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Diffusion Tensor Imaging and Neurobehavioral Outcome in Children With Brain Tumors Treated With Chemotherapy

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Abstract

Background. Childhood brain tumor survivors (CBTS) often experience treatment-related neurocognitive deficits affecting quality of life (QOL), but systemic chemotherapy contributions to outcomes are unclear. Our objective was to relate brain tissue changes to neurocognitive and QOL effects after systemic myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue in CBTS. *Procedure*. Regional brain volumes and diffusion tensor indices were correlated with neurocognitive, behavioral, and QOL measures, and compared between 8 CBTS (mean age 8.5 years, mean age at diagnosis 32 months), and 9 healthy controls (mean 9.3 years). *Results*. Overall QOL, school, and psychosocial functioning were significantly lower in patients ($P < .05$). Most patients scored within normative ranges on neurocognitive and behavioral assessment. Elevated mean diffusivity and decreased fractional anisotropy, indicating gray and white matter injury, respectively, appeared in memory and executive functioning areas. Low scores on Inhibition on the Neuropsychological Assessment–II were correlated with elevated mean diffusivity in prefrontal cortex. *Conclusions*. Brain injury, decreased QOL, and to a lesser extent, executive functioning deficits appear in CBTS treated with myeloablative chemotherapy and autologous hematopoietic progenitor cell rescue. Early cognitive and psychological assessment and intervention are warranted in this population.

Keywords

adverse effects, central nervous system tumors, chemotherapy, cognitive functioning

Introduction

At least 40% of childhood brain tumor survivors (CBTS) show posttreatment physical and neurocognitive limitations (Anderson, 2003), depending on multiple factors related to age at diagnosis, tumor type, location, and treatment. With increasing numbers of children surviving brain tumors, characterization of central nervous system injury resulting in late neurocognitive effects and ultimately, decreased quality of life (QOL) can inform nursing interventions to improve outcomes.

Cranial irradiation, a standard of brain tumor treatment, exerts detrimental effects on the developing brain (Allen, 1978; Butler & Haser, 2006; Cohen & Duffner, 1991; Grill, Kieffer, & Kalifa, 2004). Chemotherapy agents, although hypothesized to be less toxic than irradiation, appear to injure neural progenitor cells and healthy brain tissue, in addition to the targeted cancer cells (Dietrich, Han, Yang, Mayer-Proeschel, & Noble, 2006; James et al., 2008; Mignone & Weber, 2006; Wick et al., 2004). The injury has been demonstrated in both gray and white matter in children treated for brain tumors and acute lymphoblastic leukemia (ALL) with standard-dose chemotherapy in combination with cranial irradiation (Mulhern et al., 2001).

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The childhood brain tumor population shows white matter loss related to cognitive functioning (Reddick et al., 2005); specifically, associations between reduced attention (Reddick et al., 2003), impaired memory (Law et al., 2011), and decreased hippocampal volume (Nagel et al., 2004) following craniospinal irradiation. Children with ALL treated with systemic and intrathecal chemotherapy show deficits in executive functioning that correlate with white matter loss in the right frontal cortex (Carey et al., 2008). There is little direct evidence of whether brain tissue loss correlates with neurocognitive deficits for the pediatric brain tumor population treated with myeloablative chemotherapy followed by autologous hematopoietic progenitor cell rescue (AuHCR). The available data relating structural injury, and especially gray matter injury, on neoplastic intervention effects in this population, are thus sparse.

Childhood brain tumor survivors are often reported to have lower QOL than survivors of other childhood cancers, with those receiving cranial irradiation reporting lower income as adults and lower total health-related QOL (Armstrong et al., 2009; Bhat et al., 2005). When compared to survivors of ALL, CBTS reported significantly poorer physical and psychosocial health, social and school functioning, and general and cognitive fatigue (Meeske, Patel, Palmer, Nelson, & Parow, 2007). Findings are mixed as to whether and how neurocognitive deficits specifically affect QOL in this population (Baron Nelson, Compton, Patel, Jacob, & Harper, 2013).

