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NEURODEVELOPMENTAL IMPACTS ON CHILDREN TREATED FOR MEDULLOBLASTOMA: A REVIEW AND PROPOSED CONCEPTUAL MODEL

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Abstract

The population of survivors following diagnosis and treatment for medulloblastoma is thankfully on the rise. An increased focus on the quality of that survivorship has expanded the concept of cure to include efforts aimed at improving long-term cognitive outcome. It is well established in the literature that decline in overall intellect and academic performance is experienced by a majority of those undergoing treatment for pediatric medulloblastoma. This decline is believed to be secondary to decline in core cognitive abilities, which in turn are related to underlying damage to neuroanatomical substrates. A review of research on neurodevelopmental impacts following diagnosis and treatment for pediatric medulloblastoma is presented. Particular consideration is given to studies recently published that also reflect critical collaboration among those within the fields of neuropsychology and neuro-imaging. Results from the review are combined within a conceptual model upon which to guide future research and clinical efforts.

Keywords

medulloblastoma; cognitive deficits; brain tumor; model; processing speed; attention; working memory

Callouts

1. Based on the knowledge derived from studies of long term outcomes, it is important to consider medulloblastoma, as well as other pediatric cancers, as a condition resulting in life long morbidities related to the treatment for, but separate from, the primary presenting disease.
2. Intellectual and academic outcomes are considered distal markers and secondary to changes in underlying core cognitive skills.
3. While much of the research to date has focused on risk for deficits in cognitive function, attention should also be paid to resilience.
4. Consideration of the current literature on children diagnosed and treated for medulloblastoma reveals there is at least the start of a conceptual model illustrating the likely relationships between treatment, underlying

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neuroanatomical substrates, core cognitive functions, and secondary broad-spectrum abilities.

Neurodevelopmental Impacts on Children Treated for Medulloblastoma: Proposal for a Conceptual Model

Medulloblastoma is the most common form of malignant brain tumor diagnosed in children, occurs most often in the posterior regions of the brain, and is considered aggressive disease. Pediatric medulloblastoma can occur at any age but is typically diagnosed in children up to ten years of age, with a peak incidence at 5 years of age. Nearly twice as many boys are diagnosed as girls (Gottardo and Gajjar 2006; Ries 2008). Due to the tumor's tendency to spread, contemporary treatment is planned accordingly. Treatment includes maximal surgical resection, radiation therapy to the brain and spinal column, as well as the tumor bed, and several months of chemotherapy. Upon diagnosis the patient is considered to be either average risk or high risk depending on the progression of tumor and the extent to which the surgeon was able to remove tumor tissue. For example, a current multi-site treatment protocol defines a patient as standard risk if there is no evidence of metastatic disease and residual tumor is less than 1.5 cm² following surgery. The patient is considered to be at high risk if the tumor has spread or residual tumor after surgery is greater than 1.5 cm³. The assigned risk then dictates the strength of radiation therapy the patient will receive, with those at high risk receiving higher doses to the cranial spinal area (Gajjar et al. 2006).

The definitive goal of treatment is to cure the patient of the brain tumor and to prevent any relapse or progression from occurring. To accomplish this goal there have been many improvements to treatment plans based on careful research and long term monitoring of patients. Rates of survival have been steadily climbing with a recent report showing an overall 5-year survival rate of 85% for those considered average risk medulloblastoma and 70% for those considered high risk (Gajjar et al. 2006). Successful treatment has been shown to bring an unacceptable number of long term limitations in physical, cognitive, social and emotional function (Moore 2005; Mulhern and Palmer 2003; Ness et al. 2008; Schultz et al. 2007). Reducing these limitations to improve patients' quality of survival is the driving force behind many clinical research and medical teams who work together to expand the concept of cure to include improving long-term outcomes (Oeffinger and Robison 2007).

