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Neurocognitive Outcomes among Children who Experienced Seizures during Treatment for Acute Lymphoblastic Leukemia

Stephanie L. Nassar, PhD¹, Heather M. Conklin, PhD², Yinmei Zhou, MS³, Jason M. Ashford, MS², Wilburn E. Reddick, PhD⁴, John O. Glass, MS⁴, Fred H. Laningham, MD⁵, Sima Jeha, MD⁶, Cheng Cheng, PhD³, and Ching-Hon Pui, MD⁶

¹Mental Health and Behavioral Sciences, James A. Haley Veterans' Hospital

²Department of Psychology, St. Jude Children's Research Hospital

³Department of Biostatistics, St. Jude Children's Research Hospital

⁴Division of Translational Imaging Research, St. Jude Children's Research Hospital

⁵Department of Diagnostic Radiology, Children's Hospital Central California

⁶Departments of Oncology and Pathology, St. Jude Children's Research Hospital

Abstract

Background—Limited information is available regarding neurocognitive outcomes of children who experience seizures during treatment for acute lymphoblastic leukemia (ALL). Accordingly, the main objectives of this study were to determine the incidence and risk factors for treatment-related seizures among children with ALL, and the neurocognitive outcomes associated with treatment-related seizures.

Procedure—Prospective neuropsychological assessment and magnetic resonance imaging (MRI) were planned for all 498 patients with newly diagnosed ALL enrolled on the St. Jude Total Therapy XV (TOTXV) protocol at three time-points. The study database was reviewed retrospectively to identify those with treatment-related seizure. To assess neurocognitive changes associated with seizure, each patient with treatment-related seizure was matched with two cohort patients without seizure for age at treatment, gender, race, and treatment intensity.

Results—Nineteen patients developed seizure, with a 2-year cumulative risk of $3.82\% \pm 0.86\%$ (SE). No risk factors were identified to be associated with the development of seizure, with a possible exception of intensive chemotherapy used on the standard/high-risk arm as compared to the low-risk arm. Neuropsychological performance of the seizure group, as compared to normative scores and non-seizure control cohort, indicated problems in attention, working memory, and processing speed. Cognitive deficits persisted two years post-therapy, with additional declines in intellectual function observed. MRI indicated early neurotoxicity among the seizure group, as evidenced by greater leukoencephalopathy on initial exams.

*Corresponding Author: Heather M. Conklin, Department of Psychology, Mail Stop #740, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, Tennessee 38105. Telephone: 901-595-3585. Fax: 901-595-4701. heather.conklin@stjude.org.

Conflict of Interest Statement

No potential conflicts of interest.

Conclusion—Treatment-related seizures were associated with leukoencephalopathy and decreased neuropsychological performance. Prospective studies are needed to detect changes in neurocognitive status associated with long-term functional impairment.

Keywords

leukemia; seizure; cognitive late effects; working memory; leukoencephalopathy

Introduction

Advancements in systemic and central-nervous-system (CNS)-directed treatment have dramatically enhanced 5-year survival rates of children with acute lymphoblastic leukemia (ALL), the most common childhood cancer, to over 90 percent in several contemporary clinical trials [1]. However, up to 20 percent of the patients still receive prophylactic cranial irradiation (CRT), which results in cognitive late effects in approximately 60 percent of survivors [2, 3]. Risk factors associated with cognitive function decline include younger age at diagnosis, female gender, greater time since treatment, and higher treatment intensity [4–8]. Younger developing brains appear vulnerable to therapy-related neurotoxicity, as evidenced by decreased cerebral white matter volumes and increased oxidative stress in the CNS post-treatment [9]. Additionally, females may be particularly vulnerable to CNS-directed therapy, as males' neurodevelopment involves greater white matter volume increases in childhood [10].

Although elimination of CRT has reduced overall cognitive impairment in ALL survivors, intensive systemic and intrathecal chemotherapy to offset the removal of CRT can also cause impairment of acute and long-term neurocognitive outcomes and quality of life [4]. Reviews and meta-analyses of the late effects of CNS-directed chemotherapy in ALL survivors suggest that contemporary treatment negatively affects several domains of cognitive function [5–7, 11–13].

Among leukemia survivors, attention and working memory deficits predominate in subtle yet significant ways that impact daily life [8, 14]. Attention deficits in ALL survivors have been linked to smaller and abnormal cerebral white matter volumes [15]. Additionally, working memory assessment appears useful in detecting treatment-related cognitive changes, as those measurements are sensitive to cognitive decline in patients treated without CRT and have been shown to predict overall intelligence scores [14]. Detecting chemotherapy-related declines in specific cognitive abilities is necessary to develop targeted interventions and assist in the confirmation of neural pathways hypothesized to be directly related to cognitive deficits [4].

