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REVIEW
Neurocognitive Late Effects of Chemotherapy in Children: The Past 10 Years of Research on Brain Structure and Function

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Advances in the treatment of childhood cancers have greatly improved survivorship. Success has not come without cost, however, as survivors are at risk for late effects of treatment, including neurocognitive late effects (e.g., difficulties with thinking and reasoning). In the advent of chemotherapy-only protocols, researchers are examining neurocognitive sequelae of these agents to understand the specific role of chemotherapy in neurocognitive changes and the mechanism through which these occur. In this review, we examine the state of the literature on neurocognitive late effects after chemotherapy and their proposed neural mechanisms. Pediatr Blood Cancer 2009;52:159–164. © 2008 Wiley-Liss, Inc.

Key words: chemotherapy; late effects; MRI; neurocognitive; neuroradiology; neurotoxicity

INTRODUCTION

Research into neurocognitive late effects of childhood cancer began in the 1980s, and focused on populations with the most obvious late effects: patients who had experienced a clear insult to the brain from a brain tumor or cranial irradiation. Both have clear and well-documented effects on brain structure and function [1,2].

Current treatments for many childhood cancers favor chemotherapy without radiation when possible, particularly for younger children, whose developing brains are most vulnerable to its neurotoxic effects. While the neurocognitive late effects of chemotherapy alone may be relatively subtle in comparison to the effects of cranial radiation, they are still noteworthy. A significant proportion of children who are treated with chemotherapy alone show neurocognitive deficits [3–5].

The majority of research on neurocognitive late effects has been plagued by a variety of problems, including rapidly changing treatment protocols and very small or heterogeneous subject populations. Despite these unavoidable limitations, the past 10 years of research into late effects has brought advances in both neuropsychological measurement and neuroimaging techniques that are beginning to allow us to better understand how chemotherapy alone affects the developing brain. Given the growing number of childhood cancer survivors treated with only chemotherapy, it is becoming increasingly important to understand the effect of chemotherapy agents on brain development to predict risks for survivors and choose optimal treatment strategies for those newly diagnosed.

The goal of this article is to review what has been discovered about the effects of chemotherapy alone on children's brain structure and function as seen through neuroimaging and neurocognitive studies over the past 10 years and discuss future directions for research.

RESULTS OF NEUROPSYCHOLOGICAL STUDIES

Lezak [6] defines clinical neuropsychology as "an applied science concerned with the behavioral expression of brain dysfunction." Neuropsychologists conduct assessments through standardized testing to determine how brain functioning affects daily functioning, abilities, and development using a range of measures from broad indexes such as overall intellect (IQ) to very specific domains of function such as attention, executive functioning, or visual-motor integration.

Treatment protocols for childhood cancer have changed rapidly over the years, maintaining a balance between effective therapy and acceptable toxicity. As the elimination of radiation from protocols is a relatively recent phenomenon, only recent studies have truly assessed late effects of chemotherapy without radiation. Table I lists studies from the past 10 years that have focused on the neurocognitive effects of chemotherapy alone.

Overall, the literature indicates that the most common neuropsychological effects of chemotherapy alone involve deficits in visual processing [5,7,8], visual-motor functioning [3,5,9], and attention and executive functioning [4,10–12]. Difficulties in visual processing affect how a child makes sense out of visual information (e.g., being shown something without verbal explanation, understanding maps, visual-spatial skills). Visual-motor functioning involves skills like legibility of handwriting, and the ability to copy drawings. Attention refers to a child's ability to maintain concentration or focus and ignore distractions, and can affect functioning in almost all settings. Executive functioning refers to the ability to organize, plan, hold information in mind and manipulate it (e.g., mental math) and self-monitor behavior. Some studies also find minor difficulties in verbal abilities, memory, and academic achievement [7,12,13]. Between a quarter and a third of subjects show some neurocognitive decline regardless of specific chemotherapy protocol [14,15]. Additionally, it has been noted that girls do worse than boys [8,10,14], and that younger children (particularly less than 3 years old) have greater deficits [10,13]. Emerging developmental abilities may be most vulnerable to treatment, potentially accounting for some effects on the developing language system in younger children [10].

