Oxidative Stress, Motor Abilities, and Behavioral Adjustment in Children Treated for Acute Lymphoblastic Leukemia

Marilyn J. Hockenberry, PhD, RN, PPCNP, FAAN, Kevin R. Krull, PhD, Kathleen C. Insel, PhD, Lynnette L. Harris, PhD, Patricia M. Gundy, MS, Kristin B. Adkins, MA, Alice E. Pasvogel, PhD, Olga A. Taylor, MPH, Kari M. Koerner, MPH, David W. Montgomery, PhD, Adam K. Ross, BS, Adam Hill, MD, and Ida (Ki) M. Moore, PhD

Advances in primary therapy for childhood acute lymphoblastic leukemia (ALL) have resulted in increased five-year survival, which currently approaches 90% (Hunger et al., 2012). Increased overall survival has led to better appreciation of therapy-related morbidity and impaired quality of life (Barr, Feeny, Furlong, Weitzman, & Torrance, 1995; Krull et al., 2008). In contrast to the recognition of childhood cancer–related neurocognitive complications, limited research exists investigating the trajectory of fine motor and visual-motor difficulties and its impact on behavior and emotional function among children with cancer. Even less understanding exists of physiologic risk profiles for neurobehavioral problems in children with leukemia. This study investigated the influence of the oxidative stress pathway on fine and visual-motor skills, as well as behavioral adjustment in children treated for ALL. Oxidative stress results from an imbalance in the production of reactive oxygen species (ROS) and antioxidant defense systems. ROS are formed as byproducts of cellular metabolism, which in excess can result in damage to cellular structures, and antioxidant systems are the body's first line of defense against cellular injury (Roberts et al., 2010; Stenzel et al., 2010). Brain tissue is particularly vulnerable to oxidative stress because of limited antioxidant capacity, higher energy requirements, and higher concentration of lipids (Floyd, 1999).

A child's motor system experiences rapid development during the first two to five years of life, the time when ALL most commonly occurs in children. Childhood ALL treatment increases the risk for long-term fine motor problems that include peripheral neuropathy, sensory loss, reduced deep tendon reflexes, and motor function changes. Vainionpää, Kovala, Tolonen, and Lanning (1995) were among the first to describe

Purpose/Objectives: To examine associations among oxidative stress, fine and visual-motor abilities, and behavioral adjustment in children receiving chemotherapy for acute lymphoblastic leukemia (ALL).

Design: A prospective, repeated-measures design.

Setting: Two pediatric oncology settings in the southwestern United States.

Sample: 89 children with ALL were followed from diagnosis to the end of chemotherapy.

Methods: Serial cerebrospinal fluid samples were collected during scheduled lumbar punctures and analyzed for oxidative stress biomarkers. Children completed fine motor dexterity, visual processing speed, and visual-motor integration measures at three time points. Parents completed child behavior ratings at the same times.

Main Research Variables: Oxidative stress, fine motor dexterity, visual processing, visual-motor integration, and behavioral adjustment.

Findings: Children with ALL had below-average fine motor dexterity, visual processing speed, and visual-motor integration following the induction phase of ALL therapy. By end of therapy, visual processing speed normalized, and fine motor dexterity and visual-motor integration remained below average. Oxidative stress measures correlated with fine motor dexterity and visual-motor integration. Decreased motor functioning was associated with increased hyperactivity and anxiety.

Conclusions: Oxidative stress occurs following chemotherapy for childhood ALL and is related to impaired fine motor skills and visual symptoms.

Implications for Nursing: Early intervention should be considered to prevent fine motor and visual-spatial deficits, as well as behavioral problems.

