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Neurocognitive and Family Functioning and Quality of Life Among Young Adult Survivors of Childhood Brain Tumors

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Abstract

Many childhood brain tumor survivors experience significant neurocognitive late effects across multiple domains that negatively affect quality of life. A theoretical model of survivorship suggests that family functioning and survivor neurocognitive functioning interact to affect survivor and family outcomes. This paper reviews the types of neurocognitive late effects experienced by survivors of pediatric brain tumors. Quantitative and qualitative data from three case reports of young adult survivors and their mothers are analyzed according to the theoretical model and presented in this paper to illustrate the importance of key factors presented in the model. The influence of age at brain tumor diagnosis, family functioning, and family adaptation to illness on survivor quality of life and family outcomes are highlighted. Future directions for research and clinical care for this vulnerable group of survivors are discussed.

Childhood brain tumors are the second most common pediatric malignancy and the most common solid tumor during childhood (American Cancer Society, 2009). Approximately 4,030 children are diagnosed with a brain tumor each year with an estimated 2,800 of these diagnoses occurring in children younger than 15 years (Central Brain Tumor Registry of the United States [CBTR], 2010). The most common childhood brain tumor diagnoses include astrocytomas, ependymomas and medulloblastomas (CBTR, 2010). Medical treatment is often multi-modal incorporating combinations of surgical resection, chemotherapy and radiation depending upon tumor type and location.

Although brain tumors are the leading cause of death among children with cancer (Turner, Rey-Casserly, Liptak, & Chordas, 2009), advancements in medical treatments have greatly

enhanced children's ability to survive into adulthood. Five-year survival rates for pediatric brain tumor patients have increased from 54.8% in 1976 (Ries et al., 2002) to 72.1% as of 2006 (CBTR, 2010). Such improvements in survival rates have elevated the importance of functional outcomes and quality of life in the years following the completion of tumor-directed treatment in childhood brain tumor survivors. Childhood brain tumor survivors, however, have the poorest health-related quality of life among childhood cancer survivors (Zeltzer et al., 2009) secondary to a complex array of treatment-related late effects.

Depending on the location of the tumor and the types of treatments used, tumor-directed interventions greatly affect the developing central nervous systems of children and increase survivors' risk for long-term, treatment-related sequelae that often worsen over time. Pediatric brain tumor survivors generally experience significant late effects (Oeffinger et al., 2006) across multiple domains of functioning, including endocrinologic (Gurney et al., 2003), neurologic (Packer et al., 2003), and neurocognitive (Ellenberg et al., 2009; Robinson et al., 2010). For example, over 40% of pediatric brain tumor survivors experience a variety of problems related to dysfunctions in the endocrine system, including hypothyroidism, short stature, growth hormone deficiency, diabetes insipidus and obesity (Gurney et al., 2003). Additionally, 49% of childhood brain tumor survivors experience coordination difficulties and 25% of survivors develop seizure disorders (Packer et al., 2003).

The repercussions of these late effects often leave survivors unable to manage their complex health problems independently and to function in society autonomously (Gurney et al., 2009; Pang et al., 2008). In comparison to healthy sibling controls, survivors of childhood brain tumors are less likely to be married, have a college degree, or be employed (Zebrack et al., 2004). Pediatric brain tumor survivors also are less likely to live independently and are more likely to live with their family of origin than comparison controls (Ness et al., 2010). Such psychosocial sequelae increase brain tumor survivors' risk for psychological distress (Zebrack et al., 2004), place significant demand on their caregivers and families of origin (Deatrick, Mullaney, & Mooney-Doyle, 2009; Hutchinson, Willard, Hardy, & Bonner, 2009) and affect family functioning (Foley, Barakat, Herman-Liu, Radcliffe, & Molloy, 2000).

Neurocognitive Late-Effects in Pediatric Brain Tumor Survivors

Neurocognitive sequelae are arguably the most prominent of the late effects experienced by childhood brain tumor survivors. Children's brains are in a constant state of development and are vulnerable to the deleterious effects of tumor-directed treatments. In addition to the tumor's presence, each of the three widely-used treatment modalities (surgical resection, cranial radiation, and chemotherapy) can affect normal development and impact neurocognitive outcomes. For example, surgical resection and its related perioperative complications (e.g., hydrocephalus) have been shown to negatively affect neurocognitive functioning in pediatric brain tumor survivors even after controlling for other treatment-related effects (Ris & Noll, 1994). It is primarily the effects of radiation directed at the central nervous system, however, that significantly impact children's brains and cause neurocognitive late effects. Specifically, radiation disrupts the processes of myelination and white matter proliferation, which continues on into young adulthood (Casey, Giedd, & Thomas, 2000; Pfefferbaum et al., 1994), and causes demyelination and necrosis of white matter tissue (Burger & Boyko, 1991). These treatment-related insults to the developing central nervous systems can lead to declines in global intellectual functioning and core deficits in specific neurocognitive abilities.

