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Central Nervous System Injury, Neurocognitive and Quality of Life Outcomes in Children with Brain Tumors Treated with Chemotherapy

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Central Nervous System Injury, Neurocognitive and Quality of Life Outcomes in Children with Brain Tumors Treated with Chemotherapy

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Nursing

by

Mary Christine Baron Nelson

2012
Two-thirds of children diagnosed with brain tumors achieve long-term survival, and increasingly, children younger than 5-6 years at diagnosis are treated with high-dose chemotherapy protocols, delaying or foregoing cranial radiation. Intrathecal chemotherapy is associated with white matter loss, with systemic administration of certain agents also damaging healthy brain tissue. However, effects of systemic chemotherapy on the brain in children with tumors are unclear. Our first objective was to compare structural neural integrity with magnetic resonance imaging procedures in children with brain tumors (n = 7, mean age 8.3 years), treated with chemotherapy a mean of 5.4 years earlier, to age- and gender-matched healthy controls (n = 9, mean age 9.3 years). We also sought to explore the relationship between tissue loss, memory and executive functioning and quality of life (QOL) effects. Magnetic resonance imaging data were collected using a diffusion tensor imaging protocol to evaluate tissue integrity throughout the brain, and in specific regions of interest. Voxel-based morphometry was used to determine differences between groups. In addition, we used neurocognitive, behavioral and QOL assessments. Mean diffusivity and fractional anisotropy maps were obtained from normalized,
smoothed images, and the two groups were compared using analysis of covariance, with age and gender as covariates. Higher mean diffusivity values emerged in patients over controls \( (p < 0.05, \text{corrected for multiple comparisons}) \), and were especially apparent in the central thalamus, internal and external capsules, putamen, globus pallidus and pons. No significant differences emerged in fractional anisotropy values between groups. The patient group had lower brain-to-CSF ratio \( (p = .03) \), assessed with volumetric analyses. Overall QOL, school functioning, and psychosocial functioning were significantly lower in patients. The majority of patients scored within the average range on memory and executive functioning tests, and behavior assessment did not differ from controls. Significantly higher mean diffusivity, indicating long-term damage, appeared in multiple areas in patients 5 years after treatment with chemotherapy. Early intervention may provide neuroprotection or repair to alleviate the long-term consequences of the original trauma and chemotherapy-related damage.
The dissertation of Mary Christine Baron Nelson is approved.

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DEDICATION PAGE

What a journey this has been, a test of faith and endurance. “I can do all things through him who strengthens me” (Philippians 4:13). Although it seemed at times that unsurpassable roadblocks were placed in my way, the sustained support of faith, family members, friends, faculty and colleagues kept me on track for the past five years.

First and foremost, I thank my husband, Dr. Marv Nelson, who has always said, “yes, dear” to whatever path I wanted to follow for the past 22 years. His patient listening (or pretend listening) to my trials and tribulations was something I could always count on. My sons, Kevin and Andy, have grown from young high school students to young men in college during this time, and I’m so proud of their increasing independence and responsibility. My sister and best friend, Anne, also put up with my tales of challenges on many long-distance phone calls and emails. My father and brother, John, provided long-distance support, too.

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Finally, just an acknowledgement of my close friends Kim Suehiro, Ann Wetzel, Karla Wilson and Belinda Mitchell who also continually cheered me on. And a word to my wonderful mentor and friend, Dr. Kathy Meeske, who inspired me to take this path – thank you so much!
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
</tr>
<tr>
<td>Committee Page</td>
</tr>
<tr>
<td>Dedication</td>
</tr>
<tr>
<td>List of Figures and Tables</td>
</tr>
<tr>
<td>Acknowledgements</td>
</tr>
<tr>
<td>Vita</td>
</tr>
<tr>
<td>Introduction to the Manuscripts</td>
</tr>
<tr>
<td>Bibliography for Introduction</td>
</tr>
<tr>
<td>CNS Injury and Neurobiobehavioral Function in Children with Brain Tumors – a review of the literature</td>
</tr>
<tr>
<td>Bibliography for CNS Injury</td>
</tr>
<tr>
<td>Brain Structural Changes in Children Five Years After Chemotherapy for Brain Tumors</td>
</tr>
<tr>
<td>Bibliography for Brain Structural Changes</td>
</tr>
<tr>
<td>Diffusion Tensor Imaging and Neurobiobehavioral Outcome in Children with Brain Tumors Treated with Chemotherapy</td>
</tr>
<tr>
<td>Bibliography for Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>Conclusions</td>
</tr>
</tbody>
</table>
LIST OF FIGURES AND TABLES

Figures

Differentiation of Neuronal Cells 27
Functional Areas of the Brain 28
Mechanisms of Radiation/Chemotherapy Injury to Healthy Brain Tissue 29
Increased MD in deeper cortical regions 65
Diffusely increased MD 66
Regions of Interest 94
Mean FA Results 95
Mean MD Results 96
BRIEF™ Results 97
PedsQL® Results 98

Tables

Neurotoxic Effects of Cranial Radiation (CRT) and Chemotherapy on In Vitro Cells and Rodents 30
Neurotoxic Effects of Cranial Radiation (CRT) and Chemotherapy in Children 34
Effect of Cancer Treatment on Neurobiobehavioral Status in Rodents 36
Effect of Cancer Treatment on Neurobiobehavioral Status in Children 38
Tumor Types and Treatment for Patient Group (n = 7) 67
Characteristics of Patients (n = 7) and Controls 69
Brain Tissue Measurements 70
Patient Tumor Types and Treatment (n = 8) 99
Demographics of Patients (n = 8) and Controls 101

Hippocampal Volumes 102

BASC-2 Results 103
ACKNOWLEDGEMENTS

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INTRODUCTION TO THE MANUSCRIPTS

Brain tumors affect approximately one in every 30,000-40,000 children in the U.S. (Singer & Byrne, n.d.). Neurocognitive deficits are common in survivors, often contributing to decreased quality of life. Cranial radiation is more damaging to the developing brain of a child than to the fully developed adult brain; however, little is known about the effect of chemotherapy on the developing brain of a child who survives a brain tumor. The question of whether high-dose chemotherapy in children leads to brain tissue injury and loss with accompanying functional changes in the CNS as memory and executive functioning deficits was the research question addressed. This study measured brain tissue loss from high-dose chemotherapy and related that loss to neurocognitive deficits and quality of life (QOL) in children with brain tumors.

Statement of the Problem

Many childhood brain tumor survivors are left with physical and neurocognitive limitations that lead to long-term disability, impacting employment opportunities and contributing to public health care costs of nearly $92 million per year (Ness & Gurney, 2007). Often the survivors are unable to achieve their full potential as educated, independent adults with a strong social support network of friends and their own families. Neurocognitive deficits and a lack of resources often lead to an uncertain future of unemployment and social isolation. Now that more children survive these tumors, improving the quality of survivor long-term outcomes by characterizing CNS injury that causes neurocognitive late effects may ultimately lead to improved QOL.

Statement of the Purpose

The purpose of this study was to determine whether high-dose chemotherapy damages normal brain tissue, and whether such damage was associated with memory and executive functioning deficits and decreased QOL. The specific objective was to determine whether children treated with high-dose chemotherapy with autologous hematopoietic progenitor cell
rescue (AuHCR) for brain tumors displayed key areas of white matter and gray matter injury or neuronal loss from the therapeutic intervention, and whether such injury was correlated with neurocognitive deficits and decreased QOL. Brain tissue injury or loss was measured with the diffusion tensor imaging (DTI) technique of magnetic resonance imaging (MRI). Two measures of water diffusion over brain tissue, fractional anisotropy (FA) and mean diffusivity (MD), were used as markers of injury and were compared in the brain tumor patients to healthy age- and gender-matched controls. Neurocognitive deficits in the areas of memory and executive functioning and QOL were assessed using standardized tools. Gender and age at diagnosis are critical variables in neurocognitive outcome in children with brain tumors (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Waber, Tarbell, Kahn, Gelber, & Sallan, 1992); therefore, age at diagnosis and gender were considered in the analytical model. The hypothesis was that children treated with high-dose chemotherapy would show brain structural changes following treatment, and that the location and extent of damage would correlate with extent and type of neuropsychological deficits.

This study provided new information about the effect of high-dose chemotherapy with AuHCR on normal pediatric brain tissue at the cellular level in key brain regions (hippocampus, fornix, mammillary bodies, pre-frontal cortex) using the innovative, highly sensitive MRI technique of DTI. Although these four brain regions are most likely to be injured, based on their demonstrated roles in cognitive and behavioral function, other brain structures may also be injured. Further, via neuropsychological testing and QOL assessment, neurocognitive functioning and QOL were evaluated in children treated with this therapy. Because chemotherapy-only treatment regimens for children with brain tumors are relatively recent developments, there is a lack of research on the subsequent effect of this therapy.
on healthy brain tissue and patient outcome. Providing information on potential long-term effects of childhood cancer therapy enables nurses to more accurately discuss with parents the costs and benefits of treatment. Understanding CNS injury related to newer treatment regimens increases awareness of potential cognitive effects and how they affect the child and family, and assists in the development of interventions to limit these deficits, thereby enhancing outcomes and overall QOL.

**Theoretical Framework**

The theoretical framework underlying this research was drawn from several different research areas, and was based on the multiplicity of factors that influence the long-term neurocognitive outcome and QOL of childhood brain tumor survivors. Neurotoxicity as a late effect of childhood brain tumors and their treatment is a complex process that evolves from a cascade of damage to the central nervous system. The principal tenet underlying the proposed research was that chemotherapy, a potentially curative agent in brain tumor therapy, also causes late-occurring, long-lasting damage to healthy brain tissue at the cellular level (Schneiderman, 2004; Silverman et al., 2006; Wick et al., 2004). This injury ultimately leads to loss of healthy cells in areas of the brain responsible for memory and executive function, which subsequently interferes with the ability to attain good quality of life. The injurious processes of inflammation, oxidative stress, and other injury associated with chemotherapy combine to alter the delicate equilibrium of the brain and eventually to bring about a “new normal” state of allostasis. This new steady state appears to include neurocognitive deficits in areas of memory and executive functioning, which have been related to a poorer quality of life (Bhat et al., 2005; Zeltzer et al., 2008).
Age at diagnosis (a moderator), and gender (a mediator), were important contributory variables in this model. With respect to age at diagnosis, the rapid postnatal brain development that occurs during early childhood makes these children particularly vulnerable to neurocognitive damage (Kramer & Moore, 1989). Multiplication of glial cells and myelination of axons begin during gestation and continue during early childhood into young adulthood. As Kramer & Moore (1989) state, if normal developmental of the brain is interrupted by an insult, the branching and myelination processes of the developing brain can be delayed or thwarted, and ultimate brain growth and functional outcome limited. In addition, during a time of rapid growth, it requires less of an insult to make a more dramatic lasting effect (Gajjar et al., 1994; Hossain, 2005; Kramer & Moore, 1989; Vexler & Yenari, 2009).

Gender differences exist in the development and characteristics of the brain, which may influence measurement of neuronal losses related to chemotherapy. Total brain volume is about 10% larger in boys than in girls and more of that volume in boys’ brains is gray matter (Durston et al., 2001; Reiss, Abrams, Singer, Ross, & Denckla, 1996). In female brains, however, the hippocampus, globus pallidus and caudate are larger than in males, while the amygdala is smaller (Durston, et al., 2001). In females, there is more rapid development of glia and other brain tissue, along with earlier, improved language acquisition (Bartzokis, 2005). In one MRI study of normal children, gender was second only to age in accounting for the most variability in gray and white matter volumes (Wilke, Holland, Altaye, & Gaser, 2008).

The previously outlined situation-specific theoretical framework is consonant with the nursing metaparadigm of person, environment, health and nursing. Reflecting the interaction of the individual with his/her environment, and consequences on health, children undergoing treatment for brain tumors are subject to an environment of toxins given to treat the disease of
cancer, with the outcome being injury to normal cells and ultimately, a detrimental effect on their physical, social and neurocognitive health. Within the holistic view of the person and the health/illness continuum, the child journeys from acute life-threatening illness back to a new state of health that is tempered by chronic issues of survivorship, such as neurocognitive deficits and decreased QOL.

Quality of life is a multifactorial outcome that has been studied by physicians, sociologists, psychologists and nurses (Meeberg, 1992). It consists of behavioral, emotional, physical and cognitive domains, as related to abilities to meet expectations in the areas of relationships, education/employment, and the home (Meeberg, 1992). It is sometimes defined as a person’s overall satisfaction with his/her life, feeling of well-being or happiness (Taylor, Gibson, & Franck, 2008). Nurses and nurse researchers are most concerned with health-related QOL, which is often viewed as being directly influenced by medical and nursing care, even as a critical part of nursing practice (King, 2006). In the population of children with brain tumors, QOL scores are significantly lower in those who were treated before the age of 5 years (Barr et al., 1999), from which one would conclude that the more severe physical and neurocognitive deficits incurred in this population have a greater impact on QOL.

This particular area of bio-behavioral research into patient outcomes after injury resulting from treatment belongs under the umbrella of empiricism. Empiricism is a philosophy of knowledge based on observation and experience that led to the development of a controlled and systematic procedure for research (Rodgers, 2005). Empiricists believe that all knowledge comes from experience, and that we utilize our senses to gain experience. Empiricism also embraces the tenet that truth can be found through measurement, while discouraging the researcher from allowing his/her own values, beliefs or ideas to interfere with the process. The empirical
approach has been a foundation for all researchers, but is especially applicable to biobehavioral nursing research. The subjects of nursing research are most often patients, and it is usually after a period of time spent observing them and gaining nursing experience that nurse researchers develop questions about why certain things occur, and how nursing care or patient outcomes can be improved. A key component of excellent nursing practice is the ability to look for and interpret patterns – of behavior, symptoms, family dynamics, coping, etc., and then utilizing this ability to study, analyze and evaluate practice through research. Nursing research, in many cases, focuses on human response to illness, which is measureable in different ways. The quest of nurse researchers is to improve patient outcomes and quality of life, as well as to add to the body of existing evidence for practice. Avis and Freshwater (2006) state that empiricism supports evidence-based practice research (the idea that finding evidence through research is important for the scientific basis of nursing knowledge) as well as that of practical knowledge, which develops from experience and guides clinical judgment (Avis & Freshwater, 2006). In this aim, critical thinking and reflecting upon evidence is part of the intuitive process of checking ideas to see if they are consistent with experience.

**Contributions to Nursing Knowledge**

This research contributed new information to the outcomes category of nursing knowledge (Fawcett, 2005), which focuses on the results of nursing care and how to improve outcomes to the best possible endpoint. Consistent with these professional mandates, the nurse investigator is in a key position to improve health outcomes in these survivors by assessing injury to the CNS, neurocognitive deficits and diminished QOL. This knowledge ultimately informs and enables the development of interventions that improve health in the domains of neurocognitive function and QOL.
In childhood cancer, there are a limited number of studies where nursing research incorporates sociocultural, psychological and biological aspects of experiencing a life-threatening illness. As Moore (2004) states, combining biological and biobehavioral research questions provides the necessary data for development of critical interventions (Moore, 2004). This research study contributes to what is known currently about the degree of injury to the CNS after brain tumor therapy in children, for which a dearth of research exists. There is no information in the literature about loss of gray or white matter in the brain associated with neurocognitive deficits as a result of high-dose chemotherapy in children with brain tumors. Most of what is known about neurocognitive effects of this treatment has been amassed from studies done on adults, and these studies cannot be generalized to the child’s developing brain. A better, more thorough understanding of the extent of injury could lead to the development of interventions, which will improve the ability to deliver care to patients that will minimize toxicity from cancer treatments.

Following are three manuscripts prepared as a result of this dissertation research study. The first paper is a review of the literature on mechanisms of injury to the brain from cranial radiation and chemotherapy, and resulting brain tissue loss, neurocognitive deficits and quality of life outcomes in children with brain tumors. This information provides the background for the research. The second paper presents and discusses the results of diffusion tensor imaging indices and intracranial volume comparison between children with brain tumors and healthy controls. The third paper analyzes the relationship between areas of brain tissue loss, neurocognitive deficits, and QOL outcomes.
References


CNS Injury and Neurobiobehavioral Function in Children with Brain Tumors – a review of the literature

Mary Baron Nelson, Peggy Compton, Sunita K. Patel, Eufemia Jacob, Ronald M. Harper

Background and Significance

Brain tumors are the second most common type of cancer in children, affecting approximately one in every 30,000-40,000 youth in the U.S. (Singer & Byrne, n.d.). For survivors, neurocognitive deficits are common, affecting 40% - 100% of children, depending upon age at treatment, history of cranial radiation or types of chemotherapy, (Anderson, 2003) and, may not become fully realized until years after treatment has ended. Neurocognitive deficits have been linked to poor educational attainment, difficulty finding employment, and behavioral and social difficulties, all of which may contribute to poor quality of life (QOL) (Fuemmeler, Elkin, & Mullins, 2002). Central nervous system (CNS) injury after treatment of a brain tumor can be linked to the initial presence of the tumor and resulting edema or hydrocephalus, or to any therapeutic modality such as surgical intervention, cranial radiation, or chemotherapy.

