INTELLIGENCE AND ACADEMIC ACHIEVEMENT IN TEN-YEAR SURVIVORS OF CHILDHOOD MEDULLOBLASTOMA

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Advances in the treatment of childhood medulloblastoma have markedly increased survival rates in recent decades. Although survival rates have improved, research has demonstrated that significant cognitive consequences are common in patients who have survived medulloblastoma. Few studies exist that examine the extent of long-term cognitive impairment as far as 10 years after treatment. The present pilot study examined the intellectual and academic achievement in a sample of 16 ten-year survivors of childhood medulloblastoma treated with surgery and craniospinal radiation. In addition, the relationships between the medical variables of age at treatment and dose of

craniospinal radiation and cognitive and academic functioning were explored. The sample demonstrated significant cognitive impairment on measures of intellectual functioning and three measures of academic achievement. The academic domains that were most severely impaired were writing skills and practical math problem solving. The majority of participants demonstrated impairment in at least one domain of academic achievement, but the extent of achievement problems was underestimated when applying the traditional discrepancy model, in which an achievement score must be at least 15 points below the intelligence score to represent a learning disability. Age at treatment and dose of craniospinal radiation were not associated with performance on measures of intelligence and academic achievement in the present study; however, the small sample size may have limited the ability to detect significant results among these variables. The results of the present study demonstrate significant impairment in intellectual functioning and academic achievement in ten-year survivors of childhood medulloblastoma.

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CHAPTER I: INTRODUCTION

Data gathered by the National Cancer Institute indicate that brain tumors have surpassed acute lymphoblastic leukemia in recent years to become the most common form of childhood cancer (Zakhary, Keles, Aldape, & Berger, 2001). Medulloblastoma is classified as an infratentorial primitive neuroectodermal tumor (iPNET) that presents most commonly in childhood (Johnson & Latchaw, 1990). These tumors are the most frequent type of childhood malignant brain tumor, accounting for 10% to 20% of all primary central nervous system tumors and 40% of all posterior fossa tumors (Kiltie, Lashford, & Gattamaneni, 1997; Palmer et al., 2003). The survival rate for medulloblastoma was formerly very low, with studies in the 1930s reporting a survival rate of 1 out of 61 children (1.6%) at three years post-treatment (Cohen & Duffner, 1994). Studies performed within the past decade report survival rates reaching approximately 60% to 70% at five years post-treatment (Del Charco et al., 1998; Dennis, Spiegler, Hetherington, & Greenberg, 1996). The dramatic rise in survival rate is attributed to advancements in treatment of medulloblastoma. Radiation therapy contributes substantially to the improved survival rate and cure of these neoplasms.

While advances in treatment have made survival probable, significant sequelae frequently result which negatively impact the quality of life for survivors of medulloblastoma. Children who undergo radiation therapy are at increased risk for neurologic, neuroendocrine, and neuropsychological impairments (Mulhern et al., 1998) as well as social isolation and secondary cancers (Helseth, Due-Tonnessen, Wesenberg, Lote, & Lundar, 1999). Significant cognitive deficits have been documented in children treated for medulloblastoma, and these deficits are attributed primarily to whole-brain radiation (Packer et al., 1989). Factors such as younger age at time of radiation treatment, dose of radiation, and perioperative factors are associated with increased risk of neuropsychological and neurological sequelae (George et al., 2003; Mulhern et al., 1998; Palmer et al., 2003).

This pilot study was conducted as part of a larger study which examined the long-term cognitive sequelae and quality of life outcome in children who survived medulloblastoma for ten years or more (Bergeron, 2001). The purpose of this pilot study is to examine the intellectual functioning and academic achievement among a sample of 10-year survivors of childhood medulloblastoma. Age at radiation treatment and dose of radiation also were examined. Previous research demonstrates that among children treated for cancer, central nervous system (CNS) radiotherapy (specifically whole-brain radiotherapy) in combination with chemotherapy produces long-term deleterious effects in cognitive functioning when measured from three to seven years post-treatment. Reports of these impairments vary in the literature and include decrease in Full-Scale IQ, academic achievement, memory and attention, motor function, and problem solving (Dennis, Spiegler, Hetherington, & Greenberg, 1996; Johnson et al., 1994; McCabe, Getson, Brasseux, & Johnson, 1995). Studies examining these variables as far as ten years post-treatment are scarce as most long-term studies to date follow participants a maximum of five to six years post-treatment.

This study examined the intellectual functioning and academic achievement of survivors during young adulthood, a period of development when impairment in these domains critically affects an individual's educational and vocational potential. Given the lack of studies that examine these factors together as far as 10-years post-treatment, this study was designed to further elucidate the potential long-term effects of medulloblastoma treatment during childhood. The following section will describe the nature of medulloblastoma in addition to relevant factors related to typical treatment methods for the disease.

CHAPTER II: REVIEW OF THE LITERATURE

Medulloblastoma

Disease Characteristics

Bailey and Cushing defined medulloblastoma as a separate tumor in 1925 based on the belief that the tumor was comprised of embryonal stem cells with a pluripotential nature (Cohen & Duffner, 1994). The tumor commonly infiltrates the fourth ventricle of the brain and develops in the vermis or midline of the cerebellum (Deutsch, 1990). These tumors have specific biologic and histopathologic features including differentiation along varying cell lines. The prognostic importance of cell differentiation within the tumor remains unclear, as some studies report lack of differentiation to be favorable to prognosis while others report the opposite (Cohen & Duffner, 1994). Medulloblastoma was later pathologically divided into two categories called classical and desmoplastic. Classical medulloblastoma refers to a diffuse cellular tumor consisting of small round cells with very little cytoplasm which most commonly originates in the vermis of the cerebellum (Zakhary et al.). The classic tumor consists of small, undifferentiated cells. This is the most common type of medulloblastoma and approximately 80% of those diagnosed present with this type. Desmoplastic medulloblastomas are nodular tumors that have centers of dark cells that surround lighter islands (Zakhary et al., 2001). The desmoplastic tumor typically has a better prognosis in children than the classic tumor type. Prognostic factors include extent of disease at diagnosis, age, and certain histologic characteristics. Regarding extent of disease at diagnosis, it is common for up to 50% of patients with medulloblastoma to have additional tumor separated from the primary site. This is indicative of worse prognosis. In addition, factors including tumor size larger than three centimeters in diameter, local invasion, and neuraxis or systemic metastasis also indicate worse prognosis (Schold et al., 1997).

Common symptoms associated with medulloblastoma include headache, vomiting, and ataxia (Packer, Hoffman, Friedman, Kun, & Fuller, 1996). These symptoms typically result from hydrocephalus, which develops as the tumor mass obstructs the flow of cerebrospinal fluid through the ventricles. Studies report vomiting in at least 80% of newly diagnosed patients with medulloblastoma, and headache is reported in 70% (Deutsch, 1990). Other common symptoms include vertigo, papilledema, diplopia, cranial nerve palsies, head tilt, and seizures (Schold et al., 1997). Patients usually have these symptoms for less than six months, with the majority experiencing symptoms for less than two months prior to diagnosis. The most common diagnostic screening methods for medulloblastoma include computerized tomography (CT) and magnetic resonance imaging (MRI). Before the development of these tools, invasive techniques for diagnosis were utilized, such as air ventriculography and angiography, which had higher associated risk factors (Cohen & Duffner, 1994).

Treatment

Surgery. The typical treatment protocol for medulloblastoma includes three components: surgery, radiation, and chemotherapy. Improvements in these treatment methods are responsible for the increase in survival rate from no chance for survival to approximately 60 to 70 % at five years (Del Charco et al., 1998). The first form of treatment for medulloblastoma is surgery. Total resection is performed whenever it is possible without inducing damage to neural functioning. It is essential to remove as much of the tumor as possible because subsequent chemotherapy and radiation will be more effective with smaller amounts of remaining tumor, and mortality rates from total resection of medulloblastoma are low. Different survival rates correspond to different amounts of surgical resection. Total resection is not possible when the tumor also invades the brain stem, which results in less favorable prognosis. However, it is not known whether this is due in part to the remaining tumor

left behind after surgery or to the more aggressive nature of this type of unresectable tumor (Schold et al., 1997).

Techniques such as preoperative shunting to relieve hydrocephalus, corticosteroids for edema, and imaging techniques such as CT scans have greatly decreased postoperative complications and decreased the mortality rate exponentially over the past 50 years. It is estimated that between 30% to 50% of children with posterior fossa tumors require a shunt for hydrocephalus (Packer et al., 2002). Studies have reported that specific perioperative factors are strongly associated with long-term neuropsychological impairments such as decline in IQ and cognitive functioning. These factors include neurological deficits, meningitis, subdural fluid collections, and repeat craniotomy. Additional perioperative factors include hemorrhage and prolonged obtundation, or decreased consciousness (Kao et al., 1994).

Radiotherapy. The radiation protocol for medulloblastoma includes radiation of the tumor in addition to radiation of the entire cranium and spine (CS/RT). This protocol is utilized due to the tendency for malignant cells to travel through the cerebrospinal fluid (Packer et al., 2002). Significant improvement in survival of medulloblastoma patients was not achieved until the use of systematic craniospinal radiotherapy with posterior fossa doses of 50 Gy or more and spinal cord doses of 30 Gy or more (Helseth et al., 1999). In the 1960s the typical radiation protocol included doses of less than 40 Gy to the posterior fossa and 30 Gy to the spinal cord. Cohen and Duffner (1994) report recent recommendations to include 45 to 55 Gy to the posterior fossa, 40 to 45 Gy to the whole brain, and 35 to 40 Gy to the spinal cord. Schold et al. (1997) reported similar recommended ranges including 55 to 60 Gy to the posterior fossa and 24 to 40 Gy to the rest of the brain and spinal cord, emphasizing that the dose administered to the whole brain is often higher than that given to the spine. This current dosage protocol is reaching the maximum tolerable level, and

further increases in cure and survival rate are not expected to come from radiotherapy (Cohen & Duffner, 1994).

Although radiation therapy has increased survival rates the treatment often results in significant costs to health and cognitive functioning. Numerous long-term physical and neuropsychological problems have been identified subsequent to craniospinal radiation treatment. These long-term effects are specifically prevalent in children treated under the age of five. The protocol for very young children is to treat with lower doses of radiation to minimize physical and neuropsychological effects (Deutsch, 1990). Kiltie, Lashford, and Gattamaneni (1997) found that C/S RT in children under three had a deleterious effect on growth due to spinal shortening, growth hormone deficiency, premature puberty, and hypothyroidism at ten years post-treatment. Numerous additional studies cite endocrine dysfunction as a result of C/S RT (Dennis et al., 1996; Helseth et al., 1999; Vijayakumar, & Muller-Runkel, 1985). In a review article, Vijayakumar and Muller-Runkel found sequelae including growth retardation, thyroid deficiency, sterility, marrow suppression, immunological alterations, second malignancies, and pituitary hormonal deficiencies to be common in long-term medulloblastoma survivors. Neuropsychological deficits found in patients treated with radiation include impairments in intellectual functioning, academic achievement, and other cognitive abilities (Roman & Sperduto, 1995).