A sizable literature documents the deleterious effects of childhood brain tumors and treatment on intellectual functioning (IQ). For example, a consistent finding in studies of

medulloblastoma survivors is the continued decline in IQ and academic achievement over time following the completion of medical treatment (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). These declines may be the result of difficulties acquiring new information at developmentally appropriate rates (Palmer et al., 2001) with underlying problems with fundamental neurocognitive processes, such as attention and processing speed, likely contributing to these knowledge acquisition difficulties. Childhood brain tumor survivors demonstrate a wide array of deficits in specific neurocognitive abilities including problems with attention, verbal memory, working memory, and processing speed (Kiehna, Mulhern, Li, Xiong, & Merchant, 2006; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Mulhern, White, et al., 2004; Nagel et al., 2006; Palmer, Reddick, & Gajjar, 2007). Deficits in focused (Dennis, Hetherington, & Spiegler, 1998), sustained (Mulhern et al., 2001; Reddick et al., 2003), and selective attention (Reeves et al., 2006) have been found in pediatric brain tumor survivors.

The type and severity of neurocognitive late effects experienced typically are related to the tumor location (King et al., 2004; Mulhern, Hancock, Fairclough, & Kun, 1992; Papazoglou, King, Morris, & Krawiecki, 2008), patient age at diagnosis (Mulhern et al., 2001; Sands et al., 2001), and the specific combination and intensity of treatment modalities used while on therapy (Turner et al., 2009). For example, children with tumors in the third ventricle region demonstrate more difficulties with auditory verbal memory, while those with cerebellar tumors display more impairments with attention (King et al., 2004). Cranial radiation (Turner et al., 2009) and younger age during radiation therapy (Mulhern et al., 2001; Radcliffe, Bunin, Sutton, Goldwein, & Phillips, 1994; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001) are considered significant risk factors for developing neurocognitive deficits. A prospective longitudinal study of attention performance in 120 patients with primary brain tumors found that inattentiveness increased significantly following conformal radiation (Kiehna et al., 2006). Additionally, the diagnoses of craniopharyngioma, supratentorial tumors, and optic pathway tumors and subtotal resection increased the risk of attention problems (Kiehna et al., 2006). Receiving cranial radiation at a young age increases the risk for neurocognitive late effects due to its impact on future brain development (Mulhern et al., 2001) through reductions in white matter volume (Mulhern et al., 1999). Deficiencies in the development of white matter secondary to radiation therapy in childhood brain tumor survivors is associated with deficits in IQ, verbal and nonverbal reasoning (Mulhern et al., 2001), and attentional functioning (Mulhern, White, et al., 2004).

These neurocognitive late effects have a significant impact on brain tumor survivor quality of life and social functioning by impairing academic, vocational, and psychosocial functioning. In the Childhood Cancer Survivor Study, adolescent and young adult survivors of childhood brain tumors display more difficulties with depression (Zebrack et al., 2004), suicidal ideation (Recklitis et al., 2009), and somatization and have lower quality of life than other cancer survivors (Zeltzer et al., 2009). Additionally, among childhood brain tumor survivors, those with greater dysfunction on a self-report measure of neurocognitive functioning demonstrate less educational achievement, reduced income, and lower rates of full-time employment and marriage (Ellenberg et al., 2009).

Neurocognitive Late Effects Within a Family Systems Framework

Consistent with a family systems perspective highlighting the importance of family patterns of interaction for the adaptation of each family member and the interrelatedness of family members (Miller, Ryan, Keitner, Bishop, & Epstein, 2000), the entire family is affected by the diagnosis and treatment of childhood cancer. These experiences represent a potentially traumatic event that can have lasting psychological effects on each member of the family

and the family system (Alderfer, Labay, & Kazak, 2003; Alderfer, Cnaan, Annunziato, & Kazak, 2005; Barakat, Alderfer, & Kazak, 2006; Gerhardt et al., 2007). While distress generally tends to recede over time, caregivers of childhood brain tumor survivors continue to experience elevated levels of illness-related uncertainty and caregiving demand secondary to the continued management of disease late effects (Deatrick et al., 2009; Hutchinson et al., 2009).

In addition to the potential impact of the cancer diagnosis and late effects of brain tumor survivors on families, family functioning variables can impact the psychological adjustment of the survivors. Although there are competing models of family functioning, this multidimensional construct typically includes family structure or organization, communication, cohesion, problem solving and emotional expression (Alderfer et al., 2008; Miller et al., 2000). Traditional approaches to measuring family functioning involve questionnaires that assess the various dimensions of family functioning (e.g., cohesion, communication) and include measures such as the Family Assessment Device (FAD; Epstein, Baldwin, & Bishop, 1983) or the Family Environment Scale (Moos & Moos, 1986). In a sample of adolescent cancer survivors, three-fourths of the survivors with a diagnosis of posttraumatic stress disorder (PTSD) came from poorly functioning families (Alderfer, Navsaria, & Kazak, 2009).

Neurocognitive deficits in brain tumor survivors, in particular, may continue to strain the family system despite the conclusion of tumor-directed treatment and require that the family continues to care for the survivor into adulthood. For example, difficulties with attention and memory can impair communication between the survivor and family members (Papazoglou et al., 2008) and deficits in working memory and processing speed may limit the types of tasks a survivor is able to complete independently. Additionally, neurocognitive impairments reduce the likelihood of full-time employment and higher incomes (Ellenberg et al., 2009), placing the burden on families to financially provide for many childhood brain tumor survivors. Collectively, neurocognitive deficits likely impact functional outcomes and quality of life among pediatric brain tumor survivors and may increase the demand placed on caregivers and families.

