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CLINICAL INVESTIGATION **Brain**

DIFFERENCES IN SUPRATENTORIAL DAMAGE OF WHITE MATTER IN PEDIATRIC SURVIVORS OF POSTERIOR FOSSA TUMORS WITH AND WITHOUT ADJUVANT TREATMENT AS DETECTED BY MAGNETIC RESONANCE DIFFUSION TENSOR IMAGING

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Purpose: To elucidate morphologic correlates of brain dysfunction in pediatric survivors of posterior fossa tumors by using magnetic resonance diffusion tensor imaging (DTI) to examine neuroaxonal integrity in white matter.
Patients and Methods: Seventeen medulloblastoma (MB) patients who had received surgery and adjuvant treatment, 13 pilocytic astrocytoma (PA) patients who had been treated only with surgery, and age-matched healthy control subjects underwent magnetic resonance imaging on a 3-Tesla system. High-resolution conventional T1- and T2-weighted magnetic resonance imaging and DTI data sets were obtained. Fractional anisotropy (FA) maps were analyzed using tract-based spatial statistics, a part of the Functional MRI of the Brain Software Library.
Results: Compared with control subjects, FA values of MB patients were significantly decreased in the cerebellar midline structures, in the frontal lobes, and in the callosal body. Fractional anisotropy values of the PA patients were not only decreased in cerebellar hemispheric structures as expected, but also in supratentorial parts of the brain, with a distribution similar to that in MB patients. However, the amount of significantly decreased FA was greater in MB than in PA patients, underscoring the aggravating neurotoxic effect of the adjuvant treatment.
Conclusions: Neurotoxic mechanisms that are present in PA patients (*e.g.*, internal hydrocephalus and damaged cerebellar structures affecting neuronal circuits) contribute significantly to the alteration of supratentorial white matter in pediatric posterior fossa tumor patients. © 2010 Elsevier Inc.

Diffusion tensor imaging, Medulloblastoma, pilocytic astrocytoma, White matter, Sequelae.

INTRODUCTION

Pediatric survivors of posterior fossa tumors have a plethora of brain function restrictions (1). These are caused by different factors, primarily the tumor proper and secondarily therapeutic efforts. The extent and the type of brain damage caused by the tumor differ with respect to tumor biology. Whereas low-grade pilocytic astrocytoma (PA; World Health Organization [WHO] Grade 1) grows slowly and is well delineated, the growth pattern of high-grade medulloblastoma (MB; WHO Grade 4) is fast and invasive. Patients in both tumor groups are prone to develop internal hydrocephalus due to the obstruction of the aqueduct. As an unwanted effect, craniospinal irradiation with a boost to the posterior fossa and concurrent chemotherapy, commonly used to treat MB tumors, have been shown to amplify neurotoxicity in MB patients (2–5). However, the significance of the various specific neurotoxic effects in posterior fossa tumor patients is poorly understood. Therefore, newer studies aimed at analyzing the different contributions to neurotoxicity, such as impact of the tumor proper, internal pressure increase by hydrocephalus, the surgical intervention, and adjuvant treatment (6–9). Tools to assess and monitor the neurotoxic effects will be of great value in tailoring therapy individually and in rehabilitation to improve long-term outcome.

Conventional magnetic resonance imaging (MRI) can identify some long-term changes of the central nervous tissue, such as morphologic local damage, brain atrophy, and leukoencephalopathy. However, the degree of leukoencephalopathy correlates poorly with the functional deterioration observed in the patients (10). Recently, more sensitive tools to quantify the damage to brain tissue have been developed. Volumetric

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studies showed an association between neurocognitive function and the atrophy of white matter and gray matter (11–13). In the present study, we used magnetic resonance diffusion tensor imaging (DTI) to assess the integrity of cerebellar and supratentorial white matter tracts. The value of DTI for detecting structural changes in MB patients has been demonstrated recently by two research groups that showed decreased fractional anisotropy (FA) values in white matter of MB patients and found an association between the decrease of FA and loss of intelligence quotient (2, 14–17).

Diffusion tensor imaging has not yet been used in brain tumor patients of this age group who did not receive irradiation of the brain. In addition, no comparisons of FA from normal-appearing white matter of irradiated and nonirradiated brain tumor patients have been reported hitherto. The decreased white matter FA (WMFA) measured in MB patients was mainly ascribed to irradiation and chemotherapy (1, 2, 4, 5).

To test whether other neurotoxic factors, apart from adjuvant treatment, cause additional decreases of FA, this study examined two groups of posterior fossa tumor patients, including those who had (MB) and had not (PA) received craniospinal irradiation and chemotherapy.