While CRT, with and without chemotherapy, has been strongly linked to intracranial white matter changes, vascular damage, and other neuropsychological and neuroendocrine issues, chemotherapy alone has also been associated with significant neurocognitive side effects [5]. Leukoencephalopathy, as measured by magnetic resonance imaging (MRI), can be found in as many as 86 percent of patients treated with seven courses of intravenous high-dose methotrexate (HDMTX) [16].

At the end of treatment, MTX therapy has been associated with abnormal frontal lobe white matter and working memory deficits, yet the long-term effects related to these changes are not clear [14, 16–17]. Intensive CNS-directed treatment can cause homocysteine excitotoxicity and neuronal death, which may clinically present as focal neurological deficits, stroke-like episodes, or seizures [12, 18]. Despite anti-inflammatory properties, glucocorticoids such as dexamethasone and prednisone used in the treatment for ALL may also result in neuronal death and seizure [19].

Approximately 3 to 13 percent of children experience seizure during treatment for ALL [20–26]. Higher doses of intrathecal and intravenous MTX have been identified as a risk factor for seizure [25]. In a study of 384 pediatric cancer patients, seizure occurred in 47 children, of whom 16 were treated for ALL [27]. Seizure risk was higher for younger children (< 10 years), males, and patients with ALL [27]. Treatment-related seizures generally developed within the first six weeks of therapy during remission induction and consolidation treatment [21, 28–29].

Among children with CNS relapse who experienced seizure, Mulhern and colleagues [30] found weak negative correlations between seizures and overall cognitive and academic performance. CT scans of four children with ALL hospitalized for seizures after treatment with high-dose intravenous and intrathecal chemotherapy revealed diffuse periventricular white matter hypodensities and, in three of them, subcortical hyperdense foci [31]. In all four cases, MRI revealed diffuse hyper-intense white matter lesions on T2-weighted images. The authors concluded that the white matter lesions with calcification were related to leukoencephalopathy and resultant seizures [31]. Otherwise, little is known about neurocognitive changes, psychosocial outcomes, or diagnostic imaging findings of ALL survivors who experience on-therapy seizures. The current study was conducted to address this gap in the literature.

The first study objective was to estimate the risk of seizure in children treated for ALL and identify demographic and/or clinical factors associated with seizure risk. Given the omission of CRT on the TOTXV protocol, we predicted that seizure occurrence would be in the lower range as reported in the literature (roughly 5%). We also predicted that treatment intensity and premorbid seizure history would be seizure risk factors. The second objective was to assess neurocognitive changes in children with on-therapy seizures by comparing serial neuropsychological assessment across three time-points. Children with on-therapy seizures were predicted to have worsening cognitive performance across time, particularly in the domains of attention and working memory. The third objective compared the neuropsychological outcomes of children with on-therapy seizures to the normative sample, as well as to a matched control group of patients treated on the same protocol. We hypothesized post-treatment cognitive performance of children with on-therapy seizures would be significantly worse than the normative sample and the matched cohort. Our fourth objective compared the degree of leukoencephalopathy between children with seizures and the matched cohort. A greater occurrence of leukoencephalopathy among children with on-therapy seizures was predicted.

Methods

Patients and Setting

Patients included children ($N = 498$) with newly diagnosed ALL sequentially enrolled on St. Jude Total Therapy XV protocol (TOTXV, clinicaltrials.gov identifier NCT00137111) of whom a subset of 57 participants were the focus of this seizure-related study. The TOTXV protocol was designed to test whether prophylactic CRT could be safely omitted from treatment of all children with ALL [32]. Based on presenting genetic features and early treatment response, as measured by minimal residual disease during remission induction, children were assigned to low-risk or standard/high-risk groups, with increased treatment intensity for the standard/high-risk arm across remission induction, consolidation, and continuation phases [32]. Depending on presenting characteristics and leukemic cell counts in the cerebrospinal fluid, patients with low-risk ALL received 13 to 18 intrathecal treatments with methotrexate, hydrocortisone, and cytarabine. Patients with standard/high-risk ALL received 16 to 25 intrathecal treatments. Before conventional induction therapy, one course of HDMTX was given intravenously in the first week (1.0 g/m^2). During consolidation therapy, HDMTX was given intravenously every other week for four cycles (2.5 g/m^2 for low-risk group and 5.0 g/m^2 for standard/high-risk group). During continuation treatment, MTX was given intravenously weekly at 40 mg/m^2 together with daily oral mercaptopurine for 3 weeks, with pulses of vincristine plus dexamethasone at 8 mg/m^2 per day for 5 days for low-risk group, and at 12 mg/m^2 per day for 5 days for standard/high-risk group every 4 weeks. Treatment continued for 120 weeks for girls and 146 weeks for boys, interrupted by two reinduction treatments in the first 5 months of continuation treatment [8].