The interrelations between brain tumor survivor neurocognitive late effects and indices of survivor, caregiver, and family functioning, however, have received little empirical examination, representing a significant gap in our understanding of survivorship for these families. Research within pediatric traumatic brain injury (TBI) has illustrated the potential for child neurocognitive and behavioral functioning to predict child, caregiver, and family functioning, as well as family variables to predict child neurocognitive and behavioral outcomes (Taylor et al., 1999; Taylor et al., 2001). In a longitudinal study following children who experienced a TBI and their families, post-injury family functioning and family burden moderated the effect of severe TBI on child verbal skills, verbal memory and adaptive behavior 12 months after the injury (Taylor et al., 1999). The authors speculated that the neurobehavioral sequelae of severe TBI make these children more susceptible to family influences allowing family factors to influence neurocognitive performance up to a year later. Poorer family functioning may limit the family's ability to promote cognitive recovery or aid in the development of new skills to offset the neurocognitive sequelae (Taylor et al., 1999). Such findings in childhood brain injury provide an impetus to examine family variables when studying neurocognitive outcomes in childhood brain tumor survivors.

Peterson and Drotar (2006) developed a theoretical model to describe the development of neurocognitive late effects in childhood cancer survivors and notable factors that influence this process. The model depicts the associations between several constructs including premorbid child and family functioning factors, disease and treatment variables, family

adaptation to illness and management of late effects, family functioning, and survivor late effects and quality of life (see Figure 1). For example, treatment intensity and related complications may influence both the family's adaptation to their child's cancer and child outcomes, such as quality of life. Family adaptation, in turn, then influences family management of survivor late effects and the family's ability to reintegrate the survivor back into the relevant social systems of the family and school.

Peterson and Drotar's (2006) model is unique in that it incorporates a family systems framework and highlights the influence that a survivor's family may have on neurocognitive late effects. The model suggests that family adaptation and functioning and survivor neurocognitive late effects may reciprocally interact to influence survivor, caregiver, and family functioning. For example, increased neurocognitive late effects may change the family system by increasing family demand for managing both medical and neurocognitive late effects and elevating family conflict. Alternatively, positive family functioning may moderate the impact of the severity of treatment on survivor neurocognitive functioning. In the only study to address these relations in a sample of pediatric brain tumor patients, a combination of family and illness factors best predicted child IQ (Carlson-Green, Morris, & Krawiecki, 1995). Specifically, higher socioeconomic status, two available parents and mothers who engaged in fewer coping resources and were presumably less stressed predicted better IQ approximately four years post-diagnosis. Additional research is needed to further elucidate these relations and examine family functioning as a potential malleable intervention target to promote cognitive recovery from the effects of disease and treatment in childhood brain tumor survivors.

Purpose of Current Case Series

The purpose of this paper is to illustrate the utility of Peterson and Drotar's (2006) model of childhood cancer survivorship and neurocognitive late effects by presenting a series of cases that exemplify the constructs and associations depicted in the model. The selected cases are three young adult survivors of childhood brain tumors and their mothers. These cases illustrate the potential relations between treatment and disease-related variables, family adaptation to illness and late effects, survivor neurocognitive functioning, family functioning, and survivor and caregiver health-related quality of life. The current case series includes a unique combination of both quantitative and qualitative data that will inform future research and clinical care with pediatric brain tumor survivors.

Methods

Case Selection and Procedures

An intensive case analysis was conducted on selected cases of three young adult survivors (ages 18–30) of a childhood brain tumor and their mother. Multiple, in-depth case study methods are useful to explore complex phenomenon that often are understudied (Docherty, Sandelowski, & Preisser, 2006). Each survivor-mother dyad participated in three phases of a larger, parent study that examined caregiving in pediatric brain tumor survivors: a) a first quantitative phase that included measures of family functioning, caregiver demand and survivor quality of life; b) a qualitative phase that included interviews with the survivor and his/her mother that focused on issues related to family adaptation to illness and late effects, health-related quality of life, and caregiver demand and competence; and c) a second quantitative phase that occurred approximately 18 months after the first quantitative phase that included measures of survivor neurocognitive functioning and repeated family measures administered in the first phase (see Table 1 for details on the measures collected at each time point). Eligibility criteria for these phases of research included the survivor a) being greater than 5 years from diagnosis and 2 years from the completion of cancer treatment, b) being

between the ages of 18 and 30, and c) living at least part-time with his/her mother. Exclusion criteria included a) the survivor being married or in a partnered relationship, b) the survivor having a multi-system genetic condition that may affect neurocognitive function (e.g., Down Syndrome), c) survivor having cognitive or developmental delays prior to the brain tumor diagnosis, and d) non-English speaking. The selected cases represent three of the four available cases at the time of this paper's preparation who had participated in all three phases of an ongoing research project with pediatric brain tumor survivors and their mothers. The other available case was not included due to it highlighting similar issues and constructs as Survivor #1, "Sarah."