More recently, investigators have studied the physiological processes involved when giving chemotherapy and radiation to eradicate or provide prophylaxis against malignancies in the CNS. Cranial radiation, the cornerstone of pediatric brain tumor therapy for years, contributed to a 5-year survival rate of approximately 66%. However, as long-term survival was achieved, radiation to the brain was also identified as an important causative factor for neurocognitive deficits, ranging from global loss of intelligence quotient (IQ) points to attention problems (Kim, Brown, Jenrow, & Ryu, 2008; B. D. Moore, 3rd, Copeland, Ried, & Levy, 1992; Waber, Tarbell, Kahn, Gelber, & Sallan, 1992). More severe neurocognitive deficits, specifically difficulty with abstract
thinking, correlate with younger age at treatment and higher doses of radiation (Mulhern et al., 2001).

Cranial radiation may be more damaging to the developing brain of a child than to the fully developed adult brain (Silber et al., 1992). This issue has been so strongly recognized that more young children are now treated on protocols with chemotherapy alone (Dhall et al., 2008; Marachelian, Butturini, & Finlay, 2008). Yet, even less is known about late effects of chemotherapy on the child’s developing brain. The rapid postnatal brain development that occurs during early childhood makes children particularly vulnerable to neurocognitive damage (Kramer & Moore, 1989; Trask & Kosolfsky, 2000). Multiplication of glial cells and myelination of axons begin during gestation and continue during early childhood to the age of 5 to 7 years, even extending into the third decade in certain areas of the brain such as the prefrontal cortex. If normal brain development is interrupted by an insult, such as that of neurotoxic chemotherapy or cranial radiation, the branching and myelination processes of the developing brain can be delayed or thwarted, and ultimately, brain growth and functional outcome will be limited (Kramer & Moore, 1989). In addition, during a time of rapid brain growth, it requires less of an insult to make a more dramatic lasting effect (Gajjar et al., 1994; Hossain, 2005; Kramer & Moore, 1989; Vexler & Yenari, 2009).

Since radiation therapy results in deleterious consequences, high-dose chemotherapy followed by autologous hematopoietic stem cell rescue (AuHCR) has become more common as a frontline treatment for brain tumors in children less than 6 years of age (Marachelian, et al., 2008). This has resulted in a five-year survival rate (57-79%), and is within the range achieved by radiation and chemotherapy (Dhall, et al., 2008). Medulloblastoma has proven to be particularly sensitive to this treatment, resulting in improved survival and neurocognitive
outcomes in very young children (Gottardo & Gajjar, 2008). The chemotherapy agents most commonly used in high-dose regimens for childhood brain tumors are cisplatin (CDDP), cyclophosphamide (CPM), etoposide, MTX, thiotepa, carboplatin (CBDCA) and topotecan (Dhall, et al., 2008; Gardner & Finlay, 2001; Sands et al., 2010). Few studies have examined the neurotoxic effects of high-doses of this type of chemotherapy in children, focusing instead on more acute organ toxicities and survival statistics.

This paper will review the literature on the effects of cranial radiation and chemotherapy agents used to treat brain tumors in children on healthy brain tissue and discuss outcomes after treatment. There are limitations to the interpretation of the body of clinical research available on this population. Most of the research on CNS injury and neurocognitive outcomes due to pediatric cancer therapy involve subjects treated with a combination of cranial radiation, chemotherapy and corticosteroids, making it difficult to distinguish between direct and interaction effects of each intervention. Thus, included in this review are relevant research studies in animal models and in general pediatric oncology.

A literature search was performed in Pub Med and PsycINFO for the years 2000-2011, using a combination of key words: “neuronal injury, neuronal loss, chemotherapy, radiation, neurocognitive, quality of life, brain tumors in children, childhood and pediatric.” Inclusion criteria for in vitro and rodent studies were clinically relevant treatment, and for human studies were treatment for pediatric brain tumors. Exclusion criteria included duplicate or very similar findings to other papers. Some earlier important works were also included; one, a classic early paper from 1963, establishing a link between cranial radiation, CNS injury and behavior change, and a few brain tumor studies from the 1990s to demonstrate critical findings.

CNS Structure/Function
As a brief review, the CNS includes the brain and spinal cord. The brain itself is made up of neurons and glial cells that differentiate from neural progenitor cells (Figure 1). Neurons have a cell body, an axon and many dendrites, and they send (via axons) and receive (via dendrites) signals by forming synapses with other cells. Astrocytes and oligodendrocytes are types of glial cells. Astrocytes provide a supportive structure and nutrients to neurons, while oligodendrocytes form the myelin sheaths that surround and insulate axons, facilitating transmission of synaptic signaling (Kandel, 2000b). White matter consists of myelinated axons, while gray matter is largely made up of cell bodies.

Although different parts of the brain have specific functions (Figure 2), there is some overlap. Cognition, specifically, requires the interaction of thinking, memory, perception and language. Since many brain regions are involved in this process, dysfunction in one area can create a disability that may or may not be overcome (Kandel, 2000a).

The presence of a brain tumor alone, with or without resulting hydrocephalus, may injure normal brain tissue. Once the open sutures and fontanels of the infant’s skull close, the presence of a mass in the brain will cause increased intracranial pressure when it reaches a certain volume. Vasogenic edema, as a result, may cause damage to healthy brain tissue, if not treated in a timely manner (Laterra & Goldstein, 2000). Delicate brain tissue may also be injured during surgical resection of the tumor, manifesting as either traumatic brain injury or ischemic injury (Chamberlain, 2010).

**CNS Injury from Cranial Radiation and Chemotherapy**

*In Vitro and Rodent Studies of Radiation/Chemotherapy Effect on CNS*

Basic science research has provided much of the evidence regarding neurotoxic effects of cancer therapies in children. It demonstrates that both cranial radiation and certain chemotherapy
agents affect a variety of normal healthy brain cells, in addition to eradicating cancer cells. A summary of this literature is found in Table 1.

A major cause of cellular injury results from the process of oxidative stress and inflammation triggered by radiation and/or chemotherapy. Within hours to days after exposure to cranial radiation, ongoing release of pro-inflammatory cytokines from damaged cells supports a chronic state of inflammation in the rodent brain (Nordal & Wong, 2005). During the cycle of oxidative stress and inflammation, cell membrane breakdown and cell death, apoptosis (programmed cell death), demyelination, and loss of integrity of the blood-brain barrier (BBB) are common. Disruption of the BBB also contributes to edema, cell membrane breakdown and loss, as the regulatory mechanisms that control passage through this important barrier fail, creating a cycle of continuing injury.

Pathological changes in the mouse brain after cranial radiation were noted five decades ago (Ordy, Samarajski, Zeman, Collins, & Curtis, 1963) with the findings that extreme doses of cranial radiation (720 Gy) caused widespread destruction of a variety of brain cells that were gradually replaced with fluid-filled cavities within 7 months of treatment. Even significantly less (80 Gy), but still very high doses of cranial radiation, induced signs of active inflammation in the brain at 21 days after treatment (Ordy, et al., 1963). Although such high radiation doses are not used today, this 1963 study provided important early information about the chronic injurious nature of radiation.

There is evidence that several chemotherapy agents cause injury in a similar manner. Administration of intrathecal and systemic MTX has been linked to the presence of oxidative stress markers in the cerebrospinal fluid of children on treatment for ALL (Miketova et al., 2005) (I. M. Moore et al., 2008). Disruption of axonal and dendritic networks appeared in neuronal
cultures exposed to ifosfamide, vinblastin, CPM, CDDP, MTX and thiotepa (James et al., 2008) (Rzeski et al., 2004). While this may not overtly cause cell death, it renders the affected neurons dysfunctional.

Cyclophosphamide appears to be more toxic to the young, developing brain than to the adult brain, causing brain tissue loss in many more areas in younger rodents than in older ones (Rzeski, et al., 2004). Cerebellar granule cells, tiny neurons found in the cerebellum, are similarly affected by chemotherapy, and many die within 72 hours after exposure to lomustine, CDDP, VCR and topotecan (Wick et al., 2004). These cells were particularly sensitive to low concentrations of VCR. Additionally, VCR was toxic to astrocytes. Vincristine is a known potent peripheral neurotoxin (Casey, Jellife, Le Quesne, & Millett, 1973), but there has been little research on its effects on cells of the CNS.

Although cranial radiation results in generalized white and gray matter loss in the brain, its effect the hippocampus is of particular importance, since this is a primary site of neurogenesis, the generation of new neurons from progenitor cells, after the early post-natal period. Specific areas of the hippocampus where proliferating (growing and dividing) cells may be found include the subventricular zone (SVZ), subgranular zone (SGZ) and dentate gyrus (DG). A single low dose of radiation to the adult rat brain (1-3 Gy) led to significantly less brain growth over time, with an acute decrease in the number of cells in the SVZ (Amano et al., 2002). Proliferating cells decreased markedly up to 2 months after a single 10 Gy dose of cranial radiation (M. L. Monje, Mizumatsu, Fike, & Palmer, 2002). After exposure to radiation, remaining progenitor cells have a stronger tendency to differentiate into glial cells than into neurons, which may reflect an alteration of the signaling process. (M. L. Monje, et al., 2002). The exact mechanism for the failure of neurogenesis is unknown, but may be related to

15
alterations in the microenvironment of the hippocampus and the presence of pro-inflammatory cytokines, or to interference with normal molecular and cellular interactions (M. L. Monje, et al., 2002). Moreover, this reduction in hippocampal proliferating cells due to radiation given early in life persisted into adulthood (Rao, Ye, Decker, Howe, & Wetmore, 2011). These processes may help to explain the more severe neurocognitive effects of radiation found in children, as compared to adults (Rao, et al., 2011; Rola et al., 2004). Even in adults, loss of oligoprogenitor cells, precursors to the cells that form myelin, after radiation persisted for up to 7 years after therapy (Panagiotakos et al., 2007).

As with radiation, chemotherapy appears to preferentially affect cells of the hippocampus. Methotrexate injures neural progenitor cells in the hippocampus (Dietrich, Monje, Wefel, & Meyers, 2008), which is believed to account for delayed neurotoxicities (progressive cognitive dysfunction, neuropathies, cerebral atrophy, cerebellar toxicity) associated with that treatment. Systemic administration of thiotepa, an anti-mitotic agent that effectively crosses the BBB, resulted in significant neuronal loss in the mouse hippocampus (Mignone & Weber, 2006) (Dietrich, Han, Yang, Mayer-Proeschel, & Noble, 2006). Cisplatin exposure caused an increase in apoptosis of cells in the DG (Dietrich, et al., 2006), The effects of CDDP, carmustine and cytarabine, given separately and in combination, on both quiescent brain tissue cells and cancer cell lines suggest that these agents are even more toxic to neural progenitor cells than to the cancer cells, decreasing viability by up to 90% for at least 6 weeks after chemotherapy exposure (Dietrich, et al., 2006).

In summary, the literature suggests that cranial radiation results in both acute and chronic injury to a wide variety of cells, leading to demyelination and areas of necrosis of the brain. Both chemotherapy and radiation appear to target neural progenitor cells in the hippocampus,
leading to notable decreases in the number of new neurons. As a site of memory consolidation, hippocampal cell loss is detrimental to cognition. The time progression of damage to normal cells after treatment with chemotherapy indicates that CNS cell death may occur within 24 hours of treatment, and continue for up to 6 weeks, and may cause more widespread neuronal degeneration in the young brain than in the adult. The multiple mechanisms by which cell injury occurs, including cell shrinkage, axonal and dendritic disruption, and apoptosis of cerebellar granule cells and neural progenitor cells, resulting in white and gray matter loss, have also been explicated.

**Pediatric Brain Tumor Studies of Radiation/Chemotherapy Effect on the CNS**

A summary of the literature on the effects of CNS cellular injury and loss after brain tumor therapy in childhood is found in Table 2. One of the most commonly reported effects of cancer treatment evident on pathologic examination and with certain brain imaging techniques is a loss of white matter, or demyelination. After cranial radiation, demyelination appears within 5 months, with vascular structural changes and necrosis occurring about 9 months later (Oi, Kokunai, Ijichi, Matsumoto, & Raimondi, 1990). Five years after radiation, significant structural damage to the brain appeared and continued to progress (Oi, et al., 1990). After treatment with 35-40 Gy cranial radiation, normal-appearing white matter (NAWM) continued to decrease at a rate of 0.3ml/year over 5 years (Reddick et al., 2005).

The volume of the hippocampus was also affected by radiation, continuing to decrease bilaterally on magnetic resonance imaging (MRI) for 2-3 years post-diagnosis, but then returning to a normal growth pattern (Nagel et al., 2004). On autopsy examination of the hippocampi of children, a 100-fold decrease in neurogenesis after total body irradiation (13.2 Gy) and a 10-fold decrease in neurogenesis after 23.4 Gy craniospinal radiation and focal cranial radiation were
observed. As is typical in most clinical samples, these patients were also treated with chemotherapy and with corticosteroids, known inhibitors of neurogenesis, so these differences may not solely be attributable to radiation (M.L. Monje et al., 2007).

There is also evidence of gray and white matter loss in children treated for brain tumors with standard dose chemotherapy combined with cranial radiation (Mulhern, et al., 2001). With higher doses of MTX and cranial radiation, an increased incidence of leukoencephalopathy (white matter changes related to endothelial cell loss and demyelination) was seen at a median 7.5 years after therapy (Kellie et al., 2005). Those children with more severe changes had all received higher doses of radiation. Since both cranial radiation and MTX have been associated with leukoencephalopathy, an interaction effect of both treatments may exist.

**Model of Injury of Cancer Treatment to CNS**

Figure 3 demonstrates the similarities in the injurious processes of chemotherapy and radiation to healthy brain tissue. An acute cranial radiation effect is an increased expression of intracellular adhesion molecule-1 (ICAM-1) within 24 hours of exposure, which contributes to disruption of the BBB (Nordal & Wong, 2005). The integrity of the BBB is compromised by damage to vascular endothelial cells, leading to edema, further inflammation and tissue hypoxia (Kim, et al., 2008). In response to cell injury, acute and chronic oxidative stress processes damage cellular mitochondria and result in the formation of oxidative products and enzymes such as lipid peroxidase, which contribute to continuing cell membrane breakdown (Miketova, et al., 2005). Like radiation, chemotherapy induces oxidative stress in the CNS (Carey et al., 2008; I. M. Moore et al., 2000; Ward, Phipps, de Sousa, Butler, & Gumley, 2009) through the release of cytokines such as tumor necrosis factor and interleukin 1-β, contributing to demyelination (Nordal & Wong, 2005) and white matter loss.
Chronic oxidative stress secondary to radiation or chemotherapy also inhibits hippocampal neurogenesis, which appears related to memory dysfunction (Dietrich, et al., 2006; Mignone & Weber, 2006; Zhao, Diz, & Robbins, 2007). Therefore, the two common mechanisms of injury from chemotherapy and radiation resulting from oxidative stress are CNS cell injury and/or death leading to white and gray matter loss, and decreased hippocampal neurogenesis leading to a drop in the development of new neurons. These two separate mechanisms contribute to the most common neurocognitive deficits in brain tumor survivors. Damage to the hippocampus or to its progenitor cells results in memory problems, specifically with short-term memory, which can be very detrimental to learning (Squire, 2009). Loss of gray and white matter in certain areas of the brain may result in attention problems and executive functioning (Fouladi et al., 2004; Mulhern et al., 2004; Reddick et al., 2003) and decreased intelligence quotient (IQ).

CNS Cell Loss and Neurobiobehavioral Outcome

It is important to investigate the impact of CNS injury on developmental and neurocognitive outcomes. The loss of cells in cortical and subcortical regions in the brain induced by chemotherapy and radiation predict neurocognitive deficits in children with brain tumors. Life-threatening illness and aggressive treatment at a young age can affect future physical, emotional, cognitive and psychosocial health.

Neurocognitive deficits in children with brain tumors have been almost exclusively studied in those who received a combination of radiation and chemotherapy or with radiation alone. Children treated with cranial radiation before the age of 5 years have much poorer neurocognitive outcomes than those treated in older childhood and adolescence (Duffner et al., 1999). Research on rodent models of the relationship of treatment-induced CNS injury and loss
to neurocognitive deficits are summarized in Table 3.

**Rodent Models of Neurobiobehavioral Effects after Radiation and/or Chemotherapy**

In an early study of adult rodent behavior after cranial radiation, mice treated with 80 Gy demonstrated small, but significantly different behavior changes, depending on the area of the brain treated. For example, rodents who received cerebellar radiation had locomotor problems, while those radiated in the parietal areas had more difficulty with tasks involving memory (Ordy, et al., 1963). Young mice (21 days old) experienced memory retention deficits that correlated with a decrease in neurogenesis in the SGZ after a single 5 Gy dose of whole brain radiation (Rola, et al., 2004). Five consecutive days of 4 Gy whole brain radiation resulted in long-term impairment of non-spatial learning in one-month-old mice (Rao, et al., 2011).

Systemic high-dose MTX (HD-MTX) caused a loss of healthy neurons in the hippocampi of rats as well as concurrent changes in neurocognitive functioning, specifically, difficulties with spatial learning and object recognition tasks (Seigers et al., 2008). High-dose MTX-treated adult mice had an inadequate response to fear conditioning, which represented cognitive and memory deficits (Seigers, Schagen, Coppens, van der Most, & al., 2009). Mice treated with combined standard-dose MTX and 5-fluorouracil had difficulty with spatial memory tests on the day after treatment, but these deficits normalized with time (Winocur, Vardy, Binns, Kerr, & Tannock, 2006).