Diagnosis brings an immediate threat, and understandably pressing concern is with regard for medical treatment and survival. Survivorship however, can involve a continual struggle with lingering effects of treatment including the impact of surgery, radiation and chemotherapy (Bull et al. 2007; Maddrey et al. 2005). Based on the knowledge derived from studies of long term outcomes, it is important to consider medulloblastoma, as well as other pediatric cancers, as a condition resulting in life long morbidities related to the treatment for, but separate from, the primary presenting disease. An acute pediatric illness is one that has a definitive stage ending with a clear recovery, while chronic disease is one where the primary pediatric disease extends into adulthood (Oeffinger and Robison 2007). Childhood cancer is not appropriately considered within either of these health models. Instead survivors of pediatric medulloblastoma continue to experience problems secondary to their original diagnosis throughout their life span.

The impact of treatment strikes multiple organ systems and will alter functional abilities in several domains. Some deficits will not become evident until several years post-treatment. Ultimately responsible care for each survivor will require a multidisciplinary approach that is also longitudinal, proactive, and anticipatory (Oeffinger and Robison 2007). However, this ambitious standard of care will only be possible if providers have a solid understanding

of the risks faced by this population, and have the support to offer evidence based care. Continuity between pediatric services and adult services, within numerous specialties, should be viewed as a process rather than a single referral.

Survivors of medulloblastoma face many neuropsychological challenges with the type, timing and salience of particular challenges depending on individual, treatment and clinical variables. Historically assessment of broad-spectrum abilities such as intellectual outcome and academic performance, have been the benchmarks by which late effects have been measured. These studies eventually lead researchers to uncover preceding events by examining core cognitive abilities such as attention, memory and processing speed. Cross sectional studies were supported by longitudinal analyses allowing those in the field to understand developmental trends over time from diagnosis. The addition of diagnostic imaging techniques to studies of cognitive function following treatment opened a new era of research probing underlying neuroanatomical substrates of cognition, and understanding radiation dose-tissue response. Investigation of factors leading to resilience, as well as the development of cognitive remediation programs, are beginning to emerge, with much work yet to be accomplished in these areas. Review of the literature on each of these areas follows, culminating with a proposed conceptual model within which results from multiple studies can begin to be integrated.

Impact on Broad Spectrum Abilities

Nearly 40 years ago, Bloom (1969) reported a high rate of cognitive dementia among children surviving medulloblastoma. Since that time research in the area has continued to further our understanding of neurocognitive deficits that plague this growing population of survivors. Deficits in broad-spectrum abilities such as general intellect and academic achievement were among the first to be documented, and later quantified, within the oncology literature.

An early review and integrative analysis of 22 studies, representing a total of 544 brain tumor patients, confirmed cognitive deficits among those treated with cranial radiation (Mulhern et al. 1992). This paper was also important in summarizing the adverse consequences of radiation therapy and young age of the patient at time of treatment on eventual intellectual function. Children who had received cranial radiation exhibited lower intellectual function than those children who did not. Among those who had received cranial radiation, those who were younger when treated displayed significantly lower intellectual function than those who were older.

As a result of these types of findings the Pediatric Oncology Group and the Children's Cancer Group began to change medical treatment protocols to reduce the dose of radiation therapy and improved adjuvant chemotherapy. Psychology outcomes were considered important endpoints upon which to measure the impact of these treatment options. Studies that followed became increasingly specific in their aims and objectives. Protocols were designed to prospectively test hypotheses of age at treatment and radiation dose as risk factors, and patient groups became more homogeneous with respect to treatment and tumor type (Dennis et al. 1998; Deutsch et al. 1996; Mulhern et al. 1998; Ris and Noll 1994; Silber et al. 1992).

As patients were monitored from an earlier point in treatment and over longer periods of time, longitudinal studies emerged. Rather than a snapshot of patient function limited to one point in time, these studies employed sophisticated statistical analyses to detect patterns of change over time. In striking contrast to their healthy peers, in whom intellectual function was maintained over time, patients experienced significant declines in verbal, non-verbal, and general intellect as time from diagnosis increased (Mulhern et al. 2005; Palmer et al.

2001; Ris et al. 2001; Spiegler et al. 2004). Studies of academic function demonstrated similar patterns of decline over time for reading, spelling and math, with particular vulnerability in reading skills (Mabbott et al. 2005; Mulhern et al. 2005).