Chemotherapy. Advances in chemotherapy may hold a key to increasing survival for medulloblastoma patients at 10 years and beyond, as radiotherapy treatment dosage has reached a maximum tolerable level in treatment. Use of chemotherapy as adjuvant therapy for treatment of recurrent tumors in medulloblastoma has become common. (Cohen & Duffner, 1994). Cohen and Duffner indicate that medulloblastomas are typically good candidates for chemotherapy due to their rapid growth rate, high mitotic index, location, and close proximity to the ventricular cavity and subarachnoid space. The positive effect of chemotherapeutic agents such as intrathecal methotrexate

and intravenous vincristine in treating CNS tumors was first reported in the early 1960s (Cohen & Duffner, 1994).

The use of chemotherapy in the treatment of newly diagnosed pediatric brain tumors is a fairly recent addition to surgery and radiation. Use of this treatment protocol has occurred regularly for only the past two decades, due to the limitation of available drugs that were capable of effective penetration of the blood-brain barrier of the central nervous system. Studies have not produced consistent results regarding the effectiveness of chemotherapy in treating medulloblastoma. Packer et al. (2002) described three large randomized trials that examined the effects of adjuvant chemotherapy on advanced medulloblastoma. These studies depicted only moderate success in treating the disease; however, Packer et al. indicated that each of these studies had methodological flaws such as inclusion of improperly staged patients and ineffective medications. Packer emphasized that other studies have confirmed the benefits of agents such as cisplatin, cyclophosphamide, and melphalan in treating medulloblastoma. One study with robust findings was conducted by Packer et al. (1999) and utilized a treatment protocol of 23.4 Gy of CS/RT with combined post-treatment chemotherapy, which included CCNU, vincristine, and cisplatinum. They found an 80% disease-free survival rate 3 years post-treatment.

Various combinations of chemotherapeutic agents are under study, as the best combination is different according to each patient's risk factors. While deleterious cognitive effects of radiation therapy, particularly in younger children with higher doses of CS/RT, have been demonstrated, the relationship between chemotherapy and cognition is not clearly understood. In a review and meta-analysis, Cousens, Waters, Said, and Stevens (1988)

indicated that among childhood cancer survivors, those treated with combination therapy typically demonstrate greater cognitive deficits than children treated solely with chemotherapy. Anderson, Godber, Smibert, and Ekert (1997) examined the neuropsychological performance of survivors of childhood acute lymphoblastic leukemia treated with CS/RT and chemotherapy, and survivors of other childhood cancers treated only with chemotherapy. They found that children treated with combination therapy attained lower intelligence scores and demonstrated poorer academic achievement than those subjects treated with chemotherapy alone. The combined group also depicted deficits in information processing and attention. The chemotherapy group performed no differently than controls on any of these measures; however, they demonstrated subtle weaknesses for the registration of new information, compared with controls. Although the cognitive impact of chemotherapy treatment in childhood is not fully elucidated, it appears chemotherapy is associated with subtle deficits, while radiation therapy is associated with more significant impairments. Further study is warranted to further clarify the type and extent of cognitive outcome after combination surgery, radiation, and chemotherapy in children with medulloblastoma.

Intellectual Functioning in Childhood Medulloblastoma Survivors

Glauser and Packer (1991) found that 40-100% of long-term survivors of childhood brain tumors develop some form of cognitive dysfunction. Prior to the early 1980s, cognitive deficits were assessed through general accounts of school performance, presence or absence of "mental retardation," and assessments of daily functioning (Glauser & Packer, 1991). These early studies were typically retrospective and uncontrolled, and often included multiple tumor and treatment types. Assessments of cognitive deficits were based on global

descriptions of functional abilities and often reported less than 10% of long-term survivors were severely disabled (Glauser & Packer, 1991).

During the late 1970s and early 1980s, researchers began to include standardized measures of intelligence, such as the Wechsler Intelligence Scale for Children – Revised (WISC-R; Wechsler, 1974), and the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981), to assess cognitive performance among brain tumor survivors. The literature from the late 1970s to date suggests that radiation negatively affects intellectual functioning in medulloblastoma survivors. However, few studies exist which explore the impact on survivors' intelligence as far as 10-years post-treatment. A review of the literature on intellectual functioning in childhood medulloblastoma survivors follows.

Intelligence

An early study by Hirsch, Renier, Czernichow, Benveniste, and Pierre-Kahn (1979) examined cognitive deficits in 26 long-term survivors of medulloblastoma. Patients received 50 Gy of radiation to the posterior fossa and 35 Gy to the whole brain, in addition to chemotherapy. Results indicated 31% of medulloblastoma patients had FSIQ in the mentally impaired range (< 70), 58% had IQs below average (< 90), and only 11% demonstrated average or above average FSIQ scores at 5-years post-radiation. The medulloblastoma patients were compared to a group of astrocytoma patients who underwent surgery but did not undergo radiation therapy. Nineteen percent of the astrocytoma patients had IQ scores below 70, 19% demonstrated scores between 70 and 90, and 62% had average or above average FSIQ scores. The study gave evidence to suggest that CS/RT has a detrimental impact on cognition.

Findings by Duffner, Cohen, and Thomas (1983) support the evidence of Hirsch et al. (1979). Duffner et al. (1983) examined a group of 10 patients with posterior fossa tumors (medulloblastoma, n = 6) treated with combination radiation and chemotherapy. The average follow-up interval was approximately 3.5 to 4 years. Of the medulloblastoma patients, 50% (n = 3) had IQ scores < 80 at follow-up. Three medulloblastoma patients were tested prior to radiation, and their IQ scores decreased between 21 and 27 points between pre-test and follow-up, demonstrating dramatic decline. Riva, Pantaleoni, Milani, and Belani (1989) examined IQ in addition to the domain of attention in medulloblastoma (n=8) and sibling controls at an average follow-up interval of 5 years. Results demonstrated significant impairment in FSIQ, verbal and performance estimates of IQ, and attention, compared to controls.

Hoppe-Hirsch et al. (1995) also found evidence for progressive decline in intellectual functioning among survivors of childhood medulloblastoma. Their study included 59 children treated for medulloblastoma who received whole-brain radiation ranging from 25 Gy to 35 Gy, in addition to irradiation of the posterior fossa ranging from 45 Gy to 55 Gy post-surgery. They were compared to a cohort of 37 children who received surgery and focal radiation for posterior fossa tumors. Patients were tested at 1, 2, 5, and 10 years post-treatment. At one year post-treatment, no significant differences in IQ were found between the two groups. However, at 5-year follow-up, 20% of the medulloblastoma patients had IQ scores above 90, and only 10% scored above 90 on IQ tests at 10-year follow-up. Conversely, in the comparison group, 60% of participants maintained IQ scores above 90 at the 5 and 10-year follow-up sessions. While the results appear dramatic, a possible limitation

in this study may ultimately reduce the marked differences among reported percentages. The authors fail to provide total number of subjects per group for each of the follow-up testing periods (1 year, 5 years, and 10 years). The median length of follow-up was 5 years in both groups.

The literature clearly indicates that intellectual declines are common for medulloblastoma patients treated with CS/RT. Furthermore, younger ages at treatment and higher radiation dose are factors that appear to influence intellectual decline. A review of the literature on the relationship between these risk factors and intelligence among childhood medulloblastoma survivors follows.

Age at Radiation and Intelligence. Many studies have found evidence to suggest that age at time of irradiation in children with medulloblastoma is a significant medical risk factor associated with deterioration in cognitive functioning over time (Hoppe-Hirsch et al., 1990; Johnson et al., 1994; Roman & Sperduto, 1995; Silber et al., 1992). In a study assessing quality of long-term survival in medulloblastoma, Johnson et al. (1994) reported that children treated under the age of 3 have a significantly larger decrease in IQ at 5 years post-treatment (mean IQ of 65) than children treated over the age of three (mean IQ of 80). In addition, mean verbal and performance intelligence scores and achievement scores were higher in children treated over the age of three, although these results did not reach statistical significance. Similar results were found by Silverman et al. (1984) in a study comparing nine medulloblastoma survivors treated with CS/RT to healthy siblings. Patients had survived the disease for three years or longer. They found that patients treated at younger

ages, particularly under age eight, demonstrated the greatest decline relative to their siblings, while those treated at older ages showed little difference from sibling scores.

In a prospective study by Ellenberg et al. (1987), 43 children with brain tumors were followed for two IQ assessments, the last of which was at least three years post-treatment. They determined radiation therapy had a significant impact on subsequent cognitive deterioration. Age of the child was found to be inversely related to the severity of the treatment effects; however, they also found a trend toward IQ loss in older children (over seven years) who received CS/RT. There were no cognitive deficits reported for children receiving local radiation.

Similarly, Fossen, Abrahamseen, and Storm-Mathisen (1998) performed a study assessing the cognitive and psychosocial functions of 16 children with brain tumors and used a group of 15 nonirradiated acute lymphatic leukemia (ALL) patients as controls, and found a relationship between age at radiation and cognitive decline. The mean Full Scale IQ (FSIQ) of the brain tumor group was 78, with 50% of the sample falling below a FSIQ of 80. The nonirradiated ALL patients had a mean FSIQ of 109, which was significantly higher than brain tumor patients. Their results demonstrated that children under the age of four at time of radiation had the lowest psychomotor speed scores and IQ scores.

In a long-term study of 22 survivors of medulloblastoma, Mulhern et al. (1998) examined the effects of standard radiation dose and age at diagnosis on subsequent cognitive function and achievement. They found that children who were diagnosed and treated at a younger age (< 9) with radiotherapy had lower IQ on the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) or Wechsler Adult Intelligence Scale-Revised (WAIS-R),

at a median of 8.2 years at follow-up. Estimates of Verbal IQ, Performance IQ, Full-Scale IQ, and Attention Index were found to be in the low average range compared to the general population.

Alternatively, Hoppe-Hirsch et al. (1990) recognized the lack of studies in the literature that followed patients as far as 10-years post-treatment. They conducted a study at the Hôpital des Enfants-Malades in Paris which examined the intellectual functioning in a small group of medulloblastoma survivors 10 years after radiation. They found that 5 years after treatment, 58% of 55 patients had an IQ above 80. At 10-year re-evaluation, 13 patients were retested, and only 15% had an IQ above 80. Age at radiation was an important factor in their study as they found that the lower the age of treatment the lower the IQ scores. At the 10-year assessment period, only 33% of children (3 out of 13) treated between the ages of 6 and 10 had IQ scores over 80. Of those between the ages of 3 and 6, 17% had IQ scores over 80, and of those treated under the age of 3, none maintained an IQ above 80. The findings demonstrated a dramatic decrease in IQ from the 5 to 10 year follow-up period and provided convincing evidence that IQ deterioration was progressive in their sample. However, there was a large difference in the number of individuals tested at 5-year and 10-year follow-up intervals, which may have contaminated the results. Studies that follow medulloblastoma survivors for at least 10 years are needed to further confirm the findings.