Measures—The selected measures all are well-validated and have been used with pediatric oncology samples previously. During the first phase of the research (Time 1), mothers completed the General Functioning Scale from the *Family Assessment Device* (FAD GFS; Epstein, Baldwin, & Bishop, 1983), the *Bakas Caregiving Outcomes Scale* (BCOS; Bakas, Champion, Perkins, Farran, & Williams, 2006), and the *Pediatric Oncology Quality of Life Scale* (POQOLS; Goodwin, Boggs, & Graham-Pole, 1994). The FAD GFS is a well-established measure of general family functioning that encompasses the seven dimensions of family functioning delineated by the McMaster model of family functioning including problem-solving, communication, roles, affective responsiveness, affective involvement, and behavioral control (Miller et al., 2000). The FAD GFS has a range of 0–4 with higher scores indicating higher levels of general family dysfunction. The BCOS is a measure of perceived caregiver demand and assesses the impact of the survivor's brain tumor and related late effects on the mother. It has a range of 15–105 with a score of 64 indicating no change and scores lower or higher than 64 indicating a negative impact or positive impact respectively. The POQOLS is a 21-item proxy measure of health-related quality of life specific to pediatric cancer and includes three factors that comprise a total score: physical functioning, emotional distress, and response to current medical treatments. Lower scores indicate better quality of life.

During the second phase of research (Time 2), both survivors and mothers participated in semi-structured qualitative interviews that occurred in their homes. The interviews explored family functioning and adaptation, factors affecting family functioning, survivor quality of life, and caregiver competence and demand. Interviews were recorded and transcribed for thematic, qualitative descriptive analysis.

During the third phase of research (Time 3), survivors completed standardized assessments of neurocognitive functioning that assess areas typically affected in pediatric brain tumor survivors. Survivors' working memory and processing speed abilities were assessed with the *Working Memory Index* (Digit Span & Letter-Number Sequencing) and the *Processing Speed Index* (Symbol Search & Coding) from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler, 2008). Verbal learning and memory was assessed by the *California Verbal Learning Test, Second Edition, Short Form* (CVLT-II SF; Delis, Kramer, Kaplan, & Ober, 2000). Executive functioning was assessed using the *Trail Making Test* (mental flexibility) and the *Tower Test* (problem-solving, planning) from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) and the self-report version of the *Behavior Rating Inventory of Executive Function – Adult* (BRIEF-A; Roth, Isquith, & Gioia, 2005).

Also at Time 3, survivors and mothers completed the FAD GFS. Additionally, mothers completed the informant-report version of the BRIEF-A, the BCOS, the POQOLS, and the PedsQL Family Impact Module (PedsQL FIM; Varni, Sherman, Burwinkle, Dickinson, & Dixon, 2004). The PedsQL FIM assesses the impact of the survivor's health problems on

both caregiver and family quality of life. It has a range of 0–100 with higher scores indicating better quality of life.

Case Summaries

Survivor # 1: “Sarah”

Sarah is a 24-year-old Caucasian female who was diagnosed with an astrocytoma at age nine years. At diagnosis, her tumor was a large heterogeneous left frontal tumor that caused significant mass effect upon the circle of Willis, the third ventricle, the sella turcica, and the left anterior cranial fossa. The tumor measured $7.1 \times 6.4 \times 6.4$ centimeters in its anterior posterior. She underwent a near total surgical resection that left residual tumor along the inferior portion of the operative cavity at the level of the hypothalamus and suprasellar cistern and filling the region of the sella turcica. She also received 5400 centigray (cGy) of cranial radiation. Sarah experiences a number of medical late effects including mild visual impairments, hypothyroidism, growth hormone deficiency, and probable infertility. She takes several daily medications to manage these endocrine late effects. She had a documented learning disability and received educational accommodations, including additional time on tests, when she attended school. She currently lives with her mother and father, both of whom are college graduates and financially stable. Sarah is a college graduate and teaches third grade at a local private school but has few friends and little contact with same-age peers.

In general, Sarah performed in the average range across the assessed neurocognitive domains (see Table 2). Her working memory abilities were in the high average range and her processing speed abilities were in the average range. Sarah’s scores on the CVLT-II SF generally indicate average verbal memory abilities, including immediate and delayed recall. There was more variability in terms of her executive function skills on the administered tests from the D-KEFS. She demonstrated average mental flexibility and switching of cognitive sets on the Switching condition of the *Trail Making Test*. She demonstrated deficits, however, in problem-solving and planning on the *Tower Test* (scaled score = 4). Neither Sarah nor her mother reported significant concerns with executive function on the BRIEF-A.

Both quantitative and qualitative data suggest that Sarah has a good quality of life and are illustrative of her resiliency. Quantitative data from the POQOLS at both Time 1 and Time 3 presented in Table 3 indicate few difficulties related to emotional distress or physical limitations. During her qualitative interview, Sarah indicated that she is accepting of her late effects and optimistic about her health and future. She noted that she “realize[s] now that there are people who are much worse off and [she is] grateful for what [she’s] overcome.”

Data regarding the family and Sarah’s mother also indicate positive family functioning and adaptation to Sarah’s brain tumor. Sarah’s mother reported good levels of family functioning on the FAD GFS at both time points and good family and caregiver quality of life on the PedsQL FIM when considering the impact of Sarah’s brain tumor and related late effects. Sarah’s mother also reported moderate levels of caregiver demand on the BCOS at both time points. Qualitative data also support good family functioning, positive adaptation, and resilience. Sarah described her family and her mother, in particular, as her “backbone and support” and indicated that they help her with any challenges she experiences. When discussing how treatment decisions were made for Sarah’s tumor and potential side effects of radiation, Sarah’s mother stated her belief at the time that “we’ll deal with everything else but just don’t let it recur...I took the risk of radiation because I thought we could deal with the problems.” This quote exemplifies the family’s response to Sarah’s medical history and how they’ve been able to support her following the completion of treatment.