Different types of chemotherapy and administration methods likely have different levels of neurotoxicity. Methotrexate, an integral part of current leukemia and other childhood cancer treatment protocols has known neurotoxicity [16]. However, most studies of methotrexate neurotoxicity have focused on white matter hyperintensities seen on MRI or neurological events such as seizures, neither of which correlate with neurocognitive functioning

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TABLE I. Neurocognitive Effects of Chemotherapy

References	N	Neuropsychological domains assessed	Main findings
Hill et al. [13]	10 ALL survivors, 10 healthy controls	IQ Memory	Chemotherapy affects verbal and visual memory as well as IQ in children treated at a young age (5 and younger)
Brown et al. [8]	47 ALL survivors	IQ Achievement Visual-motor integration	Survivors did worse than test norms on on non-verbal tests; girls did worse than boys; no effects on achievement
Brown et al. [7]	26 cancer survivors	General development IQ Achievement	CNS chemotherapy resulted in greater neurocognitive deficits than non-CNS targeted therapy, particularly in academic achievement
Kaleita et al. [22]	30 ALL survivors	General development	Survivors similar to normal population on McCarthy
Espy et al. [12]	30 ALL survivors	IQ General development Achievement Language Visual-motor integration Verbal memory Executive functioning	Modest declines in arithmetic, visual-motor integration, verbal fluency over 4 years after diagnosis, although still within the average range
Kingma et al. [3]	20 ALL survivors, 17 ALL survivor controls and 225 healthy children	IQ Verbal learning Processing speed Executive functioning Visual-motor integration Fine motor	Minor differences between survivors and controls on verbal IQ and Trails B, but no major cognitive impairment in survivors, and no significant differences between groups of ALL survivors
Montour-Proulx et al. [20]	19 ALL survivors	IQ Memory	Verbal IQ and memory remained stable while performance IQ declined. All mean scores were lower than population means.
Buizer et al. [21]	36 ALL survivors, 39 cancer controls, 110 healthy controls	Attention	CNS chemotherapy is associated with attentional dysfunction, particularly in intensified treatment protocols, young age at diagnosis, and girls
Buizer et al. [21]	34 ALL survivors, 38 cancer controls, 151 healthy controls	Visual-motor integration	CNS chemotherapy affects visual-motor control, particularly in girls
Mahone et al. [9]	22 ALL survivors, 22 healthy controls	Timing Judgment of interval Judgment of pitch	Chemotherapy results in perceptual and motor timing deficits thought to be regulated by cerebellar-frontal pathways

[16,17]. Different corticosteroids may have differing levels of effect on neurocognitive function. Waber et al. [18] examined differences in neurocognitive effects between two different leukemia treatment protocols, finding greater neurocognitive effects from dexamethasone than prednisone. Additionally, administration method or timing of chemotherapy may also affect neurocognitive outcome. Copeland et al. [5] examined differences between intrathecally administered chemotherapy versus no specific CNS chemotherapy, finding that intrathecal therapy was associated with a few longer-term neurocognitive sequelae, but no clinically meaningful difference between these two groups. Kaleita et al. [19] assessed cognitive, motor, and behavioral functioning in children who received delayed intensification. Children who received delayed intensification (i.e., an additional 3 weeks of dexamethasone, vincristine, daunomycin, Ara C, and cytoxan) performed significantly worse on a visual-motor integration task than children who did not receive delayed intensification. The authors speculated that this difference in performance could have been due to the additional dexamethasone or vincristine therapy. Montour-Proulx et al. [20] found an effect of cumulative dosage of intrathecal methotrexate on estimated Wechsler Performance IQ in a sample of 24 leukemia survivors treated with chemotherapy only. More recently, Buizer et al. [11,21] found an association between chemotherapy and attention and visual-motor functioning in 35 ALL survivors who were treated with chemotherapy only. They noted that intensified treatment protocols had the greatest effect on attention, and that females and children who were younger at the time of diagnosis were more susceptible.