Study Design and Procedures

Cognitive scores and clinical and demographic factors were extracted from the TOTXV database and medical records. Neuropsychological assessments were conducted at three time-points: week 6 induction (initial assessment), end of therapy (week 120 continuation), and two years post therapy completion. The assessment battery has been previously described in detail [11]. MRI exams were prospectively conducted at three time-points: week 5 induction (initial exam), week 7 continuation treatment, and end of therapy (week 120 continuation). The timing of procedures, which was decided prospectively based on the TOTXV protocol, placed the first neuropsychological assessment approximately one week after the first MRI exam (Figure 1).

Intellectual Functioning—Age-appropriate intelligence tests were utilized, including the Wechsler (WAIS-III for age > 16 , WISC-III for age 6–16, WPPSI-R for age < 6) and Bayley Scales (BSID for age < 2) [33–36]. Wechsler and Bayley scores have an age standardized mean score of 100 and standard deviation of 15. Estimated Intelligence Quotient (EIQ) scores were obtained at all assessment time-points. Full Scale Intelligence Quotient (FSIQ) scores were obtained at the latter two assessments. EIQ was calculated from the Information, Similarities, and Block Design subtests using a formula provided in Sattler [37], which highly correlates with FSIQs ($r = .93$).

Academic Achievement—Academic skills were assessed for children at least 6 years of age using the Word Reading and Math Reasoning subtests from the Wechsler Individual Achievement Test [WIAT, 38]. Word Reading measures phonological awareness, speed, and accuracy of single word reading from lists. Math Reasoning assesses mathematical problem-solving abilities, including solving word problems using verbal and visual prompts. Wechsler scores have an age standardized mean score of 100 and standard deviation of 15.

Attention, Working Memory, and Processing Speed—Children between the ages of 6 and 16 were administered the WISC-III, which allowed Wechsler indices of attention, working memory, and processing speed to be examined (Freedom from Distractibility or FFD, Digit Span Total or DS, and Processing Speed Index or PSI; respectively).

The Conners' Continuous Performance Test [CPT, 39], a computerized measure of selective and sustained attention, was also administered to children aged 6 and older. During the 14-minute task, children press the space bar as quickly and accurately as possible for letters (targets), except "X" (non-target). The CPT computes indices of inattention/failure to respond to a target (Omission Errors) and processing speed (Reaction Time). Index scores are age standardized, with a percentile score calculated for Omission Errors ($M=84$, $SD=6$) and a T-score calculated for Reaction Time ($M=50$, $SD=10$).

Parental Report of Behavioral Problems and Attention Abilities—Behavioral problems and inattention symptoms were assessed using the Learning, Psychosomatic, Impulsive-Hyperactive, and Hyperactive subscales of the Conners' Parent Rating Scale [CPRS, 40]. Parents rated each item on a scale of 0 "Not True At All" to 3 "Very Much True," in regard to the intensity of the behavior problem in the past month. CPRS subscales are age and gender standardized, with a T-score ($M=50$, $SD=10$).

Leukoencephalopathy—MRI exams were classified as either normal appearing white matter or leukoencephalopathy by a neuroradiologist (F.H.L.) who was blinded to neuropsychological assessment and treatment risk arm. Images were acquired using a 1.5 Tesla whole-body MRI scanner with a standard circular polarized volume head coil (Avanto; Siemens Medical Systems, Iselin, NJ). Leukoencephalopathy, or T2 white matter hyperintensities, were best seen with a T2-weighted sequence with reduced cerebrospinal fluid. Imaging sets included most of the cerebrum, beginning at the apex of the brain, excluding the cerebellum. Imaging was obtained using oblique 4-mm-thick contiguous axial images with a 1-mm gap. T1-weighted images were obtained with a multi-echo inversion recovery sequence (repetition time between spin excitations [TR] = 8000 milliseconds [ms]; echo time [TE] = 29 ms; time between inversion and the excitation pulse [TI] = 300 ms; 7 echoes). T2/proton-density weighted images were obtained using a dual spin-echo sequence (TR/TE1/TE2 = 3500/17/102 ms, 5 echoes). Fluid-attenuated inversion recovery images were acquired with a multi-echo inversion recovery sequence (TR/TE/TI = 9000/119/2470 ms; 7 echoes).