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) procedure that is sensitive to brain tissue changes at the microstructural level. Measuring the diffusion of water between tissues is useful to determine subtle alterations in gray and white matter. Two indices, mean diffusivity (MD) and fractional anisotropy (FA), when compared to healthy controls, provide information about cellular and fiber injury across gray and white matter (MD), and changes in axonal integrity in white matter (FA). Children with medulloblastoma treated with both cranial irradiation and chemotherapy displayed brain tissue injury, as evidenced by decreased FA, that correlated with deterioration in school performance (Khong et al., 2003). Reports of DTI studies in children with brain tumors treated with surgery and high-dose chemotherapy with AuHCR are lacking.

We examined the relationships between brain tissue changes and neurocognitive deficits and QOL in CBTS treated with myeloablative chemotherapy and AuHCR. We hypothesized differences in white and gray matter or brain tissue loss in key cognitive areas, neurocognitive dysfunction, and decreased QOL in patients relative to healthy age- and gender-matched controls. Given that the hippocampus, fornix, and mammillary bodies have long been associated with roles in memory, and the prefrontal cortex with executive functioning (Kumar et al., 2005; Makris et al., 2007), we anticipated that injury in these areas would be accompanied by deficits in those cognitive skills.

Method

Design

A 2-group comparative cross-sectional design was used to assess regional FA and MD values, and scores on QOL and cognitive–behavioral questionnaires between 8 CBTS and 9 age- and gender-matched healthy controls. The relationships between indicators of tissue injury in regions of interest of the brain and specific functional outcomes (memory, executive functioning, and QOL) were evaluated in the patient group with a survey design. The institutional review board approved the study, and signed informed consent was obtained from a parent of each subject. Assent was obtained from children aged 7 to 13 years.

Sample

A small convenience sample of CBTS meeting study inclusion criteria (history of brain tumor with no current evidence of disease, previous treatment on a myeloablative chemotherapy-only regimen, current age between 5 and 13 years, off-therapy for at least 6 months, and speaking either English or Spanish) was recruited over 14 months. Exclusion criteria were residual disease, history of cranial irradiation, concurrent diagnosis of neurofibromatosis or other serious neurological anomaly, history of prolonged (> 1 week) posterior fossa syndrome postoperatively, presence of any implanted metal device, or inability to participate in neuropsychological testing due to severe developmental disability.

Of the 16 potentially eligible CBTS mailed an invitation letter, 12 (75%) responded. Among these, 2 were ineligible because of the presence of residual tumor or congenital brain malformation and 2 families declined due to distance from the institution. Therefore, 8 CBTS were available who agreed to participate, whose age and gender were used to find healthy controls. 6 of the remaining 8 had been treated for posterior fossa tumors (medulloblastoma), 1 for a third ventricular tumor (choroid plexus carcinoma), and one for a supratentorial primitive neuroectodermal tumor. Healthy controls to match the 8 CBTS were recruited from children of staff at the institution. Inclusion criteria were aged 5 to 13 years, fluency in English or Spanish, and ability to complete a 30-minute MRI without sedation. Exclusion criteria were any neurological, developmental or learning disability, inability to complete MRI without sedation, or presence of metal appliances in the body that would impair MRI interpretation.