There are a number of issues to be considered in evaluating this research. Neurocognitive testing batteries vary widely from one study to the next and are frequently updated, making it difficult to see replication of findings. Treatment protocols are also constantly being updated, so even if a study carefully focuses on one protocol, it is often quickly obsolete. It is impossible to determine the effects of any single chemotherapy agent because they are rarely administered alone. It is also impossible to separate out the effects of the disease from the treatment, as healthy patients do not receive these treatments. Furthermore, the goals of the studies often vary, which can make it seem as if discrepant results were found when that is not necessarily the case. For example, some studies have focused on demonstrating that children who receive chemotherapy without radiation remain generally cognitively intact (e.g., Kaleita et al. [22]), while others have focused on the subtle yet specific differences between children who have undergone chemotherapy

treatment and a healthy population (e.g., Mahone et al. [9]). Despite these limitations, this field of research is progressing toward a better understanding of the effects of chemotherapy on children's brains.

In general, regardless of agent used or administration method, attention and executive functioning [4,10–12], visual processing [5,7,8], and visual-motor functioning [3,5,9] emerge as important neurocognitive domains affected by current chemotherapy treatment protocols. Several studies have demonstrated that this pattern of findings is similar to that seen in patients treated with cranial radiation therapy [23]. The primary difference is in the severity of the effect. While research indicates that as a group, cancer survivors treated with chemotherapy alone experience only subtle changes in neurocognitive functioning, these changes still affect children's ability to function in their daily lives and reach their academic potential. Theory-driven research on the effect of chemotherapy on brain structure and function is necessary to inform the development of the least toxic treatment protocols and ultimately predict those at greatest risk for neurocognitive late effects.

THEORETICAL MODELS FOR NEUROCOGNITIVE CHANGE

Saykin et al. [24] note that "the greatest gap in our knowledge regarding chemotherapy-related cognitive changes is a lack of understanding of the mechanism or mechanisms that account for the observed changes." The majority of studies focus on either functional neurocognitive outcomes or structural neuroimaging. Only a few recent studies have begun to combine the examination of brain structure with function. Damage to cortical and subcortical white matter has been the most widely accepted model explaining neurocognitive changes following chemotherapy [1,2,15]. Functionally, the integrity of white matter between different brain regions is thought to be evident in neuropsychological measures such as processing speed and visual-spatial or visual-motor tasks that depend on communication between multiple regions of the brain [25]. Researchers have hypothesized that the developing brain may be more susceptible to damage because newly synthesized myelin has higher metabolic activity and lower stability, making it more vulnerable to the toxic effects of therapy. Data from neuroimaging studies support this model, and early studies combining neuroimaging and neurocognitive assessment also support this model. Saykin et al. [24] outline three nonexclusive mechanisms for this white matter damage: "(1) direct neurotoxic injury to the cerebral parenchyma, including the microglia, oligodendrocytes, and neuronal axons, producing demyelination or altered water content; (2) secondary inflammatory response, an immunologic mechanism including allergic hypersensitivity and autoimmune vasculitis; and (3) microvascular injury leading to obstruction of small and medium sized blood vessels, spontaneous thrombosis, ischemia/infection, and parenchymal necrosis." Based on the deficits displayed and preliminary MRI studies, frontal white matter is thought to be most affected [26]; specifically, fronto-cerebellar pathways [9,27].

Genetic factors may also play a role in individual differences in brain response to chemotherapy. Apolipoprotein E (APOE) is a complex glucolipoprotein that facilitates the uptake, transport and distribution of lipids. Previous studies have suggested that it plays an important role in neuronal repair and plasticity after injury. The human E4 allele has been associated with poor outcomes in various disorders with prominent neurocognitive dysfunction, including Alzheimers disease, stroke, and traumatic brain injury. A recent study investigating the relationship of the APOE genotype to neuropsychological performance in adult survivors of breast cancer and lymphoma found that those with at least one E4 allele scored significantly lower in visual memory and spatial ability domains, with a trend to score lower in executive functioning, compared with survivors who did not carry an E4 allele [28]. The authors suggest that APOE4 may be a genetic marker for increased vulnerability to chemotherapy-induced cognitive decline.

