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Neurocognitive Late Effects in Pediatric Cancer

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Abstract

As survival rates for the most prevalent types of childhood cancer have dramatically improved over the past three decades, the concept of “cure” has evolved to include optimizing the quality of life among survivors. Although significant progress has been made in addressing some adverse late effects of treatment that limit quality of life, such as endocrinopathies, other late effects remain problematic. This paper will review neurocognitive late effects as defined by problems with thinking, learning, and remembering among survivors of childhood cancer. After defining the neurocognitive phenotype that characterizes many such children, we will review the etiology and risk factors for damage to the central nervous system associated with childhood cancer and its treatment. We will then discuss methods of pharmacological, behavioral, and ecological intervention that may be helpful in reducing learning problems among surviving children. Finally, we will identify areas of future research that will be critical to the elimination of neurocognitive late effects in childhood cancer survivors and the resources needed to implement such research.

For children diagnosed with cancer in the early 1970's, the probabilities were approximately the same as to whether they would be cured or succumb to their illness. For children diagnosed in the early 1990's, the overall prognosis for survival had increased to 75% with some types of cancer exceeding 80% cure rates.[1] With improvement in survival, clinicians became more aware of late occurring adverse effects of treatment for childhood cancer. Neurocognitive late effects, defined by problems with thinking, learning, and remembering, have become an expanding area of scientific interest, especially for the two most frequent types of childhood cancer, acute lymphoblastic leukemia (ALL) and brain tumors.

Although estimates vary according to patient diagnosis and age, aggressiveness of therapy, and length of follow-up, most researchers would agree that the incidence of neurocognitive late effects is unacceptably high. Despite recent attempts to modify therapy to reduce morbidity while maintaining high cure rates, problems in neurocognitive functioning remain to be experienced by a large majority of survivors. Efforts to eliminate neurocognitive late effects have been hampered by a deficient understanding of the biological and developmental mechanisms responsible, as well as a lack of clinical trials directed at treating the deficits associated with this neurocognitive syndrome.

Several recent reviews of the literature are available which summarize contemporary findings among empirical studies and which offer methodological recommendations for improving the level of rigor among future studies.[2-6] We shall not provide another comprehensive review in this paper. Rather, we will attempt to provide an interpretation of findings within a conceptual framework that can be used to accommodate new studies as well as to guide future research. Our review of the literature will therefore be more selective, concentrating on more recent developments that are likely to have a significant impact on future research priorities.

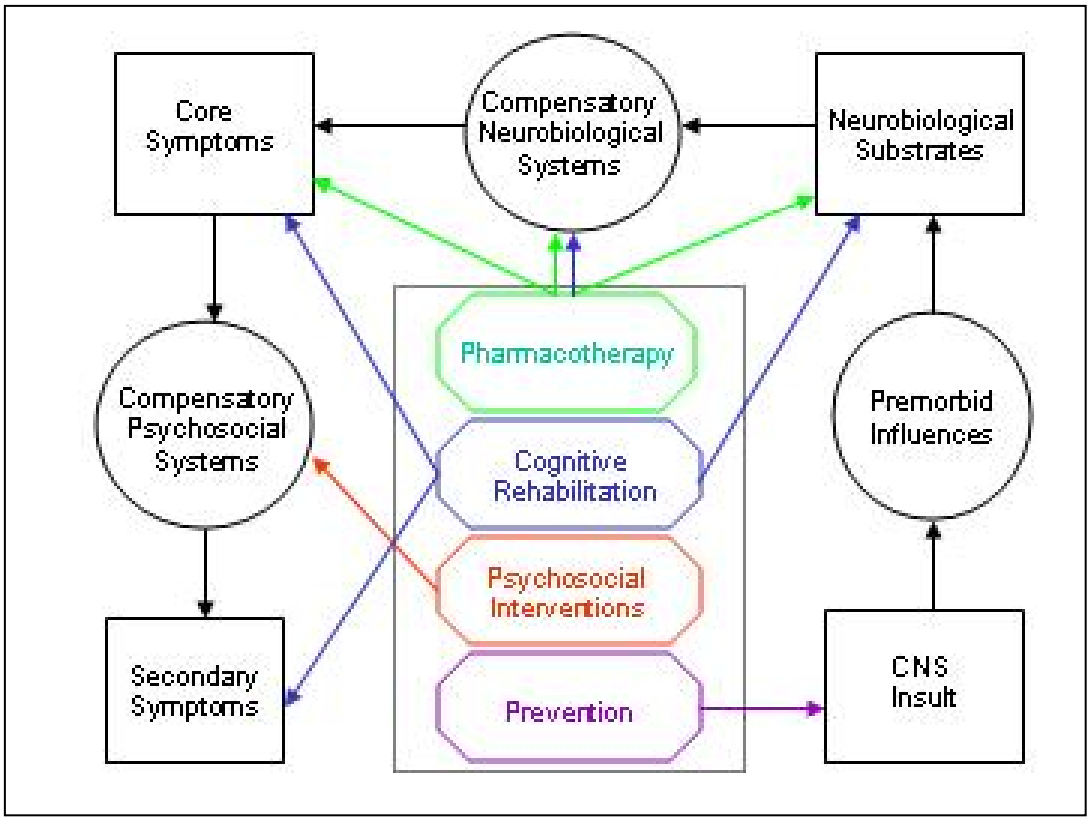

Figure 1. Conceptual Model of Factors Influencing Research Priorities. This conceptual model encompasses our approach to these research objectives. First, it recognizes the influence of premorbid factors (e.g., genetic endowment, gender, and age) at the time of central nervous system damage, the potential for both neurobiological and environmental compensatory systems, the resulting core symptoms and secondary symptoms of the neurocognitive syndrome, and the potential impact of pharmacological and behavioral interventions to modify the expression of the symptoms.