Statistical Analyses

Of the 498 children on protocol, 19 experienced on-therapy seizures, which was defined as at least one incident of Grade 2 seizure (i.e., altered consciousness). To increase the statistical power of comparisons, each of the 19 children were matched to two children on the TOTXV protocol without seizure experience ($n = 57$). Matching variables included gender, race, age at treatment, and treatment intensity.

To characterize the sample and ensure group equivalence, qualitative analyses of demographic and clinical variables were performed. Cumulative incidence was utilized to estimate the rate of seizure occurrence and identify factors associated with seizure risk. The cumulative incidence of seizure (i.e., first event) was tested between groups by using the method described by Gray [41] and the estimation was produced by using the method described by Kalbfleisch and Prentice [42]. One-way repeated measures analysis of variance (ANOVA) was utilized to assess change in the neuropsychological performance of children with on-therapy seizures across time points. One-sample t-tests were utilized to compare the neuropsychological performance of children with on-therapy seizures at each time point to published normative scores. Mixed model repeated measures ANOVA was utilized to compare the neuropsychological performance of children with on-therapy seizures to a matched control cohort across time points. Fisher's exact test was utilized to compare the rates of leukoencephalopathy classification at each neuroimaging time point between children with on-therapy seizures and the matched control cohort. An alpha level of .05 was used to assess the significance of all statistical comparisons.

Results

For the entire TOTXV sample of 498 patients, the estimated cumulative incidence rates of Grade 2 seizures were $3.21\% \pm 0.79\%$ at 1 year and $3.82\% \pm 0.86\%$ at 2 years (Figure 2). Additionally, age at diagnosis, race, and gender did not have a statistically significant effect on seizure development. Of the 19 children with treatment-related seizures, two had a prior history of seizures. However, this relationship was not statistically significant, likely due to reduced power secondary to small sample size. Treatment intensity was trending toward statistical significance, with the standard/high-risk group having a higher estimated incidence rate of seizures than the low risk group (2-year cumulative risk, 5.6 ± 1.6 v. 2.5 ± 0.9 , respectively, $p = .06$). Induction and consolidation phases had the highest frequency of seizure onset, each at 26 percent, accounting for over half of on-therapy seizures (Supplementary Table S1 for additional information on seizure onset, frequency, and severity).

For the subsample of 57 children, there were no significant differences between the seizure group and the control group with respect to age, race, gender, or treatment intensity (Table 1). Ages ranged from 2 to 18 years old, with a mean age of 8.2 across groups. There were no significant differences in dosing (mg/m^2) of dexamethasone, HDMTX, and intrathecal therapy (hydrocortisone, MTX, and Ara-C) between the two groups.

Neurocognitive Outcomes

Among the seizure group, basic reading scores significantly declined from first assessment to two years post therapy completion ($MD = -6.77$ points, $p = .05$, Table 2). However, parental report of learning problems as measured by the Conners' indicated significant improvement from first assessment to two years post therapy ($MD = -19.27$ points, $p = .01$). In contrast to hypotheses, significant change was not observed for estimated intellectual functioning (EIQ), attention, working memory, processing speed, math reasoning, or other behavioral problems from initial assessment to two years post therapy.

In comparison to published norms, at initial neuropsychological assessment, the seizure group demonstrated a significantly lower mean IQ ($M = 89.33$ vs. 100; $p = .01$, Table 3). No significant differences were observed for measures of academics, inattention, or processing speed. The Conners' Parent Rating Scale revealed significantly more psychosomatic problems in the seizure group than published norms ($M = 68.64$ vs. 50, $p < .01$). At the end of therapy, significant differences for IQ were no longer present; however, the seizure group performed significantly worse on attention and working memory tasks (FFD $M = 80.14$ vs. 100, $p = .02$; DS Total $M = 6.43$ vs. 10, $p = .03$) and their parents reported greater learning and psychosomatic problems ($M = 62.27$ vs. 50, $p = .05$; $M = 65$ vs. 50, $p = .02$, respectively) than published norms. At two years post therapy, the same pattern was observed for attention and working memory (FFD $M = 79.43$ vs. 100, $p = .01$; DS Total $M = 6$ vs. 10, $p = .02$) and parental report of psychosomatic problems ($M = 65.70$ vs. 50, $p = .03$).

