Understanding the Cognitive Impact on Children Who are Treated for Medulloblastoma

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Objective Risk-adapted treatment approaches employed within contemporary medulloblastoma treatment protocols aim to reduce the neurotoxicity directed at the central nervous system. Despite these important steps to reduce radiation dose exposure, an overwhelming majority of medulloblastoma survivors continue to experience academic failure and significant learning delays. **Methods** A review of the current literature is presented. **Results** Deficits in intellectual function, academic achievement, memory, attention, and processing speed are reported. Finally, intervention programs, including pharmacotherapy and experimental cognitive intervention studies, are discussed. A review of neuroimaging studies shows changes in brain tissue following chemotherapy and radiation treatment. **Conclusions** Declining IQ and academic struggles may be predated by difficulties with attention, memory, and processing speed. More clinical trials directed at treating and preventing neurocognitive late effects through cognitive rehabilitation are needed.

Key words brain tumor; cognitive deficits; late effects; medulloblastoma.

Medulloblastoma is a type of malignant tumor that arises predominantly in the area of the cerebellar vermis within the posterior fossa region accounting for ~10–20% of all central nervous system (CNS) tumors in children (Ries et al., 1999). Over 2000 children are diagnosed with malignant CNS tumors each year in the United States alone (Ries et al., 1999). Although the diagnosis is relatively rare, the disease leaves significant and costly impairments. Pediatric medulloblastoma is typically diagnosed in children from birth to 10 years of age, with a peak incidence at 5 years of age, and has a 2:1 male to female ratio (Gottardo & Gajjar, 2006). The tumor can completely occlude the fourth ventricle and has a propensity to disseminate along the subarachnoid space in the entire neuraxis at diagnosis. The tumor can recur either locally or have metastatic spread limited to the neuraxis. On rare occasions the tumor can spread outside the neuraxis with bone being the most common site for metastasis (Blaney et al., 2006).

The earliest clinical presentation of medulloblastoma of the posterior fossa region usually includes nonspecific symptoms of headache, lethargy, and vomiting thought to be caused by increasing intracranial pressure. These symptoms are present in 70–90% of patients at diagnosis but, because of their intermittence and subtlety, can be often overlooked for months (Blaney et al., 2006). Several clinical features impact the prognosis of pediatric medulloblastoma patients. While some studies have shown that larger tumor size has been associated with poorer prognosis (Tait, Thorton-Jones, & Bloom, 1990), others have been unable to show any consistent relation with size (Hughes et al., 1988). Extent of surgical resection and presence of metastatic disease have been consistently shown to impact survival. Patients presenting with metastatic disease at diagnosis and those with $>1.5\,cm^2$ residual disease after surgical resection experience inferior survival rates in most contemporary studies (Gattardo & Gajjar, 2006). Young age (<3 years) at diagnosis has also been identified to negatively impact outcome (Ries et al., 1999). Due to the adverse impact of radiation therapy (RT) on neurocognitive outcome in infants and young children, this therapeutic modality is used sparingly (Walter et al., 1999). Therefore, age at diagnosis impacts therapy offered to patients and thus impacts outcome (Gottardo & Gajjar, 2006).

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Over the past 10 years, treatment for medulloblastoma has undergone extensive modification. Current protocols consists of maximal surgical resection, risk-based neuraxis RT, and adjuvant chemotherapy (Gottardo & Gajjar, 2006). Due to the high metastatic potential of these brain tumors, RT includes targeting the entire craniospinal axis with an additional boost aimed at the primary tumor site. Long-term side effects following treatment for medulloblastoma have been consistently demonstrated. Research has indicated that, of the therapeutic modalities used in treating medulloblastoma, RT appears to be most related to the severity of neurocognitive deficits in survivors in a dose-related fashion (Grill et al., 1999; Kieffer-Renaux et al., 2000). Aimed at reducing adverse outcome, contemporary protocols employ a risk-adapted strategy in which treatment is stratified according to the presence of metastatic disease at diagnosis and volume of residual tumor after surgical resection (Gajjar et al., 2006; Thomas et al., 2000). Those who are considered to have average-risk disease receive a lower dose of craniospinal RT than those who are considered to have high-risk disease (Packer et al., 2006). In addition, advances in radiation delivery techniques, such as 3-dimensional conformal radiation to the primary tumor site and reduction to the clinical target volume margins, have sought to minimize the adverse consequences of radiation treatment by reducing RT dose exposure to healthy tissue (Douglas, Barker, Ellenbogen, & Geyer, 2004; Merchant et al., 2006; Wolden et al., 2003). Proton beam irradiation holds promise to even further reduce radiation exposure of healthy brain tissue (Wilson, McDonough, & Tochner, 2005; Yock & Tarbell, 2005). With several USA medical facilities implementing proton treatment, studies utilizing this therapy option for children are expected to increase in the near future.

