Developmental differences in deep gray matter nuclei tissue integrity and neuropsychological performance in healthy children and patients treated with brain radiation

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INTRODUCTION

Whole brain radiation therapy is an important treatment modality that has improved survival among children with brain malignancies. However, even at relatively low doses, radiation therapy can generate an array of adverse acute, early delayed and late effects. On a pathologic basis, radiation-induced injury can include vascular damage, demyelination, and necrosis within the brain. While the early effects of this damage can be transient, late effects have been associated with a range of clinical pathologies, including neurocognitive deficits, which can have long-term implications for learning and memory. Diffusion tensor imaging (DTI) is a non-invasive method that has provided unique information on radiation-induced white matter pathology. DTI has also provided information on normal maturation of white matter tracts as well as cortical and deep gray matter nuclei. A recent DTI study evaluating the maturation of white matter tracts and deep gray matter nuclei among children and adolescents demonstrated that ADC changes can be quite profound throughout childhood and adolescence. The aim of this prospective study was to evaluate differences in ADC over time in deep gray matter nuclei among patients receiving brain radiation compared with age-matched controls.

METHODS

Nine pediatric patients (7 boys; 11.81 ± 3.8 years, mean age ± SD at time of first exam) who received brain radiation were examined. The control group was comprised of nine healthy children (2 boys; mean age, 11.2 ± 1.8 years) with normal development. The patients were examined with DTI before or early in the course of RT (time point 1), and then at 6 (time point 2), 15 (time point 3) and 27 (time point 4) months following completion of RT. Controls were examined at the same time intervals. All subjects were evaluated with a battery of neuropsychosomatic examinations at the time of each visit. MRI was performed at 1.5 Tesla. DTI data were acquired with a single-shot spin echo planar sequence with 15 non-collinear diffusion gradient directions (b=1000 s/mm²) and two b=0 s/mm² images. The following parameters were used: 24 axial slices, 96x96 acquisition matrix, FOV 240 mm², 5 mm slice thickness, no gap. FA, ADC, and color maps were calculated from raw data using DTI Studio software. Each region of interest (thalamus (1), globus pallidus (2), putamen (3), caudate head (4), and hippocampal head (5)) was drawn on the color maps two times and the measurements were averaged. Linear mixed effects models analysis was applied for statistical evaluations, using the SPSS software. Statistical significance was set to p<0.05.

RESULTS

The overall analysis revealed a statistically significant difference in ADC as well as axial and radial diffusivity between patients and controls (p = 0.025, 0.005, and 0.017, respectively). At the individual time points, significant differences in overall ADC were also observed, with these changes observed before the start of radiation therapy (p = 0.03) (Fig. 1, Exam 1). In the individual regional analysis, the mean ADC was significantly higher in patients than in controls at all times points in regions 3 and 4, and at time point 1 and time point 4 in region 5 (hippocampal head) (Fig. 2). In the overall and regional analyses, there was a trend towards a wider range of values among patients compared with controls.

Compared to healthy children, this group of patients tended to perform better at all time points on neuropsychological tests of dexterity, memory, and motor persistence and inhibition. All subjects improved their performance on these tests over time.

DISCUSSION

Recent literature has shown that mean diffusivity of deep gray matter decreases over time, correlating with what is believed to be normal developmental maturation of these structures. In our study, a significant increase in the mean ADC value calculated over time from five separate regions comprising deep gray matter and the hippocampal head was detected between patients and age-matched controls, despite no visible pathology on conventional MR imaging. This was observed at the start of the study, and continued throughout the 27 months of observation. This suggests that while radiation may cause damage to deep gray matter, patients with brain malignancies may have abnormal development of these structures at the outset.

Interestingly, the patients did perform significantly better on neuropsychological tests of memory and motor function, clinical measures of the functionality of these regions of the brain. This suggests that DTI may detect abnormalities in deep gray matter development before they become clinically apparent. All subjects (including controls) improved their performance over time, likely due to ongoing brain maturation. Despite the appearance of DTI abnormalities at the start of the study, these differences in diffusivity could be compounded by radiation therapy. It will be important to determine the relationship of radiation dose to the differences in diffusivity over time, as well as the potential contribution of other treatments including surgery and chemotherapy.

In summary, the results presented here are highly suggestive that DTI is able to detect persistent changes in deep gray matter integrity associated with brain malignancy treated by RT. These results suggest that RT is not completely responsible for the abnormalities observed.

REFERENCES