Comparisons of cognitive performance between the seizure group and the control cohort at first assessment also revealed significantly lower estimated IQ for the seizure group ($M = 89.33$ vs. 100.74, $p = .05$, Table 4). No other significant differences in cognitive functioning or parental report were observed. At the end of therapy, the seizure group performed significantly worse on attention and working memory tasks compared to the control cohort (FFD $M = 80.14$ vs. 100.74, $p < .01$; DS Total $M = 6.43$ vs. 9.52, $p = .05$). Clinically significant differences in attention and working memory tasks, namely FFD, were evidenced after accounting for leukoencephalopathy among seizure experience (Supplementary Table S2). Additionally, parents of children with on-therapy seizures reported greater problems in the areas of learning, impulsivity, and hyperactivity ($M = 62.27$ vs. 49.69; $M = 57.45$ vs. 49.59; $M = 59.36$ vs. 48.66, respectively, $p = .04$). At two years post therapy, the seizure group performed significantly worse on a measure of overall intelligence than the control cohort (FSIQ $M = 88.92$ vs. 101, $p = .04$). A similar pattern of worse performance among the seizure group compared to the control cohort on tasks of attention and working memory was also observed at two years post therapy (FFD $M = 79.43$ vs. 101.17, $p < .01$; DS Total $M = 6.00$ vs. 10.04, $p = .02$), with additional processing speed deficits observed for the seizure group (PSI $M = 88.57$ vs. 103.92, $p = .02$). No significant differences on parental report were observed at two years post therapy.

Lastly, significant differences in rate of leukoencephalopathy on MRI were observed between the seizure and the control cohort groups at week 7 continuation treatment (56.25% vs. 12.90%, $p < .01$), and at the end of therapy (week 120 continuation end, 38.46% vs. 6.06%, $p = .01$). However, no significant differences were found on the initial MRI exam at week 5 induction (15.38% vs. 2.94%, $p = .18$).

Discussion

Two-year cumulative incidence of on-therapy seizures for children treated on the TOTXV protocol was 3.82%, which is within the lower range of 3 to 13% found in the literature. The lower incidence is likely reflective of the reduced neurotoxic effect of a chemotherapy-only protocol. Of particular interest is the lack of significant change in neuropsychological performance for children with on-therapy seizures when compared to themselves across time points. One potential explanation is that the initial neuropsychological assessment was not a true baseline, as one dose of HDMTX had been administered, which may have influenced cognitive performance. Additional factors, including acute seizure activity and anticonvulsant treatment occurring in temporal proximity to the first assessment, may have also impacted the results of early neuropsychological assessment.

Based on comparisons with the normative group and non-seizure control cohort, it appears that children with on-therapy seizures are at greater risk of neurocognitive deficits, as evidenced by poorer performance across domains of attention and working memory at the end of therapy. Additionally, those cognitive deficits persisted at two years after therapy, with the addition of processing speed deficits and lower intelligence scores for the seizure group when compared to the control cohort. These findings may indicate that children who experience on-therapy seizures may represent a higher-risk subgroup that, in part, account for the current literature that supports cognitive late effects, namely impaired attention and working memory dysfunction, in children treated for ALL [4, 8, 14]. It is possible that cognitive deficits that negatively impact alert, undistracted attention, which is required for adequate learning, may precede later declines observed in overall IQ.

Children with on-therapy seizures appeared to have experienced more significant early neurotoxicity, as evidenced by greater leukoencephalopathy on MRI than the non-seizure control cohort, which may contribute to the higher level of cognitive deficits observed. Notably, significant differences in leukoencephalopathy were observed *concurrently* with significantly worse neuropsychological performance on measures of attention and working memory among the seizure group as compared to the control cohort at end of therapy, and *temporally preceded* the similar pattern of cognitive late effects among the seizure group at two years post therapy. However, it is important to note the nonsystematic nature of the study's retrospective design, which may limit that conclusion. Overall, our observations are consistent with previous literature evidencing decreased attention and working memory abilities post-chemotherapy, as well as decrements in intelligence, which have been associated with treatment-related neuroanatomical changes such as smaller and abnormal cerebral white matter volumes [14–16, 18].

Limitations and Future Directions

One major limitation of this study is its retrospective design. A prospective, longitudinal study would allow for a more systematic investigation of the emergence of cognitive late effects, including potential mechanisms of change by closely monitoring children experiencing seizures during treatment. Additionally, the lack of correlation between parent report and performance-based measures may be one of the unfortunate yet expected

drawbacks of subjective rater measures, which have been shown to exhibit low rates of sensitivity and specificity [43].

The authors acknowledge the likely overlap of seizures and leukoencephalopathy in some patients; however, our data suggest that treatment-related seizures are associated with poorer cognitive outcomes for attention and working memory, independent of the presence of leukoencephalopathy. Therefore, seizure experience as a predictive factor of poorer cognitive outcomes has great clinical utility, especially within the context of clinical care that does not routinely include neuroimaging. Seizures may be the first or only indicator of cognitive risk that may or may not be confirmed with leukoencephalopathy on MRI.