Despite these important steps to reduce radiation dose exposure, an overwhelming majority of survivors continue to experience academic failure and significant learning delays (Mabbott et al., 2005; Mulhern et al., 2005; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001) with a large number eventually requiring special education services (Dennis, Spiegler, Hetherington, & Greenberg, 1996; Mitby et al., 2003). Thus, current treatment plans are constrained by the unsatisfactory balance between successful disease control and serious impact on cognitive abilities. Cognitive side effects can include deficits in intellectual function, academic achievement, memory, attention, and processing speed.

Intellectual Functioning

A review of the literature conducted in 1992 reported that radiation had adverse effects on intellectual functioning among patients treated for brain tumors. In 12 of 18 studies reviewed, patients receiving radiation had IQ levels 12–14 points lower than those who did not receive radiation. It was also found that children who were younger when treated with cranial radiation showed a 14-point deficit in IQ as compared with those who were older at treatment (Mulhern, Hancock, Fairclough, & Kun, 1992). In a separate review of 12 studies published in 2004, it was reported that those treated by surgery alone (astrocytoma), or with radiation of the posterior fossa only (ependymoma) showed less severe cognitive deficits than those patients treated with craniospinal RT for medulloblastoma (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004).

Evaluating the effects of cranial radiation dose and patient age on cognitive outcome, the Pediatric Oncology Group conducted a prospective and randomized clinical trial (Mulhern et al., 1998). The survivors who received reduced-dose cranial radiation (23.4 Gy), and those who were older at the time of treatment (>8.8 years), showed higher cognitive functioning than those who received standard dose (36 Gy) and who were younger at time of treatment (<8.8 years). Although enlightening, these earlier studies did not establish a pattern of change in cognitive abilities across time from treatment.

Within the normal population, an IQ score is expected to remain stable across time. However, in a longitudinal study the intellectual functioning of pediatric patients with medulloblastoma was found to decline as time from treatment increases (Palmer et al., 2003). The effects of RT began to clinically impact cognitive functioning at ~1 year post-treatment and showed a continuing pattern of decline over time. It was also found that patients who were younger at the time of irradiation were at risk of impaired cognitive functioning sooner after treatment than those who are older. Analysis of longitudinal changes in IQ scores over time revealed that younger patients experienced an immediate decline that continued over time while the older patients experienced a delay in decline for ~2 years (Palmer et al., 2003).

Because of the properties underlying the IQ score, two processes could account for the cognitive decline experienced by medulloblastoma patients. Children who show a decline in their standardized IQ scores could be losing previously acquired information as evidenced by a decline in raw scores. Or, they could continue to acquire

new information, but at a rate slower than expected when compared with normal same-aged peers. This would be evident by a slower than normal increase in raw scores. A study examining these two processes was completed (Palmer et al., 2001). As in previous literature, a significant decrease in standardized IQ scores over time since completion of RT was found. However, upon examination of the raw score pattern over time on information, similarities, and block-design subtests, a significant increase was demonstrated. The results indicated that these survivors continued to acquire new information over time, but at a rate slower than expected when compared with same-aged peer normative rates, thus resulting in a decline in standard scores. A slow rate of knowledge acquisition has direct implications on a patient's potential academic performance.