Key Words: childhood leukemia; fine motor dexterity; visual-motor integration; oxidative stress; cerebrospinal fluid

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problems in the peripheral nervous system during childhood ALL treatment; significant prolongation of the median nerve peripheral conduct time caused by vincristine (Oncovin®) therapy was discovered in a group of 38 children receiving ALL therapy. Evidently, motor changes are not restricted to the peripheral nervous system and may cause deficits throughout the motor circuitry, including the central motor system (Harila-Saari, Huuskonen, Tolonen, Vainionpää, & Lanning, 2001). Reduced motor competence is demonstrated by greater handwriting difficulties, as well as deficits in manual dexterity and strength.

Motor and sensory-perceptual function is an important indicator in determining severity of a neurologic insult and extension of impairment across specific regions of the brain. Although motor and sensory perceptual signs are often deemed "soft signs," they can be important indicators of a compromised central nervous system (CNS). Examination of fine motor function can assist in understanding the effects of ALL treatment on the brain and the long-term impact of therapy on development. Although most studies demonstrated some evidence of fine motor problems associated with manual dexterity problems during treatment (Dowell, Copeland, & Judd, 1989; Green, Knight, McCarthy, & De Luca, 2013; Jansen et al., 2005; Kingma et al., 2001; Reinders-Messelink et al., 1996, 1999, 2001; van Brussel et al., 2006), inconsistencies existed in findings following completion of ALL treatment. Many of the neurotoxic treatment-related problems disappear over time, but findings from several studies demonstrate that gross and fine motor deficits continue to be evident five years after completing therapy (Galea, Wright, & Barr, 2004; Hartman, van den Bos, Stijnen, & Pieters, 2006; Jansen et al., 2008; Kingma et al., 2001; Lehtinen et al., 2002; Marchese & Chiarello, 2004; Reinders-Messelink et al., 1996, 1999; Wright, Galea, & Barr, 2005; Wright, Halton, Martin, & Barr, 1998). Behavior difficulties, including attention problems, anxiety, depression, and social problems, among childhood cancer survivors have been reported (Brown et al., 1992; Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2005, 2006). However, inter-individual differences exist in neurobehavioral outcomes that could be associated with physiologic and/or psychological factors. A previous study by the current research team found that, in children with ALL, symptoms of hyperactivity decreased over time for participants with low oxidative stress levels but remained stable over time for participants with high oxidative stress levels (Stenzel et al., 2010).

Emerging evidence supports oxidative stress as an underlying biologic process responsible for progressive neurologic injury following chemotherapy. Growing evidence exists that alkylating agents and antimetabolites increase ROS production (Illingworth & Glover, 1971; Roberts et al., 2010; Stenzel et al., 2010). Oxidative stress induced by methotrexate (MTX) (Rasuvo®, Otrexup®, Trexall®) has been observed in tumor tissue, cell cultures, rat liver and brain, and children with ALL (Babiak, Campello, Carnieri, & Oliveira, 1998; Cetinkaya, Bulbuloglu, Kurutas, & Kantarceken, 2006; Hockenberry et al., 2013; Jahovic, Cevik, Sehirli, Yegen, & Sener, 2003; Mazor, Abucoider, Meyerstein, & Kapelushnik, 2008; Oktem et al., 2006; Rouse, Nwokedi, Woodliff, Epstein, & Klimberg, 1995; Sener et al., 2006). Oxidative stress may also be responsible for fine motor dexterity problems observed in children with ALL.

The current study assessed fine motor dexterity, visual processing, and visual-motor integration in children during chemotherapy and examined associations with behavioral outcomes and cerebrospinal fluid (CSF) markers of oxidative stress. In addition, the authors expected oxidative stress within the CNS to be associated with fine motor problems.

Methods

A prospective, longitudinal design was used to investigate a model for examining associations among CSF biomarkers of oxidative stress, fine motor, visual-motor, and behavioral adjustment in children treated for ALL. The study was approved by the University of Arizona Human Subjects Protection Program in Tuscon, Arizona, and the Baylor College of Medicine Institutional Review Board in Houston, Texas. Parent consent and child assent (for children aged 7–15 years) were obtained.