Declines in intellect were also found to vary depending on the age of the patient at the time of diagnosis. For example, those who were 6 years of age at the time of diagnosis were shown to experience immediate declines in intellect that did not slow until approximately 5 to 6 years following diagnosis. In contrast, those who were 11 years at time of diagnosis showed a delay, not experiencing declines in intellectual function until approximately 3 to 4 years following diagnosis (Palmer et al. 2003). For both the younger and older patient, these declines are thought to represent a reduced rate of information and skill acquisition, rather than a loss of previously acquired information, when compared to healthy same-aged peers (Mabbott et al. 2008; Palmer et al. 2001).

Core Cognitive Abilities

Clinical assessment of intelligence and academic performance remain important to monitoring global impacts of disease and treatment. Reliance on these measures however, is insufficient to explain the basis for declines in cognitive function experienced by survivors of medulloblastoma (Mabbott et al. 2008). Intellectual and academic outcomes are considered distal markers that arise secondary to changes in underlying core cognitive skills (Mulhern and Palmer 2003; Palmer et al. 2003; Palmer et al. 2007). Impairments in foundational skills of broad memory, working memory, attention and information processing speed have also been reported (Dennis et al. 1998; Kieffer-Renaux et al. 2000; Mabbott et al. 2008; Mulhern et al. 2004; Nagel et al. 2006; Reeves et al. 2006; Schatz et al. 2000; Spiegler et al. 2004) and may be precursors to the observed declines in intellectual function and academic function.

Measures of information processing speed are meant to capture the efficiency of processing simple perceptual or cognitive information, while broadly defined, memory is the ability to store, retain and retrieve information. Working memory is considered the ability to temporarily hold and manipulate information. Memory can also be classified in terms of the type of information or how the information is presented such as visual or verbal. Attention includes elements of vigilance, capacity for information, shifting focus, and screening out non-target information, tasks that rely on working memory and central executive processes (Sohlberg and Mateer 2001).

A retrospective review of 15 patients with posterior fossa tumors was completed using the Wide Range Assessment of Memory and Learning (George et al. 2003; Sheslow and Adams 1990). Patients were an average of 11.6 years at testing and 3.5 years from treatment. While deficits in both verbal memory and visual memory were demonstrated, verbal memory deficits were greater. Those who were younger than age 6 at diagnosis had greater deviations from population norms than those who were older than age 6 at diagnosis. Those who had been older than 6 at diagnosis showed deficits in verbal memory but their visual memory scores were within the normal range.

Early changes in verbal memory were examined in a study of 40 patients with medulloblastoma using the California Verbal Learning Test (Delis et al. 1994; Nagel et al. 2006). Patients were an average of 8.8 years at diagnosis and only 7 months from diagnosis upon testing. Each patient was matched to a healthy peer with respect to age at testing, gender, race, and parental education level. Patients performed significantly lower on initial recall, delayed recall, retention and recognition ability indicative of impairment of both encoding and retrieval. Those who were older at diagnosis retained significantly more information than their younger counterparts.

Kieffer-Renaux and colleagues (2000) examined the impact of radiation dose (25 Gy vs. 35 Gy) on verbal memory and processing speed among 36 patients with medulloblastoma. These patients were an average of 13.1 years of age and 4.3 years from treatment at evaluation. Those who had received 25 Gy cranial radiation were compared to those who had received 35 Gy. Memory was similarly impaired in both groups. Significant difficulties were evident in immediate as well as delayed recall of verbally presented information. Both groups were also significantly impaired on measures of processing speed but those who received 35 Gy cranial radiation showed slower processing speed than those receiving 25 Gy.

In a longitudinal study, Speigler and colleagues (2004) sought to determine the pattern of change or stability across multiple domains of neurocognitive function among 34 posterior fossa brain tumor patients, 30 of whom had medulloblastoma. These children were relatively young at diagnosis (average age at diagnosis of 6.1 years), and they were most recently evaluated an average of 4.71 years after diagnosis. Results confirmed previous studies showing a significant linear decline in general intellect as time from diagnosis increased (slope = -2.03), with a similar decline in information processing speed (slope = -2.11). Declines on visual memory and the ability to screen out non-target information, were also significant (slope = -1.54 and -1.86 respectively).