A recent study by George et al. (2003) examined intelligence and memory in a group of 15 children with posterior fossa tumors (medulloblastoma, n = 11; astrocytoma, n = 4) at an average follow-up interval of 3.5 years. Regarding intelligence, the authors examined FSIQ in addition to Verbal IQ (VIQ) and Performance IQ (PIQ). Through stepwise

regression, they found that age at diagnosis contributed significantly to the variability in IQ scores. They divided children into groups: < 6 years of age (n = 6) and ≥ 6 years of age (n = 9), and all three IQ estimates were significantly lower for the younger group. No significant differences were found between VIQ and PIQ scores. Memory analyses demonstrated that the overall memory scores of the patient group were significantly lower than normative means. Age at diagnosis did not show a significant relationship with IQ scores, possibly due to limitations in power due to variability in the older age group.

Although the majority of studies examining childhood medulloblastoma found a significant relationship between age at treatment and subsequent decline in cognitive function, at least two studies found no evidence to suggest a relationship. In a review article conducted by Mulhern, Hancock, Fairclough, and Kun (1992), younger age at diagnosis/treatment was related to lower post-treatment intellectual functioning in 8 of 10 studies reviewed. They cite two studies which did not find a significant relationship. The first was conducted by Kun et al. (1983) (as cited in Mulhern et al., 1992), and although no correlation was found between age at treatment and subsequent intellectual functioning, deficits in attention were determined to be significantly more common in younger patients. The second study, conducted by Kun and Mulhern (1983), also failed to find a relationship between age at treatment and long-term intellectual functioning. These conflicting findings have been explained by differences in sample selection criteria which create systematic biases, small sample sizes yielding diminished statistical power, differences among assessment tools, and methods of assignment to treatment groups (Mulhern, Fairclough, & Ochs, 1991).

Similarly, Walter et al. (1999) conducted a study at St Jude Children's Research Hospital with 29 medulloblastoma patients diagnosed under the age of four, and did not find a correlation between age at radiation and follow-up IQ scores. The treatment protocol for all children was to delay the initiation of radiation for one to two years with chemotherapy, to attempt to decrease the long-term cognitive impact. Patients were assessed with standardized measures of intelligence appropriate for their age, and testing occurred at yearly intervals following radiation for a minimum of five years post-treatment (median follow-up period = 4.8 years). Results indicated that FSIQ scores decreased significantly following radiation. The median baseline FSIQ value was 88 (range 50-111) and the median baseline FSIQ at median follow-up of 4.8 years post-treatment was 62 (range 44 to 86). The authors do not address potential reasons for the relatively low median baseline FSIQ, although it is possible that the value reflects decline related to surgery and chemotherapy. The results yielded an IQ point decline of 3.9 per year, and all children were enrolled in special education classes at the last follow-up. They compared the performance of children treated prior to 36 months of age to those treated after and found no significant differences. Despite attempts to reduce long-term cognitive effects by forestalling irradiation with chemotherapy, the IQ scores decreased dramatically overtime, with the median falling in the mentally deficient range of functioning.

Radiation Dose and Intelligence. In addition to age at radiation treatment, dose of radiation has been explored to determine its role in cognition among survivors. Numerous studies suggest a relationship between larger doses of C/S RT therapy and greater long-term deterioration in intellectual and cognitive functioning (Ellenberg et al., 1987; Grill et al., 1999; Hoppe-Hirsch, 1990; Riva, Pantaleoni, Milani, & Belani, 1989; Silber et al., 1992;

Spunberg, Chang, Goldman, Auricchio, & Bell, 1981) while some studies did not (Dennis et al., 1996; Johnson et al., 1994).

Silber et al. (1992) conducted a study that found a relationship between CS/RT dose and cognitive impairment. They studied the influences of C/S RT dose and age at treatment on neuropsychological functioning in 48 patients treated for in childhood ALL and PNET (primitive neuroectodermal tumor, which encompasses cerebral neuroblastoma, pineoblastoma, and medulloblastoma). ALL patients were treated with whole brain radiotherapy with doses of 18 Gy or 24 Gy, and PNET patients were treated with 18 Gy, 22 Gy to 24 Gy, or 32 Gy to 40 Gy. Patients were given an IQ test close to time of diagnosis and then again at least two years later. They utilized a linear regression model to analyze IQ scores, dose of C/S RT, age at treatment, and several other variables. They found patients who received the higher doses of 32 Gy to 40 Gy scored an average of 12.3 points less on an IQ test than those who received 18 Gy. Those who received 36 Gy scored an average of 8.2 points below those who received 24 Gy on average. The results demonstrate that initial IQ, age at radiation, and dose are all significant factors in prediction of IQ decline.

Additionally, Grill et al. (1999) examined long-term intellectual functioning in relation to radiation doses and volumes with a group of 31 children treated with radiation for posterior fossa tumors. The mean interval between age of treatment and time of follow-up was 5.3 years (SD = 3.3 years). They divided the patients into three groups according to craniospinal irradiation doses (0 Gy, 25 Gy, and 35 Gy). The group that did not receive CS/RT received only local posterior fossa radiation. The results showed that all groups had an overall decline in cognitive function. More importantly, they found a significant

correlation between Full Scale IQ and CS/RT dose. For the 0 Gy group, the average FSIQ was 84.5 (SD = 14.0); the 25 Gy group had an average FSIQ of 76.9 (SD = 16.6); and the 35 Gy group had an average FSIQ of 63.7 (SD = 15.4). In addition, the Verbal Comprehension scores were also inversely correlated with dosage. They cited the C/S RT dose as the main risk factor for impaired intellectual outcome and academic decline. Keiffer-Renaux et al. (2000) included more detailed testing and found greater neuropsychological impairment in a group of 36 children treated with surgery, radiation, and chemotherapy for medulloblastoma. Children received either standard CS/RT (SRT) (35 Gy, n = 13) or reduced CS/RT (RRT) (25 Gy, n = 23). The mean follow-up interval was 4.3 years post-treatment. Results demonstrated that the SRT group performed significantly worse than the RRT group on measures of FSIQ (mean score 70 vs 82, $p = 0.07$), performance IQ (67 versus 78, $p = 0.07$), fine motor function of the dominant hand, and verbal fluency.

Johnson et al. (1994) did not find a relationship between late cognitive effects and CS/RT dose in a study with 13 medulloblastoma patients. They recognized the need for more extensive evaluation of neuropsychological functioning over a longer follow-up duration. Patients in their study were tested at least 5 years post-radiation. They included 7 patients that were ≥ 10 years post-treatment and 6 patients who were 5 to 10 years post-treatment at time of testing. Patients received whole brain CS/RT ranging from 25 Gy to 45 Gy in addition to tumor site radiation ranging from 41 Gy to 56 Gy. They found no association between dose and neuropsychological outcome. In addition, there was no indication that irradiation was related to progressive intellectual decline. Survivors of more than ten years actually scored higher on tests of achievement, measured by the Wide Range

Achievement Test – Revised (WRAT-R; Jastak, Wilkinson, & Jastak, 1984). However, the authors indicate these results may be suspect due to the retrospective nature of the study, restricted variance of radiation therapy, and small sample size. Similarly, Dennis et al. (1996) examined 25 medulloblastoma survivors. Results showed that age at diagnosis and time since treatment were each predictive of cognitive status in survivors of medulloblastoma, but no radiation dose effects were reported.

The majority of the above studies suggest patients who received higher doses of CS/RT at younger ages (under age five on average) are at highest risk for intellectual decline. Children with ALL who received lower doses of radiation than brain tumor patients, or children with benign astrocytoma who were treated with surgery alone, typically comprised the control groups used in studies of intracranial neoplasms such as medulloblastoma. Children with medulloblastoma and other brain tumors have thus demonstrated greater cognitive decline than ALL due to the higher doses of CS/RT used in treatment of tumors.

Perioperative Factors and Intelligence. Perioperative factors associated with childhood medulloblastoma appear to have long-term consequences on cognitive functioning. These factors include the use of a shunt to treat hydrocephalus, meningitis, shunt infections, and repeat surgeries. It is not entirely clear which of the perioperative factors has a greater relationship to intellectual and cognitive decline over time, and different studies have found conflicting results (Glauser & Packer, 1991; Kao et al., 1994; Mulhern, Crisco, & Kun, 1983).

Kao et al. (1994) prospectively examined the impact of perioperative factors on IQ with 28 children treated for medulloblastoma. They conducted neuropsychological testing

before surgery and radiation, after completion of radiation, and at 1-year intervals following completion of radiation. They identified significant relationships between decline in IQ after treatment and adverse perioperative factors including neurologic deficits, meningitis, shunt infections, and repeat surgery. Sixteen of the 28 children presented with at least one or more of these factors, and 13 of the 16 (81%) demonstrated significant decline in FSIQ. Also important was the finding that 43.8% of these children sustained decreases of 20 IQ points or more. Of the remaining 12 children who had none of these adverse factors, only three showed significant decrease in FSIQ, and the largest decline was 13 points. Kao et al. concluded that perioperative complications may account for some of the decline in cognitive and intellectual functioning found in children with medulloblastoma, as the presence of these factors is associated with greater risk of decline in IQ.

A study by Chapman et al. (1994) lends further support to the relationship between perioperative factors and cognitive outcome. They examined the neuropsychological outcome of long-term survivors of posterior fossa tumors. They quantified and summed the following relevant perioperative factors: location of tumor, obtundation at presentation, hydrocephalus at presentation, extent of surgical intervention, and postoperative complications. Chapman et al. concluded that the perioperative summary score was as strongly associated with poor neuropsychological outcome as age at diagnosis. In addition, earlier age at diagnosis was associated with higher perioperative scores, although this association was not statistically significant. Factors contributing to the perioperative score, which were associated with younger age at diagnosis, included higher prevalence of

obtundation at presentation, hydrocephalus, and surgery involving structures outside the vermis.