**Pediatric Studies of Neurobiobehavioral Effects after Radiation and/or Chemotherapy**

A summary of the studies of the relationship of treatment-induced CNS injury and loss to neurocognitive deficits in children are presented in Table 4.

For children, school achievement is an indirect indicator of cognitive function. A report on over 800 Canadian childhood cancer survivors demonstrated that those with a history of a CNS
tumor treated with chemotherapy and cranial radiation were significantly more likely to have utilized special educational services than survivors of other cancers (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005). The academic subject accounting for the greatest difference between survivors and controls was mathematics. Children who were older at the time of diagnosis had better reading skills, and were rated more highly by their teachers for academic performance than those who were younger (Mabbott et al., 2005). Those with ventriculoperitoneal shunts for tumor-related hydrocephalus had significantly lower math scores than those without shunts. Math, spelling, reading scores, and attention continued to decline over time, possibly related to continuing, chronic white matter changes (Reddick, et al., 2003). As additional evidence of progressive deficits over time, children with medulloblastoma treated with higher doses of CRT (36-39.6 Gy neuraxis and 55.8 Gy to tumor bed) lost more IQ points per year over 5 years than those treated with a lower dose of neuraxis CRT (Mulhern et al., 2005).

Older children with germ cell tumors treated mainly with chemotherapy, while some also received cranial radiation, scored within the average range on full-scale IQ (FSIQ), verbal IQ (VIQ), reading, math and spelling (Sands et al., 2001). Younger age at diagnosis was related to lower scores in math and overall IQ (Sands, et al., 2001).

Significant correlations between white matter volume, attention and IQ have been noted in brain tumor survivors treated with chemotherapy and cranial radiation (Reddick, et al., 2003). White matter loss is strongly correlated with adverse neurocognitive outcomes (Khong et al., 2006). A decrease in white matter of just 3.3% predicted an IQ score of 85 or less, approaching borderline deficiency. Indicators of white matter loss were seen in widespread areas of the brain, including the cerebellar hemispheres, pons, medulla, frontal and parietal periventricular structure, and corona radiata in children with medulloblastoma treated with chemotherapy and cratera radiata.
radiation 1-6 years earlier (Khong, et al., 2006). Fractional anisotropy values, indicating loss of white matter integrity, correlated significantly with younger age at diagnosis, poorer school performance and longer time off-therapy (Khong et al., 2003), and with FSIQ, VIQ and PIQ (Khong, et al., 2006). These findings have been supported using alternate indicators of tissue damage with diffusion tensor imaging (DTI). Another indicator of microstructural CNS damage, the absolute diffusion coefficient (ADC), is significantly related to decreased IQ in brain tumor survivors as compared to healthy controls (Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006).

Attention problems are fairly common in survivors of childhood brain tumors. Total volume of NAWM after chemotherapy and radiation was a strong predictor of attention problems (Mulhern, et al., 2004), while 70% of the correlation between IQ and age at cranial radiation was explained by NAWM (Mulhern, et al., 2001). White matter lesions became evident in a sample of brain tumor survivors at a median time of 7.8 months after radiation, and many (73%) resolved within another 6 months. A decline in IQ was also significantly related to the presence of these lesions (Fouladi, et al., 2004).

There are few studies to date on the long-term outcome of children with brain tumors who were treated with only chemotherapy. One study showed no significant loss of IQ points over time after chemotherapy, as compared to those who received radiation (Stargatt, Rosenfeld, Maixner, & Ashley, 2007). Treatment for a brain tumor with chemotherapy before the age of 3 years resulted in mean intelligence quotient (IQ) and memory scores within the average range, but in executive functioning significantly below the standard mean (Ward, et al., 2009). Those who underwent more than one surgical resection had lower IQ, memory and executive function scores. Lower socioeconomic status was related to lower scores on IQ and memory scores.
Children with brain tumors who were an average of 3 years post-treatment showed low-average to average neurocognitive functioning after high-dose chemotherapy with AuHCR (Sands, van Gorp, & Finlay, 1998). Mean performance was in the average range for most academic skills, while fine motor skills and processing speed were in the low average range (Sands, et al., 1998). Another group treated in the same manner displayed similar performance on intelligence testing and academic achievement, and normal scores on behavioral and social-emotional functioning at a mean of 39.7 months after therapy (Sands, et al., 2010).

Quality of life in survivors of childhood brain tumors may be affected by many variables, including the treatment, frequent medical procedures and hospitalizations at a young age. Findings are mixed regarding whether impairments in specific areas of neurocognitive functioning may impact QOL. Over 80% of medulloblastoma survivors studied had impaired executive functioning, and 92% were impaired on at least one subtest of attention, but despite these findings, neither self-reported nor caregiver reported QOL was significantly diminished (Maddrey et al., 2005). A longitudinal study found that QOL scores of children with brain tumors improved so that at 12 months after diagnosis, there was no significant difference between subjects and healthy controls in any domain (Penn et al., 2008). This particular study is relevant to the resolution of effects of acute treatment on QOL, but does not measure QOL in the long-term survivor. No significant difference was seen in QOL scores between children with brain tumors treated with multimodal therapy (surgery, cranial radiation and chemotherapy) and those treated with surgery only (Benesch et al., 2009). Older children treated with a combination of cranial radiation and chemotherapy for germ cell tumors had low-average psychosocial functioning, borderline physical functioning and impaired self-esteem on measures of QOL. Age at diagnosis...
was a factor related to lower scores on psychosocial and physical domains of QOL. Studies of children with brain tumors treated on the Head Start protocols, which utilize high-dose chemotherapy regimens and AuHCR, show that QOL scores were generally positive, but younger age at diagnosis and longer time off treatment correlated with risk for behavior and attention problems (Sands et al., 2011).

As noted, there is good evidence to suggest that children treated with radiation alone or both chemotherapy and radiation have poor neurocognitive outcomes. Late effects of chemotherapy on cognitive centers in the brain in children include neurocognitive deficits in the areas of visual processing, visual motor skills and memory and executive functioning. The addition of cranial radiation therapy leads to a more global loss of IQ points. In the few studies of children with brain tumors treated with chemotherapy only, memory and executive functioning deficits were observed, but overall neurocognitive function and QOL were generally within average range.

**Implications for Practice**

Nurses are often sought out by family members to explain treatment regimens and acute and chronic effects of therapy. As the numbers of childhood cancer survivors increase, our involvement in long-term follow-up care is crucial. Educating families to recognize the signs of neurocognitive problems in children is just as important as teaching about signs of other toxicities. Nurses can educate parents to be aware of subtle difficulties in school and to discuss concerns with teachers and health care providers. These difficulties may include academic, social, mood and behavioral problems. Interaction with education specialists and teachers by the nurse to explain the possibility of neurocognitive late effects is recommended.

Standard guidelines for children who have received cranial radiation and/or MTX or high doses of cytarabine recommend regular neuropsychological testing and follow-up as needed.
Nurses should advocate for any child with a brain tumor to have a neuropsychological testing battery after treatment, and as recommended thereafter and encourage parents to be vigilant about this. Results of testing are used to develop Individualized Education Programs (IEPs) at school in order to ensure the best learning environment for each child. There is a wide range of possible interventions, ranging from simple techniques to more complex cognitive behavioral therapies, computerized interventions, and medications to improve attention and memory. Early intervention, in conjunction with newer therapies, may help to mitigate neurocognitive deficits and social problems.

**Summary and Conclusions**

Survival of a childhood brain tumor is often the result of administration of toxic therapies that not only eradicate cancer cells, but affect the healthy tissue of the child’s developing brain both acutely and in an ongoing manner. Radiation to the brain causes a progressive loss of healthy CNS cells due to a chronic state of inflammation, oxidative stress, and a loss of neural progenitor cells. Many chemotherapeutic agents cause injury to healthy brain cells by similar mechanisms. Neurocognitive deficits, often resulting in poor academic achievement and social isolation, may interfere with quality of life in this population. Educational success is directly related to social proficiency and successful transition to adulthood and independence (Gurney et al., 2009). Difficulty making friends and maintaining relationships may lead to withdrawal from social situations and subsequent isolation. Survivors of childhood brain tumors are less likely to marry or to be employed than healthy peers, and more likely to experience depression and anxiety (Anderson, 2003; Fuemmeler, et al., 2002; Gurney, et al., 2009). While there is evidence to suggest that young children treated with chemotherapy alone may encounter fewer neurocognitive deficits, there may be long-term difficulties in the areas of memory, attention and
executive functioning. Little is known about long-term neurobiobehavioral outcomes in children who were treated with high-dose chemotherapy and AuHCR, which is becoming more common as a frontline treatment. As this treatment technique gains popularity, it will be important to define its long-term effects.

There are several limitations to the state of the science upon review of the literature. There are no studies to document loss of healthy brain tissue in children with brain tumors who were treated solely with chemotherapy. Most brain tumor studies have examined children treated with a combination of radiation and chemotherapy. However, available results indicate improved QOL in those treated without radiation.

Because the number of children diagnosed each year with brain tumors is relatively small, and so many variables affect outcomes, multi-institutional studies are critical to achieve sample sizes with adequate power to demonstrate significance. Future research must seek to minimize variability in tumor location, pathology and treatment among subjects as much as possible in order to attribute certain toxicities to specific agents with more confidence. This approach will allow research to progress to develop more interventions to maximize long-term neurocognitive outcomes and quality of life.
**Figure 1.** Differentiation of Neuronal Cells

![Diagram showing the differentiation process from stem cells to early progenitor cells, then to neuron, oligodendrocyte, and astrocyte.](http://www.ninds.nih.gov/disorders/brain_basics/ninds_neuron.htm)

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**Figure 2.** Functional Areas of the Brain

Figure 3. Mechanisms of Radiation/Chemotherapy Injury to Healthy Brain Tissue

Chemotherapy
- Pro-inflammatory cytokine release

Radiation Therapy
- ICAM-1 release, altered gene expression

Oxidative Stress

Inflammation

Blood-Brain Barrier Disruption
- Cell Membrane Breakdown
- Oligodendrocyte Injury
- Neural Progenitor Cell Loss

Demyelination, White Matter Necrosis, Gray Matter Loss
<table>
<thead>
<tr>
<th>Study</th>
<th>Origin of Specimen(s)</th>
<th>Agent/Dose</th>
<th>Effect on CNS</th>
<th>Comments/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT – <em>in vitro</em></td>
<td>Adult human radiated tissues compared to non-radiated glial tissue near lesion</td>
<td>18-21 Gy focal CRT (radiosurgery)</td>
<td>Loss of oligoprogenitors 2 mos post-CRT, still seen up to 7 yrs. post-CRT.</td>
<td>Progressive degradation of myelin sheaths over time, possibly related to axonal damage. Limitation - findings may be complicated by effects of aging. Demyelination occurred prior to vascular necrosis.</td>
</tr>
<tr>
<td>Pangiotakos et al, 2007</td>
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<tr>
<td>CRT - Rodents</td>
<td>210 male rats, 6 wks of age; 30 age-matched controls</td>
<td>Random assignment to 1, 2 or 3 Gy single dose.</td>
<td>Brain weight of irradiated rats 50-62% of controls over 60 days. Apoptosis in SVZ ↑ 6 hrs post-XRT, disappeared within 2 days.</td>
<td>Single dose of CRT may cause brain growth retardation. Limitation - one-time low-dose of CRT not clinically relevant.</td>
</tr>
<tr>
<td>Amano et al, 2002</td>
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<tr>
<td>Monje et al, 2002</td>
<td>Adult rats</td>
<td>10 Gy single dose CRT (approximates 2 Gy in humans)</td>
<td>Surviving proliferating cells in DG, SGZ 38% at 1 mo post-CRT, 52% at 2 mos post-CRT compared to non-irradiated controls.</td>
<td>Radiation detrimental to neural stem cells, to signaling process for neurogenesis.</td>
</tr>
<tr>
<td>Ordy et al, 1963</td>
<td>40 female mice, 10 controls</td>
<td>80-720 Gy to various brain areas</td>
<td>7 days after 720 Gy, early cell pyknosis, vascular congestion; after 7 months, nerve cell bodies gone. 21 days after 80 Gy, pyknotic granular cells, proliferation of astrocytes, swelling of endothelial nuclei, granular cells disappeared.</td>
<td>One of first to postulate that CRT injury may be influenced by dose of radiation, time since radiation.</td>
</tr>
<tr>
<td>Pangiotakos et al, 2007</td>
<td>Adult rat brains</td>
<td>Single dose 25 Gy WBRT</td>
<td>Progenitor cells in SVZ ↓ by 89% 1 day after WBRT. 15 mos later, average # progenitor cells in irradiated rats 15% that of controls. In olfactory bulb, delayed ↓ neuroblasts after 2 weeks likely due to ↓ neurogenesis; restored after 6</td>
<td>Demonstrates effect of loss of neural progenitor cells in SVZ on non-irradiated areas of brain (olfactory bulb) outside hippocampus with no significant recovery over time.</td>
</tr>
<tr>
<td>Study</td>
<td>Age/Species</td>
<td>Radiation Details</td>
<td>Findings</td>
<td>Comments</td>
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<tr>
<td>Rao et al, 2011</td>
<td>1 month old male mice; non-irradiated controls</td>
<td>4 Gy/day WBRT for 5 consecutive days</td>
<td>Endothelial cells ↓(^a) 1 day after XRT, normal levels 2 mos later. 83.4% ↓ in migrating neurons at 72h and 1 mo post-XRT(^c) 88.3% ↓ in proliferating cells of HC at 72h(^a) and 1 mo(^b) post-XRT</td>
<td>Simulated clinical dose of XRT in children</td>
</tr>
<tr>
<td>Rola et al, 2004</td>
<td>21-day-old mice</td>
<td>2-10 Gy WBRT</td>
<td>48 h after initial dose, ↓(^c) in proliferating cells in SGZ: 35% ↓ with 2Gy, 93% ↓ with 10Gy. Loss(^c) of immature neurons: 12% after 2Gy, 75% after 10Gy. At 1, 3 mos post-WBRT, ↓ neuronal differentiation(^a). At 3 mos, ↑ activated microglia(^a), representing inflammatory response.</td>
<td>May help to explain greater impact of radiation on younger brain.</td>
</tr>
<tr>
<td>Rubin et al, 1994</td>
<td>Male rats, 225-250g</td>
<td>60 Gy CRT</td>
<td>Extensive leakage of contrast agent across BBB at 2 weeks; some resolution at 6-8 wks. WM necrosis mod-severe beginning at 24 wks post. At 24 wks post-CRT, increased leakage, cortical atrophy.</td>
<td>Limitation - large single dose of radiation not representative of real-life therapy, but given to detect injury in shortest time period possible.</td>
</tr>
<tr>
<td><strong>Chemo – <em>in vitro</em></strong></td>
<td>Non-dividing brain tissue cells and cancer cell lines</td>
<td>Carmustine 0-200µM CDDP 0-100µM</td>
<td>Carmustine, CDDP toxic to normal progenitor cells, 40-90% ↓ in normal neuron viability; also toxic to oligodendrocytes.</td>
<td>No tumor cell lines more sensitive to chemotherapy agents than normal progenitor cells were, even at low levels of exposure.</td>
</tr>
<tr>
<td>Authors</td>
<td>Experimental Model</td>
<td>Agents</td>
<td>Effects</td>
<td>Notes</td>
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<tr>
<td>James et al, 2008</td>
<td>Rat hippocampal, cortical neurons</td>
<td>Taxol, CDDP, MTX</td>
<td>Taxol-treated cells - fewer secondary dendrites, shortened primary dendrites. CDDP-treated cells - less dendritic branching, shortened dendrites. MTX-treated cells - 40% likelihood of having only one major dendrite &amp; shortened primary dendrites.</td>
<td>All agents caused degeneration of neurites, changes to actin cytoskeleton of neurons. No microglial activation seen, suggesting lack of CNS inflammation.</td>
</tr>
<tr>
<td>Rzeski et al, 2004</td>
<td>Neuronal cell cultures</td>
<td>5-100 µM doses of: MTX, Ifosfamide, CDDP, CPM, Thiotepa, and Vinblastin – 0.1-1 µM</td>
<td>Cell shrinkage, death to neurons dose-dependent with all agents. Vinblastin &gt; CDDP.</td>
<td>Limitation - concentrations of chemo agents &gt; clinical doses, but may be representative of combination therapy over several courses.</td>
</tr>
<tr>
<td>Wick et al, 2004</td>
<td>Postmitotic primary cerebellar granule neurons, astrocytes from 8-day old rat brains</td>
<td>Lomustine, CDDP, VCR, Topotecan</td>
<td>All agents ↓ cerebellar granule cell viability after 72 hours of exposure due to apoptosis: VCR &gt; topotecan &gt; CDDP &gt; lomustine. For reducing primary astrocytes: topotecan &gt; CDDP &gt; VCR &gt; lomustine. For malignant glioma cell reduction: VCR &gt; topotecan &gt; CDDP &gt; lomustine.</td>
<td>Rare study on CNS effect of VCR. Difficult to explain high sensitivity of cerebellar granule cells to certain agents as compared to astrocytes.</td>
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<tr>
<td>Chemo-rodents</td>
<td>6-8 week old mice</td>
<td>IP</td>
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<tr>
<td>Dietrich et al, 2006</td>
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<td>Carmustine - 30 mg/kg</td>
<td>CDDP - 15 mg/kg</td>
<td>Cytarabine - 0.1µm concentration in CSF (equivalent to human conventional treatment)</td>
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<td>Carmustine - 16.1-fold ↑ apoptotic cells in SVZ for at least 6 wks, 13.3-fold ↑ in CC, 3.8-fold ↑ in DG.</td>
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<td>Agents given systemically, not IT, not generally thought to cross BBB. Effect on cells of CNS is concerning as many forms of cancer treated with these agents.</td>
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<tr>
<td>Mignone &amp; Weber, 2006</td>
<td>12 6-week old mice</td>
<td>Thiotepa - 1 mg/kg, 5 mg/kg, 10 mg/kg</td>
<td>Thiotepa - 1 mg/kg, 5 mg/kg, 10 mg/kg IP vs. saline (3 mice per group)</td>
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<td>Dose-related ↓ of up to 80% of neurons of DG - 52%c at 1 mg/kg, 71-83%c at 5-10 mg/kg</td>
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<tr>
<td>Rzeski et al, 2004</td>
<td>7 day old rats</td>
<td>IP</td>
<td>CDDP - 5/10/15 mg/kg</td>
<td>CPM - 200/400/600 mg/kg</td>
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<tr>
<td></td>
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<td></td>
<td>Thiotepa - 15/30/45 mg/kg</td>
<td>Ifosfamide - 50-500mg/kg</td>
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<td>Swelling of dendrites within 4 hrs of administration of each agent. Widespread degeneration of neurons w/CDDP 5mg/kga, 10mg/kgc, 15mg/kgc w/Thiotepa 15b, 30b, 45b w/CPM 400a, 600c w/Ifosfamide 300b, 500c Appeared due to apoptosis.</td>
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<td>Limitation – chemo dosage given exceeds usual clinical doses in pediatrics, but not in HD regimens given to adults.</td>
</tr>
</tbody>
</table>
**Table 2. Neurotoxic Effects of Cranial Radiation (CRT) and Chemotherapy in Children**