The conceptual framework that forms the basis for our discussion is illustrated in Figure 1, comprised of the sources of central nervous system insult related to treatment of ALL and brain tumors, the neurobiological substrates underlying treatment and disease related central nervous system (CNS) damage, core neurocognitive symptoms resulting from CNS damage, and secondary neurocognitive symptoms that are expressed in every day activities of patients. Also included in Figure 1 are three variables that may influence the relationships between the sources of brain damage and the ultimate expression of secondary symptoms: premorbid patient influences, compensatory neurobiological substrates, and compensatory psychosocial systems. Finally, the potential therapeutic value of pharmacotherapy, cognitive rehabilitation, and psychosocial interventions is represented. In preparation for more specific discussion of

these factors, we will begin with a brief review of pediatric ALL and brain tumors and associated sources of CNS insult.

Acute Lymphoblastic Leukemia

Medical Background

Approximately 20,000 children and adolescents under the age of 20 were diagnosed with cancer in 1999.[7] The most commonly diagnosed cancer in this age group is ALL, a malignant disorder by which lymphoid cells found in the bone marrow migrate to virtually every organ system, including the CNS, via the circulatory system. ALL accounts for one-fourth of all childhood cancers and 78% of all cases of childhood leukemia.[1] In the United States, approximately 3000 children are diagnosed with ALL each year with an incidence of 3 to 4 cases per 100,000 white children. ALL is more common among white than black children, and is also more common among boys than girls with a peak incidence at 4 years of age. Although genetic, environmental, viral, and immunodeficiency factors have been implicated in the pathogenesis of ALL, the precise causes of most cases of ALL remain largely unknown.

Presenting symptoms include fever, fatigue, pallor, anorexia, bone pain and bruising. Because the symptoms of ALL can mimic a number of nonmalignant conditions, definitive diagnosis, usually made by bone marrow aspiration, is sometimes delayed. The duration of treatment varies from 30 to 36 months, and, in the modern era is usually restricted to intervention with combination chemotherapy, reserving cranial radiation therapy (CRT) for patients who experience a CNS relapse. A better prognosis is associated with female gender, age at diagnosis between 2 and 10 years, a lower white blood cell count, and an earlier positive response to treatment. Treatment can be divided into 4 phases: remission induction, CNS preventative therapy, consolidation, and maintenance. The purpose of the remission induction phase is to rapidly eradicate leukemia cells from the bone marrow and circulatory system. Consolidation may be used to intensify therapy following remission induction. Maintenance therapy is required for a prolonged period because of the presence of undetectable levels of

leukemia that, nevertheless, have the capacity to be fatal. After the completion of treatment, approximately 20% of those children who will eventually relapse will do so in the first year off therapy with a subsequent risk of relapse in the remaining patients at a rate of 2% to 3% per year for the next 3 to 4 years.

Sources of CNS Insult

CNS preventative therapy is necessary because the CNS is a sanctuary for occult leukemia. Traditionally, CNS therapy has included CRT and intrathecal chemotherapy, usually with methotrexate (MTX) or MTX combined with other drugs. However, because of the risks for neurocognitive toxicity with CRT, treatment is now usually restricted to intrathecal and systemic chemotherapy with equivalent success in the prevention of CNS relapses. An overwhelming majority of studies that have investigated the neurocognitive morbidity of CRT in leukemia patients have found significant adverse effects,[2,4] with the strongest evidence coming from longitudinally designed studies with internal control or comparison groups.

For example, the group at Children's Hospital of Los Angeles reported on 24 patients treated for ALL who had received CNS prophylactic therapy with 18 Gy CRT, intrathecal MTX, and intravenous MTX.[9] Patients were assessed with IQ testing prior to beginning CNS therapy and at 1 and 4 years later. Although IQ scores remained stable at the 1-year interval, significant declines in Full-scale, Verbal, and Performance IQ scores were noted at the 4-year follow-up testing, with a mean loss of 6 to 7 IQ points. Furthermore, 12 of the 24 children had received special educational services at the final assessment with three of the 12 having repeated a grade prior to receiving special services. These results were disappointing because of the expectation that a reduction of the traditional CRT dose from 24 Gy to 18 Gy would minimize neurocognitive toxicity.

In a unique analysis across two institutional protocols at St. Jude Children's Research Hospital, patients who had received 24 Gy CRT and those who had been randomized to receive 18 Gy CRT or no CRT were compared over time with regard to their neurocognitive

development.[10] All patients also received intrathecal MTX and intravenous MTX therapy. With a median follow-up of 6.8 to 8.4 years for the groups, only small and nonsignificant changes in IQ values were noted with no significant differences between groups. However, 22-30% of patients showed a clinically significant decline of Full-scale IQ over the study interval and scores on tests of arithmetic declined over time compared to normal expectations of same-age peers. Interestingly, one explanation for the lack of differences between CNS therapy groups were differences in parenteral MTX; the 18-Gy group had the lowest total dose, those in the 24 Gy group had approximately 1.5 times more, and those not receiving CRT received 10.7 times more MTX.