Patients

Eligibility requirements included children diagnosed with pre-B or pre-T cell ALL and being treated on or according to an existing Children's Oncology Group protocol. For continuity and validity of longitudinal neurocognitive assessments, patients were aged 2 years and 9 months to 15 years at the time of diagnosis and were English-language dominant. Exclusion criteria included children with CNS leukemia, a preexisting neurologic disorder (e.g., seizures), subsequent brain injury associated with an alteration of consciousness, or a neurodevelopmental disability (e.g., Down syndrome).

The ALL therapeutic protocols included the induction, postinduction, and continuation therapy treatments. Induction therapy involved weekly treatment with vincristine and daunomycin (DaunoXome®) (for high-risk ALL), a corticosteroid and a dose of pegylated L-asparaginase (Oncaspar®), and two intrathecal (IT) MTX (Rasuvo, Otrexup) treatments (Days 8 and 29). Postinduction therapy (6–8 months) involved several courses of asparaginase (Elspar®), high- or intermediate-dose IV MTX depending on ALL protocol assignment, vincristine, doxorubicin (Adriamycin®),

corticosteroid, cytarabine (Depocyt®), mercaptopurine (Purinethol®), and IT MTX. Continuation therapy consisted of daily mercaptopurine and weekly oral MTX (Trexall), with monthly pulses of vincristine and a corticosteroid, and an IT MTX treatment every 12 weeks for 2.5 years (female) to 3 years (male).

Procedures

Baseline measures were collected during postinduction therapy and during two follow-up sessions. The first follow-up occurred during continuation, about one year from date of baseline evaluation, and the second follow-up occurred at the end of continuation therapy, about two years from baseline. The test battery included measures of fine motor dexterity (Tiffin, 1968), visual-motor integration (Beery, Buktenica, & Beery, 2010), visual processing speed (Woodcock, McGrew, & Mather, 2001), and visual-spatial perception and construction (Korkman, Kirk, & Kemp, 2007), as well as parental ratings of behavioral functioning (Reynolds & Kamphaus, 2004).

CSF was obtained during scheduled therapeutic lumbar punctures (LPs), with the first sample collected during the diagnostic LP. Subsequent CSF samples were collected during the LP for each IT MTX treatment but prior to injection of any chemotherapy. Samples were obtained during the induction, postinduction, and continuation phases of therapy. Biomarkers of oxidative stress in the CSF consisted of oxidized phosphatidylinositol (PI) and F_2-isoprostanes (F_2-Is). Unoxidized PI, a biomarker of cell membrane disruption, was also measured (Chauhan & Chauhan, 2006; Folch, Lees, & Sloane Stanley, 1957).

Table 1. Sample Characteristics (N = 89)

Characteristic	$\bar{X}$	SD	Range
Age (years)			
At diagnosis	7.1	3.6	2.3–14.7
At baseline evaluation (postinduction)	7.2	3.5	3.1–15.2
At first follow-up evaluation (continuation)	8	3.3	4–16.3
At second follow-up evaluation (end of therapy)	9.1	3.1	5.5–17
Maternal education (years)	13.4	2.4	7–20
Paternal education (years)	12.8	2.9	5–20
IV methotrexate (Rasuvo®, Otrexup®) (g/M²)	9.4	10.9	0.039–39.3
Number of IT injections	17.7	2.8	13–24

Characteristic	n
Gender	
Female	49
Male	40
Race	
Non-Caucasian	50
Caucasian	39
Ethnicity	
Non-Hispanic	48
Hispanic	41
Treatment risk stratum[a]	
Standard	70
High	19

[a] Standard risk refers to a white blood cell count of less than 50,000/mcl and an age of 1 year to younger than 10 years. High risk refers to a white blood cell count of 50,000/mcl or greater and/or an age of 10 years or older (Smith et al., 1996).