<table>
<thead>
<tr>
<th>Study</th>
<th>Origin of Specimen(s)</th>
<th>Chemotherapy Agent(s) and Dose(s)</th>
<th>Effect on Neurons</th>
<th>Comments/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kellie et al, 2005</td>
<td>12 children with BT diagnosed &gt; 36 mos of age, median follow-up - 7.5 yrs. Mean age at diagnosis - 7.6 yrs.</td>
<td>HD MTX 8 gm/m² x 4 courses Etoposide 200 mg/m² x 4 courses CBDCA 700 mg/m² x 4 courses. Also conventional WBRT 35-50.4 Gy</td>
<td>66%: Grade I leukoencephalopathy, 33%: Grade II. Grade II treated with higher doses of WBRT. WM changes in Grade II began within 1 yr of WBRT with growing subarachnoid space, appearance of lacunae 5-6 yrs post-WBRT.</td>
<td>Difficult to attribute toxicity to either treatment modality. Limitation – small sample size, multimodal treatment.</td>
</tr>
<tr>
<td>Monje et al, 2007</td>
<td>Human hippocampi on autopsy of 3 children (2 with MBl (both 7 yo), 1 with AML (10 mo)).</td>
<td>AML – 13.2 Gy TBI, with 10 chemo agents MBl - 23.4 Gy CSRT w/boost to PF, 6 chemo agents</td>
<td>100-fold ↓ in neurogenesis compared to age-, gender-matched controls 10-fold ↓ in neurogenesis compared to controls</td>
<td>First study to demonstrate impact of CNS therapies on human hippocampal neurogenesis. Limitations – unable to assess for neuronal maturation.</td>
</tr>
<tr>
<td>Nagel et al, 2004</td>
<td>25 children w/MBl, mean age at diagnosis 8.27 yrs</td>
<td>All received 55.8Gy to tumor bed, 23.4-39.6Gy WBRT, plus adjuvant chemo: HD CPM CDDP VCR</td>
<td>Time since diagnosis related to right, left HC volume, declining until 2 yrs post-XRT, then resuming + growth. Girls had steeper ↓ in right, left HC volume.</td>
<td>First study to evaluate HC development in this population. Girls may be more affected than boys. Limitation - no control group</td>
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<td>Study</td>
<td>Description</td>
<td>Findings</td>
<td>Limitation</td>
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<td>Oi et al, 1990</td>
<td>Postmortem study of 34 children, mean age 6.5 yrs, all with glioma.</td>
<td>65% - mean dosage 40.63 Gy WBRT or WB/CSRT; 35% did not receive any treatment</td>
<td>Limitation – did not relate damage seen to XRT dose or site.</td>
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<td>32% of irradiated brains showed demyelination; 27% - necrosis or focal vacuoles; 18% - cortical atrophy; 18% - endothelial proliferation; 9% - vascular thrombosis; 5% - telangiectatic vascular proliferation, thickening. Findings of this sort rare in non-irradiated brains. Abnormalities most severe in WM.</td>
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<td>Reddick et al, 2005</td>
<td>52 children w/MBI, mean age at CRT 8.3 yrs, mean age at exam 13 yrs; 26 healthy controls</td>
<td>All received 35-40Gy CRT; 73% received one or more of: CBDCA, VP16, VCR, CPM, CCNU, topotecan, CDDP</td>
<td>Limitations - single section of imaging only where CRT dose not uniform, wide range of chemo agents also given</td>
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<td>Quadratic random coefficient model: volume of NAWM as function of time since CRT, time x age at CRT, presence of shunt. Deficit in NAWM compared to controls at one time point.</td>
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<tr>
<td>Study</td>
<td>Origin of Specimen(s)</td>
<td>Treatment</td>
<td>Effect on Neurons/Cognition</td>
<td>Comments/Limitations</td>
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<tr>
<td>Ordy et al, 1963</td>
<td>50 female mice, 10 controls</td>
<td>80-720 Gy to various brain areas</td>
<td>Difference in mean overall scores of open-field latency between subjects and controls. Beginning in month 5, bilateral parietal XRT group scored higher(^b) on open-field latency. Right cerebellar XRT group significantly slower on locomotor wheel(^b)</td>
<td>Very early study relating CRT to behavior changes. Delayed behavioral effects on mice after radiation may be due to necrosis, vascular damage after high doses of radiation.</td>
</tr>
<tr>
<td>Rao et al, 2011</td>
<td>1 month old male mice and controls</td>
<td>4Gy WBRT for 5 consecutive days</td>
<td>Impairment of non-spatial learning at 1 mo(^a) and 5 mos(^b) post-XRT</td>
<td>First study to demonstrate continued ↓ in memory behavior long-term after early fractionated CRT to young rodents.</td>
</tr>
<tr>
<td>Rola et al, 2004</td>
<td>24 21-day-old mice - 12 subjects, 12 controls</td>
<td>5 Gy WBRT to subjects, controls sham-irradiated</td>
<td>Irradiated mice had deficits in memory retention 3 mos after WBRT(^b), greater numbers of immature neurons after behavioral training than non-irradiated mice(^b)</td>
<td>Increased immature neurons in behaviorally-trained mice after WBRT likely due to learning-enhanced survival rather than physical activity of training, may lead to improved cognitive functioning. Limitation – single dose radiation not representative of pediatric therapy.</td>
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<tr>
<td>Siegers et al, 2008</td>
<td>Adult male rats</td>
<td>HD-MTX 250mg/kg, controls received saline</td>
<td>Animals treated w/MTX - longer latency time(^a) for spatial memory. Control rats had better novel recognition(^a)</td>
<td>Longer latency time indicates impaired spatial memory, failure to distinguish familiar object from novel reflects ↓ HC functioning.</td>
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<tr>
<td>Study</td>
<td>Species/Groups</td>
<td>Treatment Details</td>
<td>Behavioral Effects</td>
<td>Results/Conclusion</td>
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<tr>
<td>Siegers et al, 2009</td>
<td>Adult male rats</td>
<td>HD-MTX 250mg/kg, controls received saline</td>
<td>Rats treated w/MTX spent less time in platform quadrant&lt;sup&gt;c&lt;/sup&gt;, had less freezing behavior, indicating fear&lt;sup&gt;c&lt;/sup&gt;.</td>
<td>Results from both tests indicate retrograde amnesia, impaired memory consolidation after learning specific behaviors, due to MTX.</td>
</tr>
<tr>
<td>Winocur et al, 2006</td>
<td>25 female adult mice</td>
<td>MTX 37.5 mg/kg IP and 5FU 75 mg/kg IP each week for 3 weeks. Control mice given IP saline injections</td>
<td>Chemo-treated mice had longer latencies, more errors on spatial memory testing on day 1, but similar to controls as time went on. On delayed NMTS, chemo group had treatment x delay interaction on latency&lt;sup&gt;c&lt;/sup&gt; and error&lt;sup&gt;c&lt;/sup&gt; scores.</td>
<td>Spatial memory, conditional rule learning, longest delay of non-spatial memory test affected by chemo. Limitations – with administration of 2 drugs, cannot ascribe effects to either. Differences in spatial memory could be attributed to hyper-arousal or hyperactivity.</td>
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<tr>
<td>Study</td>
<td>Population Details</td>
<td>Treatment Details</td>
<td>Neurocognitive Effects</td>
<td>Limitations</td>
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<td>Barrera et al, 2005</td>
<td>800 childhood cancer survivors (average age at diagnosis - 2 yrs, average age at study - 12 yrs). 36.6% leukemia, 15.2% CNS tumor, 48% other cancers. 923 age-, gender-matched controls.</td>
<td>21.3% IT MTX only 15.6% CRT and IT MTX 9% CRT only</td>
<td>Those with BT, leukemia - highest odds ratios of repeated/failed grade in school; attending learning disabled program; academic problems. Those who received CRT had higher odds ratios of above categories</td>
<td>Mailed questionnaires without objective measurement, survivors had wide range of diagnoses and treatment. An imperfect downstream indicator of neurocognitive deficits.</td>
</tr>
<tr>
<td>Benesch et al., 2009</td>
<td>23 children w/MBL (78%) or ependymoma (22%) at median 56 mos after rx. 8 children w/glioma rx'd w/surgery only were controls.</td>
<td>No treatment information, only that it was multimodality</td>
<td>No significant difference in QOL scores in relation to neurocognitive testing results, no sig difference between groups on KINDL.</td>
<td>Small n; 74% were male; no treatment info.</td>
</tr>
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<td>Fouladi et al, 2004</td>
<td>127 children w/MBL or supratentorial PNET</td>
<td>36% high-risk - 36 Gy CSRT, 55.8 Gy boost 59% average risk - 23.4 Gy CSRT, 55.8 Gy boost All received HD chemo: CDDP 75mg/m² x 4 CPM 4gm/m² x 4</td>
<td>17% had WML: 32% Grade I, 68% Grade II; most common locations pons, cerebellum. 14% of pts w/WML had neurologic symptoms. Cumulative index of pts w/WML at 1 yr: 15%, at 2 yrs: 17.5%. No difference by risk group, diagnosis, cumulative dose of CPM.</td>
<td>Those with WMLs had significant cognitive decline over time as compared to those without WMLs. Limitation - cannot determine whether WMLs due to CRT, HD chemo, or combination.</td>
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<tr>
<td>Study</td>
<td>Participants and Treatments</td>
<td>Results</td>
<td>Limitations</td>
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| Khong et al, 2003            | 9 MBl survivors (mean age at diagnosis 7.8 yrs, mean age at study 10.8 yrs) 12 healthy age-matched controls. | VCR 3mg/m² x 4  
Some also received topotecan  
IQ ↓ in those w/WMLs, but not in those without; decline in math b for those w/WMLs but not without. | First study to show DTI sensitivity to neurotoxicity, may be correlated to academic performance. Limitations - small sample size, subjects treated with range of radiation doses and chemotherapy agents. |
| Khong et al., 2006           | 12 MBl, 18 leukemia survivors 55 healthy age-matched controls  
Mean age at study 13.1 yrs | CRT (30.6 - 40 Gy WBRT with 50.4 - 54 Gy boost to PF) & chemotherapy (VCR, CDDP, and/or Etoposide, CPM)  
FA ↓ by 12.4-19% in all areas in subjects as compared to controls. In children < 5yrs at treatment, 26.7% ↓ in supratentorial FA compared to controls, 23.2% ↓ in those > 5yrs at treatment. Severe deterioration in academic performance correlated with 46.2 % ↓ in supratentorial FA | Follow-up of previous study. Wide variability in range of radiation doses and chemo agents, but demonstrated differences in neurocognitive outcome related to treatment modality. |
| Mabbott et al, 2005          | 53 survivors of PF tumors, mean age at diagnosis 6.6 yrs.  
26% - reduced-dose CRT (23.4-30.2 Gy), 64% - standard-dose CRT (34-41.4 Gy), 8% - dose unknown.  
All received boost to PF of 45-55.8 Gy.  
74% received | Older age at diagnosis correlated with better reading b, school performance scores by parents b. Longitudinal analysis: decline in math a, spelling a, reading a. Parents'/teachers' school functioning ratings ↓ over time, with ↑ social a, attention b | Longitudinal data demonstrates continued academic declines over time. Limitation – mixed therapies |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Chemotherapy</th>
<th>Problems</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mabbott et al, 2006</td>
<td>8 children W/MBI (7 males, 1 female), mean age at diagnosis 7.5 yrs, mean time to study 2.5 yrs. 8 healthy controls</td>
<td>50% received 36-36.6 Gy CSRT; 50% received 23.4 Gy CSRT; 100% received PF boost to 55.4 Gy. All received either Etoposide/CDDP/CPM/VCR or CCNU/VCR/CDDP</td>
<td>Initial mean IQ 17.5 points &lt; controls; mean decline over 2.5 yrs: 8 pts. ↓ IQ related to ↑ ADC. Correlation of low IQ, low FA. FA in all ROIs lower in subjects than controls.</td>
<td>Deficits in IQ outcome related to CRT may be result of tissue compromise. FA, ADC sensitive measures of tissue damage related to loss of progenitor cells, loss of myelin. Limitations - small sample size, only one female included, higher mean IQ at baseline of control group may have skewed results.</td>
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<tr>
<td>Maddrey et al, 2005</td>
<td>16 MBI survivors, mean age at diagnosis 7.2 yrs, mean age at study 22.2 yrs.</td>
<td>All received CRT. 56% received unspecified chemotherapy.</td>
<td>Mean IQ=75, mean vocabulary score extremely low average, mean Block Design within mental retardation range. 67% - impairment in global intellectual functioning, 92% - impairment on one test of attention, 79-86% - impaired on executive function tests.</td>
<td>Limitations – small sample size, cross-sectional design, multimodal therapy without specific agents defined.</td>
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<tr>
<td>Mulhern et al, 2001</td>
<td>42 children W/MBI, mean age at diagnosis 8.2 yrs, mean age at study 13.4 yrs</td>
<td>All received 23.4-36 Gy CRT W/PF boost 49-54 Gy. 69% received chemo w/one or more of: CDDP, VP16, CPM, CBDCA, VCR, PCB, PDN</td>
<td>70% of correlation between IQ, age at CRT explained by NAWM volume; 90% for that between factual knowledge, age at CRT; 78% for verbal abstract thinking; 48% for nonverbal abstract thinking; model not significant for NAWM related to verbal memory, sustained attention</td>
<td>Limitations - small sample size, inconsistent number of studies done among subjects</td>
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<tr>
<td>Study</td>
<td>Sample Characteristics</td>
<td>Treatments</td>
<td>Results</td>
<td>Limitations</td>
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<td>Mulhern et al, 2004</td>
<td>37 BT survivors; median age at diagnosis 6.5, median time since treatment 5.7 yrs</td>
<td>18 received chemo: CDDP, CBDCA, CPM, VCR, Nitrogen Mustard, PCB, PDN. All received varying doses of focal CRT to tumor (49.2-70.2 Gy) and/or WBRT (23.4-44 Gy)</td>
<td>Subjects - lower norms on CCPT Overall index&lt;sup&gt;c&lt;/sup&gt;, and 7/10 component indices&lt;sup&gt;c&lt;/sup&gt; relative to norms. Decreased NAWM volume associated with lower CCPT scores.</td>
<td>First study to describe relationship between NAWM, attention; may be due to loss of NAWM over time after treatment or failure to develop NAWM age-appropriately. Limitations - cross-sectional, CCPT not comprehensive in assessment, ROIs didn't include some areas involved in attention.</td>
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<tr>
<td>Mulhern et al, 2005</td>
<td>111 children w/MBI, median age at diagnosis 7.4 yrs. 67% average risk (AR), 33% high-risk (HR) (w/metastatic disease or residual tumor after surgery).</td>
<td>AR - 23.4 Gy CSRT, 36 Gy to PF, 55.8 Gy to tumor bed HR - 36-39.6 Gy CSRT, 55.8 Gy to PF All received HD CPM, CDDP, VCR</td>
<td>Tested postop and at 1, 2 and 5 yrs after diagnosis. AR - mean loss of -0.4 pts/yr compared to HR w/mean loss of -8.2 pts/yr&lt;sup&gt;a&lt;/sup&gt; Those ≥ 7 yrs at diagnosis declined in reading&lt;sup&gt;b&lt;/sup&gt;, spelling&lt;sup&gt;a&lt;/sup&gt;. Those &lt; 7 declined in IQ&lt;sup&gt;b&lt;/sup&gt;, reading&lt;sup&gt;c&lt;/sup&gt;, spelling&lt;sup&gt;c&lt;/sup&gt;, math&lt;sup&gt;a&lt;/sup&gt;.</td>
<td>Multi-institutional longitudinal study, models suggest AR subjects had better overall neurocognitive function. Limitations - some missing values, more young children had complication of PF syndrome.</td>
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<td>Penn et al, 2008</td>
<td>37 children w/BT (parents of 37 children, 27 children themselves completed tool). Median age at timepoint 1 - 9.4 yrs. Matched to healthy controls</td>
<td>No information about type of treatment</td>
<td>Differences in parent report of HRQOL at 1, 6, 12 mos after diagnosis compared to controls&lt;sup&gt;b&lt;/sup&gt;. For self-report at time 1, difference in all summary scores, school domain compared to controls&lt;sup&gt;a&lt;/sup&gt;. At 6 mos, difference for total score, physical summary, school domain&lt;sup&gt;a&lt;/sup&gt;.</td>
<td>Longitudinal study, showed discrepancy between child and parent report. Limitations – small sample size, no treatment specific information.</td>
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<tr>
<td>Study</td>
<td>Sample Characteristics</td>
<td>Treatment Details</td>
<td>Intellectual Functionality Findings</td>
<td>Limitations</td>
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<td>Reddick et al., 2003</td>
<td>40 BT survivors, median age at study 12.8 yrs</td>
<td>CRT with or without chemotherapy</td>
<td>Correlations between WM volume and attention&lt;sup&gt;a&lt;/sup&gt; and IQ&lt;sup&gt;b&lt;/sup&gt;. Memory not significantly correlated to WM volume</td>
<td>Developed model of therapy where ↓NAWM correlates to attention deficits, which result in ↓FSIQ, academic achievement. Limitations – mixed therapy, chemo agents not specified.</td>
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<tr>
<td>Sands et al, 1998</td>
<td>10 BT survivors, mean age 5 yrs 8 mos, mean time off-therapy 37.8 mos.</td>
<td>5 cycles of: VCR CDDP VP-16 For bone marrow ablation: CBDCA Thiotepa Etoposide</td>
<td>Overall mean IQ 87.1 (19th %ile compared to peers). VIQ mean 88.6; PIQ mean 87.7, both low-average to borderline. 83% - high average to average on reading. 83% - impaired range on confrontational naming, expressive picture vocabulary. 77.8% within normal limits per behavioral checklist.</td>
<td>Encouraging but overall mixed results in this early study of outcomes after HD chemo without CRT. Limitation – small sample size.</td>
</tr>
<tr>
<td>Sands et al, 2001</td>
<td>43 children with CNS germ cell tumors; average age at diagnosis 14.4 yrs, mean age at study 21 yrs.</td>
<td>All received CBDCA Etoposide Bleomycin +/- CPM 67% received cranial CRT (&lt;25-55.8 Gy)</td>
<td>Age at diagnosis correlated with FSIQ&lt;sup&gt;b&lt;/sup&gt;, VIQ&lt;sup&gt;a&lt;/sup&gt;, PIQ&lt;sup&gt;a&lt;/sup&gt;, math&lt;sup&gt;a&lt;/sup&gt;.</td>
<td>This study of therapy in older children demonstrated average results in most IQ scales. Limitations – 2/3 of subjects received mixed therapy, small sample size</td>
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<tr>
<td>Sands et al, 2010</td>
<td>24 BT survivors, mean age at diagnosis 3 yrs</td>
<td>Received either VCR/CDDP/Etoposide/CPM; or those agents plus HD MTX; or VCR/CBDCA/temozol-amide; and HD CBDCA, HD thiotepa, HD etoposide</td>
<td>Time since diagnosis inversely related to FSIQ&lt;sup&gt;a&lt;/sup&gt;, VIQ&lt;sup&gt;a&lt;/sup&gt;, PIQ&lt;sup&gt;a&lt;/sup&gt;, reading&lt;sup&gt;a&lt;/sup&gt;, delayed verbal memory&lt;sup&gt;b&lt;/sup&gt;, delayed verbal recognition&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Limitation – those treated with CRT not separated from those who were not.</td>
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<td>Study</td>
<td>Description</td>
<td>Treatments</td>
<td>QOL/Neurocognitive Impacts</td>
<td>Limitations</td>
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<td>Sands et al, 2011</td>
<td>25 BT survivors; mean age at study timepoint 1 - 8.1 yrs, at T2 (n =19) – 13.5 yrs</td>
<td>CDDP VCR VP-16 CPM CBDCA Thiotepa 28% received CRT</td>
<td>General Health mean scores “at risk” at T2, high %age of children at-risk for withdrawal, social skills, leadership, somatization subscales. Younger age at diagnosis correlated w/poor adaptability, leadership skills. Longer time at follow-up correlated w/increased hyperactivity, attention problems.</td>
<td>Generally positive findings of QOL in those treated on more current protocols. Limitations – small sample size, some received CRT, no baseline assessment done prior to therapy for comparison</td>
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<td>Stargatt, 2007</td>
<td>35 children with PF tumors, mean age at diagnosis 9.5 yrs. 43% MB, 37% pilocytic astrocytoma, 14% ependymoma, 6% other. 23 completed entire study</td>
<td>34% had surgery only 6% had surgery, CRT 57% had surgery, CRT, chemo 54% received 50-59.6 Gy to tumor site 3% received 39.6 Gy</td>
<td>CRT group had ↓ IQ points from diagnosis to 3 yrs later, with no significant ↓ IQ in 1st year, ↑ in 2nd year, ↓ in 3rd yr. Loss of attention span over time in CRT group</td>
<td>Longitudinal study providing data up to 3 yrs after treatment. Limitation – mixed therapy modalities.</td>
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Ward et al, 2009 | 31 children diagnosed with BT at < 3 yrs of age. Mean age at dx 1.69 yrs, mean age at study 11 yrs. | Surgery and/or chemotherapy, agents not specified | Those with > 1 surgical procedure had ↓ PIQ\(^a\), executive functioning\(^c\). Younger age at treatment correlated with ↓ FSIQ\(^a\), VIQ\(^a\), executive functioning\(^a\). Chemotherapy not related to cognitive outcome. | Limitations – chemo agents not specified, no description of numbers of those treated with surgery vs. chemo and surgery. |