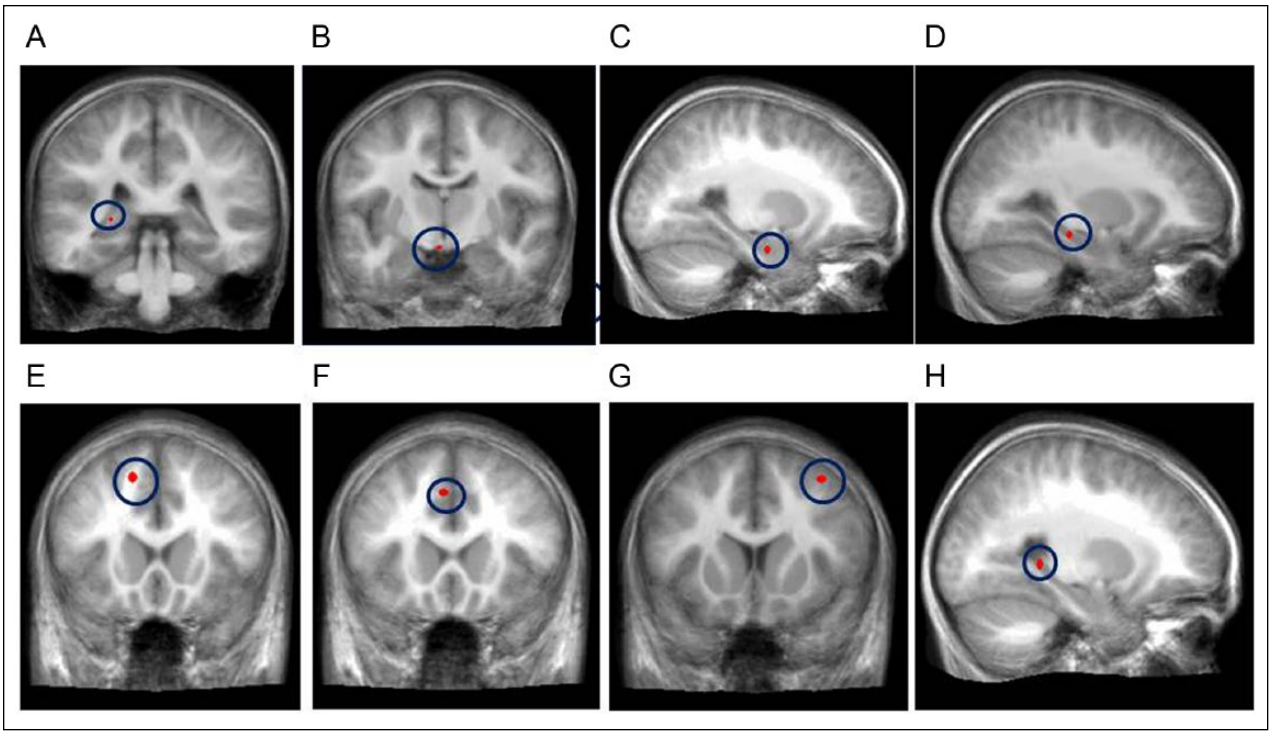

Figure 1. Regions of interest (from upper left): (A) fornix, (B) mammillary body, (C) anterior hippocampus, (D) mid hippocampus, (E) prefrontal cortex white matter, (F) superior frontal gyrus, (G) middle frontal gyrus, and (H) posterior hippocampus.

Measures

Brain Tissue Integrity. Diffusion tensor imaging assesses 3-dimensional diffusion characteristics of water within brain tissue and within coherent bundles of axonal fiber tracts (Cercignani, Inglese, Pagani, Comi, & Filippi, 2001) and was used to evaluate gray and white matter integrity throughout the brain. Voxel-based morphometry (Ashburner & Friston, 1999), derived from the T1-weighted images, was performed to obtain white and gray matter volumes in patients and controls. T1- and T2-weighted images were collected to examine FA and MD in regions of interest in the brain using a single 3.0 Tesla Philips Achieva MRI scanner. Only T1-weighted and DTI images were obtained on controls to minimize time spent in the scanner without sedation. DTI images were collected as per a previously published protocol (Nelson et al., 2014).

The left and right hippocampi were traced by the PI on normalized images for each subject using MRIcron and processed with volumetric analysis using Matrix Laboratory. Four subjects were later retraced by the PI and then by a research associate, to establish inter- and intrarater reliability. Several bilateral regions of interest were drawn on a mask image of all 17 subjects to determine mean MD and FA of each region (superior and middle frontal gyri; prefrontal cortex white matter; fornix; anterior, mid, and posterior sections of the hippocampus; and mammillary bodies) within the CBTS and control groups, as depicted in Figure 1.