IT—intrathecal

CSF samples were placed on ice immediately after collection, centrifuged for 10 minutes at 1,750 x g to remove any cellular debris, and then stored at –80°C to limit degradation. PI was extracted from CSF samples using a modified method developed by Folch et al. (1957) and separated by high-performance liquid chromatography (HPLC) with a normal-phase gradient. Lipids were extracted from the aqueous CSF with 4 ml of chloroform; methanol (2:1, v/v) was vortexed for one minute and centrifuged at 10,000 rpm for 20 minutes. The organic phase was collected and stored on ice. A second extraction of the aqueous phase with chloroform-methanol (9:1, v/v) was done to ensure complete extraction of the less polar phospholipids. The organic fractions were combined, evaporated to dryness under nitrogen, and resuspended in hexane-isopropanol (1:1, v/v) prior to HPLC separation. This method recovers 98% of phospholipids.

Mawatari and Murakami (1998) developed an HPLC method for detecting peroxidation of phospholipids in a single chromatic elution. The current authors modified that method to optimize detection using normal-phase HPLC for separation of phospholipid classes. Details of this method have been previously reported (Hockenberry et al., 2013; Ki Moore et al., 2015).

F_2-Is are a sensitive index of oxidative stress in vivo and were measured by a competitive enzyme-linked immunoassay kit. The immunoassay was validated in human urine samples with gas chromatography/mass spectrometry following solid-phase extraction, with an intra-assay correlation of $r > 0.8$. Detailed methods for F_2-I have been previously reported (Hockenberry et al., 2013).

Statistical Analysis

Descriptive statistics were calculated for patient demographics and treatment variables. Scores on measures of fine motor dexterity, visual-motor integration, visual processing speed, and visual-spatial abilities were converted to age-adjusted z-scores ($\bar{X} = 0$, SD = 1) using national population norms. For behavioral adjustment, t-scores ($\bar{X} = 50$, SD = 10) were used, which is the format given by the computerized scoring program. The authors calculated a 95% confidence interval (CI) around each mean z-score and t-score, and those intervals that did not contain the population mean (0 or 50, respectively)

Table 2. Group Performance on Fine and Visual-Motor Performance and Behavioral Outcome Measures (N = 89)

	Baseline Evaluation		Follow-Up 1 Evaluation		Follow-Up 2 Evaluation	
Performance Measure[a]	$\bar{X}$	95% CI	$\bar{X}$	95% CI	$\bar{X}$	95% CI
Fine motor dexterity						
Dominant hand	–1.19	[–1.47, –0.91]	–0.44	[–0.68, –0.19]	–0.39	[–0.7, –0.09]
Nondominant hand	–1.16	[–1.46, –0.86]	–0.42	[–0.67, –0.18]	–0.2	[–0.51, 0.1]
Both hands	–1.15	[–1.45, –0.86]	–0.57	[–0.85, –0.29]	–0.25	[–0.58, 0.09]
Visual processing speed	–0.24	[–0.45, –0.03]	–0.26	[–0.5, –0.03]	–0.03	[–0.26, 0.21]
Visual-motor integration	–0.22	[–0.42, –0.02]	–0.4	[–0.66, –0.13]	–0.37	[–0.57, –0.18]
Spatial construction	–0.16	[–0.37, 0.05]	–0.04	[–0.32, 0.24]	0.26	[–0.05, 0.57]
Spatial perception	0.1	[–0.16, 0.35]	0.44	[0.21, 0.67]	0.21	[0.01, 0.41]
Behavioral Measure[b]	$\bar{X}$	95% CI	$\bar{X}$	95% CI	$\bar{X}$	95% CI
Activities of daily living	51.39	[48.92, 53.87]	51.03	[48.67, 53.4]	50.31	[47.53, 53.09]
Aggression	47.74	[45.28, 50.21]	47.52	[45.2, 49.83]	47.07	[44.91, 49.24]
Anxiety	52.53	[49.88, 55.19]	51.94	[49.45, 54.43]	51.36	[48.31, 54.42]
Attention problems	47.97	[45.79, 50.16]	48.61	[46.13, 51.09]	47.91	[45.44, 50.38]
Atypicality	48.26	[46.11, 50.4]	48.38	[46, 50.75]	48	[45.8, 50.2]
Depression	50.92	[48.45, 53.39]	50.09	[47.9, 52.29]	49.76	[47.69, 51.84]
Functional communication	50.42	[48.32, 52.52]	49.66	[47.35, 51.96]	50.36	[47.94, 52.79]
Hyperactivity	47.95	[46.02, 49.88]	47.64	[45.39, 49.89]	47.05	[44.6, 49.51]
Social skills	51.42	[49.27, 53.56]	51.81	[49.22, 54.4]	51.25	[48.2, 54.31]
Somatic complaints	59.9	[57.18, 62.62]	57.84	[55.04, 60.65]	57.09	[53.35, 60.84]
Withdrawal	51.71	[49.05, 54.36]	51.63	[48.79, 54.46]	50.95	[47.9, 53.99]