\(^a\) \(P < .05\)
\(^b\) \(P < .01\)
\(^c\) \(P < .001\)

**Abbreviations:** ADC, apparent diffusion coefficient; ALL, acute lymphoblastic leukemia; AML, acute myelocytic leukemia; AuHCR, autologous hematopoietic stem cell rescue; BBB, blood-brain barrier; BT, brain tumor; CBDCA, carboplatin; CC, corpus callosum; CCPT, Connors Continuous Performance Test; CDDP, cisplatin; CNS, central nervous system; CPM, cyclophosphamide; CRT, cranial radiation therapy; CSRT, craniospinal radiation therapy; DG, dentate gyrus; DTI, diffusion tensor imaging; FA, fractionated anisotropy; GM, gray matter; HD, high-dose; IP, intraperitoneal; IQ, intelligence quotient; IT, intrathecal; KINDL, German QOL assessment tool; MBl, medulloblastoma; MD, mean diffusivity; MRI, magnetic resonance imaging; MTX, methotrexate; NAWM, normal-appearing white matter; NMTS, non-matching to sample learning; PCB, procarbazine; PF, posterior fossa; PIQ, performance intelligence quotient; PNET, primitive neuroectodermal tumor; ROI, region of interest; SGZ, subgranular zone; SVZ, subventricular zone; TBI, total body irradiation; VBM, voxel-based morphometry; WBRT, whole brain radiation therapy; WISC, Wechsler Intelligence Scales for Children; WM, white matter; WML, white matter lesions
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Brain Structural Changes in Children Five Years After Chemotherapy for Brain Tumors

Mary C. Baron Nelson, Paul M. Macey, Ronald M. Harper, Eufemia Jacob, Sunita K. Patel, Peggy Compton

Abstract

Two-thirds of children diagnosed with brain tumors achieve long-term survival, and increasingly, children younger than 5-6 years at diagnosis are treated with high-dose chemotherapy protocols, delaying or foregoing cranial radiation. Intrathecal chemotherapy is associated with white matter loss, with systemic administration of certain agents also damaging healthy brain tissue. However, effects of systemic chemotherapy on the brain in children with tumors are unclear. Our objective was to compare structural neural integrity with magnetic resonance imaging procedures in children with brain tumors ($n = 7$, mean age 8.3 years), treated with chemotherapy a mean of 5.4 years earlier, to age- and gender-matched healthy controls ($n = 9$, mean age 9.3 years). Magnetic resonance imaging data were collected using a diffusion tensor imaging protocol to evaluate tissue integrity throughout the brain. Voxel-based morphometry was used to determine differences between groups. Mean diffusivity and fractional anisotropy maps were obtained from normalized, smoothed images, and the two groups were compared using analysis of covariance, with age and gender as covariates. Higher mean diffusivity values emerged in patients over controls ($p < 0.05$, corrected for multiple comparisons), and were especially apparent in the central thalamus, internal and external capsules, putamen, globus pallidus and pons. No significant differences emerged in fractional anisotropy values between groups. The patient group had lower brain-to-CSF ratio ($p = .03$), assessed with volumetric analyses. Significantly higher mean diffusivity, indicating long-term damage, appeared in multiple areas in patients 5 years after treatment with chemotherapy.
Introduction

Brain tumors are the second most common type of cancer in children. Despite successful treatment, survivors often show detrimental consequences years later. Partitioning specific causes of brain injury in this population is challenging, as many variables related to a brain tumor diagnosis (i.e., tissue compression and edema, increased intracranial pressure, hydrocephalus), as well as surgical procedures to remove the tumor, may also cause long-term damage to previously healthy brain tissue, and often leave survivors with physical and neurocognitive deficits (N. E. Anderson, 2003). The relationship between neurocognitive deficits and cranial radiation has been so strongly supported (Kim, Brown, Jenrow, & Ryu, 2008; B. D. Moore, 3rd, Copeland, Ried, & Levy, 1992; Waber, Tarbell, Kahn, Gelber, & Sallan, 1992) that young children under 6 years of age are increasingly treated on protocols without radiation (Dhall et al., 2008; Marachelian, Butturini, & Finlay, 2008). Alternative treatments believed to have less impact on brain function are preferred, but less is known about the potential detrimental consequences of these on healthy neural tissue.

High-dose chemotherapy with autologous hematopoietic stem cell rescue (AuHCR) is a frontline treatment for brain tumors in very young children because it is considered less damaging than radiation therapy (Gardner & Finlay, 2001; Marachelian, et al., 2008). However, chemotherapy without radiation leads to long-term brain tissue damage, including white (Carey et al., 2008) and gray matter loss (Porto et al., 2008), and to neurocognitive deficits in adults (Dutta, 2011), as well as in children with leukemia (Carey, et al., 2008; I. M. Moore et al., 2008; Stenzel et al., 2010). Certain types of chemotherapy are toxic to oligodendrocytes (Dietrich, Monje, Wefel, & Meyers, 2008), hippocampal cells (James et al., 2008), cerebellar granule cells, and astrocytes (Wick et al., 2004). Interestingly, in vitro models demonstrate that certain
Chemotherapy agents are in fact more toxic to neural progenitor cells than to cancer cells (Dietrich, Han, Yang, Mayer-Proeschel, & Noble, 2006; Dietrich, et al., 2008; Mignone & Weber, 2006). Specifically, damage from chemotherapy to progenitor cells that play a key role in the development of memory systems and white matter integrity likely underlie the neurocognitive deficits commonly found after cancer treatment in children (Dietrich, et al., 2006; Monje, 2008). Thus, although considered less toxic to brain cells than radiation therapy, recent findings suggest that chemotherapy may also be associated with brain tissue injury and consequent long-term neurocognitive deficits in children.

The purpose of this study was to 1) examine white and gray matter volume and diffusion tensor imaging (DTI) values (MD and fractional anisotropy [FA]) in childhood survivors of brain tumors treated with chemotherapy and AuHCR, and 2) compare those values to age and gender matched healthy controls. Techniques based on quantitative measures of brain integrity and volume allow detection of pathology not visible to the eye. Specifically, diffusion tensor imaging (DTI) is a technique that provides measures of structure based on the movement of water through cells, with one measure in particular, mean diffusivity (MD), being especially sensitive to long-term, generalized cellular damage. A decrease in white and gray matter volume would indicate damage, injury, or loss of normal brain tissue cells. In addition, mean diffusion values would be high in areas with edema, loss of axons and demyelination, reflecting chronic injury (Kumar, Macey, Woo, Alger, & Harper, 2006). Decreased FA in the patient group, as compared to controls, was also expected, indicating a loss of structural integrity (Cercignani, Inglese, Pagani, Comi, & Filippi, 2001). We tested the hypotheses that brain volumes would be decreased, FA would be decreased, and MD would be increased in patients with brain tumors previously treated
with systemic high-dose chemotherapy with AuHCR, when compared to age- and gender-matched controls.

Methods

Study Design

A two-group comparative cross-sectional design was used to compare white and gray matter volumes, and FA and MD values between seven pediatric brain tumor patients (mean age 8.3 years) and nine matched healthy controls (mean age 9.3 years). The UCLA Institutional Review Board and the Children’s Hospital Los Angeles Committee for Clinical Investigations approved the study, and informed consent was obtained from parents of all subjects. Assent was obtained from subjects 7 years of age and older.

Sample & Setting

Sixteen childhood brain tumor survivors were identified by the pediatric neuro-oncology team at Children’s Hospital Los Angeles who met the following inclusion criteria: 1) history of brain tumor with no current evidence of disease; 2) previous treatment on a chemotherapy-only regimen including vincristine, cyclophosphamide, cisplatin, etoposide and topotecan with AuHCR; 3) age between 5 and 13 years at time of enrollment; 4) off-therapy for at least 6 months; and 5) speaking either English or Spanish. Exclusion criteria were 1) residual disease; 2) history of cranial radiation; 3) concurrent diagnosis of neurofibromatosis or other serious neurological anomaly; 4) history of prolonged posterior fossa syndrome postoperatively; and 5) presence of a pacemaker or other implanted metal device (making the child ineligible for MRI).

Information about the study was mailed to families of eligible subjects. Parents were instructed to return a postcard if interested in enrolling. Twelve families (75%) responded. Five were excluded because of the presence of residual tumor (1); congenital brain malformation (1):
supratentorial primitive neuroectodermal tumor (PNET) with possibility of tumor location at that site interfering with DTI interpretation (1); families unable to travel for data collection (2). Six enrolled patients had posterior fossa tumors (medulloblastoma) located in the cerebellum, and one had a third ventricular tumor (choroid plexus carcinoma).

For the comparison group, nine healthy controls were recruited from children of staff in the hematology-oncology and radiology departments at the institution. Inclusion criteria for this convenience sample were 1) fluency in English or Spanish, 2) current age between 5 and 13 years, and 3) the ability to complete a 30-minute MRI without sedation. Exclusion criteria were 1) any neurological abnormality including past history of head trauma, seizures, hyperactivity or autism, or 2) presence of dental braces or other metal appliances in the body.

Measures

Magnetic resonance imaging data were collected over a 14-month period using a 3.0 Tesla Philips Achieva MRI scanner. High-resolution T1- and T2-weighted and DTI images were collected on patients, while only T1-weighted and DTI images were obtained on controls to minimize costs and time spent in the scanner for these young children without sedation. DTI images were collected using an 8-channel phased-array head coil with spin-echo echo-planar sequence [repetition time (TR) = 8,000 ms, echo-time (TE) = 55 ms, field of view (FOV) = 260 x 260 mm, slice thickness = 1.9 mm], with a 144 x 144 matrix size, 80 axial slices and no interslice gap. Diffusion-weighted images were collected in 12 directions for each slice, with a maximum b value of 1000 s/mm², a level suitable for investigation of brain tissue within children. In addition to DTI, high resolution T1-weighted images were obtained for voxel-based morphometry (VBM) purposes with a voxel size of 1.0 x 1.0 x 1.6 mm with the parameters TR 8000 ms; TE 55 ms; 136 x 136 matrix; FOV 26 cm; slice thickness 1.9 mm.
Diffusion tensor imaging allows assessment of three-dimensional diffusion characteristics of water within the brain, and within coherent bundles of axonal fiber tracks (Cercignani, et al., 2001), and was used to evaluate gray and white matter integrity throughout the brain. Derivatives of the DTI data, mean diffusivity (MD) and fractional anisotropy (FA), were used for injury assessment. Mean diffusivity, which reflects cell size, shape and integrity, and molecular motion across tissues (Cercignani, et al., 2001; Kumar, et al., 2006) has comparatively high values in areas with edema, loss of axons and demyelination, reflecting chronic injury, and low values in areas with intracellular swelling, reflecting acute injury (Iannucci, Rovaris, Giacomotti, Comi, & Filippi, 2001; Kumar, et al., 2006). Fractional anisotropy, which reflects the structural integrity and degree of alignment within fiber tracts has comparatively low values in areas with axonal damage (Mac Donald et al., 2007), loss of structural barriers and tissue organization (Cercignani, et al., 2001; Mukherjee et al., 2002),

Voxel-based morphometry (Ashburner & Friston, 1999) based on the TI-weighted images was performed to determine regional volume differences between patients and controls. A similar approach was used to define regional differences in MD and FA values between patients and controls, using an ANCOVA model at each voxel, and with corrections for multiple comparisons across voxels.