Academic Performance

The academic failure rate is high for survivors of medulloblastoma and problems in academic performance are a common reason for neuropsychological referral. Patients who are younger at diagnosis and those who receive higher doses of RT are particularly in need of special education services (Mitby et al., 2003). In addition to special services, overall educational attainment has also been examined among cancer patients. While patients surviving Hodgkin's disease, soft tissue sarcoma, and bone tumors completed high school at the same rate as their siblings, survivors of CNS tumors were significantly less likely than their siblings to finish high school (Mitby et al., 2003). Successful completion of school is critical for future vocational choice and productivity (Butler and Mulhern, 2005). Without an education, these survivors are at great risk of losing the ability to live independent lives.

School completion is highly dependent on achievement of basic academic skills including reading and spelling. These skills have served as important endpoints in comprehensive studies of cognitive ability following treatment for medulloblastoma. From October 1996 to August 2003, patients with newly diagnosed medulloblastoma were enrolled on a collaborative risk-adapted treatment protocol (Mulhern et al., 2005). The academic skills for 111 of these patients were prospectively evaluated at multiple time points. Overall, significant declines in reading decoding skills (−2.95 points per year, $p < .0001$) and spelling skills (−2.94 points per year, $p < .0001$) were observed over time from diagnosis. Significant declines in reading decoding skills were experienced by patients with standard-risk disease and those with high-risk disease (−2.90 points per year, $p < .001$, and −3.08 points per year, $p < .001$, respectively), with no significant difference between the two groups. Those younger than 7 years at diagnosis also showed a significant loss in reading ability (−4.30 points per year, $p < .001$) as did those at least 7 years old at diagnosis or older (−1.87 points per year, $p < .01$). When directly compared, the declines experienced by those who were younger at diagnosis were significantly greater than those experienced by patients who were older at diagnosis ($p < .01$). This study was also the first to longitudinally examine the *combined* effects of risk group and age at diagnosis on academic skills within a longitudinal model with reading ability showing particular vulnerability (Fig. 1).

While measures of intellect and assessment of academic achievement remain important components of studies concerned with late effects following treatment, it is believed that changes in more basic cognitive skills such as memory, attention, and processing, may occur earlier in the cascade of events.

Memory, Attention, and Processing Speed

The ability to allocate attentional resources, to plan and organize behavior, maintain adequate information within memory, and manipulate that information in a timely manner are critical pre-requisite processes by which knowledge is acquired (Dennis, Hetherington, & Spiegler, 1998). It is speculated that for children treated for medulloblastoma the inability to acquire new information and skills at a rate comparable to healthy same-aged peers may be due to deficits in underlying core abilities such as memory, attention, and speed of processing (Palmer et al., 2001). Normal age-related development of working memory and processing speed have been found to account for nearly half of the age-related improvements in intelligence (Fry & Hale, 1996). This relation was also found in one study of cancer survivors where it was reported that up to 45% of the variance in IQ was accounted for by working memory ability and processing speed (Schatz, Kramer, Ablin, & Matthay, 2000).

Specifically examining patterns of verbal memory, a recent study compared 40 children treated for medulloblastoma with 40 demographically matched controls (Nagel et al., 2006). The children treated for medulloblastoma showed a mixed profile of verbal memory deficits including both retrieval and recognition