In a review article by Glauser and Packer (1991), several studies indicated conflicting results regarding the impact of various perioperative and medical factors on intellectual decline. A prospective study by Ellenberg, McComb, Siegel, and Stowe (1987) examined the effect of hydrocephalus on subsequent cognitive performance. Thirty-two patients, 21 with hydrocephalus and 11 without, underwent IQ testing within 1 month of diagnosis, 3 months after initial testing (approximately 1 month after radiation therapy), and at subsequent 6 month intervals for up to 4 years. Patients with hydrocephalus were divided into two groups: those with severe hydrocephalus which required shunting, and those not requiring a shunting due to resolution of hydrocephalus after tumor resection. The groups did not differ on mean IQ scores at initial testing; however, those requiring shunts had a higher mean IQ at 4 months post-diagnosis than the non-shunted group and demonstrated a statistically significant 7.1-point gain in IQ over this period. The group that did not require shunts demonstrated a 4-point gain, which was not statistically significant. They concluded that patients with more severe hydrocephalus demonstrate initial depression of intellectual functioning and thus show earlier recovery of functioning than patients with less severe hydrocephalus (not requiring shunting). Johnson et al. (1994) also examined treatment variables associated with cognitive functioning in childhood medulloblastoma survivors through neuropsychological testing performed at least 5 years post-diagnosis. They determined children who underwent shunting for hydrocephalus had higher IQ and achievement scores than those not shunted. However, this difference was only statistically

significant for reading achievement. Further study is needed to examine the relationship between hydrocephalus, shunting, and cognitive outcomes.

Summary

The literature clearly illustrates that medulloblastoma survivors treated with radiation during childhood are at risk for intellectual decline following treatment. Younger age at treatment and higher dose of radiation are risk factors which appear to affect the extent of intellectual deterioration. However, the critical age and critical dose are not clearly elucidated. The majority of studies reviewed are based on small sample sizes with varied methodologies. Differences in factors such as age at patient diagnosis, baseline performance, and type of treatment make it difficult to compare studies. It appears that intellectual decline is progressive, although this issue is not fully understood. A recent study by Palmer et al. (2003) is the first to examine the pattern of intellectual decline over a 7-year period specifically within a population of 50 medulloblastoma patients treated with 35-40 Gy of CS/RT. Although prior evidence has suggested a linear model of IQ decline ranging from approximately 2 to 4 points per year (eg., Silber et al., 1992), Palmer et al. found a quadratic model of change in IQ dependent on age at diagnosis. Their model suggests the IQ values of older (> 8.17 years) and younger patients will thus ultimately meet. Older patients appeared to maintain baseline performance until 2 years post-treatment, and then slightly decline until 4 years when they begin a more rapid rate of decline. Younger patients, according to their model, immediately decline post-treatment and over time begin to plateau. The model is provocative and the first to suggest such a pattern.

The intellectual deficits that manifest among medulloblastoma survivors can cause serious consequences in education, vocation, and other quality of life factors. While many studies have documented intellectual decline in medulloblastoma survivors, few have examined this factor 10 years post-treatment. Even scarcer is literature that examines both intellectual function and academic achievement in this population. Existing studies utilize a brief measure of achievement rather than more comprehensive test batteries. A review of existing studies that examine academic achievement in survivors of childhood medulloblastoma follows.

Academic Functioning In Childhood Medulloblastoma Survivors

Academic achievement refers to skills children learn through direct teaching (Stetson, Stetson, & Sattler, 2001). Tests designed to measure academic achievement directly assess those acquired skills. Tests of academic achievement measure how well a child is understanding subject matter in school. When there is a significant discrepancy between a child's achievement and his/her overall intellectual potential, it suggests the possibility that the child has a learning disorder. The term learning disability (LD) can be used synonymously with learning disorder. According to the National Joint Committee on Learning Disabilities (as cited in Kavale & Forness, 2000) a current definition of LD states the following:

> Learning disabilities is a general term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These disorders are intrinsic to the individual, presumed to be due to central nervous system dysfunction,

> and may occur across the life span. Problems in self-regulatory behavior, social perception, and social interactions may exist with learning disabilities but do not by themselves constitute a learning disability. Although learning disabilities may occur concomitantly with other handicapping conditions (for example, sensory impairment, mental retardation, serious emotional disturbance) or with extrinsic influences (such as cultural differences, insufficient or inappropriate instruction), they are not the result of those conditions or influences. (p. 245)

Thus, LDs interfere with an individual's ability to learn and acquire skills that are necessary for success in school and work. Identification and appropriate intervention can help individuals learn ways to adapt and succeed. There is debate regarding the most appropriate means of assessing LD, but the most common method is to quantify discrepancy scores between measures of academic achievement and intellectual potential. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; 1994), learning disorders in reading, mathematics, and written expression are diagnosed when achievement scores are substantially below the expected level given the person's age, measured intelligence, and education level. The DSM-IV indicates that "substantially below" typically refers to more than two standard deviations between achievement and intelligence scores, although they cite that often a smaller deviation of between one and two standard deviations is also used. There is significant controversy in diagnosing LD and in using current discrepancy scores between achievement and intelligence. Perhaps the most relevant problem with respect to diagnosing LD in medulloblastoma survivors is the fact that IQ is often impaired in these individuals, due to the major medical disorder and treatments

the patients underwent. The disease itself may minimize the likelihood of detecting a discrepancy between achievement and IQ, resulting in failure to detect LD and subsequent failure to intervene or qualify for special services. Thus, it is critical to examine academic achievement in addition to intellectual functioning in survivors of childhood medulloblastoma. A review of studies that have included measures of academic achievement follows.

An early study by Danoff, Cowchock, Marquette, Mulgrew, and Kramer (1982) evaluated a mixed group of 38 pediatric brain tumor patients with intelligence and academic achievement tests. There was variability in the types of tumors included in the group, and only five patients were medulloblastoma survivors. Other tumor types included the following: ependymomas, pinealomas, craniopharyngiomas, pituitary adenomas, and astrocytic gliomas. The majority (n = 37) were treated with radiation, and none were treated with chemotherapy. The authors reported the ranges of radiation used to treat the tumor sites; however, they did not provide CS/RT levels. They tested the group with a Wechsler IQ test and the WRAT (Jastak & Jastak, 1978) at an average follow-up interval of 9 years. Results demonstrate that the majority of the sample obtained follow-up IQ scores in the normal or above normal range (IQ $\geq$ 90). Unfortunately, the authors did not report or discuss achievement test results. These IQ findings and the medulloblastoma literature may not be discrepant, as the authors do not describe the IQ findings of the medulloblastoma group in isolation.

Another early study by Duffner, Cohen, and Thomas (1983) examined ten children with posterior fossa tumors treated with radiation and chemotherapy at least one year post-

diagnosis. Overall, 50% of patients demonstrated FSIQ scores less than 80. Four of the children with FSIQ scores greater than 80 required special classes due to learning problems. After controlling for the confound of motor impairments through neurological exam, the group demonstrated greater impairment in PIQ scores than VIQ scores, and the authors indicated the "discrepancy between verbal and performance aspects of intelligence testing have characterized the learning disabled child" (Duffner et al; p. 236). The authors suggested that this split in intellectual performance represents evidence of learning disabilities in the study population. They supported this evidence by adding that four of five participants with FSIQ scores greater than 80 had learning problems that required special education classes. They also assessed five group participants with the WRAT, but did not discuss the scores, nor did they use the outcomes to measure learning disabilities in the population.

Similarly, a study performed by Johnson et al. (1994) emphasized the necessity of assessing specific learning disabilities among childhood cancer survivors. They emphasized that the majority of prior studies used mainly FSIQ to examine the cognitive functioning of medulloblastoma survivors. Johnson et al. recognized the need to evaluate other measures of cognitive functioning such as academic achievement. They tested 13 long-term medulloblastoma survivors with an extensive neuropsychological test battery that assessed IQ, school achievement, and specific neuropsychological abilities. The follow-up interval was longer than five years post-treatment. They defined learning disabilities as a statistically significant discrepancy between achievement scores, measured with the WRAT-R, and "intellectual potential," assessed by the FSIQ score obtained on the WISC-R or WAIS-R. Achievement scores falling 15 points or more below the FSIQ were defined as a specific

learning disability. By those criteria, 38% (n = 5) of participants met the criteria for learning disabilities. Full-Scale IQ ranged from 41 to 89, with four participants scoring below 70. In addition, 57% were enrolled in special-education programs, 65% had repeated a year of school, 70% received a mean grade of "C" in school, and 78% admitted to problems with learning. Furthermore, intelligence and achievement scores were significantly higher in participants that received radiation after age three. There was no relationship between radiation dose and intellectual or academic performance in this study.

In a long-term study, McCabe et al. (1995) examined cognitive decline in 13 medulloblastoma patients at least 5 years post-treatment. Their comprehensive neuropsychological test battery included the examination of intellectual functioning with the WISC-R and WAIS-R and academic achievement with the WRAT-R. The results indicated the FSIQ of the sample ranged from the intellectual deficiency range to the low-average range (41-89). Performance IQ was significantly lower than VIQ for the majority of subjects. The most significant impairment was found in Arithmetic, Digit Span, Block Design, and Coding/Digit Symbol subtests. The "Freedom from Distractibility" factor was most impaired among the three factors of the test (Freedom from Distractibility, Verbal Comprehension, and Perceptual Organization). Full-Scale IQ was considered an invalid measure of intelligence in 31% of the subjects due to the discrepancy between PIQ and VIQ. On the WRAT-R, participants' obtained a median oral reading score of 71 (range 45-116), spelling median score of 66 (range 45-102), and arithmetic median score of 67 (range 45-101). Achievement scores were significantly worse than intelligence scores (more than one standard deviation) in 39% of participants, and those participants (5 of 13) met the

qualification for a specific learning disability based on federal regulations (McCabe et al., 1995).

Similarly, Seaver et al. (1994) also found significant impairment on a measure of academic achievement. Eighteen long-term survivors of childhood medulloblastoma (n = 12) or posterior fossa ependymoma (n = 6) who received CS/RT were evaluated with the WRAT-R. The tumor types were examined as a single group, rather than examined separately. Seventeen participants were given the WRAT-R, and borderline performance was found in reading recognition (mean = 75) and spelling (mean = 72). The group also demonstrated deficient arithmetic performance (mean = 66). Average performance was demonstrated by only five participants on the reading recognition section, and by four participants on the spelling and arithmetic sections. All 17 participants attended regular school rather than home schooling, but spent a mean of 41% of their education in special education classrooms.

Summary

In conclusion, evidence from the scarce literature available on academic achievement in medulloblastoma suggests that Full-Scale IQ does not depict the entire range of functioning in these children. Previous studies demonstrate medulloblastoma survivors show impairment across academic domains assessed by the WRAT, and also suggest that age of radiation treatment may impact academic performance later in life, with younger age at treatment correlating with greater impairment (Johnson et al., 1994). Few studies have examined the impact of dose of CS/RT on academic achievement, and while one found no association between dose and academic achievement or intellectual functioning, the results may have been limited by a small sample size of 13 (Johnson et al., 1994). Furthermore, as

described in the literature review, several studies have shown that higher dose has been associated with greater impairment in intellectual functioning over time, and dose of CS/RT may have a similar impact on academic achievement.