More recently, serial neurocognitive evaluations were performed on 30 children surviving ALL to 4-years post-diagnosis.[11] Patients had received CNS treatment with chemotherapy only. Although IQ scores remained stable, arithmetic achievement declined significantly as well as patients' verbal fluency and visual-motor skills. These results recapitulated earlier reports that intrathecal and/or intravenous MTX were not benign to the CNS. For example, one cross-sectional study of 47 long-term survivors of ALL treated with chemotherapy only found statistically significant declines in Performance IQ, as well as perceptual organization, and freedom from distractibility scores but no significant changes in academic achievement.[12]

It is worth noting that at least one prospective study has failed to find IQ losses among patients treated without CRT at a 3-year followup.[8] Other types of chemotherapy, such as the use of dexamethasone instead of prednisone, in the treatment of children with ALL may also confer increased risk for neurocognitive impairment.[13]

Brain Tumors

Medical Background

Pediatric brain tumors are considerably more heterogeneous than ALL in that they vary by histology as well as location. Although brain tumors can appear as a second malignancy following the treatment of ALL with cranial irradiation, the etiology of most pediatric brain tumors

is uncertain. Next to ALL, primary CNS tumors are the second most frequently diagnosed malignancy of childhood and the most common pediatric solid tumor with an annual incidence of 2.7 per 100,000 children under the age of 20 years.[1]

Among the more common symptoms of a brain tumor are morning headaches, nausea, and lethargy resulting from tumor obstruction of the ventricles and increased intracranial pressure. Tumors are oftentimes characterized as being above (supratentorial) or below (infratentorial) the tentorium, a membrane that separates the cerebellum and brain stem from the rest of the brain. Problems with balance and cranial nerve findings are more common among patients with infratentorial tumors whereas seizures are more common among patients with supratentorial tumors. Computed tomography (CT) and/or magnetic resonance imaging are critical to the diagnosis of a pediatric brain tumor, and surgical resection or biopsy of tissue is usually necessary for definitive histological diagnosis. In addition to maximal safe surgical resection of the tumor, CRT, with or without chemotherapy, is indicated for malignant tumors. Local target volumes of radiation are applied to tumors that remain confined, with whole brain fields used for tumors that are mulitfocal. For those tumors with a tendency to spread through the neuraxis, craniospinal irradiation (CSI) is used. Radiation therapists are increasingly using 3-D techniques where individual beams are altered to conform to the shape of the target, sparing a greater amount of the normal surrounding tissue.[14] The total dose delivered to the brain depends on disease and patient factors, and can be more than twice that given in the treatment of ALL.

Prognosis varies with the tumor type. For example, medulloblastoma, the most common malignant brain tumor in childhood, has a prognosis of approximately 65% long-term survival whereas children with intrinsic brain stem glioma have a prognosis of less than 10%. Although this chapter will focus on the neuropsychological toxicity, other potentially serious complications from irradiation (e.g., hormone deficiencies, growth retardation, second malignancies) as well as

hearing loss from treatment with cisplatin chemotherapy, are recognized in the brain tumor literature.

Sources of CNS Insult

In the treatment of malignant brain tumors CSI has consistently shown a link to symptoms of neurocognitive deficit. Unfortunately, upon psychological testing, 40-100% of long-term brain tumor survivors have been found to have some form of cognitive dysfunction[15] with impaired intelligence found in nearly 90% of conventionally treated medulloblastoma patients.[16] When compared to brain tumor patients who did not receive radiation therapy, those patients who did receive radiation therapy consistently scored lower on tests of intellectual functioning.[17] Evidence also indicates that the effects of CSI has an immediate impact on intellectual functioning with a continuing pattern of decline over time.[18] These declines in IQ over time appear more severe for those who receive greater doses of CSI. Children treated for medulloblastoma with 23.4 Gy performed better on tests of intellectual and academic ability than those treated with 36 Gy.[19,20]

Extent of tumor resection is used in staging individual patients, with those who did not receive total resection of primary tumor tissue generally considered at higher risk. Extent of surgical resection has been found to have a positive relation with intellectual function[21] as well as no relation at all.[22] These equivocal findings could be due to variability in how total resection was defined and diagnosed, and the corresponding treatment the patient received based on their resection status.

Despite seizure activity being a common symptom, especially in supratentorial tumors, it is rarely considered in studies of neurocognitive function within pediatric oncology populations. Seizures are often successfully treated with anticonvulsant medications. However, these medications may themselves be linked to behavioral problems.[23] Accurate documentation of seizure activity and anticonvulsant use is therefore an important consideration when interpreting the cognitive functioning of brain tumor patients.

Increased intracranial pressure from the process of hydrocephalus can result when tumor obstructs the flow of the cerebral spinal fluid. Compression of tissue at both local and remote sites throughout the brain can result. Although it has been reported that acute hydrocephalus has had no lasting effects on cognitive functioning,[3] these studies have generally described hydrocephalus as being promptly treated with placement of shunts or surgical removal of the obstruction. However, there has been at least one study to find brain tumor patients with hydrocephalus at diagnosis to be at higher risk for intellectual deficits than those with no hydrocephalus at diagnosis.[24] In addition, hydrocephalus in other pediatric populations has been associated with problems of neurocognitive functioning including memory, attention and perceptual performance.[25] The long-term effects of hydrocephalus within the setting of childhood cancer requires additional examination.

Core and Secondary Symptoms of the Neurocognitive Phenotype

Within our model, secondary symptoms include broad-spectrum abilities measured by tests of academic achievement and intellectual functioning. These secondary symptoms can produce limitations in age-appropriate activities of daily living such as school performance, employment, independent living, and quality of life among subsets of surviving patients.[26-28] These problems were the first to be quantified in the neuro-oncology literature and remain important endpoints in any pediatric oncology Phase III clinical trial where CNS treatment is initiated.