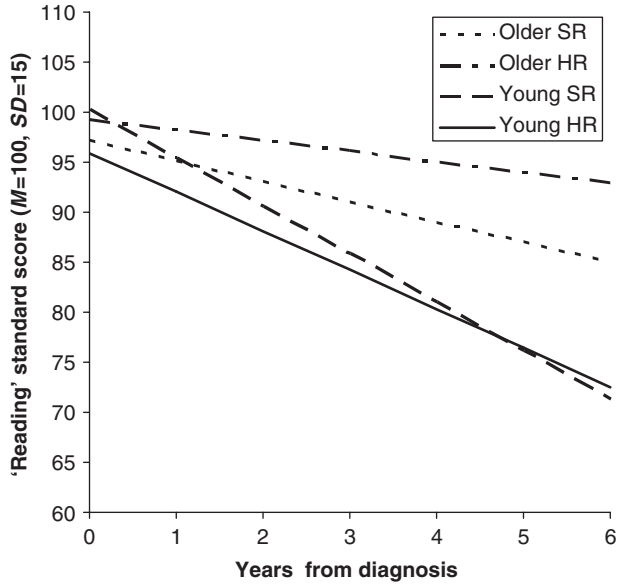

Figure 1. Predicted mean changes in 'reading' for combined age/risk groups. The older/average risk group demonstrated a decline in reading of −2.05 points per year ($p<.001$), while the older/high risk group demonstrated a nonsignificant decline of −1.05. The younger/average risk and younger/high risk patients demonstrated a significant decline (−4.81, $p<.001$, and −3.90, $p<.001$, respectively). Data originally described in Mulhern et al., 2005.

impairments. Examining change in verbal memory over time, patients with posterior fossa tumors have shown an overall decline in ability following treatment (Copeland, DeMoor, Moore, & Ater, 1999; Mulhern et al., 2001). Similar deficits in attention have been demonstrated. Examining dose- and age-effects in relation to attention, it was found that like IQ, younger patients (<8 years of age at diagnosis) and those who received higher dose of craniospinal RT (36 Gy) experienced greater deficits in attention than those who were older and who had received lower doses (Mulhern et al., 1998).

In an effort to understand the pathophysiology that underlies these cognitive changes among children treated for medulloblastoma, the number of imaging studies utilizing magnetic resonance imaging (MRI) techniques has increased rapidly. The ability to quantify brain parenchyma has been developed and is termed quantitative MRI. Because of the increased sensitivity at detecting change in tissue characteristics, this technology holds promise for longitudinal assessments of treatment response and long-term post-treatment follow-up. With quantitative MRI, the opportunity exists to detect subtle brain pathology that may otherwise be missed. Greater accuracy in detection of change translates to earlier treatment and more informed treatment decisions for the patient, and perhaps an increased chance of survival.

Imaging Studies

Studies utilizing neuroimaging have shown changes in brain tissue following chemotherapy and radiation treatment, with particular vulnerability being detected in the white matter of the brain (Mulhern et al., 1999; Reddick et al., 1998, 2005; Shan et al., 2006). Glial cells serve a supportive role by providing structure and insulation for the axon of the nerve cells. Within the white matter of the brain, a type of glial cell called oligodendrocyte, form a fatty sheath that surrounds portions of the neuronal axon and acts to dramatically increase the speed of nerve conduction (Barkovitch, 2000). This sheath is referred to as myelin. Myelination normally takes place rapidly after birth and continues into the third decade of life (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). It is believed that exposure to radiation can disrupt this developmental process (Coderre et al., 2006).

Utilizing computerized tomography (CT) several CNS abnormalities such as cerebral atrophy, focal and diffuse white matter lesions, and enlarged ventricles, have been demonstrated among children who have received radiation treatment (Constine, Konski, Ekholm, McDonald, & Rubin, 1988). Quantitative MRI studies allow volumetric measures of various brain tissues to be derived from processing MRI data. Applying quantitative MRI techniques, researchers examined volumetric differences associated with cranial radiation in 15 medulloblastoma patients compared with 15 age-matched astrocytoma patients (Reddick et al., 1998). Both patient groups received surgery, but only the medulloblastoma patients received radiation. The irradiated patients showed significantly less normal appearing white matter (NAWM), whereas gray matter was not found to differ between the two groups.