Neurocognitive and QOL Assessment. Neurocognitive measures were selected to assess memory and executive functioning, based on established validity and reliability with broad pediatric populations (Embry et al., 2012; Mottram & Donders, 2005), and included the CVLT-C (California Verbal Learning Test–Children's Version) to assess verbal memory, and a developmental Neuropsychological Assessment–Second edition (NEPSY-II) memory for designs test to assess nonverbal memory. The NEPSYII Inhibition test evaluated Inhibitory control and Switching, components of executive functioning. The Behavior Rating Inventory of Executive Function parent report (BRIEF; Gioia, Isquith, Retzlaff, & Espy, 2002) provided summary scores of behavioral regulation index, metacognition index, and global executive composite. The Behavior Assessment System for Children–2 parent report (BASC-2; Reynolds & Kamphaus, 2004), provided 4 summary scores: externalizing problems, internalizing problems, behavioral symptoms index, and adaptive skills.

The PedsQL 4.0 Generic Core Scale (Varni et al., 1998) was used to self-evaluate QOL in all subjects; a parent of each child also completed the parent proxy

report. Scores from physical, emotional, social, and school functioning domains were obtained, together with a psychosocial functioning composite score. Total QOL score was derived from all 4 domains.

Procedures

Following informed consent, child and parent completed the PedsQL Generic Core Scale. Parents completed the BRIEF and BASC-2 while subjects underwent MRI and/or neuropsychological testing. Diagnosis and treatment history were abstracted from medical records. The MRI protocol followed, lasting 1 hour for CBTS, and including T1- and T2-weighted and pre- and postcontrast images for clinical surveillance purposes, in addition to DTI. For controls, the protocol took 30 minutes to complete, and included only T1-weighted and DTI images; no contrast was administered. Five patients received propofol anesthesia for the MRI, as was standard for their routine scans, and the remaining 3 patients and 9 controls used MRI-compatible movie goggles for distraction. Images were de-identified and coded for analysis after review by a neuroradiologist.

Image Processing. The MRI data were processed according to a protocol published previously (Nelson et al., 2014).

Data Analyses. Data were analyzed using the Statistical Package for Social Sciences, Version 17 (SPSS, IBM Corp.). *T* tests were performed to determine differences in mean hippocampal volumes, mean FA and MD in each region of interest, and mean scores on the BASC-2, BRIEF, and PedsQL between CBTS and controls. Pearson correlation analyses explored relationships between DTI values and neurocognitive, BASC-2, BRIEF, and PedsQL, scores in the CBTS group.

Results

Childhood brain tumor survivors and controls were similar in demographics, except that parents of healthy controls had significantly higher education levels (4 years of college or more) compared to parents of CBTS (community college or lower; $P = .01$), and fewer children in the home ($P = .01$). Demographic and treatment information is shown in Table 1.

A pediatric neuroradiologist evaluated the MRI scans for clinical abnormalities, and in CBTS, for evidence of recurrent disease. Although no CBTS had recurrence of the primary brain tumor, one had a stable low-grade glioma of the right hippocampus (a second brain tumor) and another had a midline arteriovenous malformation, both of which caused no symptoms and had been noted on previous scans. No abnormal findings were noted in healthy controls.

Imaging

White and gray matter volumes, when considered separately, trended lower in CBTS than controls, but results were not significant. Hippocampal volumes were very similar in patients and controls (Table 2). Mean diffusivity was significantly higher in CBTS than controls in all regions of interest (prefrontal cortex, hippocampus, fornix, mammillary bodies) analyzed by Statistical Parametric Mapping–Version 8 (SPM-8), possibly reflecting long-term damage to tissues. Fractional anisotropy was significantly lower in CBTS than controls in the majority of regions analyzed, indicating decreased axonal integrity in these areas (Table 3).

Neurocognitive Function

Executive Functioning. No significant differences between CBTS and controls emerged on parent report of executive functioning via the BRIEF. Childhood brain tumor survivors were categorized as more "at-risk" for the BASC-2 subcategory of "atypicality" than controls ($P = .01$), but all other subscales were similar between groups. Female CBTS were rated significantly higher by their parents on internalizing problems ($P = .03$) than male CBTS.