[a] Fine motor dexterity and visual-motor performance scores presented in age-adjusted standard scores (population $\bar{X}$ = 0, SD = 1), with 95% CI for the participants. Lower scores reflect worse performance.

[b] Behavioral ratings presented in age-adjusted standard scores (population $\bar{X}$ = 50, SD = 10), with 95% CI for the participants. Higher scores reflect more problematic behavior.

CI—confidence interval

Note. Baseline evaluation occurred after postinduction therapy, the first follow-up occurred after continuation therapy, and the second follow-up occurred at the end of therapy.

were interpreted as being significantly different from the normal population. Pearson correlation was used to test for associations among measures of motor abilities and CSF biomarkers. Some motor and visual-motor problems recovered after the postinduction phase of therapy. Therefore, Pearson correlation was used to determine associations between performance on motor measures at the first follow-up and behavioral measures at the end of therapy (second follow-up). All analyses were conducted using SPSS®, version 20.

Results

Table 1 presents demographic and clinical characteristics of the 89 participants. Participants were aged an average of 7.1 years at diagnosis, and 49 participants were female. Patients received an average cumulative IV MTX dose of 9.4 g/M^2, and number of IT MTX injections ranged from 13–24.

Participants' scores were significantly lower than the population means for fine motor dexterity symptoms at baseline following induction therapy (see Table 2). Performance improved during the course of therapy; scores for nondominant ($\bar{X}$ = –0.2, 95% CI [–0.51, 0.1]) and both hands ($\bar{X}$ = –0.25, 95% CI [–0.58, 0.09]) were within the average range at the second follow-up by the end of therapy. Performance for the dominant hand remained significantly below expectations by the end of therapy ($\bar{X}$ = –0.39, 95% CI [–0.7, –0.09]). Visual processing speed demonstrated a pattern of low performance following induction ($\bar{X}$ = –0.24, 95% CI [–0.45, –0.03]) and postinduction ($\bar{X}$ = –0.26, 95% CI [–0.5, –0.03]) therapy, but performance was within the expected range by the end of therapy ($\bar{X}$ = –0.03, 95% CI [–0.26, 0.21]). Visual-motor integration was also below expectations following induction therapy ($\bar{X}$ = –0.22, 95% CI [–0.42, –0.02]) and remained that way until the end of therapy ($\bar{X}$ = –0.37, 95% CI [–0.57, –0.18]). No difficulties were observed in spatial perception or construction during the course of treatment.

Following induction, parental rating of hyperactivity was below the norm ($\bar{X}$ = 47.95, 95% CI [46.02, 49.88]), and rating of somatic complaints was elevated ($\bar{X}$ = 59.9, 95% CI [57.18, 62.62]). Following postinduction therapy, rating of hyperactivity ($\bar{X}$ = 47.64, 95% CI [45.39, 49.89]) and aggressive behavior ($\bar{X}$ = 47.52, 95% CI [45.2, 49.83]) were below norms, and rating of somatic complaints ($\bar{X}$ = 57.84, 95% CI [55.04, 60.65])

remained elevated above norms. This pattern continued until the end of therapy. No differences were noted in ratings of emotional or social behaviors.