The association between quantitative MRI measures and assessment of cognitive functioning has been studied (Mulhern et al., 1999). The study examined cognitive functioning of a group of patients with medulloblastoma, who were treated with surgery, radiation, and in some cases chemotherapy. A group of low-grade astrocytoma patients, also with tumors of the posterior fossa region but who were treated with surgery alone, were used as a comparison control group. In order to experimentally control for age-related differences in head size at the time of quantitative MRI, subjects were age-matched. This resulted in 18 age-matched pairs (mean age difference = 3.7 months). For the medulloblastoma group, all IQ scores were found to be significantly lower than expected in the general population. However, mean IQ values of the astrocytoma control group were

within normal population range. When compared, patients in the medulloblastoma group had significantly lower mean Full Scale IQ values than those in the astrocytoma control group. The medulloblastoma patients also demonstrated significantly lower volume of NAWM than the astrocytoma control patients, but no significant difference was found between the groups on cerebral spinal fluid or cortical gray matter. The study also reported that among the medulloblastoma group, as NAWM increased, IQ performance improved.

Neurocognitive performance of 42 survivors of childhood medulloblastoma was examined in relation to NAWM volume and time since treatment with RT (Mulhern et al., 2001). This study developed a mediational model that, after statistically controlling for the effects of time from treatment, demonstrated NAWM volume explained a significant amount of the variance in the relationships between age at RT and IQ. A disturbance to white matter integrity was therefore considered a plausible neurological substrate involved in the cognitive declines experienced by this population.

Building on past research, a further examination of the relationship between NAWM volume and additional neurocognitive abilities was completed (Mulhern et al., 2004). In addition to measures of intellect, measures of sustained attention, memory, and achievement were obtained from a group of 40 medulloblastoma survivors. A developmental model was derived which demonstrated that the primary consequence of reduced NAWM among pediatric patients treated for brain tumors is decreased attentional abilities, leading to declining IQ and academic achievement (Mulhern et al., 2004).

Diffusion tensor magnetic resonance imaging (DTI) quantifies the diffusion of water molecules in the brain. When white matter microstructure is disrupted, the abnormality is detected and can be quantified as fractional anisotropy or FA. Lower FA occurs when there is a disruption to diffusion, indicating pathology (Khong et al., 2006). Examining the integrity of white matter among pediatric cancer survivors, a group of researchers from China utilized DTI (Khong et al., 2006). Subjects included 12 survivors of medulloblastoma, and acute lymphoblastic leukemia (ALL) survivors who received ($n = 9$) and who did not receive ($n = 9$) cranial radiation. Compared with age-matched healthy controls, it was found that those who had been treated for medulloblastoma had the greatest difference in white matter FA, followed by those ALL patients who had been treated with radiation, and then those who had not received radiation as part of their treatment for ALL. The differences in white matter FA measures were also highly correlated with Full Scale, Verbal, and Performance IQs. The results indicate that FA is a useful biomarker of treatment-induced white matter damage. Longitudinal and prospective DTI studies of children being treated for medulloblastoma are needed to determine the relative timing of changes in FA, intellect, and other cognitive abilities.

Children treated for medulloblastoma often experience functional memory deficits (Kieffer-Renaux et al., 2000). In an effort to understand the neuropathology underlying these deficits, examination of longitudinal patterns of hippocampal volume was completed (Nagel et al., 2004). Twenty-five pediatric patients underwent 159 serial MRI examinations over a period of 5 years from diagnosis of medulloblastoma. Right and left hippocampal volumes were obtained via manual tracing of 1.5 mm contiguous coronal slices through the structure. It was found that both right and left hippocampal volumes showed a decrease after treatment. This abnormal pattern continued until ~2–3 years post-diagnosis when hippocampal volumes demonstrated a return toward a normal, positive growth pattern. Further analyses revealed that volume loss occurred predominately in the posterior regions of the hippocampus. Female gender, low parental education, shunt placement, and positive seizure history were all found to have a significant negative impact on hippocampal growth. While previous studies have demonstrated that hippocampal integrity is crucial to the acquisition of new memories (Suzuki and Clayton, 2000), the specific relationship between hippocampal volume and memory function has yet to be determined. This is believed especially true in pediatric populations. Additional research is needed to specifically examine the relationship between longitudinal volumetric measures of the hippocampus and memory performance among those who are treated for medulloblastoma.