In summary, Sarah's neurocognitive functioning is mostly intact and she has a high quality of life. Examining her outcomes through the framework of Peterson and Drotar's (2006) model, several aspects of the model are highlighted by this case. First, Sarah's older age at diagnosis likely contributed to her experiencing fewer neurocognitive late effects and deficits. Sarah still displays some neurocognitive deficits, however, related to executive function and planning. Second, her high-achieving and well-functioning family appears to have been able to mitigate the impact of her particular difficulties with planning and problem solving and compensate in such a way as to help her achieve her potential. The family has been able to access resources and manage her late effects in a positive manner. Despite these efforts Sarah still demonstrates some social and developmental deficits that are fairly typical in childhood brain tumor survivors.

Survivor #2: "Kim"

Kim is a 19-year-old Caucasian female who was diagnosed with a posterior fossa medulloblastoma at age three years. At diagnosis, Kim's tumor was a heterogeneous enhancing posterior fossa mass measuring approximately 3.0 centimeters in its greatest dimension that was situated in the fourth ventricle. Her medical treatment consisted of gross total surgical resection and 2340 cGy of cranio-spinal radiation with a boost to the posterior fossa region bringing her cumulative radiation dose to 5500 cGy. She also was treated with multi-agent chemotherapy. Seven to eight months after beginning her tumor-directed treatment, Kim demonstrated evidence of severe radiation injury marked by significant speech and motor difficulties. Kim experiences a significant number of late effects including dysarthria, alopecia, moderate hearing and vision deficits, several endocrine-related problems, and difficulties with emotion and behavior regulation. She often has emotional outbursts at home and receives a number of external services, including occupational and physical therapies and vocational services. Kim currently lives with her mother and younger sister. Her mother was a health care provider, but no longer works in order to care for Kim full-time. Kim's father is not a part of the family following her parents' divorce after the conclusion of Kim's medical treatment and is a source of conflict and distress for both Kim and her mother.

Kim's performance on the administered measures of neurocognitive function showed significant deficits across all domains assessed (see Table 2). Kim's neurocognitive presentation appears consistent with the types of neurocognitive late effects seen in survivors who were treated with cranial radiation at a very young age. Her working memory and processing speed abilities both were in the extremely low range and she demonstrated poor verbal memory abilities on both immediate and delayed recall tasks. She also demonstrated extremely low abilities on administered measures of executive function, including significant deficits with mental flexibility, switching, and planning and problem solving. Both Kim and her mother noted at-risk-to-clinically significant concerns related to executive function as measured through her behaviors on the BRIEF-A.

Qualitative and quantitative data suggest that Kim's quality of life is poor (see Table 3). The high scores on the different indices of quality of life on the POQOLS at both time points indicate significant problems related to emotional and behavioral problems and poorer physical functioning. Kim also appears to be struggling with developmental issues on top of her chronic medical and neurocognitive difficulties. Kim's responses during the qualitative interview reveal the ongoing tension between her neurocognitive functioning and her desire for autonomy. She noted that she "doesn't always need the help. If you're willing to help me, great, I love help but I don't always need it. And it's aggravating to me when people like right ahead go and try to help me."

Kim's quote also suggests conflict between Kim and family members who may be providing help or support. Kim's tumor and subsequent late-effects appear to have had a profound impact on the family as evidenced by both the quantitative and qualitative data. Both Kim and her mother reported moderate difficulties related to general family functioning on the FAD GFS at Time 3 and Kim's mother reported low family and caregiver quality of life secondary to Kim's tumor on the PedsQL FIM. Additionally, Kim's mother endorsed a negative impact and high levels of caregiver demand on the BCOS at both time points. The interview with Kim's mother contained themes related to the conflict of providing developmentally- and age-appropriate care while accounting for Kim's significant neurocognitive limitations and behavioral difficulties. She also expressed regret regarding the decision to administer cranio-spinal radiation during cancer treatment because of the significant late effects as evidenced by the following quote: "If somebody said to me, here are your options, you only do chemo and its 30% survival but you won't have an invalid so to speak. Or you do radiation and chemo and you might have an 85% survival but her quality of life is such that you may not be able to enjoy the load. I would have done chemo alone." This perspective contrasts greatly with the notion expressed by Sarah's mother.

Examining Kim's experiences through the framework of the theoretical model, such outcomes might be expected given her young age at diagnosis and the amount and types of therapies that she received that insulted her developing central nervous system. Although Kim's family has been able to access external resources for her and involve her in valuable activities outside the family, this is not sufficient to mitigate the contribution of her neurocognitive deficits on her poor quality of life. Family conflict and high levels of caregiver demand likely make it difficult for Kim's family to address the tension between her deficits and need for independence and appropriately promote increased autonomy and enhance her quality of life.