F_2-I, oxidized PI, and unoxidized PI levels in the diagnostic CSF samples were not associated with motor dexterity, visual processing speed, or visual-motor integration at any of the three assessment points. CSF concentration of F_2-I during induction was negatively correlated with motor dexterity symptoms ($r = –0.29$, $p < 0.05$) and visual-motor integration problems ($r = –0.23$, $p < 0.05$) at the postinduction assessment. CSF concentration of F_2-I during postinduction therapy was significantly associated with motor dexterity symptoms at the second follow-up at the end of therapy ($r = –0.339$, $p < 0.05$). As shown in Table 3, oxidized and unoxidized PI concentrations during induction, postinduction, and continuation were negatively correlated with motor dexterity problems at the end of therapy. The number of IT MTX injections received was not associated with performance on the motor dexterity, visual processing speed, or visual-motor integration measures. However, greater total dose of IV MTX received was significantly and negatively associated with visual-motor integration abilities at the first ($r = –0.213$, $p < 0.05$) and second ($r = –0.24$, $p < 0.05$) follow-up assessments.

As summarized in Table 4, fine motor dexterity problems at the first follow-up assessment were associated with a range of behavioral problems, including anxiety, somatic complaints, atypicality (i.e., behaviors commonly considered odd or strange), and attention problems, at the second follow-up assessment at the end of therapy. Poor visual processing speed at Year 1 was associated with increased attention problems ($r = –0.29$, $p < 0.05$) at the end of therapy, and poor visual-motor integration was associated with higher hyperactivity ($r = –0.23$, $p < 0.05$) and lower functional communication ($r = 0.29$, $p < 0.05$) at the end of therapy.

Table 3. Correlations Among CSF PI Biomarkers and Fine Motor Dexterity

	Peak Area		F1[a]	F2[b]
Treatment Phase	$\bar{X}$	SD	p	p
Induction				
Oxidized PI	8.23	9.57	NS	–0.24
Unoxidized PI	48.39	57.11	NS	–0.27
Postinduction				
Oxidized PI	18.04	17.06	NS	–0.3
Unoxidized PI	112.96	103.69	NS	–0.32
Continuation				
Oxidized PI	8.88	8.25	–0.31*	–0.34
Unoxidized PI	57.67	60.25	–0.32*	NS

[a] Occurred at the end of continuation therapy

[b] Occurred at the end of therapy

CSF—cerebrospinal fluid; F—follow-up; NS—not significant; PI—phosphatidylcholine

Note. Mean and SD were divided by 100,000.

Discussion

Results of the current study demonstrate that children undergoing chemotherapy for ALL experience fine motor dexterity problems within months of diagnosis, which persist throughout the course of therapy. Visual processing speed was also initially lower than expected but improved and normalized by the end of therapy. Visual-motor integration, a relatively complex task dependent on visual-spatial perception and fine motor dexterity, followed a similar pattern as motor dexterity and worsened with time. Because spatial perception and construction tasks did not show impairment at any time during treatment, visual-motor integration problems are likely directly related to poor motor dexterity.

Symptoms of impairment in fine motor dexterity appear to be related to oxidative stress and associated disruption in cell membrane integrity in the CNS. F_2-Is are prostaglandin-like compounds formed by free radical peroxidation of arachidonic acid and are established markers of oxidative injury (Frere, Chang-Ileto, & Di Paolo, 2012). Although F_2-I is a gold standard measure of oxidative stress, phospholipids were more strongly associated with fine motor problems in the current study.