Utilizing the California Verbal Learning Test (Delis et al. 1994), verbal memory function was examined among 38 survivors of medulloblastoma an average of 1.97 years from the time of their treatment, and 8.34 years at the time of their diagnosis (Reeves et al. 2006). Twenty-six patients were considered average risk and treated with 23.4 Gy while the remaining 13 were considered high risk and treated with 36 Gy cranial spinal radiation. All verbal memory outcomes were below the population average. Though clinically significant, these deficits failed to reach statistical significance at the a priori criterion of $p < 0.01$. However, total recall and both short and long delay recall obtained values $p < 0.05$, and had moderate effect sizes. Attention was also measured using the Conner's Continuous Performance Test (Conners 2000). Eight of the 11 attention variables were significantly below than population averages. Consistent with previous studies of attention within pediatric brain tumor populations (Dennis et al. 1998; Mulhern et al. 2001; Mulhern et al. 2004; Reddick et al. 2003), patients' responses were slow and irregular. These attention deficits reflected slow processing speed and poor selective attention rather than impulsivity.

In a longitudinal study of information processing Australia researchers prospectively evaluated 35 patients with posterior fossa tumors (Stargatt et al. 2007). Patients were an average of 9.47 years of age at diagnosis and received neuropsychological evaluation upon diagnosis and annually for 3 years. When compared to healthy population norms, deficits in processing speed were noted at each evaluation time point. A smaller study of 18 patients with posterior fossa tumors documented similar results (Briere et al. 2008). Patients in this study were an average of 6.25 years at diagnosis and were evaluated at approximately 3 and 5 years post diagnosis using the Wechsler Intelligence Scales for Children - Third Edition (Wechsler 1991). At 3 years post diagnosis, processing speed had already fallen on average 1.7 standard deviations below population norms. At 5 years post diagnosis, processing speed remained low and deficits in attention had emerged as evidenced by the group's declining ability to screen out non-target information. In this group of patients, it was clear that processing speed was affected first followed by difficulties in attention.

Researchers within developmental psychology and pediatric oncology share a common goal to understand how intellectual function is related to core cognitive functions in children. Both processing speed and working memory increase rapidly at an early age and continue to show improvement throughout childhood, eventually reaching adult levels of performance

during late adolescence (Fry and Hale 2000). In parallel with this pattern of improvement is the rate of knowledge and skill acquisition among children, indicating strong relationships between intelligence, processing speed and working memory.

The pathways by which processing speed, working memory and intelligence are related have been studied within the healthy population (Fry and Hale 1996, 2000). Study participants included a large group of children and adolescents (n=214) aged 7 through 18 years. Results supported a developmental cascade model. Age related improvements in intelligence were found to be the product of improvements in processing speed and working memory capacity. Processing speed also predicted working memory. Additional analyses determined unique and shared variance between the variables (Fry and Hale 2000). Ninety-seven percent of the age related improvement in working memory was accounted for by processing speed, and together working memory ability and processing speed accounted for 80% of age related improvements in intelligence. Processing speed by itself was not sufficient to account for changes in intelligence but rather influenced intelligence through its effect on working memory.

Two studies to date have explored these relationships within pediatric oncology populations (Mabbott et al. 2008; Schatz et al. 2000). The developmental cascade model proposed by Fry and Hale (1996) was used as the basis to investigate the influence of processing speed and working memory on intelligence among long term survivors of acute lymphoblastic leukemia (ALL; n=27) matched with healthy comparison participants (Schatz et al. 2000). All of the ALL patients received intrathecal methotrexate chemotherapy. Fifteen were also treated with 18 Gy cranial radiation, while 3 received 24 Gy cranial radiation. Patients who received cranial radiation showed slower processing speed and poorer working memory capacity than those who had not received cranial radiation and the healthy controls. Differences in intelligence between the cranial radiation group and their matched healthy controls were accounted for by differences in working memory, with processing speed as an important moderating variable for working memory. However, processing speed could not fully account for differences in working memory between the cranial radiation and matched controls. Therefore the authors concluded there is a potential for additional mediating variables.