Survivor # 3: "Kevin"

Kevin is a 26-year-old Caucasian male diagnosed with a posterior fossa medulloblastoma at age five years. Kevin's tumor was a mass in the mid-posterior fossa that measured 4.0×5.2 centimeters and had necrotic areas. It extended from the foramen magnum to the tentorium and resulted in compression of the brain stem. His tumor-directed treatment included gross total surgical resection, multi-agent chemotherapy and 2340 cGy of cranio-spinal radiation with a boost to the posterior fossa region bringing his total dose to 5880 cGy. Kevin also had a ventroperitoneal (VP) shunt placed secondary to hydrocephalus and developed posterior fossa syndrome with cerebellar mutism following treatment that required extensive rehabilitation. Kevin has several medical late effects secondary to his brain tumor and treatment including growth hormone deficiency, hearing loss, seizures, and a stroke. Kevin had a lumboperitoneal shunt placed several years after treatment concluded and a VP shunt revision approximately seven years ago. Additionally, he developed three meningiomas that required surgical resection two-to-three years prior to his participation in this research. Kevin attended a specialized high school due to learning disabilities. He currently lives with his mother, step-father and younger brother. Kevin works part-time as a bagger at a local grocery store.

Similarly to Kim, Kevin demonstrated significant neurocognitive late effects across the domains assessed (see Table 2). Working memory, processing speed, verbal memory, and executive function abilities all were in the extremely low range. However, neither Kevin nor his mother reported significant concerns related to executive function on the BRIEF-A, suggesting that Kevin is able to function adaptively despite his neurocognitive deficits. During his interview, Kevin acknowledges his limitations but still expresses a belief in moving forward in a positive manner. Such resilience is exemplified by this quote: "Throughout my life basically, it all, and in grade school, kindergarten, high school, middle

school basically, just some things were challenging for me. But I tried to make the best out of it.”

Kevin’s quality of life appears to be relatively good based on the quantitative and qualitative data (see Table 3). On the POQOLS, Kevin’s mother reported few difficulties with emotional problems at both time points but did note some physical challenges and limitations related to fatigue at Time 3. Quantitative data also suggest positive family functioning and adaptation to Kevin’s brain tumor and associated problems as evidenced by the lower scores on the FAD GFS at both time points and the higher score on the PedsQL FIM. Despite indicating that Kevin’s tumor and related late effects have had a moderately negative impact on her life and resulted in increased caregiver demand (BCOS scores of 49 and 50), Kevin’s mother expressed appreciation for the treatment that saved his life. Referring to radiation’s persistent, deleterious effects, she indicated that she “wouldn’t change what I did. But I really know that radiation is the gift that keeps on giving. You don’t, I wouldn’t change, I wouldn’t not give him the radiation.” Despite Kevin having similar neurocognitive and medical sequelae from cranio-spinal radiation to Kim, Kevin’s mother expresses a very different attitude about the radiation and subsequent late effects than Kim’s mother.

Kevin’s mother reiterates Kevin’s positive adaptation further in her qualitative interview. She notes that she is struck by “his overall resilience and how I am just amazed at how he just takes things. He said ‘Mom, after everything I’ve been through, I feel like Superman.’” This case illustrates the potential reciprocal relations between survivor and family functioning. There appears to be an interaction between Kevin’s optimism and resilience and his mother’s reframing and positive beliefs about his medical treatment, as they both seem to influence one another.

In summary, Kevin has significant neurocognitive deficits but a good quality of life. Examining this case through the theoretical model of survivorship, the contributions of age at diagnosis and the number of therapies to the level of neurocognitive late effects are evident. In contrast to Kim and her family, Kevin’s family has demonstrated a more positive adaptation to his medical history and late effects and more successfully promoted appropriate activities and levels of independence that contribute to his better quality of life.

Summarizing the Cases within the Model of Survivorship

In examining all three cases within the context of Peterson and Drotar’s (2006) model of pediatric cancer survivorship (see Table 4), the first clear theme is the detrimental influence of a younger age at diagnosis on neurocognitive functioning in survivors. Consistent with previous research findings (e.g., Mulhern et al., 2001), the two survivors in this case series who were diagnosed and treated at age five years or younger demonstrated extremely poor neurocognitive functioning across all domains assessed. The second theme relates to families’ ability to adapt to their child’s illness and subsequent late effects and their beliefs about these things. Reframing beliefs about the curative yet harmful medical therapies that survivors endured and perceiving their experiences from a positive frame seems to influence current survivor, caregiver and family functioning. The families in this case series with a more positive adaptation seemed better able to work together to effectively compensate for the survivor’s cognitive deficits and have better survivor, caregiver and family quality of life.

Discussion

Pediatric brain tumor survivors are at significant risk for developing neurocognitive late effects that can have tremendous consequences for survivors and their families. Research on

the neurocognitive late effects in survivors of childhood brain tumors indicates that declines in global intellectual functioning (Palmer et al., 2001), processing speed (Mabbott et al., 2008), working memory (Dennis et al., 1998), verbal memory (Nagel et al., 2006), and attention (Mulhern, White, et al., 2004) are most pronounced. Receiving cranial radiation, particularly when younger than age 8, greatly increases the risk for developing neurocognitive late effects across several domains of functioning (Mulhern et al., 2001; Radcliffe et al., 1994; Ris et al., 2001).

Although the associations between survivor neurocognitive late effects and survivor and family psychosocial outcomes have received little empirical examination, these deficits likely contribute to the outcomes of survivors (Ellenberg et al., 2009; Penn et al., 2010) and family members (Deatrick et al., 2009). With survival rates for children treated for pediatric brain tumors improving and advances in curative treatments, such as proton radiation, holding promise in reducing the severity of neurocognitive late effects (Merchant et al., 2008), it becomes critically important to identify all the potential mechanisms that may mitigate the impact of tumor-directed therapy and improve quality of life in this group of vulnerable childhood cancer survivors.

