Decrease in white matter volumes and commensurate deficits in neuropsychological performance following radiation therapy in children

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INTRODUCTION

Treatment paradigms for primary brain tumors and acute lymphoblastic leukemia which include radiation therapy have improved long term patient survival. However, radiation therapy administered to the brain can generate a range of adverse acute, early delayed and late complications that may lead to tissue atrophy, demyelination, necrosis, and vascular abnormalities[1]. While early effects may be transient, late effects have been associated with a range of neurocognitive deficits, which can have long-term implications for learning and memory. The aim of this longitudinal volumetric MRI study was to evaluate changes in gray and white matter lobar volumes among children who received brain radiation, with the focus on early-delayed effects of radiation. Changes in neuropsychological performance were evaluated in all patients and control subjects.

METHODS

Twenty six pediatric patients (20 males; mean age 11.8 years (range 3.9-18.95 years)) who received radiation to the brain were examined at the initiation of radiation therapy, and approximately at 6, 15 and 27 months following completion of radiation therapy. Diagnoses included ALL (N=2) and primary brain tumors (N=24). A control group was comprised of 51 children (26 males; mean age 12.3 (years range 6.2 to 18.3 years)). Among the pediatric patients, 1st, 2nd, and 3rd follow-up scans were performed in 58%, 13%, and 13%, respectively. For the control subjects, 1st, 2nd, and 3rd follow-up scans were performed in 82%, 27%, and 4% respectively. MR images were acquired at a 1.5 Tesla GE LX scanner using a quadrature head coil. Axial images were obtained with a 3-D volumetric radiofrequency spoiled gradient echo (SPGR) sequence, partitioned into 124, 1.5-mm contiguous slices. The image data were imported into the program BrainImage for visualization, processing, and quantitation. The 3D volume dataset was parcellated according to cerebral lobe separating gray matter, white matter, and CSF proportions for each voxel in the volume. Linear mixed effects (LME) models analyses were used to evaluate the differences between groups (patients, controls), sexes, and the effects of age (at baseline) and time since the baseline (and their respective group interactions) on the resultant gray and white matter volumes from the frontal, temporal, parietal, and occipital lobes. Overall analyses included all available data; early-delayed effects of radiation were evaluated using the data from the baseline and the 1st follow-up scans. Total brain volume was controlled for in all of the analyses. All participants completed a neuropsychological assessment at each visit, including measures of attention, executive function, memory, language, and visual and motor skills.

RESULTS

Table 1 summarizes the results of overall statistical analyses (p values) in lobar gray and white matter (all available data were used and total brain volumes were summed from both hemispheres). The LME analyses did not show any significant differences in lobar volumes between the sexes.

LME analyses of the initial two visits showed that, in controls, gray matter volumes were stable over the examined age range in the frontal lobe (but decreased with age in patients), decreased with age in the occipital lobe (but did not change with age in patients) and the parietal lobe (in both groups), and increased with age in the temporal lobe (but did not change with age in patients). No differences in lobar gray matter volumes between the first two visits were detected in controls. However, in patients, a small but significant increase in frontal (by 6%, p=0.001), and parietal (by 4.3%, p=0.024) gray matter volumes was detected at the first follow-up examination.

Table 1	**Group**	**Age**	**Time**	**Group*Age**	**Age0*Time**
Gray Matter Volume					
Frontal	**0.017**	**<0.001**	0.091	**0.024**	NS
Parietal	NS	**<0.001**	**0.038**	NS	NS
Temporal	**0.003**	0.078	NS	NS	NS
Occipital	NS	**0.015**	NS	NS	NS
White Matter Volume					
Frontal	**0.008**	**<0.001**	0.067	**0.010**	NS
Parietal	**0.007**	**0.005**	**0.037**	NS	NS
Temporal	NS	0.067	**0.017**	NS	**0.014**
Occipital	NS	NS	NS	NS	NS

Analysis of white matter volumes demonstrated age-related volume increases in the frontal lobes (in both groups). Temporal lobe white matter increased in patients while stable volumes were detected in controls. Parietal lobe white matter volumes increased in controls and were stable in patients. No age-related changes in occipital white matter were detected in either group. No differences in lobar white matter volumes between the first two visits were detected in controls. However, in patients, white matter volume decreased in the frontal (by 6%, p=0.069), parietal (by 4.8%, p=0.04), and temporal lobe (by 13.5%, p=0.003).

Results from the neuropsychological testing demonstrated significantly impaired performance on visual selective attention, verbal working memory, verbal recall, and motor speed in patients (Visual Matching, Auditory Working Memory, Memory for Words, Block Design, Purdue Pegboard, Bead Memory; all tests, group: p<0.001). Children receiving radiation treatment at younger ages had the most significant deficits (group x age: p≤0.001).

DISCUSSION

The main findings of this study are significant lobar gray and white matter volume changes in patients, 6 months after completion of brain radiation treatment. White matter volume reductions following radiation have been reported previously[2,3]. In agreement with literature data, we demonstrate decreases in frontal, parietal, and temporal white matter. Our data also extend findings of previous studies in children receiving brain radiation, showing that radiation induces predominantly white matter loss.[1] While long-term effects of (whole brain) radiation may manifest as cortical thinning[4]; significant increases in frontal and parietal gray matter volumes detected in our study at 6 months after radiation may represent early radiation injury manifesting as edema, perhaps artificially inflating gray matter volumes. Our findings of both frontal gray and white matter involvement are also consistent with a previous DTI study that suggested a higher susceptibility of the frontal lobe to radiation injury[5].

Consistent with data in the literature, we also demonstrate significant age-related changes in gray and white matter volumes in healthy children[6]. However, several comparisons indicated significant differences in age-related volumetric changes between patients and controls (e.g. in the frontal and parietal lobe gray matter).

Intellectual and neurocognitive deficits have also been associated with decreases in white matter volumes.[2] Results of our neuropsychological testing confirmed previous literature findings that patients receiving RT initiated at younger ages, have the most significant deficits.[3] The resultant deficits on tasks associated with the frontal lobe (motor and executive functions) as evidenced by neuropsychological test findings, are corroborated by the concomitant decrease in frontal lobe white matter volumes in these patients.

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