Future studies will benefit from advanced neuroimaging, such as diffusion tensor imaging (DTI). DTI is likely to assist with early identification of subtle cerebral white matter damage by examining neural pathways associated with attention and memory (e.g., the prefrontal cortex) in relation to chemotherapy-induced neurotoxicity, impaired neuropsychological performance across treatment, and cognitive late effects in childhood cancer survivors [44]. Early identification would better inform patient treatment plans with enhanced physician insight on when regimen-related accommodations are needed, such as modifying the timing or dosing of chemotherapy administrations to minimize white matter damage or seizure risk without compromising a favorable treatment outcome.

Earlier identification of children at risk for seizure may also allow healthcare professionals to develop preventive measures against lasting therapy-related CNS impairments. For patients and their caregivers, early identification of treatment-related neurocognitive deficits may signal the need for earlier intervention focused on remedial and compensatory strategies to minimize functional impairment. Recent empirical findings support post-chemotherapy interventions that lessen cognitive late effects [6], including both pharmacologic (e.g., methylphenidate, donepezil, modafinil) [45–47] and non-pharmacologic methods, such as therapist delivered cognitive remediation or computerized cognitive training [48–50]. While stimulants and other pharmacologies should not be considered in patients with poorly controlled seizures as it may be dangerous, they may be useful neuroprotective agents for patients without seizures that evidence early white matter damage on neuroimaging.

Conclusions

Despite the limitations of this study, the current findings point to a relationship between on-therapy seizures, leukoencephalopathy, and deficits in neurocognitive functioning, specifically attention, working memory, and processing speed skills, which may lead to overall declines in intellectual function. However, these findings also raise questions about the neurobehavioral mechanisms, including neuroanatomical pathways, involved in cognitive late effects associated with seizures. Future research on theoretically driven neurobehavioral processes is necessary to unravel these mechanisms within the context of leukemia therapy so that we may improve caregiver education, treatment planning, and treatment monitoring for a growing number of survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

ALL	Acute Lymphoblastic Leukemia
ANOVA	Analysis of Variance
Ara-C	Cytarabine (arabinofuranosyl cytidine)
BSID	Bayley Scales of Infant Development
CNS	Central Nervous System
CPRS	Conners' Parent Rating Scale
CPT	Conners' Continuous Performance Test
CRT	Cranial Irradiation
CT	Computed Tomography
DS	Digit Span Total
DTI	Diffusion Tensor Imaging
EQ	Estimated Intelligence Quotient
FFD	Freedom From Distractibility
FSIQ	Full Scale Intelligence Quotient
g/m²	grams per meters squared
HDMTX	High-Dose Methotrexate
IQ	Intelligence Quotient
M	Mean
MD	Mean Difference
mg/m²	milligrams per meters squared
mm	millimeters
ms	milliseconds

MRI	Magnetic Resonance Imaging
MTX	Methotrexate
PSI	Processing Speed Index
SD	Standard Deviation
SE	Standard Error
TE	Echo Time
TI	Time Between Inversion and Excitation Pulse
TOTXV	St. Jude Total Therapy XV
TR	Repetition Time Between Spin Excitations
WAIS-III	Wechsler Adult Intelligence Scale – Third Edition
WIAT	Wechsler Individual Achievement Test
WISC-III	Wechsler Intelligence Scale for Children – Third Edition
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence - Revised

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Figure 1.

Points of Cognitive Assessment and Neuroimaging Exams as a Function of Therapy *Note:* Ind=Induction; Cons=Consolidation. Measurements included neuropsychological and neuroimaging exams across three time points. Neuropsychological assessments were conducted after one dose of HDMTX (week 6 induction), at end of therapy (week 120 continuation end – no intrathecal therapy for approximately 72 weeks, no HDMTX for approximately 120 weeks, no corticosteroids for approximately 20 weeks), and at two years post therapy completion. MRI exams were conducted after one dose of HDMTX (week 5 induction), after five doses of HDMTX (week 7 continuation), and at end of therapy (week 120 continuation end).

Figure 2.

Cumulative Incidence of Grade 3 Seizure on TOTXV

Note: Estimated 1-year and 2-year cumulative incidence rates of Grade 3 (i.e., altered consciousness) and higher seizures were $3.21\% \pm 0.79\%$ and $3.82\% \pm 0.86\%$, respectively, for the entire TOTXV sample.