Levels of achievement and learning disabilities play a significant role in the educational development and employment opportunities of the child, and must be further examined with more detailed academic achievement measures to provide more comprehensive understanding of the nature and extent of the impairments. The most common academic achievement measure utilized by studies to date appears to be the WRAT. While the WRAT is useful in screening for basic spelling, arithmetic, and reading recognition, the test does not permit thorough examination of written expression, reading comprehension, or mathematical problem solving skills. A test which examines these skills more comprehensively is the Woodcock Johnson-Revised (WJ-R; Woodcock & Johnson, 1990). It is necessary to more comprehensively examine academic skills, in conjunction with intellectual functioning, to gain a more comprehensive understanding of the individual's academic attainment and potential learning diasabilities.

Purpose of Study and Hypotheses

Purpose

The purpose of this study was to examine the intellectual functioning and academic achievement of ten-year survivors of childhood medulloblastoma. The study also explored the impact of age at radiation treatment and dose of radiation on intellectual functioning. The participants were assessed with measures of intelligence and academic achievement. In addition, demographic and medical information were collected from each participant. This

study was designed to provide a more comprehensive picture of academic achievement at 10-years post-treatment, a time when the majority of survivors were in young adulthood.

The literature on cognitive functioning in medulloblastoma is sparse. Existing studies have relied primarily on measures of intelligence at follow-up intervals of five years or less. Few studies have examined academic achievement in medulloblastoma survivors, and those that exist have utilized a brief measure, the WRAT-R (Johnson et al., 1994; McCabe et al., 1995, Seaver et al., 1994), which does not allow for comprehensive evaluation of critical academic skills. In the current study, the inclusion of more comprehensive measures of academic achievement was intended to provide insight into the educational and vocational potential of medulloblastoma survivors at a significant length of time after treatment with CS/RT. This will be the first known study to assess academic achievement factors of reading comprehension, practical mathematical problem solving, and written dictation in 10-year medulloblastoma survivors.

Therefore, it is the intent of this study to expand the current understanding of the long-term intellectual functioning and academic achievement of childhood brain tumor survivors. Knowledge regarding the long-term cognitive outcome of cancer treatment in this population may assist physicians to make critical decisions regarding treatment options, and timing of treatment options. In addition, families will be able to use this information to better prepare for their child's future by planning appropriate educational interventions to maximize the child's potential.

Hypotheses

Specific Aim I: To examine the intellectual functioning of 10-year medulloblastoma survivors.

Hypothesis 1: Participants will demonstrate significant deficits in intellectual functioning. The mean estimated FSIQ score of participants will be significantly below the normative mean.

Specific Aim II: To examine the academic achievement of 10-year medulloblastoma survivors.

Hypothesis 2: Participants will demonstrate significant deficits in academic achievement. The mean Passage Comprehension, Applied Problems, and Dictation scores will be significantly below the normative means.

Specific Aim III: To examine the relationship between age at CS/RT treatment and intellectual and academic functioning in 10-year medulloblastoma survivors.

Hypothesis 3: Participants treated with CS/RT at five years or younger will demonstrate greater impairment in intellectual functioning and academic achievement than participants treated at older ages. The younger participants (≤ 5) will have a significantly higher proportion of impaired estimated FSIQ and achievement means than those treated with CS/RT at older ages.

Specific Aim IV: To examine the relationship between dose of CS/RT and intellectual and academic functioning in 10-year survivors of medulloblastoma.

Hypothesis 4: Participants treated with ≥ 40 Gy CS/RT will demonstrate greater impairment in intellectual functioning and academic achievement than participants treated with < 40 Gy CS/RT. Those treated with higher doses of CS/RT (≥ 40 Gy) will have a significantly higher proportion of impaired estimated FSIQ and achievement means than those treated with lower doses.

CHAPTER III: METHODS

Subjects

The medulloblastoma patients were identified through the patient database of the Neuro-Oncology clinic at Children's Medical Center of Dallas, Texas. Seventy-six children under the age of sixteen were treated for medulloblastoma at Children's Medical Center between 1980 and 1989. Of those, 30 survivors were identified in the patient database; of those, 19 had survived for ten years or more. All 19 were contacted and asked to participate in the study; 16 agreed, 3 refused. Of the 16 that were included, 3 were excluded from data analyses. Two were unable to complete neuropsychological testing due to pervasive cognitive deficits and/or severe visual problems. Another subject spoke Spanish as a primary language and scores on testing were determined to be inaccurate. All subjects met the inclusion and exclusion criteria listed below.

Inclusion Criteria: Participants were included in the current study if they met the following criteria:

1. Received diagnosis of medulloblastoma between birth and 16 years of age.
2. Postdiagnosis interval of ten years or more.
3. No recurrence of disease at time of evaluation.

Exclusion Criteria: Participants were excluded from the current study if they met any of the following criteria:

1. History of traumatic brain injury, stroke, or gross neurological disorder unrelated to medulloblastoma.
2. Presence of any other major medical illness that interfered with or impaired neuropsychological functioning.
3. English was not the primary language

Materials

All subjects were administered a battery of neuropsychological tests and self-report measures as part of a larger study. The present study examined subtests of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997), or Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991), depending on the subject's age (WAIS-III to 11 subjects; WISC-III to 2 subjects), and Woodcock-Johnson Psychoeducational Battery – Revised (WJ-R; Woodcock & Johnson, 1990). Additional medical variables were obtained from the clinical database and medical chart review at Children's Medical Center at Dallas, Texas. Other data, such as demographic variables, were obtained through self-report questionnaire forms.

Instruments

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III).

The WAIS-III is a test of general intelligence for individuals ranging in age from 16 to 89 years (Wecshler, 1997). The WAIS-III provides a global measure of Full Scale IQ (FSIQ) in addition to Verbal IQ (VIQ) and Performance IQ (PIQ). The test is also comprised

of four factor indices: Verbal Comprehension (VCI), Working Memory (WMI), Perceptual Organization (POI) and Processing Speed (PSI). The IQ and index scores are based on a mean of 100 and standard deviation of 15. Individual subtests comprise the index and IQ scores, which provide scaled scores based on a mean of 10 and standard deviation of 3. The measure has been demonstrated to be a reliable and valid measure of intelligence. The average internal consistency reliability for the IQ scales and factor indexes are high and range from $r = .88$ to $r = .97$, and the FSIQ has the highest average internal consistency reliability of all IQ and index scores ($r = .98$; The Psychological Corporation, 1997).

Subtests of the WAIS-III were administered to subjects over age 16. The current study examined two subtests from the WAIS-III: Vocabulary and Block Design. As part of a larger study, an extensive battery of neuropsychological tests was administered to examine a wide variety of cognitive domains. In order to permit time for the study of multiple domains, an estimate of FSIQ was derived from the Vocabulary and Block Design subtests. Sattler (2001) provided tables for conversions from WAIS-III and WISC-III dyad short form sum of scaled scores to the appropriate Deviation IQs that were used in the current study. Sattler (2001) cited that the popularity of the Vocabulary and Block Design short form has been substantiated statistically, as both subtests have moderate correlations with FSIQ ($r = .80$ and $r = .66$ for the average of the 13 age groups in the standardization sample, respectively; and have high reliabilities ($r = .93$ and $r = .89$ for the average of the 13 age groups, respectively; The Psychological Corporation, 1997). Further evidence supporting the use of these two subtests as a short-form was supported by a study from Ringe, Saine, and Cullum (1999) which found excellent correlation (.94) between an estimated IQ from the

Vocabulary and Block Design subtests and Full Scale IQ in a population of mixed neurological and psychiatric patients (n = 63). Furthermore, they conducted multiple regression analyses which demonstrated that the Vocabulary and Block Design subtests accounted for 90% of the variance in FSIQ scores among the sample.

The Vocabulary subtest assesses word knowledge by requiring the subject to verbally define a set of words of increasing complexity. The Block Design subtest is a measure of visuospatial ability in which the subject is required to construct a figure from blocks to match a novel geometric design presented to them on a stimulus card. The internal consistency reliability for the Vocabulary and Block Design subtests is high: r = .93 and .86 respectively (The Psychological Corporation, 1997). Subtest raw scores were converted to age-corrected standard scaled scores based on normative data provided in the WAIS-III manual. The age-corrected scaled scores were then summed and converted into an estimated FSIQ based on the method and tables found in Sattler (2001, p. 256-257, 828).

Wechsler Intelligence Scale for Children-Third Edition (WISC-III).

The WISC-III is a widely used test of general intelligence for children ranging in age from 6 to 16 (Wechsler, 1991). The test assesses a variety of verbal and nonverbal abilities in order to derive a variety of IQ and index scores. The test is comprised of three intelligence scores (FSIQ, VIQ, and PIQ) and four factor index scores (Verbal Comprehension, Freedom from Distractibility, Perceptual Organization, and Processing Speed) based on standard scores with a mean of 100 and standard deviation of 15. The IQ and factor scores are comprised of individual subtests' scaled scores which have a mean of 10 and a standard deviation of 3. Like the WAIS-III, the WISC-III has consistently demonstrated excellent

reliability and validity. The IQ scores all have internal consistency reliabilities above $r = .90$, and the FSIQ has an average internal consistency reliability of $r = .96$ across all age groups in the standardization sample (Sattler, 2001). Two subtests of the WISC-III, the Vocabulary and Block Design subtests, were given to two subjects in the current study who met the age criterion. The correlations between the WISC-III and WAIS-III are high and justify using both to account for the age differences in the current study. According to the administration manual, both tests were administered to a sample of 184 16-year-old individuals in a testing interval ranging from 2 to 12 weeks. The correlation coefficients for the FSIQ, Vocabulary, and Block Design subtests were $r = .88$, .83, and .80 respectively (The Psychological Corporation, 1997).

The Vocabulary and Block Design subtests are administered in the same fashion as described in the WAIS-III description above. The internal consistency reliability of both subtests is high ($r = .87$). Subtest raw scores were converted to age-corrected standard scaled scores based on normative data provided in the WISC-III manual. The age-corrected scaled scores were then summed and converted into an estimated FSIQ based on the method and tables found in Sattler (2001, p. 256-257, 774).

Woodcock Johnson Psychoeducational Battery – Revised: Tests of Achievement (WJ-R ACH).