On neurocognitive testing, 3 CBTS scored below average (>1 SD below the normative mean) on the NEPSY Inhibition component (INI) of executive functioning, and 2 of the 6 children eligible (>6 years old at study) scored below average on the NEPSY Switching component (INS) (Table 4). Those CBTS scoring below average were older at testing ($P < .05$) and had been off-therapy longer ($P < .05$) than those who scored better. Childhood brain tumor survivors who were 2 years of age or younger at diagnosis scored lower on the Switching portion of the NEPSY Inhibition test ($P < .01$), and girls performed significantly better than boys on the Inhibition portion ($P < .05$).

Memory. All CBTS scored within 1 SD of the normative mean for verbal memory (CVLT-C long delay free recall score) and only 1 CBTS scored below average on nonverbal memory (Memory for Designs long delay score; Table 4).

Quality of Life. Childhood brain tumor survivors rated their QOL as significantly lower on 2 of the 4 subscales of the PedsQL and on the psychosocial summary and total overall scores when compared to healthy controls (Table 5). Parents of CBTS rated their children significantly lower on physical functioning and overall QOL

Table 1. Demographics.

	Childhood Brain Tumor Survivors (n = 8)	Healthy Controls (n = 9)
Age, years, M ± SD (range)	8.5 ± 1.3 (5-13)	9.3 ± 2.6 (6-13)
Gender, n (%)		
Males	3 (37.5)	3 (33.3)
Females	5 (62.5)	6 (66.7)
Ethnicity, n (%)		
Hispanic	5 (62.5)	1 (11.1)
Caucasian	1 (12.5)	5 (55.6)
Asian	1 (12.5)	1 (12.5)
African American	0	2 (25)
Mixed	1 (12.5)	0
Age at diagnosis, months, M ± SD (range)	31.8 ± 16.5 (14-55)	
Time off treatment, years, M ± SD (range)	5.4 ± 2.9 (2.5-11.4)	
Hydrocephalus at diagnosis, n (%)		
None	3 (37.5)	
Mild	2 (25.0)	
Moderate	3 (37.5)	
Tumor type, n (%)		
Supratentorial primitive neuroectodermal tumor	1 (12.5)	
Medulloblastoma	6 (75.0)	
Choroid plexus carcinoma	1 (12.5)	
Tumor location, n (%)		
Posterior fossa	6 (75.0)	
Parieto-occipital	1 (12.5)	
Occipital horn of ventricle	1 (12.5)	
Chemotherapy, n (%)		
Vincristine	8 (100)	
Cisplatin	8 (100)	
Cyclophosphamide	8 (100)	
Etoposide	8 (100)	
Carboplatin	8 (100)	
Thiotepa	8 (100)	
Temozolomide	3 (37.5)	
Methotrexate	3 (37.5)	

Table 2. Intracranial Contents and Hippocampal Volumes.

Brain Tissue Measured	CBTS (n = 8), Volume (L) ± SD	Controls (n = 9), Volume (L) ± SD	*P*
Total brain volume	1.18 ± 0.77	1.25 ± 0.94	.13
Total gray matter	0.85 ± 0.05	0.87 ± 0.05	.39
Total white matter	0.34 ± 0.04	0.38 ± 0.05	.06
Total intracranial volume	1.63 ± 0.22	1.50 ± 0.25	.27
Total CSF volume	0.44 ± 0.25	0.25 ± 0.28	.14
Gray: White ratio	2.52 ± 0.23	2.30 ± 0.23	.07
Brain: CSF ratio	3.91 ± 2.87	8.83 ± 4.53	.02
Brain: Total intracranial volume ratio	0.74 ± 0.12	0.85 ± 0.13	.08
Right hippocampus	0.0025 ± 0.021	0.0026 ± 0.021	.30
Left hippocampus	0.0025 ± 0.014	0.0026 ± 0.022	.24

Abbreviations: CBTS, childhood brain tumor survivors; CSF, cerebrospinal fluid.

compared with controls. Quality of life scores were not significantly correlated to scores on neurocognitive assessment. Younger age at study was related to poorer child rating of social functioning ($P < .01$). Female CBTS rated themselves significantly lower than males ($P = .02$) on emotional functioning.

Table 3. Regional Fractional Anisotropy (FA) and Mean Diffusivity (MD).