Initially, some attributed these deficits to the nonspecific effects of chronic illness or school absenteeism. However, subsequent studies have objectively measured deficits in intellectual development and academic achievement relative to healthy age peers as well as other pediatric patients with cancer treatment not involving the CNS.[29,30] More recently, studies have sought to define the changes in underlying, core mental processes that secondarily result in changes in IQ and achievement. Many of the core symptoms are defined by the term "executive functions", including the ability to allocate attentional resources and to plan and

organize behavior, thought to be dependent upon pre-frontal lobe integrity. Other, more widely distributed functions, such as mental processing speed, the ability to sustain attention, to learn and retrieve new information efficiently, and to use previously learned information to provide a context for new learning, also appear to be negatively affected.[31-35] The increasing sophistication of such studies is evidenced by the fact that more recent investigations of attentional functioning are theoretically-driven, based upon cognitive models of normal development of attention and learning.[31,32]

One recent longitudinal study by Palmer and colleagues[18] has unequivocally demonstrated that declining IQ, the single most commonly occurring symptom among affected patients,[2-5] was not due to loss of previously acquired information but instead due to a failure to acquire new information at a rate commensurate with age peers. Forty-four patients with pediatric medulloblastoma had completed 150 psychological examinations of intellectual ability. Changes in patient IQ performance corrected for age (scaled scores) was compared to uncorrected performance (raw scores). A significant decline in IQ scaled scores was demonstrated over time since start of radiation treatment. Upon examination of raw scores a significant increase was found over time since start of radiation treatment. However, this increase, indicating acquisition of new information and skills across time, was less than expected in the normal healthy population therefore resulting in a decline in IQ scaled scores. Memory and attention are critical pre-requisite processes by which knowledge is acquired[36] and in a recent study up to 45% of the variance in IQ was accounted for by working memory ability and processing speed.[37] It is speculated that the inability to acquire new information and skills at a rate comparable to healthy same-age peers may be due to deficits in underlying core abilities such as memory and speed of processing.[18]

Identifying the core mechanisms by which patients experience a loss in academic and intellectual function is critical for developing efficacious intervention programs. Examples of standardized tests that are currently available to objectively evaluate the patient's school failure,

intellectual development, and potentially underlying problems with attention, memory, and processing speed are described in Table 1. An important component in the quest for successful interventions is to examine the neurobiological substrates associated with cognitive changes.

Insert Table 1 about here

Neurobiological Substrates

Neuropathological Changes

Studies utilizing neuro-imaging have shown changes in brain tissue following chemotherapy and radiation treatment. Utilizing computerized tomography (CT) to study patients with brain malignancies, several CNS abnormalities such as cerebral atrophy, calcifications, focal and diffuse white matter lesions, and enlarged ventricles, have been qualitatively defined.[38] Late effects of treatment-related CNS injury in ALL survivors include diffuse and multifocal white matter abnormalities, demyelination, breakdown of the blood-brain barrier, microvascular occlusion, and calcifications in cortical gray matter and basal ganglia.[39]

While it has been well documented in the literature that treatment for pediatric cancer is associated with several CNS abnormalities, the underlying cellular and subcellular mechanisms of such change require additional research. It is generally accepted however, that damage to the microvasculature, as well as accompanying injury to glial cells is involved.[40] Glial cells serve a supportive role by providing structure and insulation for the axon of the nerve cells. Within the white matter of the brain, oligodendrocytes, a type of glial cell, form a fatty sheath called myelin that surrounds portions of the neuronal axon and acts to dramatically increase the speed of nerve conduction.[41] Myelination normally continues after birth into the third decade of life[42] and exposure to CRT can disrupt this developmental process, ending in demyelination, and

ultimately white matter damage. In addition, immature oligodendrocytes are thought to be more vulnerable to injury than the mature counterparts.[43]

With the advent of biomedical image computation programs related to magnetic resonance imaging (MRI), neuro-imaging has advanced from a qualitative to a quantitative science.[44] The ability to quantify brain parenchyma has been developed and is termed quantitative MRI (qMRI). With qMRI the opportunity exists to detect subtle brain pathology that may otherwise be missed. Because of its increased sensitivity at detecting change in tissue characteristics, this technology holds promise for longitudinal assessments of treatment response and long-term post treatment follow-up. Greater accuracy in detection of change translates to earlier treatment and more informed treatment decisions for the patient, and perhaps an increased chance of survival.

For reasons outlined above, white matter appears to be especially prone to CRT damage.[45] Applying qMRI techniques, volumetric measures of white matter and other tissues have been examined in association with cranial radiation.[46] It was demonstrated that irradiated patients had significantly less normal appearing white matter volume than their non-irradiated matched counterparts, whereas gray matter volume was not found to differ between the two groups. A longitudinal study of 26 medulloblastoma patients with 178 MRI exams found normal appearing white matter volume to decline over time from start of treatment with CRT.[47] This was in stark contrast to the expected increase of normal maturation. While making an important initial contribution to the literature, these studies generally defined radiation dose by the amount given as the craniospinal volume. However, more precise measurement of tissue CRT dose exposure is available through the construction of dose contour maps and dose volume histograms. These methods provide an accurate measure of dose exposure for each specific area of the brain, or each identified structure of interest. Utilizing this technology, more precise studies of how radiation exposure may impact tissues, and any corresponding function of those tissues, are now possible.

Chemotherapy, especially high dose MTX, is also associated with white matter injury.[48] As demyelination occurs, axons near the lesions become swollen without an inflammatory response.[49] These changes are characterized as leukoencephalopathy. The quantity of leukoencephalopathy, as well as the amount of affected white matter, was found to increase in proportion to additional courses of high dose methotrexate during treatment.[50] The time course of MTX-induced leukoencephalopathy in an individual patient is illustrated in Figure 2. The cognitive effects of resolving areas of white matter hyperintensity are at present unknown.