The WJ-R ACH (Woodcock & Johnson, 1990) is comprised of a battery of tests which assess a range of cognitive abilities, scholastic aptitudes, and achievement. The battery was standardized with 6,359 subjects ranging in age from 24 months to 95 years. The test is divided into a Standard Battery and Supplemental Battery and permits focus on four

domains of achievement: reading, mathematics, written language, and knowledge (Spreen & Strauss, 1998). The Standard Battery has nine subtests, and three were selected for the current study. Passage Comprehension, Applied Problems, and Dictation subtests were administered to subjects to assess reading, arithmetic, and writing achievement, respectively. In the Passage Comprehension subtest, the subject is asked to verbally provide an appropriate word to complete a short passage after silently reading the passage to him/herself. The Applied Problems test assesses the individual's ability to solve practical math problems. The problems are presented visually and read to the individual and they are required to recognize the correct problem solving procedure, identify relevant data, and perform simple calculations (paper and pencil are permitted). The Dictation test assesses the individual's skill in a variety of domains such as knowledge of punctuation, capitalization, spelling, and word usage. All responses are given in written format by the examinee on the Dictation subtest (Spreen & Strauss, 1998). Internal consistency reliability coefficients are reported for each of these three scales based upon age group. For Passage Comprehension, Applied Problems, and Dictation, the median reliability coefficients across the age groups are: r = .90, .91, and .91, respectively (Woodcock & Johnson, 1990). A variety of derived scores can be obtained from the raw scores including age equivalents, grade equivalents, relative mastery indices, percentile ranks and standard scores. For the current study, raw scores were transformed to standard scores for comparison with IQ scores.

Procedure

All subjects (or their legal guardian) gave informed consent prior to participating in the study. This study was approved by the Institutional Review Board of the University of

Texas Southwestern Medical Center. All participants were mailed a packet of demographic questionnaires which the participant was asked to fill out and bring to his/her neuropsychological evaluation. Participants were scheduled to attend a neuropsychological testing session which lasted approximately three to four hours. Demographic information was obtained during the scheduled session if patients and their families had not filled out the forms mailed to them. One of two trained graduate students administered and scored all tests in standardized format. Breaks were given to participants as needed to prevent fatigue during the testing battery. All tests were double-scored by the two graduate students to ensure accuracy and consistency. Furthermore, data were double entered into a Microsoft Access 97 (1996) database to ensure accuracy. Following testing, patients were informed they would be contacted to attend a feedback session at a later date.

Statistical Analyses

All data were analyzed with the Statistical Package for the Social Sciences for Windows, version 12.0 (SPSS, 2003). The following statistical analyses were conducted to explore the hypotheses.

Hypothesis 1: Ten-year survivors of medulloblastoma will demonstrate deficits in intellectual functioning.

Hypothesis 1 was evaluated with a one-sample Student's *t*-test. The mean of the sample was considered to be significantly impaired if it were significantly below the normative mean. Findings were considered significant at the $p < .05$ level. Additionally, descriptive analyses were conducted to demonstrate the mean and standard deviation of the

sample estimated IQ, as well as the percentage of subjects that fell within each descriptive category (e.g., Average, Low Average, Borderline) based on estimated IQ.

Hypothesis 2: Ten-year survivors of medulloblastoma will demonstrate deficits in academic achievement.

Hypothesis 2 was evaluated by a series of one-sample Student's *t*-tests that compared the mean score of each academic subtest (Passage Completion, Applied Problems, Dictation) to the normative mean. The mean of the sample was considered to be impaired if it were significantly below the normative mean ($p < .05$). In addition, further analyses were conducted to explore the extent of the sample that met criteria for LD based on the standard 15-point discrepancy formula. For each subject, all three achievement scores were subtracted from the estimated IQ score and were considered to meet criteria for LD if there was a 15-point discrepancy between any achievement score and the estimated FSIQ. Further exploratory analyses were conducted to determine how many subjects (percentage) had below average performance in each area of academic achievement (standard score < 85).

Hypothesis 3: Ten-year medulloblastoma survivors who were treated with CS/RT before the age of 5 will have greater impairment in intellectual functioning and academic achievement demonstrated by a significantly higher proportion of impaired estimated FSIQ and achievement means than the older group.

Hypothesis 3 was tested with four one-sample Chi-Square tests. Subjects were divided into two age categories (≤ 5 and > 5). Subjects were also divided according to

estimated IQ scores and the three achievement scores (< 85 and ≥ 85). Separate Chi-square analyses were conducted to determine the relationship between age and IQ and WJ-R Passage Comprehension, Applied Problems, and Dictation scores. Estimated IQ scores and achievement scores were considered impaired if the standard score were < 85.

Hypothesis 4: Ten-year medulloblastoma survivors who received higher doses of CS/RT (≥ 40 Gy) will demonstrate greater impairment in intellectual functioning and academic achievement than participants treated with lower doses, demonstrated by significantly higher proportion of impaired estimated FSIQ and achievement means in the high-dose group.

Hypothesis 4 was tested in the same manner as Hypothesis 3. Four one-sample Chi-Square tests were conducted. Subjects were divided according to dose of CS/RT (< 40 Gy versus ≥ 40 Gy). IQ scores were divided into impaired versus non-impaired categories, and the three achievement scores were divided into impaired versus non-impaired categories. Separate Chi-square analyses were conducted to determine the relationship between dose of CS/RT and IQ and WJ-R ACH Passage Comprehension, Applied Problems, and Dictation scores. Estimated IQ scores and achievement scores were considered impaired if the standard score were < 85.

CHAPTER IV: RESULTS

Descriptive Data

Table 1 provides the demographic information for the sample. The sample consisted of 6 males and 10 females, ranging in age from 13.6 to 27.9 years, with a mean age at assessment of 22 years (SD = 3.7). The average years of education across the group was 12.3 (SD = 2.4). Sixty-three percent (n = 10) of the subjects were female. Regarding racial composition, 62.5% (n = 10) were Caucasian, 18.75% (n = 3) were African American, and 18.75% (n = 3) were Hispanic. Fourteen (87.5%) of the subjects had never married or had children and were residing with a parent or other family member. In terms of socioeconomic status, caregivers of the 14 subjects residing at home reported household income respectively: 29% had a yearly income less than $25,000, 43% had a yearly income between $25,000 and $75,000, and 29% had a yearly income greater than $75,000.

Treatment variables are provided in Table 2. The mean age at diagnosis of the sample was 7.2 years (SD = 4.6), with a range from 1 to 15 years. The average length of survival was 14.6 years (SD = 3.7), with a range from 11 to 20 years. The mean dose of CS/RT used to treat subjects was 37.9 Gy (SD = 3.7), with a range from 30.4 Gy to 45.0 Gy. The subjects received a mean radiation boost to the posterior fossa of 15.5 Gy (SD = 3.2), with a range from 10.0 Gy to 21.6 Gy. Gross total resection of the tumor was achieved in half of the subjects. Chemotherapy was used in the treatment regimen of 56% (n = 9) of subjects. Of those, one received low-dose methotrexate, and the others received varying combinations of methotrexate, vincristine, cisplatin (CDDP), cyclophosphamide (CTX), lomustine (CCNU), and etoposide (VP-16). Additionally, 31% (n = 5) had post-operative

complications, 63% required placement of a shunt (n = 10), and 19% (n = 3) had progression of the tumor and required a second surgery and chemotherapy.

This pilot study is part of a larger study on the long-term cognitive sequelae and quality of life of children who survived medulloblastoma for at least 10 years (Bergeron, 2001). As a part of the larger study, comparisons of participants and nonparticipants were performed to determine if there were differences between the sample and other survivors who did not participate in the study. The nonparticipant sample included 15 patients who either refused to participate (n = 3), or were lost to follow-up (n = 12). Student *t*-tests were conducted to examine potential differences in demographic and treatment variables between participants and nonparticipants. Results are shown in Table 3. No significant difference was found regarding the following variables: age at the time of the study, age at diagnosis, age at radiation treatment, and time since diagnosis, t (28) = -4.1, .59, .67, -1.31, respectively, p = .683, .563, .510, and .201, respectively. Additionally, no significant difference was found between cranial radiation dose, t (25) = -.06, p = .954, or posterior fossa boost dose, t (24) = -.20, p = .846.

Additionally, to further explore sample representativeness, Pearson chi-square tests were conducted to examine the categorical variables between the participant and nonparticipant samples (Table 4). There was no significant difference across the gender and racial compositions of each group, χ^2 (1, N = 30) = 1.16 and .27 respectively, p = .282 and p = .605 respectively. Similarly, no significant discrepancies were found between the groups with respect to treatment variables (gross total resection, chemotherapy, post-operative

complications, shunt, or progression of tumor), χ^2 (1, N = 30) = .15, .01, .37, .48, and .03 respectively, p = .696, .961, .544, .491, and .855, respectively.

Analysis of Hypotheses

Hypothesis 1. The first hypothesis predicted that the sample of ten-year medulloblastoma survivors would demonstrate impairment in intellectual functioning depicted by a significantly lower estimated FSIQ than the normative mean. This hypothesis was tested by a one-sample Student *t*-test. A significant difference between the estimated IQs of the medulloblastoma sample and the normative mean was found, with the medulloblastoma group performing significantly below the normative mean of 100, t (12) = -4.46, p = .001. The average estimated IQ of the medulloblastoma group was at the cutoff between the Borderline and Low Average range (M = 79.6, SD = 16.48; see Table 5). Seventy-seven percent of ten-year medulloblastoma survivors demonstrated impairment in estimated FSIQ, defined by an estimated FSIQ score below 85. In the normative population, only 16% demonstrated the same level of impairment. The sample was then divided based on Wechsler intelligence classifications, and 85% of the medulloblastoma survivors were found to have estimated FSIQs that placed them within the Low Average to Extremely Low categories (Table 6). Only 21% of the normative population fall within those classifications.

Further exploratory analyses demonstrated similar results for the Vocabulary and Block Design subtests (see Table 5). The Vocabulary mean scaled score was 7.31 (SD = 4.46) with 50% of the sample depicting impairment on this subtest (scaled score < 7), t (12) = -2.18, p = .05. The Block Design mean scaled score was 5.62 (SD = 2.50), which fell within

the significantly impaired range, and 62% of the sample were impaired on this measure (scaled score < 7), t (12) = -6.32, p < .001. Exploratory analyses were done to attempt to discover if impairment in Block Design could be attributed to motor impairment, rather than poor visuospatial ability. As depicted in Table 7, individuals who demonstrated motor impairment on a finger tapping test as part of the larger study (defined by a T score ≤ 35; n = 5) were compared to those who did not (T > 35; n = 7) on the Wechsler Block Design subtest (Bergeron, 2001). Results indicated that there were no significant differences between the scores of the two groups, suggesting the impairment found in Block Design was related to visuospatial problems rather than motor impairment. A *t*-test was conducted to determine if the mean performance on Vocabulary was significantly different from Block Design. The difference was not significant, t (12) = 1.35, p = .202. Thus, the first hypothesis was supported by the data, as the medulloblastoma sample demonstrated significant impairment in estimated Full-Scale IQ scores compared to the normative mean.