Most recently Mabbott and colleagues (2008) completed a study of core neurocognitive functions with 64 patients treated for posterior fossa tumors and 10 with non-CNS tumors. Here again, the roles of processing speed, working memory, and sustained attention in predicting intellectual outcomes were studied by analyzing the unique contributions of each. Thirty-two patients were treated with surgery and radiation therapy, with both cranial spinal radiation and a boost to the posterior fossa (n=23) or radiation to the posterior fossa only (n=9). An additional 32 patients were treated with surgery alone, while 10 non-CNS solid tumor patients were included as a comparison group. Patient groups were an average of between 4.54-6.85 years of age at diagnosis and were an average of between 4.5 and 6.3 years from diagnosis at evaluation. No group differences were found for sustained attention or working memory tasks. However, those patients who received radiation therapy exhibited slower information processing speed than those patients treated with surgery alone or who had a non-CNS tumor. Sustained attention did not predict intellectual outcome after adjusting for treatment was considered. Working memory and treatment modality shared a significant impact on intellectual outcome, while processing speed exerted a unique contribution. The authors concluded that the impact of cranial radiation treatment on intellect may derive primarily from impaired processing speed. Information processing speed may be the first deficit to emerge following treatment, a finding that is supported by Briere and colleagues (Briere et al. 2008). Further, the authors suggested that this impaired

speed of information processing may result from damage to the white matter structures of the brain.

Impact on the Brain

Recent studies have used diagnostic neuroimaging to augment behavioral studies of long-term impact of treatment. Age at the time of treatment remains prominently and consistently reported (Reddick et al. 2005; Reddick et al. 2000). Age is directly related to the developmental process of myelination in the brain. As the child develops, a portion of the brain's neuronal axons are surrounded by a covering called myelin, allowing for faster conduction of electrical impulses (Barkovitch 2000). These myelinated axons constitute the white matter of the brain. Unlike gray matter (unmyelinated) that develops rapidly and peaking at approximately 4 years of age, the process of white matter development continues into the second decade of life (Pfefferbaum et al. 1994). Age is therefore directly related to white matter maturity.

Of great significance, white matter is extremely vulnerable to injury from cranial radiation and chemotherapy, especially during rapid myelination (Moore 2005). Magnetic resonance imaging (MRI) has documented changes to the white matter areas of the brain following treatment for medulloblastoma. With the development of biomedical image computation programs, white matter can be quantified (Mulhern et al. 1999; Reddick et al. 1998). An initial study found that medulloblastoma patients, who were treated with cranial radiation exhibited significantly less normal appearing white matter volume than did astrocytoma patients who had been treated with surgery alone (Mulhern et al. 1999).

A subsequent longitudinal study (Reddick et al. 2000) found no significant difference in the rate of white matter loss between children with medulloblastoma who were older and those who were younger at the time of treatment with cranial radiation therapy. Following treatment, both patient groups lost white matter volume at a similar rate. However, since younger children begin treatment with a lower volume of white matter, they experience greater deviation from the expected development trajectory (Reddick et al. 2005). Perhaps those who are older at treatment and therefore more neurologically mature or intact, have greater opportunity for compensation and can better withstand the impact of cranial radiation. Reddick and colleagues (2000) also investigated the impact of radiation dose amounts on white matter tissue. Patients who received the reduced dose (23.4 Gy) had a slower rate of white matter loss when compared to those who had received the higher standard dose (36 Gy). Palmer and colleagues (Palmer et al. 2002) confirmed this dose-tissue response among medulloblastoma patients, finding greater deviations from normal development in the posterior regions of the corpus callosum, the area receiving the highest doses of radiation exposure (Palmer et al. 2002).

These quantitative MRI changes were found to be linked to neuropsychological performance among survivors of medulloblastoma. Specifically, data from 42 survivors of childhood medulloblastoma were evaluated to determine whether observed white matter volume, as measured within an index slice, mediated the relationship of age at the time of radiation therapy and neurocognitive performance (Mulhern et al. 2001). Longer time from treatment was significantly associated with poorer performance on tests of intellectual function. After statistically controlling for the effects of time following treatment, these analyses revealed that white matter volume explained a significant amount of variance in the relationship between age at radiation treatment and intellectual outcome.