Peterson and Drotar's (2006) theoretical model of neurocognitive late effects in childhood cancer is a promising model that could greatly advance research in pediatric brain tumor survivors and inform clinical care. The model is unique in that it identifies disease and treatment-related variables as well as individual child and family systems variables as being influential in the development and management of neurocognitive late effects. Given that family variables have the ability to affect neurocognitive recovery from pediatric brain injuries (Taylor et al., 1999), it is important to understand the family contributions to neurocognitive late effects in childhood cancer. Few investigations, however, have empirically studied the relations presented in the model in pediatric brain tumor survivors. The case series presented in this paper represents an initial examination of the aspects of this model and a first step in exploring the role of the family in the development of neurocognitive late effects in childhood brain tumor survivors.

Findings from this case series provide initial support for the relations noted in the model and highlight several key variables and processes. First, the presented cases emphasize the importance of disease and treatment variables such as age at diagnosis and the presence of multiple treatment modalities, particularly cranial radiation, in the development of neurocognitive late effects. Younger age at the time of diagnosis and treatment is likely to continue to be a significant risk factor for neurocognitive late effects regardless of advancements in treatments due to the nature of brain development. Children diagnosed with brain tumors at young ages will require early interventions to offset the deleterious consequences of curative therapies.

Second, this case series illustrates the complex interrelations between survivor and family variables. Family functioning variables, such as cohesion and conflict, seem instrumental in determining how the family is able to apply resources towards the survivor in order to compensate for neurocognitive deficits and promote better quality of life. The families in this case series who were able to work together to address their child's difficulties and limitations seemed more successful in promoting developmentally appropriate levels of autonomy, which in turn led to better quality of life for the survivors. Additionally, this case series highlighted the role of caregiver demand and the potential influence of survivor deficits on caregiver and family functioning. The type and severity of survivor deficits likely influences the degree of demand experienced by caregivers. Survivors who exhibit more significant behavioral or cognitive difficulties may exacerbate the demand placed on caregivers. Increased caregiver demand likely taxes caregiver and family resources to such a

degree that caregivers' and family's efforts to meet the neurocognitive and developmental needs of the survivor become less helpful or potentially counterproductive.

Finally, family adaptation to the traumatic nature of the survivor's brain tumor diagnosis, related treatment and the subsequent late effects seems associated with how well the family is able to move forward and support the survivor's transition into young adulthood. The families in this case series that demonstrated aspects of posttraumatic growth and were able to reframe their beliefs about the brain tumor and treatment seemed better able to utilize their resources in order to support their survivor. Maintaining negative thoughts and beliefs about the treatment and late effects, however, seemed to hinder compensatory efforts.

The limitations of this case series should be considered when interpreting the study's findings. Although the combination of quantitative and qualitative data provide a unique depiction of the associations between family variables and survivor outcomes, this study's small sample size precludes the ability to draw broad conclusions. Additionally, this study included survivors who were many years from diagnosis and the conclusion of treatment and did not examine the interrelations between family functioning, neurocognitive functioning and quality of life from diagnosis onward. The reliance on data from the survivors' mothers and the absence of their fathers' perspectives also is a limitation. Finally, the family functioning and quality of life measures are not specific to families affected by pediatric brain tumors and may not adequately assess the unique issues experienced by this group.

Future Directions

The findings from this case series indicate a number of future directions in order to advance both research and clinical care with pediatric brain tumor survivors. First, due to their significant impact on the lives of childhood brain tumor survivors and their families, brief batteries to screen for neurocognitive late effects should be incorporated into treatment protocols and routine clinical care. Such screeners could identify survivors and families at risk for poor psychosocial outcomes and quality of life and those in need of intervention and resources. Such batteries could include elements of brief standardized neuropsychological tests (e.g., Digit Span) and self- and informant-reports of functioning (e.g., BRIEF).

Second, future research should investigate the interaction between family functioning and neurocognitive functioning in pediatric brain tumor survivors. Studies with larger samples sizes will allow for a complete examination of the reciprocal relations between these factors in order to better understand how they influence one another. Longitudinal prospective studies, in particular, that follow survivors and their families from the point of diagnosis through survivorship are greatly needed to determine whether or not positive family functioning and adaptation moderate the effects of disease and treatment on neurocognitive functioning. Such research designs could address the limitations of the research presented in this paper.

Third, both research and clinical work with childhood brain tumor survivors and their families should include family functioning measures specific to the key issues related to the experiences of families with a pediatric brain tumor survivor. Such measures should assess the impact of late effects on the family and how the family manages these late effects. Additionally, perceptions of caregiver demand and competence, as well as families' ability to support appropriate levels of survivor autonomy, are important constructs worthy of assessment within this population. However, no current measures are ideal for these purposes. The Family Management Measure (Knafl et al., In press) is a promising measure for families with a child with a chronic illness and assesses parental perception of how families manage their child's medical condition but it is not specific to pediatric brain tumor

survivors and their unique challenges. Additional measures are warranted to better assess these important issues in families of childhood brain tumor survivors.