TABLE 1

Age, Race, Gender, and Treatment Intensity across Groups at Diagnosis

	Total	Seizure Group	Cohort 1	Cohort 2	p-value
N	57	19	19	19	
Age					0.99 ^A
Mean (SD)	8.26 (4.72)	8.27 (4.80)	8.26 (4.81)	8.23 (4.82)	
Median	7.66	7.21	8.00	7.66	
Range	2.07–18.73	2.07–18.73	2.09–17.12	2.14–18.73	
Race [n (%)]					0.68 ^P
White	42 (73.7)	14 (73.7)	13 (68.4)	15 (78.9)	
Black	14 (24.6)	5 (26.3)	5 (26.3)	4 (21.1)	
Other	1 (1.8)	0 (0)	1 (5.3)	0 (0)	
Gender [n (%)]					0.99 ^P
Male	39 (68.4)	13 (68.4)	13 (68.4)	13 (68.4)	
Female	18 (31.6)	6 (31.6)	6 (31.6)	6 (31.6)	
Treatment Intensity [n (%)]					0.99 ^P
Low	21 (36.8)	7 (36.8)	7 (36.8)	7 (36.8)	
Stand/High	36 (63.2)	12 (63.2)	12 (63.2)	12 (63.2)	

Note: P-values indicate that groups are equally distributed across relevant demographic and clinical variables using Analysis of Variance (A) or Pearson's Chi-Square Test (P).

TABLE 2

Means and Standard Deviations on Cognitive Measures for Seizure Group across Time Points

	First Assessment	End of Therapy	Two Years Post	<i>p</i>
Wechsler EIQ	89.33 (10.10)	90.73 (19.82)	94.33 (18.84)	0.50
Wechsler FSIQ	--	88.20 (21.29)	88.92 (18.35)	--
FFD	--	80.14 (17.86)	79.43 (15.11)	0.06
PSI	--	86.29 (24.31)	88.57 (18.04)	0.82
DS Total	--	6.43 (3.60)	6.00 (4.00)	0.38
WIAT				
Basic Reading	93.33 (7.39)	90.80 (22.38)	86.56 (22.26)	0.05*
Math Reasoning	91.83 (16.19)	87.00 (19.30)	89.67 (22.47)	0.29
Conners' CPT				
Omissions	86.15 (21.79)	89.43 (12.69)	83.04 (21.33)	0.76
Hit RT	51.04 (9.69)	50.84 (13.81)	53.27 (15.59)	0.83
CPRS				
Learning	63.27 (23.43)	62.27 (18.66)	44.00 (9.21)	0.01*
Psychosomatic	68.64 (17.29)	65.00 (19.54)	65.70 (20.39)	0.90
Impulse-Hyper	56.36 (15.36)	57.45 (11.47)	50.30 (9.81)	0.41
Hyperactive	59.73 (20.56)	59.36 (17.03)	46.60 (9.34)	0.06

Note: Significant *p*-values are asterisked, which indicate change in the neuropsychological performance of children with on-therapy seizures across time using one-way repeated measures analysis of variance; EIQ = Estimated Intelligence Quotient, FSIQ = Full Scale Intelligence Quotient, FFD = Freedom from Distractibility, PSI = Processing Speed Index, DS = Digit Span, WIAT = Wechsler Individual Achievement Test, CPT = Continuous Performance Test, RT = Reaction Time, CPRS = Conners' Parent Rating Scale.

TABLE 3
Cognitive Comparisons between Seizure Group and Published Norms across Time Points

	Norms	First Assess	<i>p</i>	End Therapy	<i>p</i>	Two Years Post	<i>p</i>
Wechsler EIQ	100 (15)	89.33 (10.10)	0.01*	90.73 (19.82)	0.15	94.33 (18.84)	0.31
Wechsler FSIQ	100 (15)	--	--	88.20 (21.29)	0.11	88.92 (18.35)	0.06
FFD	100 (15)	--	--	80.14 (17.86)	0.02*	79.43 (15.11)	0.01*
PSI	100 (15)	--	--	86.29 (24.31)	0.18	88.57 (18.04)	0.14
DS Total	10 (3)	--	--	6.43 (3.60)	0.03*	6.00 (4.00)	0.02*
WIAT							
Basic Reading	100 (15)	93.33 (7.39)	0.07	90.80 (22.38)	0.22	86.56 (22.26)	0.10
Math Reasoning	100 (15)	91.83 (16.19)	0.27	87.00 (19.30)	0.06	89.67 (22.47)	0.20
Conners' CPT							
Omissions	84 (6)	86.15 (21.79)	0.71	89.43 (12.69)	0.89	83.04 (21.33)	0.30
Hit RT	50 (10)	51.04 (9.69)	0.82	50.84 (13.81)	0.85	53.27 (15.59)	0.50
CPRS							
Learning	50 (10)	63.27 (23.43)	0.08	62.27 (18.66)	0.05*	44.00 (9.21)	0.06
Psychosomatic	50 (10)	68.64 (17.29)	<0.01*	65.00 (19.54)	0.02*	65.70 (20.39)	0.03*
Impulse-Hyper	50 (10)	56.36 (15.36)	0.19	57.45 (11.47)	0.05*	50.30 (9.81)	0.92
Hyperactive	50 (10)	59.73 (20.56)	0.14	59.36 (17.03)	0.09	46.60 (9.34)	0.27