Similar results were found in a later study of 40 long term survivors who were an average of 6.5 years of age at, and 5.7 years from the time of treatment (Reddick et al. 2003). White matter volume was significantly related to intellectual outcome. Furthermore, working

memory and sustained attention were found to be significantly related to intellectual outcome. After controlling for working memory and attention, the relationship between white matter and intellectual outcome was diminished, supporting the hypothesis that these variables mediated the relationship.

Though extremely valuable, quantitative volumetric measures cannot detect the process of change to white matter at the cellular level. Diffusion tensor imaging (DTI) is a magnetic resonance technique that detects the microstructural properties of white matter. This technique allows researchers to probe the white matter tissue at a level not available with use of conventional magnetic resonance imaging. Diffusion tensor imaging yields several measures, one of which is fractional anisotropy (FA), an index of the integrity of the white matter tissue. Higher FA values indicate greater integrity of the white tissue. As a child ages FA increases in a non-linear pattern, corresponding to increasing myelination of axons. The association between FA within specific brain regions and the development of cognitive functions was studied among 23 healthy children (Nagy et al. 2004). A significant positive relationship was found between working memory and white matter maturation within the left frontal lobe.

DTI studies are now emerging within the pediatric brain tumor literature as well (Khong et al. 2003; Khong et al. 2005; Khong et al. 2006, 2007; Mabbott et al. 2006; Qui et al. 2007). The first pilot study utilizing DTI evaluated 9 medulloblastoma survivors (Khong et al. 2003). Although this tissue appeared normal on conventional MRI, the DTI images showed a significant reduction in white matter integrity in multiple areas of the brain. Younger age at treatment, longer time since treatment and deterioration of school performance were all significantly related to reduced FA. The same group of researchers later studied white matter FA in 20 children surviving medulloblastoma who had been treated with cranial spinal radiation with boosts to the posterior fossa (Khong et al. 2005). Measures of FA were compared to those of healthy age matched control participants. The medulloblastoma survivors displayed lower FA values than the control participants of the same age. Those who were younger age at treatment and who had received larger radiation doses showed the greatest differences. These results lend further support to the notion that white matter is a neuroanatomical substrate for treatment-induced neurotoxicity.

Khong and colleagues (2006) were the first to examine the association between intellectual outcome and DTI measures among 12 medulloblastoma patients, 9 ALL patients who had received cranial radiation therapy, 9 ALL patients who did not, and 52 age and demographically matched healthy comparison children. Since FA increases with age, each patient was compared to an age-matched control group. The percent difference between the patient's FA and that of their corresponding control group was significantly related to general intellect, verbal intellect and non-verbal intellect. The authors concluded that FA is a useful clinical predictor of cognitive outcome but noted that their cross-sectional design did not allow evaluation of potential developmental trends in FA and IQ.

Later that same year an additional study examining the association between intellectual outcome and DTI among patients surviving medulloblastoma was released (Mabbott et al. 2006). Four patients were treated for high-risk disease with standard dose cranial spinal radiation (36-36.6 Gy), while 4 were treated for average-risk disease with reduced dose (23.4 Gy). A healthy control group was also recruited for comparison. Relative to the control group, FA was significantly lower in the patient group in 5 of the 6 regions of interest; the genu of the corpus callosum, the posterior and anterior limbs of the internal capsule, and inferior frontal and high frontal white matter, but not in the parietal white matter. To determine the association between general intellect and white matter integrity, a mean FA value using all regions of interest was calculated. With the exception of one patient, low IQ

was associated with low FA. Although this group of researchers used a different statistical approach to examining the relationship between FA and intellectual outcome, the results nevertheless replicate those of Khong et al. (2006). The authors offer valuable discussion with regard to the possible meaning(s) behind the decreased FA values following radiation treatment among these patients and caution that mechanisms other than demyelination should also be considered. These include a failure or disruption to normal myelin development, and radiation induced damage to astrocytes.