Also showing abnormal development following treatment is the main commissure of the brain, the corpus callosum (Palmer et al., 2002). Following diagnosis, 35 patients underwent 239 MRI exams over a period of 4 years. Quantitative analyses showed that total midsagittal corpus callosum area significantly decreased 18.0 mm^2/year. Significant declines were also observed in corpus callosum subregions: genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium. The greatest deviation from normal development occurred in the posterior most subregions, the isthmus and the splenium. These subregions, associated with fibers

traversing from the temporal, posterior parietal, and occipital lobes, are normally expected to have the highest rate of growth during childhood (Giedd et al., 1999). Examination of dosimetry fields in this group of patients demonstrated that these regions received the highest total dose of irradiation. Since development of word and letter recognition in the left hemisphere requires transcallosal white matter connections between visual areas performing basic feature analysis (Beversdorf, Ratcliffe, Rhodes, & Reeves, 1997), abnormal development of the corpus callosum, especially in the posterior regions, may play a role in the reading deficits experienced with this population.

Identification of the underlying pathology contributes a great deal of information that can now be combined with existing knowledge, aiding in the development of efficacious cognitive rehabilitation programs and tested within intervention studies.

Intervention Studies

Following risk-adapted treatment approaches aimed at reducing the neurotoxicity directed at the CNS, implementation of efficacious intervention programs may be considered the second line of defense against cognitive decline following treatment. Each patient experiences a varying degree of impairment. Those who are at increased risk for specific cognitive deficits must be accurately identified, and services designed to counteract these deficits should be made available.

Intervention programs can include pharmacotherapy, cognitive therapy, experimental interventions designed relative to the specific deficits or combinations of deficits that this population demonstrates, or the utilization of programs already commercially available. Despite the large body of literature describing the cognitive sequelae impacting survivors of childhood cancer, only two ongoing studies were found that offered intervention programs to neutralize deficits among long-term survivors. The pilot data of these studies has been published with promising results and are discussed below (Butler & Copeland, 2002; Thompson et al., 2001).

The effectiveness of the psychostimulant methylphenidate to improve attention deficits among cancer survivors has been examined. In a double-blind, placebo-controlled study, patients given 0.6 mg/kg methylphenidate showed significant improvement on measures of attention when compared with those receiving placebo (Thompson et al., 2001). A multicenter follow-up study, funded by the National Cancer Institute with the primary site located at St. Jude Children's Research Hospital, utilizing a trial of two doses of methylphenidate and placebo in the home and school environments, is currently in progress. Parent and teacher ratings of behavior, as well as objective testing of the patients, will allow the evaluation of pharmacotherapy effects on academic achievement and social relations.

Cognitive rehabilitation is a term used to describe therapeutic services intended to restore lost cognitive functions, or to teach the patient skills to compensate for cognitive losses that cannot be restored. A pilot study implemented a multiple-session program aimed at improving attention deficits among 21 cancer survivors (Butler & Copeland, 2002). The program combined attention process training developed for those undergoing brain injury rehabilitation (Sohlberg & Mateer, 1986), metacognitive strategies from educational psychology, and cognitive behavioral strategies from clinical psychology. Those who received the pilot intervention showed statistically significant improvements on measures of vigilance attention and concentration, while those who were in the control sample did not show any difference in performance over the same time period.

Utilizing a prophylactic approach, such as providing intervention training during treatment, needs further development (Butler & Mulhern, 2005; Moore, 2005). Waiting until the patient develops known vulnerabilities in cognitive performance is no longer acceptable. Given the high demands on the patient and their families during treatment however, requires the researcher and service provider team to be creative, flexible, and knowledgeable regarding the patient's medical treatment regimen.