Note: Significant *p*-values are asterisked, which indicate a difference between the neuropsychological performance of children with on-therapy seizures to published norms at each time point using one-sample *t*-tests; EIQ = Estimated Intelligence Quotient, FSIQ = Full Scale Intelligence Quotient, FFD = Freedom from Distractibility, PSI = Processing Speed Index, DS = Digit Span, WIAT = Wechsler Individual Achievement Test, CPT = Continuous Performance Test, RT = Reaction Time, CPRS = Conners' Parent Rating Scale.

TABLE 4

Cognitive Comparisons between Seizure Group and Matched Cohort across Time Points

	First Assessment		p	ES	End of Therapy		p	ES	Two Years Post Therapy		p	ES
	Seizure	Cohort			Seizure	Cohort			Seizure	Cohort		
Wechsler EIQ	89.33 (10.10)	100.74 (16.54)	0.05*	0.75	90.73 (19.82)	100.41 (16.37)	0.14	0.56	94.33 (18.84)	101.64 (16.48)	0.29	0.43
Wechsler FSIQ	--	--	--	--	88.20 (21.29)	97.61 (13.14)	0.21	0.61	88.92 (18.35)	101.00 (15.65)	0.04*	0.74
FFD	--	--	--	--	80.14 (17.86)	100.74 (12.82)	<0.01*	1.47	79.43 (15.11)	101.17 (17.52)	0.01*	1.28
PSI	--	--	--	--	86.29 (24.31)	100.74 (16.14)	0.14	0.79	88.57 (18.04)	103.92 (12.96)	0.02*	1.09
DS Total	--	--	--	--	6.43 (3.60)	9.52 (2.52)	0.05*	1.12	6.00 (4.00)	10.04 (3.58)	0.01*	1.10
WIAT												
Basic Reading	93.33 (7.39)	102.45 (13.83)	0.10	0.71	90.80 (22.38)	102.04 (13.59)	0.22	0.69	86.56 (22.26)	101.53 (15.30)	0.07	0.88
Math Reasoning	91.83 (16.19)	104.65 (14.64)	0.08	0.86	87.00 (19.30)	100.46 (12.98)	0.07	0.91	89.67 (22.47)	100.20 (14.49)	0.22	0.64
Conners' CPT												
Omissions	86.15 (21.79)	72.49 (30.67)	0.22	0.47	89.43 (12.69)	84.42 (17.54)	0.51	0.30	83.04 (21.33)	78.32 (18.01)	0.19	0.25
Hit RT	51.04 (9.69)	44.42 (14.82)	0.37	0.47	50.84 (13.81)	47.42 (10.22)	0.50	0.31	53.27 (15.59)	52.52 (11.13)	0.61	0.06
CPRS												
Learning	63.27 (23.43)	50.03 (9.36)	0.19	0.92	62.27 (18.66)	49.69 (12.68)	0.04*	0.87	44.00 (9.21)	46.71 (11.39)	0.37	0.25
Psychosomatic	68.64 (17.29)	67.17 (18.10)	0.74	0.08	65.00 (19.54)	56.41 (17.19)	0.16	0.48	65.70 (20.39)	68.71 (16.25)	0.48	0.17
Impulse-Hyper	56.36 (15.36)	50.23 (9.46)	0.22	0.54	57.45 (11.47)	49.59 (11.17)	0.04*	0.70	50.30 (9.81)	47.00 (10.95)	0.35	0.31
Hyperactive	59.73 (20.56)	49.13 (8.60)	0.17	0.83	59.36 (17.03)	48.66 (10.94)	0.04*	0.84	46.60 (9.34)	47.47 (13.82)	0.70	0.07

Note: Significant *P*-values are asterisked, which indicate a difference between the neuropsychological performance of children with on-therapy seizures to a matched non-seizure cohort across time points using mixed model repeated measures analysis of variance; ES = Effect Size (.8 = large, .5 = moderate, .2 = small; Cohen, 1988); EIQ = Estimated Intelligence Quotient, FSIQ = Full Scale Intelligence Quotient, FFD = Freedom from Distractibility, PSI = Processing Speed Index, DS = Digit Span, WIAT = Wechsler Individual Achievement Test, CPT = Continuous Performance Test, RT = Reaction Time, CPRS = Conners' Parent Rating Scale.