Longitudinal studies are needed to understand developmental changes in white matter microstructure and its relationship to core cognitive abilities among patients diagnosed with medulloblastoma. To date no such studies exist in the literature. FA may be a critical biomarker of treatment-induced white matter damage, allowing early detection and identification of those at risk for neurocognitive deficits, and evidence-based initiation of appropriate intervention. It may also be a useful application in testing the effectiveness of potential neuroprotective drugs or treatment alterations (Khong et al. 2006).

Resilience

While much of the research to date has focused on risk for deficits in cognitive function, attention should also be paid to resilience. Though research usually reports findings derived from groups of patients, it is important to remember that considerable variability still exists among individuals within those groups. Not all patients follow the expected trends with regard to poor neurocognitive outcomes. Aside from treatment factors possible explanations lie in examination of patients' home, school, and community environments.

A recent longitudinal study provides some perspective examining several aspects of recovery among 109 children with severe or moderate traumatic brain injury (TBI), along with 80 children with orthopedic injuries not involving the brain for comparison (Taylor et al. 2002). In addition to measures of behavior, academic achievement and child status, family environment was also studied. Family environment, as measured by socioeconomic status and stressors within the family, were significantly related to patterns of recovery among patients with a TBI. Those from more advantaged home environments were found to have positive socialization patterns during the first year of recovery, compared to no improvement or a decline in socialization behavior among those from less advantaged homes. In addition, low stress was found to facilitate recovery of math skills among those with a severe TBI. Possible mechanisms responsible for the association between low family stress, more advantaged socioeconomic status, and positive recovery patterns were discussed. The authors speculated that opportunities to communicate effectively, learn compensatory skills, obtain appropriate support, and provide greater cognitive stimulation may be responsible.

The potential influences of family environment, including levels of stress, parental coping, and socioeconomic status, have been considered within the pediatric brain tumor literature (Mabbott et al. 2005; Mulhern and Palmer 2003; Palmer et al. 2007; Taylor and Alden 1997) but little applicable data exists. Children with brain insults are more dependent on their families, a fact that highlights the even greater importance of a positive and supportive family life. In addition, demographic variables such as parental education can account for significant amount of variance in a child's intellect (Vanderploeg et al. 1998). Identification of the associated paths by which family environment impacts outcome, could suggest ways to work with the family (Taylor and Alden 1997). Efforts to reduce familial stress, influence positive coping skills, educate parents on critical issues impacting treatment and recovery, and improving access to cognitive remediation resources have the potential to benefit the patient's eventual outcome.

Accommodations within school environment may also reduce the impact on academic performance and facilitate rehabilitation (Butler and Haser 2006; Butler and Mulhern 2005; Nagel et al. 2006; Palmer and Leigh in press; Palmer et al. 2007). Slowed processing speed will require extended time for completing assignments, homework and tests. Reliance on memory recall ability could be avoided by providing tests in multiple choice format rather than essay or short answer formats. Adaptations for verbal memory deficits could include suggestions for classroom lectures to be recorded, and written material to be provided that corresponds to daily class content. These modifications require that teachers and school staff be informed of the patient's condition and treatment related risks and their response to be positive and accommodating. Empowering parents with the knowledge and support they require may help them become more independent in advocating on behalf of their child. Combined with effective intervention programs, modifications to family and school environments is likely to result in maximal gains for the child (Butler and Mulhern 2005)

A Proposed Conceptual Model

Consideration of the current literature on children diagnosed and treated for medulloblastoma reveals there is at least the start of a conceptual model illustrating the likely relationships between treatment, underlying neuroanatomical substrates, core cognitive functions, and secondary broad-spectrum abilities (Figure 1). This model can be used to guide research objectives and clarify priorities in the area of neurodevelopmental impacts following treatment for medulloblastoma. The model can be modified and updated based on subsequent research from both within and outside pediatric oncology literature. Much can be learned from our colleagues in fields such as traumatic brain injury, dyslexia, central nervous system rehabilitation, developmental psychology, and aging, among others.