A final future direction for research and clinical care involves incorporating family-based elements into cognitive remediation interventions or other interventions directed at improving survivor and family outcomes and quality of life. Cognitive remediation represents a promising intervention approach for survivors of childhood cancer affected by either disease or treatments involving the central nervous system. A recent Phase 3 randomized controlled clinical trial of a cognitive remediation program with this at-risk group of survivors demonstrated improvements in academic achievement and parent-rated attention but did not show improvements in other domains such as working memory or verbal memory (Butler et al., 2008). The authors speculated that greater emphasis on including family elements into the remediation program might have yielded more robust findings (Butler et al., 2008). Such speculation is supported by the promising results seen with a family-based problem-solving intervention for pediatric TBI that showed improvements in behavioral and social outcomes (Wade, Carey, & Wolfe, 2006).

Interventions tailored to the needs of pediatric brain tumor survivors that incorporate family-based elements are needed to improve outcomes with this population. Such interventions would work to promote resiliency in both the survivor and the family by identifying and reframing negative beliefs about the disease and treatments. Incorporating elements of cognitive remediation and cognitive-behavioral therapy into a family-based intervention could bolster the resources and skills of families in order to help them compensate for survivor neurocognitive deficits and support the survivor in regaining functioning and increased autonomy.

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Figure 1.
Hypothesized Model of Neurocognitive Late Effects and Family Functioning. (Adapted from Peterson and Drotar, 2006).

Table 1

Summary of Research Design and Measures.

Phase	Survivor Measures	Mother Measures
Time 1 (First Quantitative)	No measures	Family Assessment Device - General Functioning Scale Bakas Caregiving Outcome Scale Pediatric Oncology Quality of Life Scale
Time 2 (Qualitative)	Qualitative Interview	Qualitative Interview
Time 3 (Second Quantitative)	WAIS-IV Digit Span WAIS-IV Letter-Number Sequencing WAIS-IV Coding WAIS-IV Symbol Search CVLT-II, SF D-KEFS Trail Making Test D-KEFS Tower Test BRIEF-A Self-Report	Family Assessment Device - General Functioning Scale Bakas Caregiving Outcome Scale Pediatric Oncology Quality of Life Scale PedsQL FIM BRIEF-A Informant-Report

BRIEF-A: Behavior Rating Inventory of Executive Function, Adult Version; CVLT-II, SF: California Verbal Learning Test, Second Edition, Short Form; D-KEFS: Delis-Kaplan Executive Function System; PedsQL FIM: PedsQL Family Impact Module; WAIS-IV: Wechsler Adult Intelligence Scale, Fourth Edition.

Table 2

Survivors Performance on Administered Measures of Neurocognitive Function at Time 2.

Variables	“Sarah”	“Kim”	“Kevin”
WAIS-IV Working Memory Index	111	63	53
WAIS-IV Processing Speed Index	100	59	59
D-KEFS Trail Making Test: Switching	10	1	1
D-KEFS Tower: Achievement	4	2	5
CVLT-II, SF: Trials 1–4 Recall <i>T</i> score	56	28	12
CVLT-II, SF: Short Delay free recall standard score	−0.5	−1.0	−2.5
CVLT-II, SF: Long Delay free recall standard score	0.0	−2.0	−1.0
BRIEF-A: GEC <i>T</i> score (Self/Mother)	37/38	62/78	53/56

BRIEF-A: Behavior Rating Inventory of Executive Function, Adult Version; CVLT-II, SF: California Verbal Learning Test, Second Edition, Short Form; GEC: Global Executive Composite; D-KEFS: Delis-Kaplan Executive Function System; WAIS-IV: Wechsler Adult Intelligence Scale, Fourth Edition.

Table 3

Family Functioning and Quality of Life of the Three Survivors.

Variables	“Sarah”	“Kim”	“Kevin”
FAD GFS: mother report (Time 1/Time 3)	1.5/1.0	1.83/2.33	1.25/1.08
FAD GFS: survivor report (Time 3)	1.33	2.17	2.5
BCOS (Time 1/Time 3)	50/50	47/32	49/50
PedsQL FIM total score (Time 3)	84.72	43.75	75
POQOLS Emotional Expression (Time 1/Time 3)	6/9	34/35	16/13
POQOLS Physical Functioning (Time 1/Time 3)	17/19	46/41	N/A/28

BCOS: Bakas Caregiving Outcome Scale; FAD GFS: Family Assessment Device General Functioning Scale; PedsQL FIM: PedsQL Family Impact Module; POQOLS: Pediatric Oncology Quality of Life Scale.

Table 4

Case Series Summary within Model of Survivorship.

	Individual & Treatment Factors	Presumed Family Adaptation	Family Functioning	Survivor Outcomes
"Sarah"	• Older age at diagnosis	• Positive beliefs & reframing	• Good family functioning	• Mostly intact neurocog
	• 2 therapy modalities		• Less caregiver demand	• High QoL
"Kim"	• Younger age at diagnosis	• Negative beliefs • Focus on negative	• Significant family & caregiver demand	• Significant neurocog deficits
	• 3 therapy modalities		• Family conflict	• Poor QoL
"Kevin"	• Younger age at diagnosis	• Positive beliefs & reframing	• Good family functioning	• Significant neurocog deficits
	• 3 therapy Modalities		• Less caregiver demand	• Good QoL

Neurocog: Neurocognitive; QoL: Quality of life.