Investigation of genetic polymorphisms also holds promise for furthering our understanding of the mechanisms behind chemotherapy-induced neurocognitive changes [29]. Genetic factors have the potential to affect the neurotoxicity of treatments, potentially making one more or less vulnerable to poor neurocognitive outcomes after certain types of cancers and their treatments. Some identified genetic factors have been hypothesized to affect metabolism of specific chemotherapeutic agents or play a role in neural vulnerability. For example, common polymorphisms of methylene tetrahydrofolate reductase (MTHFR), a folate-metabolizing gene, have been associated with a decrease of folate levels in response to methotrexate (an antifolate metabolite), and increased levels of homocysteine (an excitotoxin). Researchers have hypothesized that free oxygen radical mediated damage secondary to increased homocysteine and folate depletion may be a potential cause of neurocognitive problems associated with cancer treatment. Specifically, the polymorphism MTHFR-677-TT has been associated with better medical outcome in at least one study, and may play a role in late neurocognitive effects [30]. A recent study [31] investigated the role of MTHFR polymorphisms in attention deficit hyperactivity disorder after treatment for ALL and found that certain genotypes related to lower folate levels (specifically A1298C) were strongly associated with inattentive symptoms in survivors. Further genetic studies such as these will be important in understanding the variability in neurocognitive outcomes after chemotherapy.

RESULTS OF NEUROIMAGING STUDIES

Newer techniques such as functional MRI (fMRI), MR spectroscopy, single-photon emission computerized tomography (SPECT) and diffusion tensor imaging (DTI) are offering more sensitive and specific ways to examine brain structure and function. Studies have begun to combine sensitive neuroimaging techniques and neurocognitive testing to evaluate both structure and function. Recent studies that focused exclusively on chemotherapy or included a specific group of patients who received only chemotherapy are reviewed below. Many studies have suggested that the effects seen are largely the result of methotrexate, although a few studies have demonstrated similar white matter issues in children whose chemotherapy protocols did not include methotrexate [11].

Basic structural magnetic resonance imaging (MRI). Methotrexate neurotoxicity (usually from intrathecal administration) is a fairly well-established phenomenon which has been associated with transient T2 hyperintensities in the white matter that resolve by the end of or within a year or so of treatment [16,17,32,33]. These hyperintensities are thought to be the result of cerebral edema, can produce stroke-like symptoms and/or seizures, but resolve quickly [16,34]. Younger children seem more susceptible to these effects [32]. Studies have found no association between hyperintensities on MRI and neurocognitive functioning [16,20]. However, recent research does show associations between other MRI findings and

neurocognitive performance. Paako et al. [32] found associations between white matter changes and attention in leukemia survivors, but the group of 33 survivors included 15 who had received cranial radiation.

In perhaps the largest published study to combine basic structural neuroimaging technology and neurocognitive outcome measures, Reddick et al. [35] examined 112 ALL survivors between ages 6 and 18 (84 of whom had received chemotherapy only) and 33 healthy sibling controls. Neurocognitive measures of intelligence, attention, and academic achievement were performed and MRIs were obtained and segmented to yield tissue volume measurements. Performance on most neurocognitive measures deviated significantly from population normative data, with the greatest area of difficulty noted on measures of attention. Children who were treated on protocols involving combined chemotherapy and radiation therapy performed more poorly on measures of academic functioning than those treated with chemotherapy alone. Patients who had received chemotherapy alone had larger volumes of white matter than patients who had received treatment with cranial irradiation, but their volumes remained significantly smaller than those of the control group. Smaller white-matter volumes were associated significantly with larger deficits in attention, intelligence, and academic achievement.