PATIENTS AND METHODS

Patients

Because our study aimed at measuring neurotoxic long-term effects, all patients had completed therapy at least 1 year before assessment. MB patients had received adjuvant treatment including craniospinal irradiation with boost to the posterior fossa and chemotherapy (Table 1), whereas PA patients had not. None of the patients showed signs of tumor recurrence. The local institutional review board approved the study. All patients and/or their guardians gave written, informed consent.

Seventeen MB and 13 PA patients were included in the DTI analysis. The demographic data are summarized in Table 1. Seven MB patients had to be excluded from the initial group of 24 because of severe distortions in the diffusion-weighted images in the brain region adjacent to a metal-containing valve that had been implanted to regulate cerebrospinal fluid drainage.

Table 1. Patient characteristics

Characteristic	Medulloblastoma patients	Pilocytic astrocytoma patients
Total number	17	13
Age (y)	14.7 (8.5)	13.3 (7.6)
Age at diagnosis (y)	9.9 (5.8)	10.9 (3.5)
Time since diagnosis (y)	3.8 (4.8)	1.9 (3.5)
Male	10	6
Female	7	7
Adjuvant treatment		—
Craniospinal irradiation (Gy)	24–32	—
Boost to posterior fossa (Gy)	18–30	—
Chemotherapy	CCNU, carboplatin, vincristine, cyclophosphamide, methotrexate, etoposide	—
Leukoencephalopathy		
Grade 1	11	—
Grade 2	5	—
Substituted GH	1	—
Substituted TH	8	—
Substituted HC	1	—
Midline tumor site	15	7
Hemispheric tumor site	2	6
Metastases	5	—

Abbreviations: CCNU = 1-(2-chloroethyl)-3-cyclohexyl-L-nitrosourea; GH = growth hormone; TH = thyroid hormone; HC = hydrocortisone.

Adjuvant treatment of medulloblastoma patients was carried out according to the HIT (''Hirntumor'') protocols of the German Speaking Society of Pediatric Oncology and Hematology. Displayed are median age and interquartile range from 25th to 75th percentile (in parentheses), number of male and female patients, number and grade of occurrence of leukoencephalopathy, number of patients with substituted hormones, number of midline and hemispheric tumor localization as documented by the attending radiologist (derived from T1- and T2-weighted MRI studies), and number of patients with metastases.

Control subjects

Control subjects were selected from a cohort of patients who received MRI because of clinical indications like headache but did not show any pathologic findings in structural imaging. Patients and controls were matched for their age. For those younger than 18 years, the ages of the matched pairs differed by less than 12 months. The age difference was allowed to be greater in patients older than 17 years because the influence of age on FA is believed to be less important after adolescence. Median age of the control group was 14.8 years for MB patients (interquartile range from 25th to 75th percentile, 11.1 y; 12 male, 5 female) and 13.3 years for PA patients (interquartile range from 25th to 75th percentile, 7.5; 8 male, 5 female).

Data acquisition

All imaging was performed with a 3-T MRI system equipped with an eight-channel head coil (Signa Excite; GE Healthcare, Milwaukee, WI). Diffusion tensor MRI using single-shot spin-echo echo-planar imaging (repetition time [TR]/echo time [TE] = 9,000 ms/100 ms) was accelerated by a factor of 2 with the parallel imaging ''array spatial sensitivity encoding technique,'' using a slice thickness of 4 mm (no gap) and an acquisition matrix of 256 × 256, providing a resolution of 1 mm × 1 mm × 4 mm (voxel volume of 4 mm^3). The diffusion gradients were applied in 25 directions at a b-factor of 1,000. One image set was acquired without use of a diffusion gradient (b = 0). For total brain coverage 25–28 sections were obtained, resulting in a total of 650–728 images acquired in approximately 5 min. For diagnostic purposes conventional imaging included axial T2-weighted fast spin-echo sequences (TR/TE, 4,000 ms/100 ms; 3 mm-sections; in-plane resolution of 0.4 mm × 0.8 mm) and T1-weighted inversion-recovery fast spin-echo sequences (TR/TE, 2,000 ms/15 ms; inversion time, 860 ms; 5-mm sections; in-plane resolution of 0.4 mm × 0.8 mm). T2-weighted images were used to assess the severity of white matter changes and atrophy and to rate leukoencephalopathy (18).

Image processing

The image data were converted from DICOM to Analyze format using MRIcro (freeware; www.sph.sc.edu/comd/rorden/mricro.