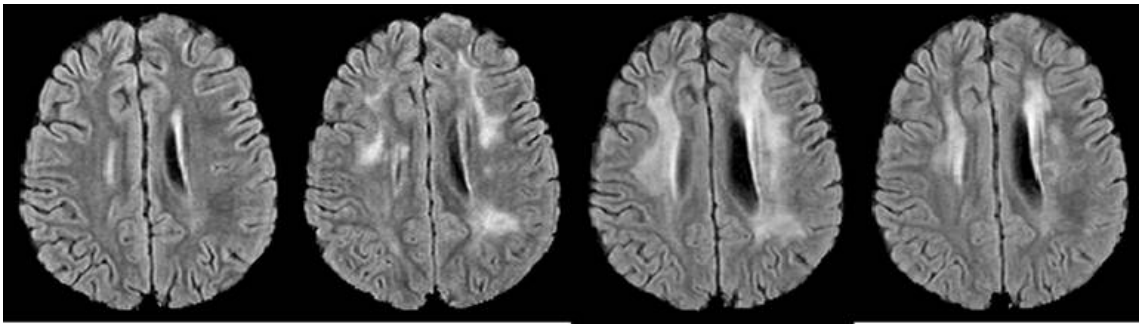

Figure 2. MRI FLAIR (fluid attenuated inversion recovery) images of changing patterns of leukoencepalopathy in ALL associated with HDMTX (high dose methotrexate). From left to right: Week 7 (1 HDMTX), Week 18 (4 HDMTX), Week 44 (7 HDMTX), and Week 132 (end of treatment). The transverse images show periventricular white matter abnormalities increasing to 35% of total white matter volume at Week 44 and then decreasing to 15% at the end of treatment (Reddick et. al., Quantitative MR measure of MTX neurotoxicity in children, in press).

Leukoencephalopathy can be transient during treatment with permanent damage emerging as a late effect of treatment. The intensity of remaining leukoencephalopathy was found to vary by individual patient. The clinical course of this pathology is gradual, characterized by decreased alertness and, eventually, intellectual decline.[49]

Neurocognitive Correlations

The volume of the cerebral hemispheres is about one-half myelin; however, patterns of myelination differ across brain regions. Brain stem and cerebellar areas myelinate first, followed by the cerebral hemispheres, and finally, the anterior portions of the frontal lobes. This process is believed to parallel the maturation of brain functions associated with these areas.[42] Demyelination, the loss of myelin tissue, is frequently observed in the CNS following

treatment.[45] Frontal lobe white matter has extensive links to more posterior cortical and subcortical areas of the brain. The right frontal lobe is especially rich in myelin. Therefore, global white matter pathology might disproportionately affect functions associated with this region, such as attention and visuospatial ability.[51]

Considering the role and distribution of myelin in the brain, the neurocognitive impairments of long-term survivors are somewhat intuitive. For example, the diffuse loss of myelin in survivors might be expected to be associated with widely distributed functions in the brain such as attention and information processing speed. Indeed, a recent study demonstrated that deficits in the speed of information processing were correlated with the volume of white matter loss among older adults.[52] Brain volumetry studies within pediatric cancer have also found secondary functional consequences, such as IQ and academic achievement declines, of tissue loss[17,53] In one study, 18 pediatric patients previously treated for medulloblastoma, with CSI with or without chemotherapy following surgery, were matched on the basis of age at the time of evaluation to 18 patients treated for low grade tumors of the posterior fossa who were treated with surgery alone. Evaluations were conducted with age-appropriate neurocognitive testing and qMRI of normal appearing white matter. Patients treated for medulloblastoma had significantly less normal appearing white matter and significantly lower IQ scores than their low grade controls. In addition, normal appearing white matter has a positive and statistically significant relationship with IQ. [17] In a more recent study from the St. Jude Group, 53 patients who had completed CRT with or without chemotherapy for medulloblastoma were evaluated by qMRI and neurocognitive testing. Analysis of MRI data with an automated segmentation algorithm developed from an artificial neural network revealed that smaller volumes of normal appearing white matter were predicted by a younger age at evaluation, higher CRT dose, and increased time from completion of CRT. Furthermore, volumes of normal appearing white matter were positively correlated with IQ values.[53] The investigators have concluded from these two studies that inhibition of normal white matter development and/or loss of white matter volume at least partially explains intellectual and academic deficits among children who survive medulloblastoma. Current efforts are being aimed at identifying the effects of this tissue loss on core functions of the syndrome (e.g., processing speed, attention).

Premorbid Influences

Gender

The most convincing data relating to gender as a risk factor for increased neurotoxicity has come from the work of the Dana Farber group with patients treated for ALL,[54-56] although this effect had been reported incidentally in other papers.[10] When gender effects have been investigated and have had significant effects on cognitive function, female gender confers a greater risk. Waber's initial study utilized a control group with solid tumors who had not received CNS therapy to assess the risks associated with CNS prophylaxis. Measures of intellectual and academic functioning, including a test of reading comprehension were obtained for both groups of children. The ALL group performed below average norms on all measures, while the solid tumor group performed above average on all measures. Group differences indicated that the ALL group was more cognitively impaired than the solid tumor group, and females in both groups were more impaired than males. In addition, the correlation between age, socioeconomic status, and cognitive impairment within the ALL group differed as a function of gender. Specifically, early age of diagnosis and low SES were associated with more severe cognitive impairment in females, while these factors did not reliably correlate for males. It was concluded that the major risk factor for CNS toxicity among children treated for ALL was gender with females at greater risk than males.

Providing further support to the role of gender, these results were confirmed in a more recent study which also demonstrated clear dose-related, gender-dependent effects of treatment on cognitive functioning in ALL survivors.[55] Both male and female children showed decreased performance on measures of language-based academic skill and memory for digit strings. Conversely, only girls demonstrated global decline of cognitive function (i.e., lower IQ). Systemic chemotherapy was associated with this decline in IQ for girls, indicating that systemic as well as CNS chemotherapy should be evaluated as a risk factor for cognitive impairment.

Most recently, the same group has published a comparison of patients surviving ALL who had been treated with intrathecal MTX, conventional dose MTX or high dose MTX with or without 18 Gy CRT. Females receiving high dose MTX with CRT were more impaired than males receiving the same combination therapy and more impaired than other females receiving conventional MTX with CRT.[56] Researchers speculate that global deficits might be associated with diffuse axonal injury, a neurotoxicity

that might be both endocrine-dependent and worsened by large doses of chemotherapy. However, more research is needed to clarify the relationship between gender, treatment type, and cognitive outcome.