Procedures

Families were asked to arrive one hour before MRI registration time to complete the informed consent and/or assent process. Consent was obtained in a private conference room. The MRI protocol lasted one hour for patients, and included T1- and T2-weighted and pre- and post-contrast images for clinical surveillance purposes, in addition to the DTI scans. For controls, the MRI protocol took 30 minutes to complete. Five patients received propofol anesthesia for the
MRI, as was standard for their routine scans, and the remaining 2 patients and 9 controls utilized MRI-compatible movie goggles for distraction during the scan. After completion of the scans, parents were reimbursed for parking and lunch, and received a merchandise gift card, while children received a merchandise gift card in appreciation for their participation. All children were able to complete the study.

After images were assessed by a neuroradiologist, they were then de-identified and coded by a research assistant before being copied onto flash drives for analysis by the primary investigator.

Data Analysis

Demographic data were processed using Statistical Package for Social Sciences, version 17 (SPSS, IBM Corp.). The MRI data were processed using SPM8 and custom MATLAB software. After conversion from DICOM to NIFTI format, each subject’s anatomical T1 images were segmented into gray matter, white matter and cerebrospinal fluid (CSF) using the unified segmentation procedure (Ashburner & Friston, 1997). The procedure also calculated the spatial normalization parameters for warping images into a common space Montreal Neurological Institute (MNI), space. Segmented gray matter images in MNI space were smoothed with a Gaussian filter with 10 mm kernel, and voxel-based analyses were performed based on the SPM8 linear modeling.

Whole brain tissue volume was quantified for each subject, as well as gray matter volume, white matter volume, total intracranial volume, CSF volume, gray-to-white ratio, brain-to-CSF ratio, and brain-to-total intracranial volume.

Diffusion tensor imaging scans were analyzed with the SPM8 Diffusion Toolbox. The diffusion tensor was calculated at each voxel, from which whole-brain maps of FA and MD were
derived. The b0 images from the DTI series were co-registered to the T1 anatomical scans, and indices were spatially normalized using the T1 parameters. The normalized FA and MD images were smoothed with a 10 mm Gaussian filter, and analyzed with a voxel-based approach in SPM8.

Results

Sample Characteristics

Seven brain tumor survivors (mean age 8.3 years ± 3 years) (Table 1) and 9 age- and gender-matched control subjects (mean age 9.3 years ± 2.5 years) were included in these analyses. The patient and control groups were similar in demographics, except there were fewer adults (p < .05) and children (p < .02) in the home in the control group than in the patient group (Table 2).

Whole Brain Analysis

The anatomical scans were evaluated by a pediatric neuroradiologist for clinical abnormalities, and in patients, for evidence of recurrent disease. Although no patient had recurrence of the primary brain tumor, one patient had a stable low-grade glioma of the right thalamus, and another had a midline arteriovenous malformation (AVM) that had been noted on previous scans. None of the controls had abnormal findings.

Of the intracranial overall tissue compartment volume measurements, brain-to-CSF ratio significantly differed (p = .03) in patients from controls (Table 3), indicating a smaller brain tissue volume in patients.

With age and sex as covariates, DTI analyses showed significantly higher MD in the patient vs. the control group at p < 0.05, with family-wise error correction for multiple comparisons. These findings reflect a very large effect size, and are indicative of chronic injury.
Widespread brain regions showed increased MD, including the internal and external capsules, putamen, globus pallidus and pons, suggesting a global effect of damage (Figure 1). Mean diffusivity was likewise increased throughout the cerebral white matter, mainly involving the long and short association fibers (subcortical u fibers, arcuate fasiculus, cingulum, superior and inferior longitudinal fasculi), the external and extreme capsules, and the centrum semiovale (Figure 2). Gray matter nuclei with increased MD were the medial and lateral nuclei of the globus pallidus, putamena, claustrum, and central thalamus including the interthalamic adhesion. At the same threshold ($p < 0.05$, with family-wise error correction), there was no significant difference in FA values between patients and controls.

Therefore, our hypotheses that brain volumes would be decreased, FA would be decreased and MD would be increased in patients with brain tumors previously treated with systemic high-dose chemotherapy, relative to matched controls, were partially supported. Although FA values did not differ, MD was increased in widespread regions throughout the brain, and brain-to-CSF ratio was smaller in patients compared to controls, indicating a smaller brain tissue volume in patients.

**Discussion**

In this study, children treated with chemotherapy for brain tumors displayed indicators of injury across multiple brain regions up to 11 years after completion of treatment. Significantly elevated MD, reflecting greater water diffusion and decreased tissue density, suggests the presence of long-term damage to tissue, rather than an acute inflammatory process. These changes appeared most notably in deep cortical brain structures that exert essential influences on other brain regions (Nieuwenhuys, Voogd, & van Huijzen, 2008) and are likely related to the history and effects of a brain tumor and subsequent surgery, as well as the administration of
systemic high-dose chemotherapy. The specific source cannot be determined based on this cross-sectional study.

The areas of the brain most affected are those that serve as essential pathways in the transmission of information between brainstem, cerebellum and thalamus to frontal and other cortical areas (Carpenter & Sutin, 1983; Guillery, 1995; Humphries, Stewart, & Gurney, 2006; Nieuwenhuys, et al., 2008). The injury largely involved white matter, possibly reflecting a loss of myelin in these tracts, which supports other findings of white matter loss in children treated with chemotherapy (Aukema et al., 2009; Carey, et al., 2008; Reddick, Laningham, Glass, & Pui, 2007), and of oligodendrocyte loss after chemotherapy in vitro (Dietrich, et al., 2006).

Injury to fiber pathways during surgical resection involving the cerebellum may have caused long-term damage in the pons, thalamus and white matter projection tracts, since 6 of the 7 patients had cerebellar tumors, and all patients underwent surgical resection. Alternatively, initial injury in the cerebellum due to the tumor and resulting hydrocephalus and edema may never have resolved. A third scenario may be that the acute injury of the tumor evolved into a chronic process over time due to inflammation and oxidative stress, exacerbated by the administration of systemic high-dose chemotherapy. The chemotherapy agents used to treat these 7 children damage healthy cells of the central nervous system, causing cell membrane disruption and apoptosis, which trigger the response of oxidative stress. In neuronal cell cultures, cisplatin and cyclophosphamide caused cell shrinkage and death in a dose-dependent fashion, and in a rodent model, the same agents caused widespread apoptosis of neurons (Rzeski et al., 2004). Vincristine, topotecan and cisplatin decreased viability of cerebellar granule cells, and reduced the number of primary astrocytes in rodents (Wick, et al., 2004). In a clinical setting, systemic administration of cisplatin and cyclophosphamide caused organ damage to the kidneys and heart...
respectively, through oxidative stress mechanisms (Sudharsan, Mythili, Selvakumar, & Varalakshmi, 2005; Turner & Lysiak, 2008).

Our findings suggest that MD is the best indicator of injury after chemotherapy. The combined findings suggest that radiation may cause more myelin injury, while chemotherapy causes more glial injury. Rapidly dividing cells, such as glial cells, are targeted by chemotherapy, and certain agents cause pyknosis of glial nuclei (Dietrich, et al., 2008; Morris, Hopewell, & Morris, 1995). Cisplatin and methotrexate administration to rodent neurons disrupted the branching of dendrites and interfered with the actin cytoskeleton, which results in cellular stress and neuronal dysfunction (James, et al., 2008; Rzeski, et al., 2004), and ultimately would affect the supporting glial cells. Inflammation and disruption of the intracellular matrix are underlying factors causing increased brain water diffusion, according to studies of brain pathology (Cloak, Chang, & Ernst, 2004). An interesting explanation for the source of injury is chronic process of oxidative stress and inflammation causing injury to glia after high-dose chemotherapy.

The lack of significant differences in FA between the groups may indicate generalized injury to neurons, dendrites and glial cells, and possibly disrupted axonal microstructure in the patient group (Kumar, et al., 2006). The finding contrasts with reports in the childhood brain tumor population that FA was the most sensitive indicator of injury after brain tumor treatment involving radiation (Khong et al., 2003). In this report, combined chemotherapy and radiation treatment, fractional anisotropy was significantly lower in the pons, medulla, corona radiata, and periventricular white matter in children with medulloblastoma treated with chemotherapy and craniospinal radiation (Khong, et al., 2003; Khong et al., 2006). Mean diffusivity was slightly lower in the pons in patients vs. controls, but higher in all other areas, and significantly higher in
the cerebellum. Since the majority of our patients had cerebellar tumors, we chose not to consider cerebellar FA and MD differences due to the history of surgical intervention in that area.

In this population of young patients (mean 2.6 years of age at diagnosis), it is not possible to know whether any recovery from initial injury occurred over time, although there is evidence for plasticity and resilience in the young brain (Chugani, Muller, & Chugani, 1996). Long-term outcome in children with various brain injuries is often inconsistent and contradictory (V. Anderson, Spencer-Smith, & Wood, 2011), and difficult to predict. Diffuse insults, such as those found in this study, tend to have poorer recovery than focal insults (V. Anderson, et al., 2011). Abnormal DTI values in what appears to be normal brain tissue on MRI may have clinical indications of increased disability in spite of the lack of gross injury (Moll et al., 2011).

Conclusion

Indications of chronic brain injury appear in children successfully treated for brain tumors with chemotherapy, but not radiation, an average of five years prior. While the study is small, very few studies are available to date on effects of high doses of systemic chemotherapy on the young brain. The injury and cell loss may be attributable to chemotherapy, or a result of general pathological changes associated with the condition of having a cerebellar lesion, or a combination of both that has culminated in a chronic injurious process. Future longitudinal studies are recommended, to document changes in mean diffusivity before and after surgery for a brain tumor, then subsequently after chemotherapy has been administered, and later after all treatment has ended for several years. Limitations of this study are the small sample size and the cross-sectional design.
The number of children with brain tumors who are treated with chemotherapy alone and not cranial radiation is currently small, and there is little information about the effects of high doses of systemic chemotherapy on the young brain. As more children are treated in this manner to avoid or delay cranial radiation, careful monitoring of brain structure will be required to establish the long-term consequences of this treatment approach, as well as partitioning the extent of damage done by the presence of a tumor and resection. This is the first study to document microstructural damage, as evidenced by increased mean diffusivity in the brain of this population treated in the manner, as compared to healthy controls. For now, clinicians should be aware that chemotherapy may potentially have long-term consequences on brain structure.
Figure 1. Increased MD in deep cortical regions.
Highlighted areas represent significant regions of increased mean diffusivity. The areas are concentrated in the subsulcal white matter, the insula, basal ganglia and central thalami.
Figure 2. Diffusely increased MD.

Highlighted areas represent significant regions of increased mean diffusivity, including short association fibers and centrum semiovale.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at Diagnosis</th>
<th>Years off therapy</th>
<th>Tumor Type/Location</th>
<th>VP Shunt</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>54 months</td>
<td>3.5</td>
<td>Choroid plexus carcinoma, left occipital horn</td>
<td>no</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan Temodar</td>
</tr>
<tr>
<td>02</td>
<td>27 months</td>
<td>2.5</td>
<td>Desmoplastic medulloblastoma, 4th ventricle</td>
<td>yes</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan</td>
</tr>
<tr>
<td>03</td>
<td>14 months</td>
<td>11.4</td>
<td>Medulloblastoma, posterior fossa</td>
<td>yes</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan</td>
</tr>
<tr>
<td>04</td>
<td>16 months</td>
<td>4.5</td>
<td>Desmoplastic medulloblastoma, posterior fossa</td>
<td></td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan</td>
</tr>
<tr>
<td>05</td>
<td>55 months</td>
<td>4.75</td>
<td>Primary leptomeningeal PNET involving left cerebellum, 4th ventricle, infundibulum, bilateral cerebellar-pontine angle</td>
<td>no</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan Methotrexate Temodar</td>
</tr>
<tr>
<td>06</td>
<td>19 months</td>
<td>3.3</td>
<td>Desmoplastic medulloblastoma, posterior fossa</td>
<td>no</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan Methotrexate</td>
</tr>
<tr>
<td>07</td>
<td>28 months</td>
<td>8</td>
<td>Primitive neuroectodermal tumor, posterior fossa</td>
<td>yes</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of Patients (n = 7) and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients n = 7</th>
<th>Controls n = 9</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at study</strong></td>
<td>8.33 years</td>
<td>9.3 years</td>
<td>.539</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td>.518</td>
</tr>
<tr>
<td>3 male</td>
<td>6 male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 female</td>
<td>3 female</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td>.303</td>
</tr>
<tr>
<td>1 Caucasian</td>
<td>4 Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Hispanic</td>
<td>2 Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Asian</td>
<td>1 Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mixed</td>
<td>2 African</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian/Hispanic</td>
<td>American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent Education</td>
<td></td>
<td></td>
<td>.058</td>
</tr>
<tr>
<td>(3 = community college; 4 = 4 years of college; 5 = graduate/professional school)</td>
<td>3.14</td>
<td>4.44</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Brain Tissue Measurements

<table>
<thead>
<tr>
<th>Brain Tissue Measured</th>
<th>BT $n = 7$</th>
<th>Controls $n = 9$</th>
<th>$P$</th>
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</thead>
<tbody>
<tr>
<td>Total Brain Volume</td>
<td>1.88 +/- 7.74</td>
<td>1.25 +/- 1.00</td>
<td>.167</td>
</tr>
<tr>
<td>Total Gray Matter</td>
<td>8.48 +/- 5.41</td>
<td>8.74 +/- 5.5</td>
<td>.354</td>
</tr>
<tr>
<td>Total White Matter</td>
<td>3.39 +/- 3.53</td>
<td>3.79 +/- 5.19</td>
<td>.100</td>
</tr>
<tr>
<td>Total Intracranial Volume</td>
<td>1.63 +/- 2.22</td>
<td>1.51 +/- 2.65</td>
<td>.341</td>
</tr>
<tr>
<td>Total CSF Volume</td>
<td>4.44 +/- 2.5</td>
<td>2.58 +/- 2.94</td>
<td>.195</td>
</tr>
<tr>
<td>Gray: white ratio</td>
<td>2.52 +/- 2.3</td>
<td>2.33 +/- 2.24</td>
<td>.130</td>
</tr>
<tr>
<td>Brain: CSF ratio</td>
<td>3.91 +/- 2.87</td>
<td>8.86 +/- 4.85</td>
<td>.026</td>
</tr>
<tr>
<td>Brain: Total Intracranial Volume ratio</td>
<td>7.41 +/- 1.19</td>
<td>8.48 +/- 1.33</td>
<td>.113</td>
</tr>
</tbody>
</table>
References


Diffusion Tensor Imaging and Neurobiobehavioral Outcome in Children with Brain Tumors Treated with Chemotherapy

Mary C. Baron Nelson, Peggy Compton, Paul M. Macey, Sunita K. Patel, Eufemia Jacob, Jennifer Ogren, Fred Dorey, Sharon O’Neil, Jonathan Finlay, Ronald M. Harper

Abstract

Survivors of childhood brain tumors often experience treatment-related neurocognitive deficits that impact quality of life (QOL). Cranial radiation is detrimental to healthy young brain tissue and contributes to neurocognitive problems. However, chemotherapy may also impact neuropsychological functions, a consequence of chronic neural injury and reduction in relative brain volume. The objective of this study was to determine tissue loss, memory and executive functioning and QOL effects of systemic high-dose chemotherapy for brain tumors in children. We used volumetric measures of brain injury, and neurocognitive, behavioral and QOL assessments in 8 children with brain tumors (mean age 8.5 years, diagnosed at a mean age of 32 months), and 9 healthy controls (mean age 9.3 years). Data indicates that overall QOL, school functioning, and psychosocial functioning were significantly lower in patients. However, the majority of patients scored within the average range on memory and executive functioning tests, and behavior assessment did not differ from controls. Neurocognitive deficits and decreased QOL appear in pediatric brain tumor patients treated with chemotherapy, and that treatment may have long-term psychological consequences. Early intervention may provide neuroprotection or repair to alleviate the long-term consequences of the original trauma and chemotherapy-related damage.

Introduction

Depending on a variety of factors, at least 40% of childhood brain tumor survivors are left
with physical and neurocognitive limitations (Anderson, 2003). These limitations often lead to long-term disability, which impacts employment opportunities and contributes to public health care costs of nearly $92 million per year (Ness & Gurney, 2007). With increasing numbers of children surviving brain tumors, characterizing central nervous system (CNS) injury that results in late neurocognitive effects and ultimately, decreased quality of life (QOL) may lead to interventions to improve outcomes.

Cranial radiation, 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). Although hypothesized to be less toxic than radiation, there are emerging data that suggest that many chemotherapy agents used in treatment of childhood brain tumors injure neural progenitor cells and healthy brain tissue, as well as the cancer cells targeted by such treatment (Dietrich, Han, Yang, Mayer-Proeschel, & Noble, 2006; James et al., 2008; Mignone & Weber, 2006; Wick et al., 2004). Both gray and white matter injury appear in children treated for brain tumors and acute lymphoblastic leukemia (ALL) with standard dose chemotherapy in combination with cranial radiation (Mulhern et al., 2001).