Hypothesis 2. The second hypothesis proposed in this study stated that the sample would demonstrate deficits on three measures of academic achievement. Results are shown in Table 8. The performance of the sample on the Passage Comprehension subtest was below average (M = 83.08, SD = 18.62) and was significantly discrepant from the the normative mean of 100, t (12) = -3.28, p = .007. Forty-six percent of the 13 subjects tested demonstrated an impairment on this measure of reading comprehension. A statistically significant discrepancy also was found between the mean performance of the sample on Applied Problems and the normative mean of 100. The Applied Problems mean standard

score was 78.46 (SD = 11.82), which was indicative of mild to moderate impairment, t (12) = -6.57, $p < .001$. Furthermore, sixty-nine percent of the sample had scores which were indicative of impairment. Likewise, the medulloblastoma sample performed significantly below the normative mean on the Dictation test. The Dictation mean was 72.62 (SD = 13.88) which was indicative of mild to moderate impairment, t (12) = -7.11, $p < .001$. Seventy-seven percent of the sample had impairment in written expression, as assessed by the Dictation subtest.

Exploratory analyses were conducted to determine the proportion of the sample that demonstrated a 15-point discrepancy between their estimated FSIQ score and any of the achievement scores (achievement < FSIQ). The most common method of classifying learning disabilities is to examine whether this 15-point discrepancy is present. As elaborated in Chapter 2, however, this classification likely underestimates the extent of learning problems in medulloblastoma survivors given the impairment in their overall IQ. In the current study the proportion of individuals who demonstrated the 15-point discrepancy was compared to those who demonstrated impairment by standard scores (Table 9). The results demonstrated that when classifying learning disabilities based on the 15-point discrepancy, only 8% (n=1) of the sample were classified as having impairment in Passage Comprehension, while 46% (n=6) were classified as impaired based on a Standard Score cut-off of 85. Similarly, 15% of the sample was found to have a mathematics learning problem based on the 15-point discrepancy while 69% had impairment with the Standard Score classification. Regarding written expression as assessed by Dictation, the percentages were 46 and 77, respectively.

The data support the second hypothesis that the medulloblastoma survivors would perform significantly below the normative mean on all three measures of academic achievement. Additional analyses demonstrated that more participants were classified as impaired on the achievement measures when focusing on the performance of the achievement tests separately from the estimated FSIQ.

Hypothesis 3. The third hypothesis stated that subjects who received CS/RT before the age of 5 would have significantly greater impairment in intellectual functioning and academic achievement than those who underwent CS/RT after age 5. Subjects were divided into two age categories (≤ 5 and > 5). Subjects were also divided according to estimated IQ scores and the three achievement scores (< 85 and ≥ 85). The dichotomous variables were then compared by four separate Chi-square tests. None of the Chi-square tests were statistically significant, which was likely attributable in part to the small sample size (see Table 10). Thus, the results do not support the hypothesis that individuals who received CS/RT at or before the age of 5 have greater impairment in intellectual functioning and academic achievement.

Hypothesis 4. The fourth and final hypothesis stated that subjects who received higher doses of CS/RT (≥ 40 Gy) would have greater impairment in intellectual functioning and academic achievement than those who received lower doses of CS/RT (< 40 Gy). Subjects were divided according to low and high intellectual performance and academic achievement on the measures in the same manner as Hypothesis 3. Dose of CS/RT was not

available for one subject and the sample size for this analysis was n = 12. The dichotomous variables were compared by four Chi-square tests, none of which were statistically significant (see Table 11). The results did not support the hypothesis. The small sample size may have interfered with the ability to detect a significant result.

CHAPTER V: DISCUSSION

Assessing the long-term cognitive outcome of childhood medulloblastoma survivors is of critical importance in understanding the clinical prognosis and treatment implications of the disease. The advancement of surgical techniques, radiation therapy, and chemotherapy, has dramatically improved the survival rate after a diagnosis of medulloblastoma. Although the survival rate has substantially increased, clinical reports and current research demonstrate that cognitive sequelae are frequent and often significant. Cognitive impairment has been attributed primarily to whole-brain radiation therapy, although surgery and chemotherapy treatment also appear to have effects that are not yet clearly understood, but appear to be more subtle than the effects of radiation. Studies have demonstrated that survivors of childhood medulloblastoma are at significantly greater risk for impairment in overall intellectual functioning (Hoppe-Hirsch et al., 1995). Additionally, younger age at radiation and higher dose of radiation are both associated with greater impairment in intellectual functioning in several studies (Grill et al., 1999; Hoppe-Hirsch et al., 1990; Johnson et al., 1994; Roman & Sperduto, 1995).

The research examining academic functioning in long-term survivors of medulloblastoma is scarce, but some studies indicate that learning problems and disabilities are prevalent (Duffner, Cohen, & Thomas, 1983; McCabe et al., 1995; Seaver et al., 1994) and increase with younger age at radiation (Johnson et al., 1994). Most studies have not examined survivors more than 5 years post-treatment, and thus the functioning of individuals in the second decade of survival has gone largely unexplored. The goals of the current study were to 1) examine long-term intellectual and academic functioning of medulloblastoma

survivors, and 2) explore whether age at treatment and dose of radiation impact long-term intellectual and academic functioning. To that end, all of the individuals who survived medulloblastoma for at least 10 years were identified from a large regional children's hospital. Of those, 16 agreed to participate, and 13 were able to complete the neuropsychological testing. Given the small number of participants available, this study was conducted as an exploratory pilot study and as part of a larger study which examined the neuropsychological and psychosocial functioning in this population. The findings and limitations of the current study will be discussed in the following sections.

Intellectual Functioning

The results supported the hypothesis that the mean performance on the estimated measure of overall intelligence would be significantly below the normative mean. The mean IQ estimate of the medulloblastoma survivors in the present study was at the cutoff between Borderline and Low Average range (M = 79.6, SD = 16.48). Sixty-two percent had estimated FSIQ scores that were in the Borderline or Extremely Impaired ranges (n = 8; estimated IQ < 80), 23% were in the Low Average range (n = 3; estimated IQ = 80-89), and 15% were in the High Average range (n = 2; estimated IQ = 110-119). These findings support previous research that has demonstrated substantial impairment in intellectual functioning among most survivors of medulloblastoma at shorter follow-up intervals (Duffner, Cohen, and Thomas, 1983; Fossen, Abrahamseen, and Storm-Mathisen, 1998). Although there was no pre-treatment IQ testing data available to permit examination of progressive intellectual decline in the current study, the percentage of participants with IQs significantly below the normative mean suggests decline has likely occurred in the majority

of the sample, which is consistent with prospective studies examining decline over time (Hoppe-Hirsch et al., 1995).

In addition to impairment in overall estimated IQ, the sample demonstrated impairment on the measures of verbal ability and performance ability comprising the estimated IQ, also consistent with the literature. Fifty percent of the sample demonstrated impaired performance (scaled score < 7) on the Vocabulary subtest, and 62% demonstrated impaired performance on Block Design. The literature examining the difference between verbal and performance IQ among medulloblastoma survivors suggests, after controlling for motor impairment, that performance IQ is often more impaired than verbal (Duffner, Cohen, & Thomas, 1983; McCabe, 1995). A t-test was conducted to determine whether there was a significant discrepancy between the verbal and performance subtests in the medulloblastoma sample, and no significant difference was found.

Academic Achievement

In addition to overall intellectual functioning, indices of academic achievement were also assessed among the participants. The second hypothesis predicted the mean performance of the medulloblastoma survivors on three measures of academic achievement would be significantly impaired when compared to the normative means. Each measure assessed a different domain of academic achievement including reading comprehension, math problem solving, and dictation. The results were consistent with the hypothesis, as the participants' mean performance on each measure was significantly below that of the normative mean. The results are also consistent with the sparse literature available that examined the academic achievement of less than ten-year survivors of medulloblastoma.

Three studies suggested that survivors have a higher rate of learning disabilities, more frequently need special education, and demonstrate greater impairment on achievement as assessed by the WRAT compared to the normative population (Johnson et al., 1994; McCabe et al., 1995; and Seaver et al., 1994).

The current study participants' performance on Dictation was nearly two standard deviations below the normative mean, depicting the area of greatest impairment among the group. The Applied Problems and Passage Comprehension subtests were also greater than one standard deviation below the mean. There is controversy regarding how to define and diagnose learning disabilities in the population as a whole, as well as among populations with intellectual and academic impairment, such as survivors of brain tumors. To explore the prevalence of the medulloblastoma group that met traditional criteria of LD, captured by a 15-point discrepancy between FSIQ and an achievement score, all participants' academic achievement scores were subtracted from their estimated FSIQ scores (Table 8). When compared to the number of participants whose academic achievement scores fell below average based on the criterion of a standard score of 85, many participants with learning disabilities were not captured by the discrepancy method. Given that the majority of the population had estimated FSIQ scores that fell below average, it appears the discrepancy method would not capture the full range of their learning problems. Examining the long-term medulloblastoma survivors' academic functioning scores separate from the IQ score may capture their functioning more accurately.

Furthermore, in accordance with the literature, a large number of the participants, sixty-nine percent, relied upon special education services during their school years. This is

substantially higher than the average rate of 12% of students across the state of Texas that utilize special education (Texas Education Agency, 1998). Several studies have documented similarly high rates of special education services among this population. Johnson et al. (1994) reported that 57% of 10 medulloblastoma survivors included in their study required special education services. Hoppe-Hirsch et al., (1995), documented that 80% of survivors required special education services at 10-year follow-up, although they did not report their sample size. Other studies cite medulloblastoma survivors as spending a mean of 41% to 60% of their education in special education services (Mulhern et al., 1998; Seaver et al., 1994). The significant extent of impairment found in academic achievement in the current study, in addition to the high percentage of participants that relied upon special education, further suggests the consequences of treatment for medulloblastoma during childhood are long-standing and negatively impact the intellectual and academic course of development.

Impact of Age at CS/RT and Dose on IntellectualFunctioning

The potential associations between the treatment-related variables of age at CS/RT and CS/RT dose and cognitive functioning were also explored. The hypotheses, which held that younger age at CS/RT and higher dose of CS/RT would be associated with greater impairment in intellectual functioning and academic achievement, were not supported. The small sample size limited the statistical analyses that could be performed to explore these relationships. There was a limited range of age at treatment and narrow range of dose, in addition to multiple identical scores among the data, making correlational analyses inappropriate.

Despite the lack of association in the present study, the literature regarding survivors of medulloblastoma suggests that age at CS/RT has a significant impact on cognitive functioning. Younger age at treatment, particularly below age five, appears to have a more detrimental impact on functioning (Ellenberg et al., 1987; Fossen, Abrahamseen, & Storm-Mathisen, 1998; Hoppe-Hirsch et al., 1990). It was expected that those treated below age 5 in the current study would demonstrate even greater impairment in intellectual functioning and achievement than those in the literature, given the longer length of time since treatment and the apparent progressive nature of decline over time. Future studies should include larger sample sizes to further explore the critical age of treatment.