Age at Treatment

A younger age at treatment is often found to be a critical risk factor, with this group showing significantly greater declines in age-adjusted scaled scores of intellectual functioning over time than their older counterparts. For example, children who were older (>8.85 years) when treated for medulloblastoma experienced less neurotoxicity than those who were younger at treatment (<8.85 years) exhibiting greater performance on tests of intellectual functioning.[19] In a longitudinal study of intellectual development over time since radiation treatment, medulloblastoma patients who were ≤8.02 years experienced significantly greater declines in age-adjusted scaled scores of factual knowledge and nonverbal abstract thinking as well as an overall estimate of full-scale IQ than those who were >8.02 years.[18]

It has been suggested that age at treatment is a proxy variable for underlying neurodevelopmental maturity.[17,53] While development of cortical gray matter peaks at approximately age 4 years, cortical white matter volume continues to rise until about age 20 years.[57] Therefore, those who are younger at radiation treatment generally have less fully developed white matter. However, since both younger and older patients have been shown to lose white matter volume at a similar rates,[47] the younger irradiated patients continue to display reduced total white matter volume following radiation treatment. These deficits in white matter volume among younger patients have also been associated with increased intellectual morbidity.[17,47,53]

Compensatory Neurobiological Systems

The concept of "brain reserve capacity" has been proposed to explain individual variation in the behavioral manifestation of signs and symptoms of brain damage.[58] Using a model derived from adult studies of progressive neurologic diseases that result in dementia (Alzheimer's Disease, Parkinson's Disease, AIDS), he proposes that each individual has a unique threshold for tolerance of brain damage before signs and symptoms are noted. Cumulative effects of brain insults remaining below the threshold allow the individual to remain asymptomatic whereas clinical symptoms become apparent once the threshold is reached. Patients with greater brain reserve capacity will be

more resilient (i.e., have a higher threshold) to the effects of any specific brain insult than those with lesser reserve capacity. Brain reserve capacity can be estimated neuroanatomically (CT, MRI) by normal brain volume and functionally by intellectual and educational attainment.

The concept of brain reserve capacity discussed did not make reference to childhood brain damage or brain tumors.[58] However, it is relevant to the present research discussion in that it provides a useful framework to explain variability in cognitive function among patients who have received virtually identical medical treatment. Several hypotheses follow from the reserve capacity model that have received some support. One hypothesis is that patients who are more cognitively and neurologically intact prior to a particular form of therapy, such as CRT, will have a better functional outcome. An analysis of IQ function 4 years following treatment for childhood brain tumor revealed that postoperative IQ was the best predictor, accounting for 62% of the variance alone.[22]

Damage to brain parenchyma during and following treatment gradually develops over time. A recent study investigated the possibility for reorganization of function among 61 right handed adult patients who underwent treatment for brain tumors and were experiencing slow onset of damage.[59] When compared to healthy controls, it was found that the brain tumor patients recruited additional left frontal regions of the brain for language function other than the traditional language areas. They also recruited frontolateral areas in the non-dominant hemisphere for language function. This study provides a step toward understanding plasticity of function among adults and could be used as a foundation for pediatric studies.

Compensatory Psychosocial Systems

Although patients with varying types of CNS treatments may express similar core neurocognitive symptoms, considerable variability exists in their actual academic performance. Aside from treatment factors, one possible explanation is that the home, school, and community environments of patients have differences in their ability to compensate for core deficits and thus affect the intensity of secondary symptoms such as achievement in school. For example,

among healthy samples of children, sociodemographic factors such as ethnicity and parental education can account for up to 28% of the variance in IQ.[60] Among children previously treated for ALL, several studies have demonstrated that socioeconomic status is correlated with IQ and other neurocognitive outcomes with patients coming from families with higher socioeconomic status having better performance.[8,32,61]

One implication of these relationships is that the patient's environment may modify the intensity of the expression of secondary neurocognitive deficits, even among children with similar core deficits. Can patients who experience enriched environments following treatment overcome their deficits more easily? One could speculate that the patient who had interactions with teachers that were taught about the patient's specific area of deficit, and who were skilled in assisting the patient to practice these weak areas of function, would be more successful in learning to overcome and compensate for their deficits. In addition, it is speculated that having better informed parents with access to extracurricular resources to supplement their child's education would increase the child's eventual outcome. This is an important area of study that could be implemented with a favorable cost-benefit ratio. However, we are unaware of any current efforts to examine these possibilities.

Interventions for Neuropsychological Deficits

Although research on the patterns and risks for neuropsychological and educational deficits among survivors of childhood cancer has been progressing for the past three decades, the development of empirically validated interventions for these deficits has not been as rapid. Broadly speaking, interventions can be divided into two approaches: those intended to avoid or reduce the neuropsychological toxicity of therapy directed toward the CNS, and those intended to minimize or rehabilitate deficits that cannot be avoided.

A formal plan of prospective surveillance of neuropsychological status should be set forth for each patient based upon known or suspected developmental risk for problems. This assumes that a qualified psychologist has been identified as a consultant to the institution. For

example, a young adult with a supratentorial low grade glioma treated with surgery alone may require formal assessment only once or twice during the two year period following diagnosis with the focus being whether there is evidence of loss of abilities. On the other hand, a young child with the same tumor and treatment should have a neuropsychological evaluation scheduled at the completion of therapy and three to five years later, whereas an infant with a brain tumor should probably be evaluated every six months until the age of three or four years and then yearly until five years post therapy. Such plans should not depend upon the presentation of symptoms because presymptomatic assessments oftentimes allow for early educational interventions that may minimize deficits.

