the radiation dose, was detected in the genu of the corpus callosum ($p=0.073$), posterior limb of the internal capsule ($p=0.097$), and the frontal white matter ($p=0.019$).

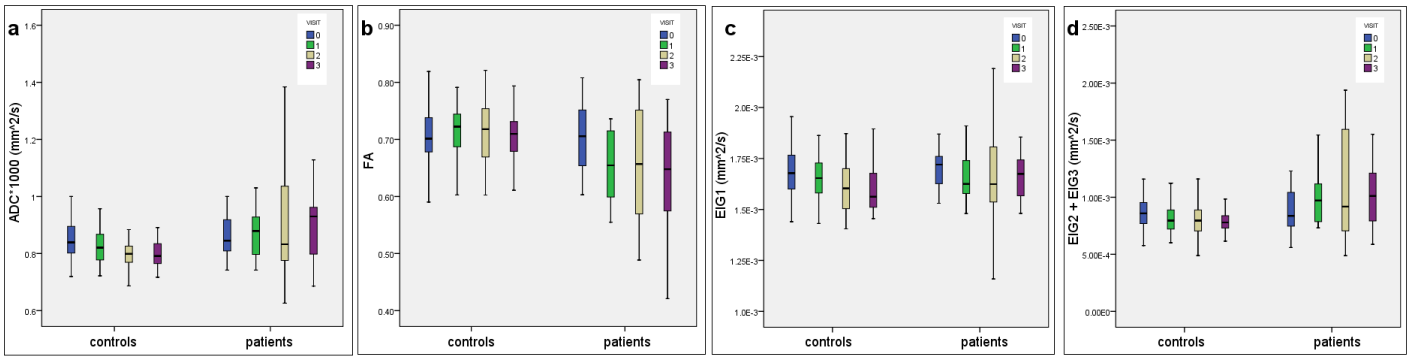

Fig 1. Genu of the corpus callosum: ADC (a), FA (b), axial (c) and radial (d) diffusivities in healthy children and RT patients at baseline (visit 0) and the three follow-up visits.

Discussion and Conclusions

In this prospective longitudinal study, late effects of radiation treatment on white matter microstructure were assessed using DTI. Healthy children showed regional age-related increases in FA and decreases in ADC, in agreement with earlier cross-sectional studies [2-4]. However, widespread white matter abnormalities (increased ADC and decreased FA) were detected in several of the examined brain regions in patients. While abnormal FA and ADC values were detected with DTI, all evaluated regions of interest had a normal appearance on conventional MRI, suggesting high sensitivity of the DTI technique for the detection of radiation injury. It has to be noted that some of the patients examined in our study received chemotherapy and were treated surgically, in addition to radiation. Therefore, some of the observed differences between healthy children and the patients may be attributed to adverse effects of other treatment modalities. Of the examined brain regions, the most prominent group differences were detected in the genu of the corpus callosum, at all examined time points. Our results therefore suggest a higher radiosensitivity of the genu of the corpus callosum to early delayed and late radiation injury compared to other examined white matter regions in our protocol, consistent with previous findings in adult [5] and children patients treated with radiation [5]. Reduction in FA corresponding to reduced radial diffusivity may suggest reduced compactness or density of fiber bundles and/or demyelination.

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