In adult women with breast cancer, standard dose chemotherapy is accompanied by memory and executive function difficulties (Myers, Pierce, & Pazdernik, 2008), which are correlated with specific volume loss in the prefrontal cortex and parahippocampal gyrus (Inagaki et al., 2006). While no similar studies exist for the pediatric brain tumor population, children with leukemia treated with chemotherapy alone showed deficits in executive functioning that correlated with white matter loss in the right frontal cortex (Carey et al., 2008). Although studies of white and gray matter loss in the childhood brain tumor population are limited, neuroimaging research in similar cognitive disorders shows a decrease in white and gray matter, specifically in areas
responsible for memory and cognitive function, including the hippocampus, fornix, mammillary bodies, anterior cingulate, right frontal cortex, and pre-frontal cortex (Inagaki, et al., 2006; Khong et al., 2003; Kumar et al., 2009; Serber et al., 2008; Spoletini et al., 2008).

Gender and age may play a significant role in neuropsychological and QOL outcomes in pediatric cancer. Girls have lower scores on health-related quality of life after childhood cancer treatment (Blaaubroek et al., 2007; Geenen et al., 2007). Furthermore, young females appear to be the most vulnerable to neurotoxic effects of chemotherapy and radiation (von der Weid et al., 2003; Waber, Tarbell, Kahn, Gelber, & Sallan, 1992). The more pronounced neurological changes after treatment may result from the more rapid development of glia and other brain tissue in females, with myelination leading in males, accompanied by improved language acquisition (Bartzokis, 2005). The sex differences mandate control of gender in this study.

The purpose of this study was to determine the relationship between microstructural brain tissue loss to neurocognitive deficits and decreased QOL in children with brain tumors treated with chemotherapy. We hypothesized that children treated with high-dose chemotherapy with autologous hematopoietic progenitor cell rescue (AuHCR) for brain tumors would display key areas of white matter and gray matter injury or brain tissue loss (in the hippocampus, fornix, mammillary bodies and pre-frontal cortex) relative to healthy age- and gender-matched controls, and that these injuries would be accompanied by neurocognitive dysfunction and decreased QOL. We anticipated that lowered memory performance and executive functioning would be associated with injury in the hippocampus and prefrontal cortex, respectively. We measured brain tissue injury and loss in these areas with fractional anisotropy (FA) and mean diffusivity (MD) measures, followed by volumetric analysis. Memory, executive functioning and QOL were evaluated with standardized tools. Gender, current age, and age at diagnosis for patients were
evaluated as contributing variables on all outcomes (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Schmithorst, Holland, & Dardzinski, 2008).

Methods

Design

To evaluate brain tissue injury in childhood brain tumor survivors treated with systemic high-dose chemotherapy with AuHCR, a two-group comparative cross-sectional design was used to compare regional FA and MD values between 8 pediatric brain tumor patients (mean age 8.5 years ± 1.3 years) and 9 matched healthy controls (mean age 9.3 years ± 2.6 years). The relationship between extent of white and gray matter loss in regions of interest in the brain and specific functional outcomes such as memory and executive functioning and QOL, was evaluated in the patient group with a survey design. These measures of brain structure were then explored as predictors of neuropsychological findings in the areas of memory and executive functioning, as well as QOL. The study was approved by the Institutional Review Boards at both Children’s Hospital Los Angeles and the University of California, Los Angeles.

Sample

A small convenience sample of patients meeting study inclusion criteria was recruited over 12 months from the brain tumor population at Children’s Hospital Los Angeles (CHLA). A letter of inquiry was mailed to 16 families of children identified as potentially eligible for study participation by the pediatric neuro-oncology team, with instructions to return a postcard if interested in enrolling. Twelve families (75%) responded, and of these, two were found to be ineligible because of the presence of residual tumor (1) and a congenital brain malformation (1), and two additional families were unable to travel to the institution for data collection. Six of the remaining 8 had posterior fossa tumors (medulloblastoma) located in the cerebellum, one had a
third ventricular tumor (choroid plexus carcinoma), and one had a supratentorial primitive neuroectodermal tumor (PNET). Age of patients at diagnosis, number of years off-therapy at time of enrollment, types and locations of tumors, presence of ventriculoperitoneal shunt, and chemotherapy received for each patient are presented in Table 1.

The final patient sample consisted of 8 brain tumor survivors who met the following inclusion criteria: history of brain tumor with no current evidence of disease; previous treatment on a chemotherapy-only regimen including Vincristine, Cyclophosphamide, Cisplatin, Etoposide and Topotecan; currently between the ages of 5 and 13 years; off-therapy for at least 6 months; and speaking either English or Spanish. Exclusion criteria were residual disease; history of cranial radiation; concurrent diagnosis of neurofibromatosis or other serious neurological anomaly; history of prolonged posterior fossa syndrome postoperatively; presence of a pacemaker or other implanted metal device (that would interfere with MRI); or inability to participate in neuropsychological testing due to aphasia, mutism, extreme developmental disability, or altered level of consciousness.

For the comparison group, nine healthy controls were recruited from children of staff in the hematology-oncology division and radiology department at CHLA. Inclusion criteria for this convenience sample were ages 5-13, fluency in English or Spanish, and the ability to complete a 30-minute MRI without sedation. Exclusion criteria were any neurological abnormality including past history of head trauma, seizures, hyperactivity or autism, or presence of dental braces or other metal appliances in the body.

**Measures**

*Brain tissue integrity*

Diffusion tensor imaging allows assessment of three-dimensional diffusion characteristics
of water within brain tissue, and within coherent bundles of axonal fiber tracks (Cercignani, Inglese, Pagani, Comi, & Filippi, 2001), and was used to evaluate gray and white matter integrity throughout the brain. A derivative of DTI procedures, mean diffusivity (MD), which reflects cell size, shape and integrity, and molecular motion across tissues (Cercignani, et al., 2001; Kumar, Macey, Woo, Alger, & Harper, 2006) was used for injury assessment. Mean diffusivity values are high in areas with edema, loss of axons and demyelination, reflecting chronic injury, and low in areas with intracellular swelling, reflecting acute injury (Kumar, et al., 2006). Fractional anisotropy (FA) measures any deviation from uniformity of diffusion in all directions, and reflects structural integrity and degree of alignment of fiber tracts (Cercignani, et al., 2001). Voxel-based morphometry (Ashburner & Friston, 1999), derived from the T1-weighted images, was also performed to obtain differences in volume between patients and controls.

To examine FA and MD in regions of interest of the brain following brain tumor treatment with chemotherapy, T1- and T2-weighted and diffusion tensor imaging data were collected using a single 3.0 Tesla Philips Achieva MRI scanner. Only T1-weighted and DTI images were obtained on controls to minimize costs and time spent in the scanner for these young children without sedation. DTI images were collected with spin-echo echo-planar sequence [repetition time (TR) = 8,000 ms, echo-time (TE) = 55 ms, field of view (FOV) = 260 x 260 mm, slice thickness = 1.9 mm], with a 144 x 144 matrix size, 80 axial slices and no interslice gap. We collected diffusion-weighted images in 12 directions for each slice, with a maximum b value of 1000 s/mm², a level suitable for investigation of brain tissue within children. In addition to DTI, high resolution T1-weighted images were obtained for voxel-based morphometry (VBM) purposes with a voxel size of 1.0 x 1.0 x 1.6 mm with the parameters TR 8000 ms; TE 55 ms; 136 x 136 matrix; FOV 26 cm; slice thickness 1.9 mm.
Neurocognitive Assessment

Neuropsychological measures were selected to assess memory and executive functioning, based on their established validity and reliability with broad pediatric populations (Mottram & Donders, 2005), and ease of administration. The majority of the selected measures are components of the standardized neurocognitive screening battery currently in use by the Children’s Oncology Group (Embry et al., in press). Completion of assessment took approximately 60 minutes.

The CVLT-C® (California Verbal Learning Test® – Children’s Version) is a widely used, validated test of verbal learning and memory in children 5-16 years of age, and includes 8 recall and 4 recognition measures. Performance on the long-delay free recall task was selected as the most appropriate indicator of verbal memory for use in the data analysis.

The NEPSY II Memory for Designs Test was used to assess non-verbal memory. The test has standardized norms for ages 5-16 years, and has an internal reliability coefficient of > 0.9 (Brooks, Sherman, & Strauss, 2009). Performance on the delayed total task was used as the best representation of non-verbal memory functioning.

The NEPSY II Inhibition Test assesses inhibitory control and switching, which are elements of executive functioning, and is used for children aged 5-16 years. The Inhibition Test has an internal reliability coefficient of > 0.8 (Brooks, et al., 2009). The Inhibition INI combined scaled scores and the Switching INS combined scaled test scores were converted to z scores for analysis.

The Behavior Rating Inventory of Executive Function (BRIEF™) (Gioia, Isquith, Retzlaff, & Espy, 2002) Parent Report is a parent questionnaire that assesses executive functioning in children 5-18 years of age, in 9 areas: emotional control, shifting, inhibition of
impulses, initiation, self-monitoring, planning and organization, working memory, organization of materials and task monitoring (Caron et al., 2009). It does so with good internal consistency (.82-.98), and test-retest reliability (.72-.84) (Mahone et al., 2002). The three summary T scores, Behavioral Regulation Index (BRI), Metacognition Index (MI), and Global Executive Composite (GEC) were used for analysis.

The Behavior Assessment System for Children, 2nd edition (BASC 2) (Reynolds & Kamphaus, 2004) is a parent evaluation of their child’s behavior and executive functioning. The four summary T scores, Externalizing Problems (EP), Internalizing Problems (IP), Behavioral Symptoms Index (BSI), and Adaptive Skills (AS) were used in the analysis.

Quality of Life Assessment

We used the PedsQL™4.0 Generic Core Scale to evaluate QOL in all subjects, and a parent of each also completed the parent proxy report. This tool, used extensively in children with cancer and survivors of childhood cancer, was designed to measure health-related quality of life between the ages of 2-18 years (Varni et al., 1998). Scores from each domain (physical, emotional, social and school functioning) were included in the analysis. In addition, a psychosocial functioning score was calculated from the emotional, social and school domains, and a total QOL score was derived from all 4 domains for use in the analysis.

Procedures

Families were asked to arrive one hour before MRI to complete the informed consent and/or assent process, obtained in a private conference room. Following the consent process, both child and parent completed the PedsQL™ Generic Core. Parents completed the BRIEF™ and BASC-2, during which time the patients underwent further testing with a neuropsychologist (CVLT-C®, NEPSY-II Memory for Designs, NEPSY-II Inhibition tests). Specifics of diagnosis,
treatment history and complications were abstracted from the patients’ charts by the primary investigator.

The MRI protocol followed, lasting one hour for patients, including T1- and T2-weighted and pre- and post-contrast images for clinical surveillance purposes, in addition to the DTI scans. For controls, the MRI 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 three patients and 9 controls used MRI-compatible movie goggles for distraction during the scan. After scan completion, parents were reimbursed for parking and lunch, and received a merchandise gift card, while children received a merchandise gift card. All children were able to complete the study.

Images were then de-identified and coded by a research assistant before being copied onto flash drives for analysis by the primary investigator.

**Image Processing**

The MRI data were processed using SPM8 and custom MATLAB software. After conversion from DICOM to NIFTI format, each subject’s anatomical T1 images were segmented into gray matter, white matter and cerebrospinal fluid (CSF) using the unified segmentation procedure (Ashburner & Friston, 1997). The procedure also calculated the spatial normalization parameters for warping images into a common space Montreal Neurological Institute (MNI), space. Segmented gray matter images in MNI space were smoothed with a Gaussian filter with 10 mm kernel, and voxel-based analyses were performed based on the SPM8 linear modeling.

Diffusion tensor imaging scans were analyzed with the SPM8 Diffusion Toolbox. The diffusion tensor was calculated at each voxel, from which whole-brain maps of FA and MD were derived. The b0 images from the DTI series were co-registered to the T1 anatomical scans, and
indices were spatially normalized using the T1 parameters. The normalized FA and MD images were smoothed with a 10 mm Gaussian filter, and analyzed with a voxel-based approach in SPM8.

The left and right hippocampi were traced by the primary investigator (PI) on normalized images for each subject using MRIcron and processed with volumetric analysis in MATLAB. Four subjects were re-traced by the PI, and then by J.O. to establish inter- and intra-rater 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). These ROIs are depicted in Figure 1.

Data Analyses

Demographic data were processed and analyzed using the Statistical Package for Social Sciences, version 17 (SPSS, IBM Corp.). T-tests were performed to determine differences in hippocampal volumes and scores on the BASC-2, BRIEF™ and PedsQL™ between patients and controls. Pearson correlation analyses were calculated to screen for relationships between variables, then linear regression analysis further explored significant correlations while controlling for age at diagnosis and gender.

Results

Eight patients (Table 1) and nine controls participated in the study. Despite attempted matching of subjects by age and gender, the resulting control group was slightly older and more frequently male than the patients (Table 2).

The MRI scans were evaluated by a pediatric neuroradiologist for clinical abnormalities, and in patients, for evidence of recurrent disease. Although no patient had recurrence of the
primary brain tumor, one patient had a stable low-grade glioma of the right thalamus and another had a midline arteriovenous malformation (AVM) that had been noted on previous scans. No abnormal findings were noted in the healthy controls.

Hippocampal volumes did not significantly differ in patients and controls (Table 3). Mean diffusivity was significantly higher in patients than controls in all regions analyzed by SPM8 (pre-frontal cortex, hippocampus, fornix, mammillary bodies), reflecting long-term damage to tissues (Figure 2). Data from a subsample of the current sample reported elsewhere also demonstrated higher MD in deep cortical regions of the brains of patients as compared to controls. These regions included the thalamus, basal ganglia and pons (Baron Nelson et al, TBD). Fractional anisotropy was significantly lower in patients than controls in the left (p < .01) and right (p < .05) middle frontal gyrus, left superior frontal gyrus (p < .05), right (p < .01), left mammillary body (p < .0001) and left prefrontal cortex white matter (p < .01), and right middle hippocampus (p < .002), indicating decreased axonal integrity in these areas (Figure 3).

No significant differences between patients and controls emerged on parent report of executive functioning via the BRIEF™ (Figure 4). Patients were categorized as more “at-risk” for the BASC-2 sub-category of “atypicality” over controls (p = 0.01), but all other subscales were similar between groups (Table 4). Thirty-eight percent of patients scored below average (scaled score of 6 or above, or 9th percentile and above) on the NEPSY Inhibition and Switching components of executive functioning and those patients were older at testing (p < .05) and had been off-therapy longer (p < .05) than those who scored higher. Children who were 2 years of age or younger at diagnosis scored lower on the Switching portion of the NEPSY Inhibition test (p < 0.1). Higher INI z score was related to female gender (p < .05).
Thirty-eight percent of patients scored below average (z score of -1.0 or above, or 1 SD below the mean and above) on verbal memory, and 25% scored below average on non-verbal memory. Patients with poorer scores on memory were also older at testing ($p < .05$) and had been off-treatment longer ($p < .01$) than those who scored in the average or above average ranges.

On the QOL assessment, both children with brain tumors and their parents rated their QOL as lower on each of the 4 subscales and total overall scores than those of healthy controls (Figure 5). Children in the patient group self-reported their social functioning and school functioning as significantly poorer than healthy controls, and their total overall QOL score was lower. They also rated their psychosocial functioning as lower. Their parents rated them significantly lower on physical functioning ($p = .01$) and total overall QOL also ($p = .05$) than parents of healthy controls. Quality of life scores did not significantly differ in patients who performed below average on neurocognitive testing, or in those who were 3 years old or younger at diagnosis. Younger age at study was related to poorer child rating of social functioning ($p < .01$).

Children are considered to be “at-risk” when their PedsQL™ scores or those of their parents’ rating are more than one standard deviation below the mean for their specific population (Varni, Burwinkle, Seid, & Skarr, 2003). As compared to published PedsQL™ means for children with brain tumors (S. N. Palmer, Meeske, Katz, Burwinkle, & Varni, 2007), 50% of this patient self-assessed with scores that were “at-risk” in psychosocial functioning; 37.5% were at-risk in emotional functioning; 25% were “at-risk” in social functioning and total QOL score; and 12.5% rated themselves “at-risk” in physical and school functioning. Of interest, none of the parents scored their children as “at-risk” on the parent-proxy report in any category.
To understand what role demographic factors played in neurocognitive outcome and QOL, a standard multiple regression analysis was performed between the dependent variables (child’s total QOL score, INI z score, INS z score, CVLT-C® long delay free recall z score, Memory for Designs delayed total recall z score) and the independent variables (age at study, gender and parent education) for all 17 subjects. Parent education, gender and age at study were not predictive for neurocognitive or QOL deficits in the whole subject group, nor were parent education, age at diagnosis or time off therapy predictive in the patient group.

In the patient group, linear regression explored the predictive power of brain volumes and DTI indices on neurocognitive and QOL outcomes, controlling for age at diagnosis and gender. None of the DTI indices (FA and MD) in the regions of interest significantly predicted memory or executive functioning assessment results, or QOL outcome. When results were transformed to categorical variables and nonparametric analyses run, however, there were significant correlations found between verbal memory score (CVLT-C® long delay free recall z score) and right posterior hippocampus MD (Kendall’s tau correlation coefficient .775, p < .05; Spearman’s rho correlation coefficient .775, p < .03). The BASC-2 Behavior Symptoms Index, encompassing Atypicality, Withdrawal and Attention Problems, was a significant predictor of the Child’s PedsQL emotional functioning score (R² .927, Beta -.636, p = .02). In addition, the Global Executive Composite score of the BRIEF™ significantly predicted the Child’s PedsQL school functioning score (R² .686, Beta -.872, p = .05).