Contemporary treatment protocols for children with for cancer generally show an enlightened concern for the potential neurotoxicity of therapy, especially among very young patients. The elimination of CRT, delay of CRT until the patient is older, or CRT dose/volume reduction to spare more normal brain are frequently considered approaches. Several studies have documented benefit of CRT dose reduction in terms of IQ and achievement functioning in survivors of ALL and brain tumors.[2,3,20,30] The benefits of more recent technological improvements, such as the use of 3-dimensional conformal CRT, are not yet known. However, with ever increasing cure rates, this approach to toxicity reduction is likely to continue to be very active.

If neuropsychological impairments are unavoidable, one may attempt to minimize the impact by direct intervention with cognitive rehabilitation or pharmacotherapy, and/or through more indirect approaches involving manipulations of the patient's environment. Cognitive rehabilitation is a term used to describe interventions intended to restore lost cognitive functions or to teach the patient skills to compensate for cognitive losses that cannot be restored. Although some evidence for efficacy is available from the child closed head injury literature, we are aware of only one program in the United States that is attempting to validate a standardized,

20-session program of cognitive rehabilitation for survivors of ALL and brain tumors in a seven institution consortium funded by the National Cancer Institute.[62]

Pharmacotherapy, especially the use of psychostimulants such as methylphenidate (Ritalin), has recently received interest. Impressive gains in activity level and quality of life were shown in one study of adult glioma patients treated with methylphenidate at the University of Texas/M.D. Anderson Cancer Center.[63] A subsequent study at our institution investigated the acute effects of methylphenidate on the cognitive functioning of pediatric patients treated for cancer.[64] In this double-blind, placebo-controlled study, patients given 0.6 mg/kg methylphenidate showed significant improvement on measures of attention when compared to those receiving placebo. Our current study, funded by the National Cancer Institute, expands upon these findings by conducting a 3-week crossover trial of two doses of methylphenidate and placebo in the home and school environments to establish the potential for efficacy prior to 12 months of treatment. Parent and teacher ratings of behavior as well as objective testing of the patients will allow the evaluation of effects on academic achievement and social relations.

Finally, one should not minimize the potential positive impact of optimal communication and education of the patient's caregivers.[65] Routine communication between the cancer treatment center and the patient's school should be the standard of care, especially in cases in which subtle neurological (e.g., hearing loss in the speech frequencies, visual field cuts) or neuropsychological deficits (e.g., problems with attention, memory, or processing speed) can obviously impair the patient's ability to function in a normal classroom environment. Because all of the deficits listed above are unobservable to teachers, there may be a tendency to misinterpret the patient's behavior in the absence of knowledge of the deficits. For example, we have experience with children labeled as having attitude problems, or as being daydreamers or unmotivated to learn when, in fact, the patient had real disabilities that were unknown to the teacher. Although parents can have an important role in facilitating communication between the cancer center and the school, we have found that a telephone call or visit from a representative

from the cancer center teacher or social worker can have a profound impact on the adaptation of the classroom environment to meet the patient's needs.

Priority Areas for Future Research

In November of 2000, a report from the Brain Tumor Progress Review Group, jointly sponsored by the National Cancer Institute and the National Institute for Neurological Disorders and Stroke, articulated four priority areas for pediatric research.[66] Two of these related to the neuropsychological functioning of surviving children. In particular, an emphasis was placed on more accurate assessment of risks for deficits, the development of more precise methods of assessing functional and structural damage to the developing nervous system, and the development of methods to prevent, minimize or rehabilitate deficits that cannot be avoided. These points will be elaborated in the following section.

More fine-grained analyses of cognitive impairments in survivors will continue to expand upon our understanding of specific cognitive phenotypes and risks for these deficits among our patients. For example, the objective assessment of "executive functions" and processing speed may provide us with early harbingers of impending changes in intellectual development and academic achievement. The addition of recent quantitative neuro-imaging techniques will facilitate our understanding of the biological substrates underlying neurocognitive deficits. However, the theoretical frameworks used to conceptualize these more specific neurocognitive processes differ across studies, as do the tools and methods used to measure cognitive processes. There is little agreement as to which conceptual model of cognitive processes is best applied or how to operationally define the cognitive processes delineated by different models. For this reason, *it is critical that future researchers clearly describe their materials, methods, and the conceptual models they use to select tests and interpret results.* This allows for comparison of cognitive outcomes across studies and cancer diagnoses.

Despite our growing knowledge about neuropsychological outcomes, our understanding of the neurobiological mechanisms underlying adverse outcomes and our ability to extrapolate

interventions from our understanding of these mechanisms is quite rudimentary. *Future research efforts would benefit from the use of animal analogue models and quantitative neuroimaging (e.g., fMRI, PET) to better characterize biological changes in normal tissue and their correlation with neuropsychological deficits.* Unlike the adult cancer setting, central nervous system damage in the developing child rarely results in dementia but rather a slowing in the learning of new skills and information compared to healthy age peers. Furthermore, these learning problems may not be evident until a particular skill that is normally expected to emerge does not. It is this dynamic system that makes pediatric neuroscience both more complex and more exciting in terms of the potential for plasticity. However, many of the most relevant contemporary research questions require animal models.

Pediatric oncologists and radiation oncologists are generally aware of the risks of brain tumor therapy for neuropsychological deficits, especially in very young children, and treatment protocols are now purposefully designed to reduce toxicity as well as to increase survival. Unfortunately, not all apparent reductions in treatment aggressiveness (e.g., reduction of RT total dose) result in measurable benefit to the patient and some patients, despite these efforts, will have unavoidable neuropsychological deficits. Furthermore, it is obvious that the empirical literature currently gives little guidance in terms of pharmacological, cognitive, or environmental interventions to rehabilitate neuropsychological deficits in survivors. It is understandable that correlational and descriptive studies were needed in the past to document the incidence and prevalence of deficits among different subgroups of survivors. However, *future neuropsychological research should give a higher priority to studies of interventions to prevent, minimize, or rehabilitate neuropsychological deficits.* Intervention research in the context of clinical trials is expensive, labor-intensive, and time-consuming but these barriers can be overcome in collaborative, multi-institutional trials.