Limitations

There were a number of limitations to the current study. The first and perhaps most significant was the small number of available subjects, resulting in a sample size of 13. Although this number is similar to the sample sizes of many studies in the literature, it significantly limited the statistical analyses that could be performed to test hypotheses. Before the study began, it was the intent of the investigator to utilize a larger sample size, closer to 30 participants, but due to recruiting difficulties, and severe developmental disabilities and language barriers, the optimal number of participants was not possible. This limitation is largely due to the low incidence of this disease, and future studies should consider multi-site collaboration to increase the sample size such that within-group comparisons can be explored more effectively.

The cognitive test battery also presented a limitation to the study. An abbreviated measure of IQ was used in order to save time for the administration of a comprehensive

neuropsychological battery. As a result, the reliability and validity of the FSIQ is reduced from that of a full WAIS-III or WISC-III, and the ability to make comparisons between VIQ and PIQ was significantly limited. Similarly, three subtests of the WJ-R ACH were selected to assess three areas of achievement in the interest of time. While the combination of those subtests provided a more comprehensive exploration of academic functioning than previous studies, they could not capture the full range of achievement. Therefore, future studies should utilize a more thorough battery of academic functioning assessment instruments in order to continue to clarify areas of impairment. In particular, since impairment in Dictation skills was widespread, more in-depth assessment of written language might be useful.

The current study did not exclude participants who were experiencing depression or other psychiatric disorders at the time of the evaluation. However, measures were included as part of the larger study to assess for psychiatric disorders (Bergeron, 2001). The study by Bergeron found that two participants were reporting symptoms consistent with depression which may have impacted performance on intellectual and academic achievement.

Another limitation of this study was the lack of a control group for comparison. This study was conducted as a descriptive pilot study, and was designed to explore the intellectual and academic characteristics of a unique population. As a result, the lack of a comparison group limited the analyses and generalizations that could be made. Several comparison groups would be useful. First, another long-term survivor group of childhood cancer, such as ALL, that received chemotherapy but not radiation, would serve to clarify the role of chemotherapy on cognition. In addition, a group that received surgery, but not radiation or chemotherapy would also help explore the potential cognitive impact of surgery compared to

the other groups. To more accurately explore the hypothesis regarding impact of CS/RT dose, it would be helpful to compare the sample to other groups who received varying doses of CS/RT such as 0 Gy, 18 Gy, and 24 Gy. A healthy normal control group, or a group of matched-siblings, would be useful in comparing intellectual and academic achievement as an alternative to using normative means.

An additional limitation relates to the generalizability of the current findings. All of the subjects were recruited from a single medical site. However, as depicted by Table 3, *t*-test comparisons of participants and non-participants on demographic and treatment-related variables did not produce significant discrepancies. Furthermore, the characteristics of the sample are similar to those found in the existent literature, which suggests that the sample appears to be representative of the larger population of childhood medulloblastoma survivors.

Conclusions

The purpose of this study was to examine the intellectual and academic functioning of ten-year survivors of childhood medulloblastoma, and to explore whether treatment-related variables of age at radiation and radiation dose were related to cognitive functioning among the survivors. These goals were pursued with the intent of providing further information regarding the cognitive sequelae of treatment to patients and their families, as well as to health care providers who make decisions regarding treatment protocols for medulloblastoma.

The results clearly demonstrate that the population had significant deficits in intellectual functioning and in academic achievement, particularly in practical math problem solving and written skills. While a significant percentage of the sample demonstrated below

average performance on the measures of academic achievement, the extent of impairment was not captured when using the discrepancy method for determining LD. It would appear that a minority of participants experience learning problems based on the discrepancy method, when in actuality, the majority of the sample experienced impairment in achievement in at least 1 of 3 domains, and 69% relied upon special education services during their educational years according to self-report.

Treatment-related variables of age at CS/RT and dose of CS/RT were also examined. The literature suggests that both younger age at treatment and higher dose of CS/RT, particularly above 35 Gy, are associated with decreased intellectual and academic functioning among long-term survivors. The data in the current study did not fully support the hypotheses. Given the small sample size, the ability to detect a significant relationship between these variables and cognitive functioning was likely limited. Furthermore, the sample demonstrated a narrow range of CS/RT from 30 to 40 Gy. Further examination with a larger sample size and greater range of CS/RT dose (25 to 45 Gy) is necessary to optimally explore these hypotheses.

Table 1:

Demographic Variables of Sample

Variable	Medulloblastoma Sample			
	n	Mean	SD	Range
Age (years at assessment)	16	22.2	3.7	13.6-27.9
Education (years)	16	12.3	2.4	8-16
	n	%		
Gender (female)	10	62.5		
Race				
African American	3	18.75		
Caucasian	10	62.5		
Hispanic	3	18.75		
Marital Status (never married)	14	87.5		
Children	1	6.3		
Reside with Caregiver	14	87.5		
Household Income				
0-25K	4	29		
25K-75K	6	43		
75K-100K	2	14		
> 150K	2	14		

Table 2:

Treatment Variables

Variable	Medulloblastoma Sample		
	Mean	SD	Range
Age at Diagnosis (years)	7.2	4.6	1-15
Survival (years)	14.6	3.7	11-20
Cranial Radiation Dose (Gy)	37.9	3.7	30.4-45.0
Posterior Fossa Boost (Gy)	15.5	3.2	10.0-21.6
	n	%	
Gross Total Resection	8	50	
Chemotherapy	9	56	
Shunt	10	62.5	
Post-Operative Complications	5	31	
Progression of Disease	3	19	

Table 3:

T-test Comparisons of Participants and Non-participants on Demographic and Treatment Variables

Variable	Group							
	Participants			Non-Participants				
	n	Mean	SD	n	Mean	SD	t	p
Age (years)	16	21.9	3.6	14	22.5	4.4	-.41	.683
Age at Diagnosis (years)	16	7.3	4.5	14	6.3	4.2	.59	.563
Age at Radiation (years)	16	7.5	4.4	14	6.5	4.2	.67	.510
Survival (years)	16	14.6	3.5	14	16.2	2.9	-1.31	.201
Cranial Radiation Dose (Gy)	14	37.9	3.7	13	38.0	4.9	-.06	.954
Posterior Fossa Radiation Dose (Gy)	14	15.5	3.2	12	15.8	5.4	-.20	.846

Table 4:

Chi-Square Comparisons of Participants and Non-participants on Demographic and Treatment Variables

Variable	Group			
	Participants	Non-Participants		
	%	%	χ^2	p
Gender (female)	63	43	1.16	.282
Race (minority)	37	29	.27	.605
Gross Total Resection	50	57	.15	.696
Chemotherapy	56	57	.01	.961
Post-Operative Complications	31	21	.37	.544
Shunt	63	50	.48	.491
Progression of Disease	19	21	.03	.855

Table 5:

Severity and Frequency (%) of Impairment on Measures of Intelligence

Measure						
Intelligence	n	Mean (SD)	Range	Percent Impaired*	*t*	*p*
Vocabulary (Scaled)	13	7.31 (4.46)	1-15	50 (n=7)	-2.18	.05
Block Design (Scaled)	13	5.62 (2.50)	2-10	62 (n=8)	-6.32	<.001
Estimated FSIQ (Standard)	13	79.62 (16.48)	60-112	77 (n=10)	-4.46	.001

*For Scaled Scores impairment = < 7, for Standard Scores impairment = < 85.

Table 6:

Participants Grouped by Classification Rating for Wechsler Estimated FSIQ

Estimated IQ		Wechsler Tests	
	Classification	n	%
110-119	High Average	2	15
90-109	Average	0	0
80-89	Low Average	3	23
70-79	Borderline	4	31
60-69	Extremely Low	4	31

Table 7:

T-test Comparison of Motor-impaired versus Non-Motor-Impaired Participants on Visuospatial Measure

Variable	Group					
	Impaired*		Non-Impaired			
	n	Mean (SD)	n	Mean	SD	*t*	*p*
Block Design	7	5.4 (3.8)	5	5.7	(1.7)	-.17	.870

* > 1.5 SD below normative mean for Finger Tapping score (dominant hand)

Table 8:

Severity and Frequency (%) of Impairment on Measures of Academic Functioning

Measure

Academic Functioning (Standard Scores)	n	Mean(SD)	Range	Percent Impaired*	*t*	*p*
Passage Comprehension	13	83.08 (18.62)	39-114	46 (n=6)	-3.28	.007
Applied Problems	13	78.46 (11.82)	60-100	69 (n=9)	-6.57	<.001
Dictation	13	72.62 (13.88)	53-94	77 (n=10)	-7.11	<.001

*Impairment = SS < 85.

Table 9:

Frequency of Learning Disability Based on Discrepancy Scores (IQ – Achievement ≥ 15 points) Versus Standard Scores (Achievement < 85)

Measure	% Learning Disability by 15 pt Discrepancy	% Learning Disability by Standard Scores
Passage Comprehension	8 (n=1)	46 (n=6)
Applied Problems	15 (n=2)	69 (n=9)
Dictation	46 (n=6)	77 (n=10)

Table 10:

Chi-Square Analysis of Intellectual Functioning and Academic Achievement by Age at CS/RT

IQ/Ach Functioning	Age at CS/RT			
	≤ 5 years	> 5 years		
Estimated FSIQ	n (%)	n (%)	χ^2	p
< 85	5 (38.5)	5 (38.5)		
≥ 85	0 (0)	3 (23)	2.44	.118
Passage Comprehension				
< 85	3 (23.1)	3 (23.1)		
≥ 85	2 (15.3)	5 (38.5)	.627	.429
Applied Problems				
< 85	4 (31)	5 (38)		
≥ 85	1 (8)	3 (23)	.442	.506
Dictation				
< 85	5 (38.5)	5 (38.5)		
≥ 85	0 (0)	3 (23)	2.44	.118

Table 11:

Chi-Square Analysis of Intellectual Functioning and Academic Achievement by CS/RT Dose

IQ/Ach Functioning	CS/RT Dose			
	< 40 Gy	≥ 40 Gy		
Estimated FSIQ	n (%)	n (%)	χ^2	p
< 85	4 (33)	5 (42)		
≥ 85	2 (17)	1 (8)	.444	.505
Passage Comprehension				
< 85	2 (17)	3 (25)		
≥ 85	4 (33)	3 (25)	.343	.558
Applied Problems				
< 85	3 (25)	5 (42)		
≥ 85	3 (25)	1 (8)	1.50	.221
Dictation				
< 85	4 (33)	5 (42)		
≥ 85	2 (17)	1 (8)	.444	.505

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VITAE

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