Both cross sectional and longitudinal studies have clearly shown deficits in the broad-spectrum abilities of intellectual outcome and academic performance following treatment for medulloblastoma (Figure 1, hexagons). These deficits are considered distal markers and secondary to the less studied but yet still critical core cognitive functions including, but not limited to, information processing speed, attention and working memory. More work is needed to partial out the relationships between processing speed, working memory and attention, and applied to those within pediatric oncology. Therefore, at the present time these three core cognitive abilities remain grouped together (Figure 1, ovals) until causal relationships are identified. Difficulty with sustained attention may stem from an inability to hold mental representations in order to guide behavior, an ability associated with (Gathercole and Alloway 2006) or even causally related (Dennis et al. 1998) to working memory. The association between processing speed and attention also needs further examination. In addition, measures of academic achievement could also be deconstructed to add more detail to the model. For example, in the area of reading subskills such as auditory attention, orthographic skills, phonological processing and sequencing can have an impact on reading decoding,

Though multiple risk factors have been discussed in the literature, three are prominently and repeatedly identified: young age of the patient at the time of diagnosis, treatment with cranial radiation and increased time from treatment. Young age at treatment is considered to directly reflect neurodevelopmental maturation (Figure 1, rectangle), which in turn has an impact on developing core cognitive abilities. Examining the relationships between neurodevelopment and corresponding core cognitive functions is vital to characterizing the mechanisms by which disease and treatment lead to the cascade of cognitive deficits following treatment. Detection of reliable biomarkers will allow for early identification of those who may be at particular risk for cognitive decline. Currently, cranial radiation dose and method of delivery vary according to protocol, risk status, and treatment center. Additional methods of risk classification as well as new methods of treatment delivery are

being developed, which may further reduce radiation dose exposure and related risk (Gajjar et al. 2004; Merchant et al. 2008). Additional risk variables have also been identified but their impact on cognitive outcome has not been as extensively substantiated. Children treated with radiation therapy who have other medical complications (i.e. increased intracranial pressure, endocrine deficiencies) may be at even greater risk for neuronal damage, with a cumulative impact on cognitive function. Intervening early within the developmental cascade may in turn alter the developmental trajectory possibly reducing longer-term risk.

Intervention programs are labor intensive and costly and thus cannot be applied as a preventative measure for every child. Accurate identification of patients at risk is critical. Confirming the timing and order of events from the point of diagnosis onwards will also help to recognize the type(s) of intervention from which this population would most benefit, and when intervention would be most effectively applied (Figure 1, broken lines). With additional research, application of efficacious interventions could be evidence based and resources more precisely allocated. Information gained from future studies on resilience will add to the efforts in developing efficacious intervention programs. Interventions that target the family could be initiated following diagnosis, while those directly applied to the patient could begin prior to the emergence of the more functionally significant deficits. Communication with the patient's school could begin prior to the school re-entry following treatment with regular follow-up and teacher education. The population of survivors is growing rapidly and we have a responsibility to forge ahead in validating methods to improve their quality of survival.

Future Directions

The proposed conceptual model has been compiled from several studies. However, each of these studies has employed various measurements, methodologies and patients. Retrospective designs do not allow establishment of the timing of events as they prospectively unfold and thus may influence interpretation of final results. The model will need to be tested with large-scale longitudinal studies that prospectively test these relationships. Caution must be taken when multiple approaches have been used and then described as similar outcome. For example, while one study may use simple reaction time tests as a measure of processing speed, another may use a task that more heavily relies on motor function or is also strongly related to attention. The makeup of the patient groups is also an important consideration when making generalizations from various research findings. Associations between some core cognitive functions may be stronger for older children than for those who are younger and therefore can be a source of variance within studies of cognitive outcome. The model proposed, like all conceptual models, should be viewed as a preliminary springboard for future studies aimed at improving the lives of those children diagnosed with pediatric medulloblastoma.

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Figure 1. Proposed conceptual model to understand neurodevelopmental impacts of diagnosis and treatment of pediatric medulloblastoma. Solid lines: Associations derived from review of the present literature. Broken lines: Suggested areas of future research.