What, then, are the resources need to remove barriers and facilitate the implementation of the above recommendations? One issue involves the training of clinical neuroscientists to

prepare them to attack these problems. Historically, pediatric psychologists, clinical child psychologists and, less frequently, pediatric neuropsychologists, have taken the lead in developing investigations in the area of neurocognitive problems of children surviving cancer. However, *a new model of a hybrid clinical neuroscientist will likely be needed* to take the research to the next level. Investigators trained in human development, developmental neurobiology, molecular biology, and pediatric neuropsychology who can interface with investigators from diverse clinical (e.g., diagnostic imaging, hematology/oncology, neurology,) and basic science (e.g., pharmacology, biochemistry) departments will be best prepared to lead such an effort. The use of advanced training awards, such as the Cancer Research Training and Career Development awards from the National Cancer Institute, may provide one route for such innovative advanced training at the postdoctoral or junior faculty level.

A second stubborn issue that has undeniably limited research on neurocognitive late effects in childhood cancer is the *inconsistent availability of third-party payment for clinical neuropsychological testing*. Despite the fact that routine surveillance testing in high risk groups of children has long been promoted as a standard of care within the cooperative groups, medical necessity as defined by managed care panels, prevents most children with cancer from obtaining such services with coverage, especially in the absence of being able to establish a mental health diagnosis. A coordinated national approach to this problem, perhaps through the National Institutes of Health, is seriously needed. One would hope that a legislative approach to this problem would not be necessary. However, with the growing and significant numbers of childhood cancer survivors reaching the age of majority, this and other quality of life issues (e.g., medical and life insurance, employment) of childhood cancer survivorship may eventually evolve into a political agenda.

Conclusions

This paper has attempted to highlight the most important issues relevant to neurocognitive late effects in childhood cancer by using a conceptual model newly developed by

the authors. Within this model, sources of CNS insult experienced by patients treated for ALL and brain tumors are discussed as well as the neurobiological factors underlying CNS damage. Various compensatory mechanisms that can modify the expression of core symptoms (e.g., problems with attention, processing speed) and secondary symptoms (e.g., declining IQ, academic failure) are also described. One goal is that this model may be a useful framework for the development of future research agendas and to integrate the results of past and future studies. We have recommended better description of methodologies in future studies, the use of animal analog models and quantitative neuro-imaging to better elucidate mechanisms of CNS damage, and an increased emphasis on clinical trials testing interventions for neurocognitive late effects. Reaching these goals will be expedited by developing novel models of hybrid neuroscientists and by removing barriers to third party payment for protocol-driven clinical neuropsychological evaluations of patients. The discovery of effective interventions will facilitate the achievement of our ultimate goal for survivors of childhood cancer; that is, returning them to the quality of life that they would have had if they had never had cancer.

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Figure Captions

Figure 1. Conceptual framework guiding the discussion of neurocognitive late effects in childhood cancer with the purpose of integrating existing research and identifying areas of research priority for the future.

Figure 2. MRI FLAIR (fluid attenuated inversion recovery) images of changing patterns of leukoencephalopathy in ALL associated with HDMTX (high dose methotrexate). From left to right: Week 7 (1 HDMTX), Week 18 (4 HDMTX), Week 44 (7 HDMTX), and Week 132 (end of treatment). The transverse images show periventricular white matter abnormalities increasing to 35% of total white matter volume at Week 44 and then decreasing to 15% at the end of treatment (Reddick et. al., Quantitative MR measure of MTX neurotoxicity in children, in press).

Table 1. Examples of Core and Secondary Symptoms and Recommended Methods of Quantitative Assessment

Type of Problem	Objective Assessment Method	Description
Secondary Problems		
School failure	Standard tests of academic achievement (e.g., Wechsler Individual Achievement Test[1])	Individually administered tests of reading recognition (word attack), reading comprehension, spelling, math computation and reasoning. Patient's achievement scores are compared to those of age-peers in the general population.
Suspected IQ loss	Standard tests of intellectual development (e.g., Wechsler Intelligence Scale for for Children-III[2])	Individually administered test of intellectual development including verbal and nonverbal skills, processing speed, and freedom from distractibility. Patient's scores are compared to those of age-peers in the general population.
Primary Problems		
Attention	a) Standardized behavioral tests of sustained, Selective, divided attention, and reaction time (e.g., Stroop[3], Continuous Performance Test[4]) b) Standardized parent and teacher inventories Of patient's behavior (e.g., Conners' Parent And Teacher Report Forms[5])	Many of these tasks were originally designed for diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). However, most patients surviving brain tumors or ALL with academic problems will exhibit inattention rather than hyperactivity. These tests allow for comparison to age and gender adjusted performance in the general population.
Memory	Standardized tests of verbal and nonverbal Short-term and long-term memory	Even among patients without attentional deficits, many will have problems in learning and recalling new information. Tests like the

Table 1. (Continued)

Type of Problem	Objective Assessment Method	Description
	(e.g., Children's Memory Scale[6], Wide Range Assessment of Memory and Learning[7])	these allow for comparisons of learning efficiency and accuracy of recall to age peers in the general population so that the sources of these problems can be identified.
Processing Speed	Some indications of processing speed can Be derived from the Wechsler scales. However, More pure measures are derived from tests of Reaction time (e.g., Continuous Performance Test) or on experimental tests that are, unfortunately, not standardized.	Processing speed is closely linked with the general integrity of the CNS And is associated with performance on tests of memory and attention.

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