Interventions that have been developed specifically to offset language and reading impairments in several pediatric populations are now commercially available and warrant exploration with children undergoing treatment for medulloblastoma. One such commercially available intervention program is called Fast ForWord, developed by a group of scientists and now distributed by Scientific Learning Corporation, Oakland, California. The Fast ForWord program is a computer-based training system developed in response to scientific research on the development of reading ability and reading deficits. By using a game-like format that incorporates modified speech, these software programs seek to rapidly improve language, reading, and learning skills through an intensive training schedule and adaptive programming. After the completion of several laboratory trials, the effectiveness of the Fast ForWord programs was tested with

500 children (4–14 years old) who were receiving speech and language services from 60 speech and language professionals at 35 sites (Tallal et al., 1996). Pre- and post-intervention standardized testing revealed that the children's skills of receptive and expressive speech and language had significantly improved. The generalizability of these findings was affirmed by results of a study of children who had specific language disorders in addition to other comorbid conditions such as attention deficit disorder and pervasive developmental disorder (Tallal, Merzenich, Miller, & Jenkins, 1998). All children experienced significant improvements on tests of language development and reading following intervention.

Imaging studies, evaluating the functional response to the Fast ForWord intervention, were also conducted (Temple et al., 2003). Following the intervention period, children diagnosed with dyslexia showed improved reading performance and oral language skills. In addition, activity increased in their occipitotemporal area during a simple phonologic task (i.e., letter rhyming). Activity patterns within the temporoparietal and inferior frontal areas also increased to levels comparable with nonimpaired control subjects. These studies show that behavioral interventions can improve reading performance in children with deficits and that fMRI is a useful method for investigating the neural correlates of response to intervention.

Adaptations in the patient's learning environment, combined with cognitive rehabilitative programs, may provide the maximum gains in outcome (Butler & Mulhern, 2005). For example, while it has been found that survivors of medulloblastoma have impaired memory retrieval, their ability to recognize material was less impaired (Nagel et al., 2006). This has important implications for the patient's classroom settings. These children should not be given essay or short answer format tests. These types of tests highly depend on having intact retrieval ability. Since these children have been found to have retrieval deficits, they would be placed at a disadvantage, especially compared with their healthy peers. Rather, these children should be given tests in true/false and multiple-choice formats. This will help these patients access information using a recognition strategy, improving academic outcome. Similarly, mnemonic strategies that utilize recognition skills such as reminder lists may prove helpful in activities of daily living. Clinical examination of these low-cost adaptations within the school environment could prove valuable to the survivors of childhood cancer.

The need to establish cost-effective and evidenced-based intervention programs is critical to utilizing limited health care resources in the most efficient manner possible. Costs of providing an intervention program can include service professional salaries, facility expense, overhead costs such as utilities and cleaning, or even expenditures related to patient travel to and from the intervention location. Outcomes can range from a specific target behavior of the patient, health-related quality of life, reduction in future service utilization following the intervention, to overall patient satisfaction. Clinical significance should also be considered along with statistical significance when evaluating outcomes of intervention trials. Small subject pools may prohibit establishing statistically significant change, while evaluation of clinical significance, an evaluation of practical meaning to the patient, may illuminate important benefits. In addition, disability does not just affect the patient. Assessment of caregivers and family members are important components to also consider when evaluating the success of an intervention program. Combining and summarizing these components of an intervention program can be completed in the context of cost-consequences analysis (Gage, Kaye, Owen, Trend, & Wade, 2006). This approach could provide researchers and administrative decision-makers detailed descriptions of multiple outcomes from several perspectives to aid in the allocation in health care dollars.

Conclusions

This review has attempted to highlight salient issues relevant to understanding the cognitive impact on children treated for medulloblastoma. While a valiant effort by the physicians who medically treat these children have resulted in contemporary protocols aiming to reduce neurotoxicity of treatment, more work is needed on counteracting the deficits in cognitive performance often experienced following treatment. Declining IQ and academic struggles may be predated by difficulties with attention, memory, and processing speed. Studies utilizing MRI have demonstrated disruption to white matter integrity and utility. Studies aimed at identifying mechanisms of CNS damage and the relation to performance are promising and deserve further investigation. More clinical trials directed at treating and preventing neurocognitive late effects are also needed, and these trials must include an assessment of economic cost and defined benefits to the patients and their caregivers. The discovery and validation of effective

interventions will facilitate the achievement of the definitive goal for survivors of medulloblastoma, ensuring an independent and fulfilling quality of life.

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