	FA, Mean ± SD			MD, Mean ± SD		
Region of Interest	CBTS (n = 8)	Controls (n = 9)	*P*	CBTS (n = 8)	Controls (n = 9)	*P*
Left middle frontal gyrus	0.206 ± 0.015	0.243 ± 0.024	<.002	0.00131 ± 0.00019	0.00086 ± 0.00004	<.0001
Right middle frontal gyrus	0.213 ± 0.031	0.244 ± 0.018	<.03	0.00124 ± 0.00016	0.00089 ± 0.00006	<.0005
Left superior frontal gyrus	0.214 ± 0.013	0.228 ± 0.011	<.03	0.00134 ± 0.00017	0.00091 ± 0.00004	<.0001
Right superior frontal gyrus	0.223 ± 0.024	0.242 ± 0.013	NS	0.00135 ± 0.00019	0.00091 ± 0.00004	<.0001
Left prefrontal cortex WM	0.303 ± 0.026	0.341 ± 0.019	<.01	0.00114 ± 0.00014	0.00079 ± 0.00025	<.0001
Right prefrontal cortex WM	0.304 ± 0.018	0.339 ± 0.017	<.02	0.00117 ± 0.00020	0.00080 ± 0.00026	<.0001
Left fornix	0.346 ± 0.055	0.372 ± 0.020	NS	0.00145 ± 0.00035	0.00101 ± 0.00020	<.01
Right fornix	0.322 ± 0.036	0.352 ± 0.022	NS	0.00146 ± 0.00035	0.00107 ± 0.00018	<.01
Left mammillary body	0.282 ± 0.031	0.309 ± 0.025	NS	0.00251 ± 0.00031	0.00170 ± 0.00014	<.0001
Right mammillary body	0.257 ± 0.028	0.278 ± 0.023	NS	0.00279 ± 0.00033	0.00190 ± 0.00017	<.0001
Left anterior hippocampus	0.241 ± 0.023	0.238 ± 0.013	NS	0.00134 ± 0.00016	0.00096 ± 0.00039	<.0001
Right anterior hippocampus	0.244 ± 0.010	0.250 ± 0.017	NS	0.00126 ± 0.00019	0.00093 ± 0.00026	<.0001
Left mid-hippocampus	0.278 ± 0.036	0.305 ± 0.018	NS	0.00140 ± 0.00021	0.00096 ± 0.000057	<.0001
Right mid-hippocampus	0.259 ± 0.022	0.280 ± 0.016	<.04	0.00136 ± 0.00021	0.00098 ± 0.000046	<.0001
Left posterior hippocampus	0.292 ± 0.051	0.317 ± 0.029	NS	0.00178 ± 0.00044	0.00125 ± 0.00030	<.01
Right posterior hippocampus	0.289 ± 0.029	0.314 ± 0.028	NS	0.00155 ± 0.00037	0.00115 ± 0.00023	<.02

Abbreviations: CBTS, childhood brain tumor survivors; NS, nonsignificant; WM, white matter.

Table 4. *z* Scores[a] on Neuropsychological Battery (CBTS Only).

	n	Mean	SD	Range
NEPSY INS (switching)	5	−1.47	1.61	−3.33 to 0.33
NEPSY INI (inhibition)	8	−1.17	1.37	−3.33 to 0.67
CVLT-C long delay free recall	8	0.00	1.00	−1.00 to 2.00
Memory for designs delayed	8	0.00	1.26	−2.00 to 2.00

Abbreviations: CBTS, childhood brain tumor survivors; CVLT-C = California Verbal Learning Test–Children's Version.
[a]*z* scores have a mean of 0 and a standard deviation of 1.

Table 5. Quality of Life Scores.