**Discussion**

This study demonstrated significant findings of elevated MD and decreased FA in key brain areas related to memory and cognition in children with brain tumors treated with chemotherapy. Quality of life was impacted, with patients scoring themselves significantly lower
on psychosocial, school and total QOL scores than controls. In parent assessments of behavior and executive functioning, however, there were no major differences between groups. Furthermore, the majority of the patient group placed in the average to above average range on tests of memory and executive functioning compared to published norms. At the same time, a higher portion of the patients obtained scores below age-expected levels than is typically observed in the normative sample, particularly for executive functioning. Of note, those who scored most poorly in neurocognitive testing did not demonstrate significantly lower QOL than those who scored better. Therefore, our first hypothesis of differences in DTI indices of CNS injury between the two groups, accompanied by neurocognitive dysfunction and QOL was partially supported.

Regression analyses did not find support for our second hypothesis, that hippocampal and prefrontal cortex tissue loss would predict memory and executive functioning impairments. However, nonparametric analyses did find a significant correlation between hippocampal MD and score on the verbal memory test.

Diffusion tensor imaging findings indicate loss of axonal integrity and chronic, long-term damage to healthy brain tissue in the prefrontal cortex and hippocampal structures. Children in this study were a mean of 5.4 years off therapy, so this finding was not indicative of an acute injurious process. Related literature on childhood brain tumors and DTI suggests that FA is a good indicator of brain tissue loss, but in studies done only in those treated with combination therapy, including cranial radiation. There have been reports of decreased FA 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). Children with brain tumors treated with high-dose
chemotherapy and radiation demonstrated changes in brainstem FA over 5 years later, with some measurements reversing initial declines to ultimately return to baseline by 4 years and others maintaining a lower FA over time (Hua et al., 2011). No studies were found in children with cancer resulting in increased MD after treatment; however, a study in adult women treated with chemotherapy for breast cancer demonstrated significant increase in MD in frontal white matter (Deprez et al., 2011). We believe that this is the first study to demonstrate indication of brain tissue loss with significantly elevated MD in the hippocampal structures and prefrontal cortex in children with brain tumors treated with high-dose chemotherapy.

In addition, injury to the basal ganglia as evidenced by increased MD in our related work (Baron Nelson et al, TBD), may affect learning. The basal ganglia are involved in goal-directed and procedural learning (Hollerman, Tremblay, & Schultz, 2003; Kreitzer, 2009). These types of learning depend upon reinforcement from positive and negative outcomes, eventually leading to decision-making based on previous experience (Ratcliff & Frank, 2012). Injury to this area would likely result in difficulty with test-taking and other activities of learning.

The majority of patients (62.5%) scored in the average- to above average-range on neuropsychological testing in areas of memory and executive functioning, which concurs with findings of less severe neurocognitive deficits in the population of children treated with chemotherapy (Sands et al., 2010). Younger age at diagnosis did not predict poorer neurocognitive outcomes, which was also aligned with others’ findings (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Sands, et al., 2010). Parent education was not predictive of neurocognitive outcomes in this small study. Although parent education was significantly higher in the control group, the results of the BASC-2 and BRIEF™ were not different between groups. This is consistent with the literature regarding parent education and executive function.
and behavior in childhood cancer (Campbell et al., 2008). Maternal education has been significantly correlated with brain tissue volume and memory functioning in children with acute lymphoblastic leukemia (Kester, Tanaka, & Koovakkattu, 2010).

In spite of relatively normal neurocognitive performance, as indicated by the low average to average overall scores, parent-proxy and child report of QOL was significantly lower in selected domains as compared to controls. Lower QOL is a finding consistent with the literature on brain tumor survivors treated with multimodal therapy, including cranial radiation (Cardarelli et al., 2006; Eiser, Greco, Vance, Horne, & Glaser, 2004; Meeske, Patel, Palmer, Nelson, & Parow, 2007). However, it does not concur with findings of comparatively normal QOL in the population treated with chemotherapy alone (Sands et al., 2011). Lower QOL scores in our patient sample may be reflective of their young age at study and the experience of serious illness and frequent hospitalizations in very young childhood. Although the patient group did not score differently from controls on the BASC II items assessing depression, there is an established relationship between mammillary body injury and depression (Bernstein et al., 2012; Kumar, et al., 2009). The mammillary bodies had the highest MD values of any of the ROIs studied, and therefore may have been among the structures most damaged. Periodic screening for depression in these children is advisable. In addition, the fact that up to half of patients in the study scored in the “at-risk” category in several QOL domains is worrisome, and adds to the case for close follow-up in the future.

Hippocampal volumes were similar in patients and controls, and DTI indices in hippocampal structures were not predictive of lower scores on nonverbal memory. Yet, the majority of patients scored in the average-to-above average range on memory testing. It is possible that, despite existing injury, as represented by higher MD, patients are able to
compensate sufficiently to perform reasonably well on cognitive tests, at least for the limited timeframe involved in this short battery of neurocognitive testing. Monetary compensation for study participation may have contributed to increased effort resulting in better performance. The lower QOL self-reports may suggest that such compensation is harder to maintain in more expansive areas of functioning in daily life.

Cognitive functioning in children is also influenced by many variables, including the home environment, parents’ education, family value of education, available resources, quality of education and the child’s motivation and general health. Certainly, school functioning appears to be one of the more compromised areas of QOL as reported by patients themselves, as compared to controls. The other QOL domain in which considerable differences existed was psychosocial functioning, likely contributing to decreased overall QOL.

While longer time off-treatment was not a variable in our original hypotheses, it appeared to be a factor in memory and executive functioning performance. This is consistent with reports in the literature that longer time off treatment and older age are often indicators of poorer neurocognitive function (Maddrey et al., 2005; Schwartz et al., 2010). In some cases, this may be the result of older treatment protocols that included higher doses of cranial radiation. Cognitive decline in children after brain tumor treatment with radiation is attributed to difficulty learning new information, and not a loss of knowledge that had already been gained (S. L. Palmer et al., 2001). It has also been related to loss of white matter over time (Reddick et al., 2003). There is a lack of research on long-term neurocognitive outcomes of children treated with chemotherapy alone, but our study suggests that this population may also experience a decline in function over time.
Limitations of this study were the small sample size and the inexact matching of controls, resulting in a 9-month mean age difference between subjects and controls. Also, while parent-report measures such as the PedsQL™, BASC-2 and BRIEF™ were administered to both groups, neurocognitive testing was limited to the patient group only, and thus prevented comparison to the control group. The control group was likely more geographically and ethnically similar than the reference group on which published neurocognitive norms are based. In addition, 3 of the 8 patients were 5 years old, and could not complete the Switching portion of the NEPSY II Inhibition test and portions of the BRIEF, making it more difficult to assess executive functioning. Because of the small sample size, it was not possible to analyze the data with multiple regression to determine significant predictors of outcome.

**Conclusions**

Despite very large effect sizes of markers of injury in childhood brain tumor survivors treated with chemotherapy, there was only a modest relationship of injury with difficulties in memory and executive functioning. Whereas the injury findings suggest that all patients show a significant degree of long-term brain structural change, more than half of them had average to above average scores on neurocognitive assessment, suggesting that neural function was either unaffected by the injury, or compensated for by neuroplasticity. Without objective information on brain tumor survivors’ pre-morbid neurocognitive function, it is not possible to know how much function may have been lost due to the disease and treatment process.

Consistent findings of poorer neurocognitive function in those children who are further out from treatment are concerning, and must be addressed with long-term supportive services. Longitudinal studies and long-term follow-up would allow exploration of why some patients recover function when others may not, or at least not to the same extent. In addition to
neurocognitive testing, future studies should include additional measures providing more information on functioning in daily life, such as grade reports and teacher reports, to provide a more comprehensive picture of learning and cognition not based on a single session of testing.

Moreover, even the more cognitively high achieving patients scored themselves significantly lower than controls on all aspects of quality of life except physical functioning. The questions remain as to why QOL is perceived as low in these patients who were so young at diagnosis and treatment, and what interventions may be helpful to improve their social, emotional and school functioning. These children may also be at risk for depression as they get older related to damage to mamillary bodies. In addition, elevated MD in the hippocampus indicated tissue injury to that structure. The hippocampus plays a role in fear and anxiety (Bishop, 2007), and in maintaining appropriate social responses and emotions such as empathy (Immordino-Yang & Singh, 2011). Hippocampal damage may be a factor in diminished social and emotional QOL.

While psychosocial support is often available during cancer treatment, survivors may not have access to this support after treatment ends. Families may not see a need for continued support as a child resumes his normal activities. Periodic assessment of neurocognitive and QOL status throughout childhood and adolescence could identify problems early on and provide necessary referrals. With improved methods of administering cranial radiation, treatment protocols with high-dose chemotherapy, and increasing use of biotherapies, it is important to define long-term neurocognitive and QOL outcomes and to determine causative factors for poor outcomes. Determination of these will enable the development and implementation of appropriate early interventions to improve outcomes in survivors of childhood brain tumors.
Figure 1. Regions of Interest

Clockwise from upper left: fornix, mammillary body, anterior hippocampus, mid hippocampus, posterior hippocampus, middle frontal gyrus, superior frontal gyrus, prefrontal cortex white matter
**Figure 2.** Mean FA Results

* p < .05; ** p < .01; *** p < .005; **** p < .0001

MFG – middle frontal gyrus; SFG – superior frontal gyrus; PFCWM – prefrontal cortex white matter; MB – mammillary bodies; Ant HC – anterior hippocampus; Mid HC – middle hippocampus; Post HC – posterior hippocampus
**Figure 3.** Mean MD Results

* $p < .05$; ** $p < .01$; *** $p < .005$; **** $p < .0001$

MFG – middle frontal gyrus; SFG – superior frontal gyrus; PFCWM – prefrontal cortex white matter; MB – mammillary bodies; Ant HC – anterior hippocampus; Mid HC – middle hippocampus; Post HC – posterior hippocampus
Figure 4. BRIEF™ Results*

*BRIEF™ Behavior Regulation Index (BRI) includes Inhibit, Shift, Emotional Control; Metacognition Index (MI) includes Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor; Global Executive Composite (GEC) is a combination score of BRI and MI.
Figure 5. PedsQL® Results
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at Diagnosis</th>
<th>Years off therapy</th>
<th>Tumor Type/Location</th>
<th>VP Shunt</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>54 months</td>
<td>3.5</td>
<td>Choroid plexus carcinoma, left occipital horn</td>
<td>no</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Etoposide Topotecan</td>
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<tr>
<td>02</td>
<td>27 months</td>
<td>2.5</td>
<td>Desmoplastic medulloblastoma, 4th ventricle</td>
<td>yes</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan</td>
</tr>
<tr>
<td>03</td>
<td>14 months</td>
<td>11.4</td>
<td>Medulloblastoma, posterior fossa</td>
<td>yes</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan</td>
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<tr>
<td>04</td>
<td>16 months</td>
<td>4.5</td>
<td>Desmoplastic medulloblastoma, posterior fossa</td>
<td>no</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan</td>
</tr>
<tr>
<td>05</td>
<td>55 months</td>
<td>4.75</td>
<td>Primary leptomeningeal PNET involving left cerebellum, 4th ventricle, infundibulum, bilateral cerebellar-pontine angle</td>
<td>no</td>
<td>Vincristine Cisplatin Cyclophosphamide Etoposide Topotecan Methotrexate Temodar</td>
</tr>
<tr>
<td>06</td>
<td>42 months</td>
<td>5.5</td>
<td>Primitive neuroectodermal tumor (PNET), right parieto-occipital area</td>
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<td>07</td>
<td>19 months</td>
<td>3.3</td>
<td>Desmoplastic medulloblastoma, posterior fossa</td>
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<td>Vincristine Cisplatin Cyclophosphamide Etoposide</td>
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<td>---------------------</td>
<td>-------------------------</td>
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</tr>
</tbody>
</table>
| **08** | 28 months | 8  | PNET, posterior fossa | yes | Vincristine
|     |      |    |                     |                          | Cisplatin
|     |      |    |                     |                          | Cyclophosphamide
|     |      |    |                     |                          | Etoposide
|     |      |    |                     |                          | Topotecan

Topotecan
Methotrexate
Table 2. Demographics of Patients (n = 8) and Controls

<table>
<thead>
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<th></th>
<th>Patients n = 8</th>
<th>Controls n = 9</th>
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<tbody>
<tr>
<td>Age at study</td>
<td>8.47 years (SD 1.3)</td>
<td>9.3 years (SD 2.6)</td>
<td>.69</td>
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<tr>
<td>Gender</td>
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<td>6 male</td>
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</tr>
<tr>
<td></td>
<td>4 female</td>
<td>3 female</td>
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</tr>
<tr>
<td>Ethnicity</td>
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</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>1 Asian</td>
<td>1 Asian</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 mixed</td>
<td>2 African American</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasian/Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent Education</td>
<td>2.88</td>
<td>4.44</td>
<td>.02</td>
</tr>
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</table>

(1 = some high school; 2 = high school grad; 3 = community college; 4 = 4 years of college; 5 = grad/prof school)
Table 3. Hippocampal Volumes

<table>
<thead>
<tr>
<th>Area of Measurement</th>
<th>Patient Volumes (mm$^3$) ± SD</th>
<th>Control Volumes (mm$^3$) ± SD</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Hippocampus</td>
<td>.002476 ± .02088</td>
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### Table 4. BASC-2 Results

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**BASC-2 Externalizing Problems includes Hyperactivity and Aggression; Internalizing Problems includes Anxiety, Depression and Somatization; Behavioral Symptoms Index includes Atypicality, Withdrawal and Attention Problems; Adaptive Skills includes Social Skills, Activities of Daily Living and Functional Communication**
References


CONCLUSIONS

Children who survive brain tumors are at risk for physical, neurocognitive and psychosocial long-term effects from the cancer and its modalities of treatment including surgery, chemotherapy and cranial radiation. The presence of a space-occupying lesion in the brain causes injury from edema and compression of delicate brain tissue. Surgical intervention may disrupt critical white matter tracts and pathways that connect different parts of the brain. Cranial radiation causes both acute and chronic injury to the brain, and is especially toxic to the young child’s developing brain. Chronic processes of oxidative stress and inflammation lead to continuing brain tissue losses over time. Less is known about the long-term effects of systemic chemotherapy to the brain, particularly in children with brain tumors, but there is evidence that many chemotherapy agents are toxic to healthy brain tissue as well as to cancer cells. White matter loss and injury to progenitor cells have been described as a result of chemotherapy administration. Loss of myelin interferes with the transmission of signals throughout the brain, impacting attention and IQ, and a loss of progenitor cells likely leads to memory dysfunction and difficulties with learning.

The injurious processes described eventually result in a new state of allostasis in the brain of the child who has survived a brain tumor. This new state is often different from the pre-diagnosis state, possibly with physical, neurocognitive and/or psychosocial dysfunction. These issues frequently affect overall quality of life in a negative way.

Indications of chronic brain injury, found in our study and evidenced by elevated MD in many areas, appeared in this sample of children successfully treated for brain tumors with chemotherapy, but not radiation, an average of five years prior. These findings contribute to the limited amount of data available on effects of high doses of systemic chemotherapy on the young
brain. Brain tissue injury and cell loss may be attributable to chemotherapy combined with general pathological changes associated with the condition of having a cerebellar lesion that has culminated in a chronic injurious process. This is the first study to document microstructural damage in this specific population, as evidenced by increased MD in the brain, as compared to healthy controls. Elevated MD is an indicator of damage to the intracellular matrix of the brain, or the glial cells, and one explanation for our findings may be that glia are injured more significantly by chemotherapy than other brain cells. This is an area that bears further investigation.

While children treated with chemotherapy in general do not experience neurocognitive effects and poor QOL to the extent those treated with cranial radiation do, our finding that older age at study and longer time off treatment was related to more severe memory and executive functioning deficits necessitates further exploration. Longitudinal studies in this population would provide needed information about whether injury from chemotherapy is progressive, similar to that of radiation.

Few significant relationships were found between brain tissue damage in specific areas and neurocognitive test scores, although there was a significant correlation between elevated MD in the prefrontal cortex and basal ganglia and decreased total QOL scores by child report. This may have implications for social and emotional issues in the future as these children enter adolescence. The child self report of QOL was significantly lower than published means in the population of children with brain tumors, placing them “at risk” in several categories. As these children were an average of 8.3 years at the time of the study, these findings are concerning. Long-term follow-up and provision of ongoing supportive services are necessary to identify
problems early and provide interventions to improve social, emotional and school functioning in these patients who were so young at diagnosis and treatment.

The greatest limitation to this study was the small sample size. The relatively small number of children diagnosed each year with brain tumors, and the many variables of tumor location and treatment limited the sample, and thus the ability to perform stepwise regression to more fully explore factors involved in outcome. Multi-institutional studies are critical to achieve sample sizes with adequate power to demonstrate significance. Future research in this population must seek to minimize variability in tumor location, pathology and treatment among subjects as much as possible in order to attribute certain toxicities to specific agents with more confidence. Longitudinal studies are recommended to investigate the possible progressive nature of injury from chemotherapy, and also to monitor QOL. Studies such as these will not only provide a foundation for development of interventions to maximize long-term neurocognitive outcomes and quality of life, but also more evidence that long-term follow-up and supportive services are needed for these children.