F_2-I levels in CSF increased from the diagnostic LP to the induction sample, and further increased following induction and postinduction therapy. Although F_2-I concentration at diagnosis was not associated with motor dexterity, levels in CSF during and following induction significantly correlated with subsequent motor dexterity problems. MTX has been observed to induce oxidative stress. Given the timing between increased F_2-I and treatment phase in the current study, MTX may be responsible for oxidative stress and subsequent impaired motor dexterity.

Arachidonic acid is a polyunsaturated fatty acid found in PI and other phospholipids that comprise cellular membranes in the brain, muscle, and liver. In the current study, the authors found an increase in CSF levels of oxidized and unoxidized PI over time compared to the diagnostic CSF sample. This pattern is suggestive of oxidative injury, resulting in disruption of cellular membranes within the CNS, and is likely because of the mediating effect of F_2-I (Milne, Musiek, & Morrow, 2005; Montuschi, Barnes, & Roberts, 2004). Although phosphoinositides are quantitatively a minor class of lipids, they have a crucial role in synaptic function. In addition, dysregulation of PI metabolism has been implicated in synaptic malfunction associated with a

variety of brain disorders. Oxidized and unoxidized PI following induction were predictive of impaired motor dexterity at the end of therapy, supporting the notion that CNS-based injury is responsible for fine motor dexterity problems that could potentially involve dysregulation of neurotransmission (Frere et al., 2012).

Motor functioning following postinduction therapy was related to behavioral adjustment at the end of therapy. Fine motor dexterity was significantly correlated with anxiety and somatic complaints at the end of therapy, and visual-motor integration was associated with hyperactivity and poor functional communication. Visual-motor integration is a complex task that involves perception of visual-spatial relations combined with fine motor dexterity required to reproduce designs and patterns. In the current study, impaired visual-motor integration following postinduction therapy was associated with symptoms of increased hyperactivity and reduced functional communication at the end of therapy. Hyperactivity is often viewed as reduced control over motor systems. Functional communication includes not only expressive language and speech, but also written communication. Therefore, early deficits in complex motor control can affect functional behavior as children continue to develop. This association suggests that behavioral problems that emerge over time are related to neurocognitive limitations as opposed to social or environmental interactions. Further research is needed to evaluate this connection between neurocognitive deficits and behavioral problems.

Slowed visual processing speed following postinduction therapy was associated with increased attention problems at the end of therapy. Attention is a cognitive construct that is heavily dependent on processing speed because slower rates of information processing require more sustained attentional effort. In the current study, visual processing speed appears to normalize by the end of therapy, but the impact on the broader domain of attention remains. That finding is consistent with work by Krull et al. (2013), demonstrating that many children treated with chemotherapy for ALL have sustained attention problems on direct assessment at the end of therapy.

The current study is not without limitations. The sample size is relatively small compared to other reported ALL outcome studies; however, the vast majority of those studies are cross-sectional and do not include longitudinal data beginning shortly after diagnosis. All children received vincristine, a known neurotoxic agent, and the contributions of this agent to changes in dexterity were not evaluated. The children also received oral corticosteroids, which can cause behavioral problems. However, corticosteroid therapy was most intense during the induction and postinduction phases of treatment and consisted of only monthly pulses during continuation when the first and second follow-up sessions were completed. The battery of assessment measures is also brief and more focused than other reports in the literature, a consequence of limited choices and time for assessment of young children during treatment of a major medical condition.

Table 4. Correlations Between Fine Motor and Visual-Motor Performance at Follow-Up 1 and Behavior Ratings at the End of Therapy

	Neurocognitive Performance		
Behavior	**Dexterity**	**VP**	**VMI**
Activities of daily living	NS	0.22	NS
Aggression	NS	NS	NS
Anxiety	–0.42**	NS	NS
Attention problems	–0.349**	–0.29*	NS
Atypicality	–0.54**	–0.23*	NS
Depression	NS	NS	NS
Functional communication	0.24*	0.25*	0.3*
Hyperactivity	–0.35**	NS	–0.23*
Social skills	NS	NS	NS
Somatic complaints	–0.34**	NS	NS
Withdrawal	–0.26*	NS	–0.23*