Domain	CBTS, Mean ± SD	Control, Mean ± SD	*P*	Parent CBTS, Mean ± SD	Parent Control, Mean ± SD	*P*
Physical	73.4 ± 19.4	88.9 ± 9.8	.05	81.6 ± 13.6	96.5 ± 6.3	.01
Emotional	61.3 ± 25.7	73.3 ± 19	.29	75.0 ±18.3	79.4 ± 14.9	.59
Social	65.6 ± 28.2	83.9 ± 18.3	.13	82.5 ± 10.7	91.1 ± 9.3	.10
School	70.6 ± 15.2	86.7 ± 8.7	.02	76.3 ± 19.6	90.0 ± 10.6	.09
Psychosocial	65.8 ± 15.5	81.3 ± 12.5	.04	77.9 ± 14.1	86.9 ± 7.3	.12
Total score	68.4 ± 15.4	83.7 ± 11.1	.03	79.2 ± 13.7	90.1 ± 5.9	.05

Abbreviation: CBTS, childhood brain tumor survivor.

Relationship of Brain Structural Change and Neurobehavioral Outcome. In the CBTS group, there were 2 correlations of significance: INI *z* score was negatively correlated with left middle frontal gyrus MD (Pearson correlation −.71, $P = .05$), demonstrating that lower Inhibition scores were associated with higher MD values in that area of the prefrontal cortex; and both INI *z* scores and Memory for Designs long delay *z* scores were negatively correlated with years off-therapy (Pearson correlation −.85, $P = .01$ and Pearson correlation −.75, $P = .03$), respectively, indicating a relationship between poorer scores on the Inhibition component of executive functioning and memory, and longer time off treatment.

Discussion

Microstructural brain tissue changes, as indicated by elevated MD and decreased FA, appeared in key brain areas

related to memory and executive functioning in CBTS treated with high-dose, marrow-ablative chemotherapy without cranial irradiation. The majority of CBTS placed in the average- to above-average range on tests of memory and executive functioning, relative to published norms. However, approximately one-third of CBTS (33% for Inhibition, 37% for Switching) obtained scores that were more than 1 SD below the age-expected mean for executive functioning, whereas only 16% of the general population would typically obtain scores below this level. In general, QOL scores were lower in the CBTS as compared to control group, as rated by both subject and parent; of note, those who scored most poorly in neurocognitive testing did not demonstrate significantly lower QOL than those who scored better. Thus, in this CBTS sample, DTI indices of central nervous system injury were present and accompanied by neurocognitive dysfunction and poorer QOL.

We found limited support for our second hypothesis of a correlative relationship between lowered memory and executive functioning performance, and injury in the hippocampal structures and prefrontal cortex of CBTS, respectively. A significant correlation did appear between low performance on the Inhibition test of executive functioning and elevated MD in an area of the prefrontal cortex, but not between memory tests and those structures associated with memory function.

There have been reports of decreased FA, at a mean of 3.8 years after diagnosis, in the cerebellar hemispheres and frontal lobes of children who underwent surgical resection of cerebellar tumors without additional treatment, and in those treated with surgical resection, chemotherapy and cranial radiation (Rueckriegel et al., 2010). Childhood brain tumor survivors treated with high-dose, but nonmyeloablative, chemotherapy and cranial irradiation showed changes in brainstem FA over 5 years later; some measurements returned to baseline by 4 years after initial declines, while others maintained a lower FA over time (Hua et al., 2011). Our findings of lower FA in the prefrontal cortex may result from having had a posterior fossa tumor (6 of 8 patients) or from surgical resection. However, no DTI studies in children with cancer have discussed increased MD after treatment. A study in adult women treated with chemotherapy for breast cancer found a significant increase in MD in frontal white matter (Deprez et al., 2011). This preliminary finding needs further exploration to determine whether elevated MD indicates a different type of cellular loss or injury that may be unique to chemotherapy effects.

The memory testing findings support reports of less-severe neurocognitive deficits in CBTS treated with chemotherapy without cranial irradiation (Sands et al., 2010). Younger age at diagnosis did not predict poorer neurocognitive outcomes after treatment, that excluded cranial irradiation, which also supports findings of others (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Sands et al., 2010). DTI indices in hippocampal structures, indicative of tissue change or injury, were generally not predictive of lower scores on memory testing. It is possible that, despite existing injury as represented by higher MD, CBTS were able to compensate sufficiently to perform reasonably well on neurocognitive tests, at least for the limited time frame involved in this short battery of testing. It is encouraging that CBTS treated in this manner display normal memory outcome, despite injury indicated in hippocampal areas.