Lesnik et al. [27] examined 10 ALL survivors treated with chemotherapy only, and found morphometric changes in the cerebellar vermis and prefrontal association cortices, concurrent with neurocognitive deficits in visual-spatial attention, short-term memory, and visual-motor organization and coordination. A very recent study by Carey et al. [26] used voxel-based morphometry (VBM) and neuropsychological testing in a population of 9 leukemia survivors treated with chemotherapy alone, and 14 age-matched healthy controls. They also found reduced white matter in the frontal lobes of survivors, and neuropsychological performance correlated with white matter volume. Together, these studies provide compelling evidence for the role of white matter in neurocognitive changes secondary to cancer treatment.

Perfusion MRI and SPECT

Paako et al. [36] found small brain perfusion defects that were apparent on SPECT but not perfusion MRI in 5 of 17 ALL patients treated with chemotherapy alone, up to 8 years after treatment. The authors attributed these defects to the neurotoxicity of methotrexate.

Magnetic Resonance Spectroscopy (MR spectroscopy)

Chu et al. [37] found that MR spectroscopy was able to detect metabolite changes in the absence of structural white matter changes in leukemia survivors. These changes were thought to be the effect of intravenous high dose methotrexate. However, as with the hyperintesities in white matter seen on structural MRI, metabolite changes resolved after treatment.

Functional MRI (fMRI)

Zou et al. [38] used blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to examine 16 brain tumor and leukemia survivors 2–9 years after completion of therapy, some of whom had received radiation therapy and some who had received only chemotherapy. They found decreased activation in the primary visual cortex survivors as compared to controls, with more significant effects in brain tumor survivors than leukemia survivors. However, no studies have used fMRI to focus on children who have received chemotherapy only.

Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) is a relatively new, non-invasive, MRI technique,which provides information about the connections between different parts of the brain. Basic MRI can show structural lesions, but DTI provides biological information on the tissue's microstructure, for example, degree of myelination [39]. DTI has been used to demonstrate subtle abnormalities in white matter when conventional MRI fails to find any differences [40]. DTI can offer much more subtle information like how chemotherapy has affected the myelination of children's brains rather than simply whether or not a structural lesion or significant atrophy has occurred. As a neuroimaging measure with potential to identify subtle white matter damage, it is the methodology most often used in the newest studies of cancer survivors. For example, Khong et al. [41] studied 30 survivors of childhood ALL and medulloblastoma using DTI on a 1.5 T imager and the Hong Kong Wechsler intelligence scales, and found an association between fractional anisotropy (FA; a measure of water diffusion) and IQ measures. However, none of these DTI studies have focused exclusively on patients who have undergone chemotherapy alone as a treatment.

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

Overall, the question of what chemotherapy does to the developing brain is a still new area of exploration. While it clearly has been established that chemotherapy alone is typically much less neurotoxic than cranial radiation, chemotherapy alone does appear to have subtle effects on specific neurocognitive functions, most commonly including attention and executive functioning [4,10–12], visual processing [5,7,8], and visual-motor functioning [3,5,9], which are more prominent in children who are younger at time of treatment, and in girls versus in boys. As there are a wide range of neurocognitive outcomes after chemotherapy, studies examining individual variability will be important, and the investigation of genetic polymorphisms will play a critical role in this endeavor. The potential moderating role of psychosocial factors (such as family functioning, parental distress, and mood) also merits attention, as there is evidence from the literature on traumatic brain injury that psychosocial factors contribute significantly to the variability in neurocognitive outcomes in those populations [42,43]. Models such as these have applicability to cancer survivors, though they have yet to be applied. Based on the literature thus far, neurocognitive late effects are most likely attributable to white matter changes, and recent studies have already begun to combine sophisticated neuroimaging techniques with specific neurocognitive batteries. Future research should strive to refine these techniques in combination to evaluate outcome after specific treatment protocols in order to better understand the mechanisms behind neurocognitive changes. Prospective, longitudinal studies which examine genetic polymorphisms at baseline and document neuroimaging and neurocognitive changes over time will be necessary to elucidate risk factors for poor neurocognitive outcome.

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