* $p < 0.05$; ** $p < 0.01$

NS—not significant; VMI—visual-motor integration; VP—visual processing

Implications for Nursing and Conclusions

The current study demonstrates that children undergoing chemotherapy for childhood ALL are at risk for early onset and persistence of fine motor dexterity and visual-motor problems that appear to be related to CNS treatment-related neurotoxicity. Pediatric oncology nurses are in an ideal position to advocate for ongoing assessment of motor abilities among children receiving CNS-directed treatment and referral for physical or occupational therapy when appropriate. Early assessment of motor abilities is important because problems with fine motor dexterity and visual-motor integration appear to affect development of functional behavior. Early interventions designed to improve fine motor dexterity and visual-motor integration are lacking. Findings from the current study support the need to test the efficacy of early interventions designed to improve fine motor dexterity and prevent future problems with visual-motor integration and behavior. The association between early motor symptoms and CNS biomarkers of oxidative stress suggest the potential role of antioxidants in limiting the cascade of reactive oxygen species and peroxidation injury of lipid membranes. However, prior to any clinical trial, preclinical studies are

Knowledge Translation

Children with leukemia are at risk for early onset and persistence of fine motor dexterity and visual-motor integration problems that appear to be related to central nervous system neurotoxicity.

Early identification of problems with fine motor dexterity and visual-motor integration may affect development of functional behavior.

Early motor symptoms and their relationships with central nervous system biomarkers of oxidative stress merit further investigation of the role of antioxidants in limiting the cascade of reactive oxygen species and peroxidation injury of lipid membranes.

necessary to ensure that antioxidants do not limit the efficacy of the primary cancer therapy.

The number of IT MTX doses was not associated with any measures of motor function, and total dose of IV MTX received was associated only with visual-motor integration at the first and second follow-ups. These findings suggest that there may be individual differences in susceptibility to chemotherapy-related CNS injury. Differences in susceptibility could be because of epigenetic changes in regulation of gene activity and expression involved in oxidative stress and oxidant defense that could be linked to diminished motor abilities among children with ALL. Additional studies are needed to characterize epigenetic factors that could identify children with ALL who are at greatest risk for fine and visual-motor skills, as well as behavioral adjustment problems.

Marilyn J. Hockenberry, PhD, RN, PPCNP, FAAN, is a professor in the School of Nursing at Duke University in Durham, NC; Kevin R. Krull, PhD, is a member in the Department of Epidemiology and Cancer Control at St. Jude Children's Research Hospital in Memphis, TN; Kathleen C. Insel, PhD, is a professor in the College of Nursing at the University of Arizona in Tucson; Lynnette L. Harris, PhD, is an associate professor at the Baylor College of Medicine in Houston, TX; Patricia M. Gundy, MS, is a principal research specialist in the College of Nursing at the University of Arizona; Kristin B. Adkins, MA, is a psychological associate at the Baylor College of Medicine; Alice E. Pasvogel, PhD, is an assistant research scientist in the College of Nursing at the University of Arizona; Olga A. Taylor, MPH, is a senior research coordinator at the Baylor College of Medicine; Kari M. Koerner, MPH, is a research specialist, David W. Montgomery, PhD, is a research professor, and Adam K. Ross, BS, is a research technician, all in the College of Nursing at the University of Arizona; Adam Hill, MD, is a palliative care fellow in the Palliative Care Program at Indiana University Health in Bloomington; and Ida (Ki) M. Moore, PhD, is a professor and biobehavioral health science division director in the College of Nursing at the University of Arizona. This study was supported by the National Institute of Nursing Research at the National Institutes of Health (NR010889). Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Oncology Nursing Forum* or the Oncology Nursing Society. Moore can be reached at imoore@email.arizona.edu, with copy to editor at ONFEditor@ons.org. (Submitted January 2015. Accepted for publication April 8, 2015.)

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