Whereas the injury findings suggest that all CBTS show a significant degree of long-term brain structural change, the overall normal scores on neurocognitive assessment suggest that neural function was either less affected by injury, or that neuroplasticity compensated for structural deficits. Without objective information on CBTS' premorbid neurocognitive function, it is not possible to know how much function may have been lost due to the disease and treatment process.

Relatively normal neurocognitive performance, however, did not predict good QOL scores. Lower QOL is a finding consistent with the literature on CBTS treated with multimodal therapy, including cranial irradiation (Cardarelli et al., 2006; Eiser, Greco, Vance, Horne, & Glaser, 2004; Meeske et al., 2007). However, there is a report of comparatively normal QOL in CBTS treated with high-dose marrow-ablative chemotherapy alone (Sands et al., 2011). When compared with published PedsQL means for children with brain tumors (Palmer, Meeske, Katz, Burwinkle, & Varni, 2007), 4 CBTS in this study scored >1 SD lower in psychosocial functioning, 3 in emotional functioning, 2 in social functioning and total QOL score, and 1 in physical and school functioning. Low QOL scores in our CBTS sample may reflect their young age at diagnosis and at study, difficulty with continuing to compensate in the more expansive areas of functioning in daily life, and the experience of serious illness with frequent hospitalizations in very young childhood.

Gender played a significant role in outcome in certain areas, where girls were rated as having better executive functioning skills, but poorer emotional QOL, and were rated as more likely to internalize problems by their parents. Gender may contribute significantly to neurocognitive and QOL outcomes in pediatric cancer, with girls scoring lower on health-related QOL (Blaaubroek et al., 2007; Geenen et al., 2007), and showing more neurotoxic effects of treatment than boys (von der Weid et al., 2003; Waber, Tarbell, Kahn, Gelber, & Sallan, 1992). More pronounced neurological changes in girls after treatment may result from the more rapid development of glial and other neuronal brain tissue in females, with myelination leading in young girls (Bartzokis, 2005). Long-term female cancer survivors, studied in a large cohort, had

significantly poorer long-term QOL across multiple domains (Zeltzer et al., 2008), so this demographic group of survivors should have close psychological follow-up.

While time off-treatment was not a variable in our original hypotheses, we observed poorer scores on executive functioning and memory with longer time off-treatment. There is a paucity of research on long-term neurocognitive outcomes of CBTS treated with chemotherapy alone, but our study suggests this population may also experience decline in function over time, as do children treated with cranial irradiation, and merits further longitudinal investigation.

Limitations of this study include the small sample size and neurocognitive testing collected on the CBTS only, thus preventing comparison of all assessments with controls. Our analytical approach was largely exploratory in nature, and our results require replication. Certainly precluded was statistical power to perform subgroup or multiple regression analyses to determine significant predictors of outcome. The varying time since treatment means that the brain of each child had a different duration of exposure to mechanisms of structural alterations, whether they were developmental or resulting from treatment effect.

Childhood brain tumor survivors treated with high-dose chemotherapy and AuHCR a mean of 8 years prior to this study displayed evidence of brain tissue changes in key areas related to memory and executive functioning; however, their scores on neurocognitive testing in these areas were, for the most part, within published norms. Quality of life self-assessment was significantly lower in CBTS than controls, despite many years off treatment and relatively good neurocognitive outcome.

Conclusion

The findings of altered brain structure associated with neurocognitive and other psychological function give a biological underpinning to the symptoms observed in CBTS. While psychosocial support is often available during cancer treatment, survivors often have less access to such services after treatment ends. Periodic assessment of neurocognitive and QOL status throughout childhood and adolescence could identify problems early and lead to timely referrals and intervention. With improved methods of administering cranial irradiation, treatment protocols with high-dose marrow-ablative chemotherapy, and increasing use of biological therapies in this population, it is important to define more current long-term neurocognitive and QOL outcomes and to determine causative factors for poor outcomes. Determination of these factors will enable development and implementation of appropriate early interventions to improve outcomes in survivors of childhood brain tumors.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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