

LYMPHOID NEOPLASIA

Long-term decline in intelligence among adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiation

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Key Points

- Adult survivors of childhood ALL treated with cranial radiation demonstrate a decline in verbal intelligence during an interval of 28 years.
- This decline was associated with current attention problems, but not gender, radiation dose, or age at radiation exposure.

Survivors of childhood acute lymphoblastic leukemia (ALL) treated with cranial radiation therapy (CRT) are at risk for cognitive impairment, although whether impairment progresses with age into adulthood is unknown. We report change in intelligence for 102 adult survivors of childhood ALL (age range, 26.6-54.7 years) during a median interval of 28.5 years. Survivors demonstrated lower Performance intelligence (mean, 95.3; standard deviation, 16.5; $P = .005$) but not Verbal IQ (mean, 97.4; standard deviation, 15.44; $P = .09$) at initial testing. Verbal intelligence declined an average of 10.3 points ($P < .0001$) during the follow-up interval with no decline in Performance intelligence. Decline was associated with current attention problems ($P = .002$) but not gender, CRT dose, age at CRT exposure, or years between testing. Results suggest long-term survivors of childhood ALL treated with CRT are at risk for progressive decline in verbal intellect, which may be driven by attention deficits. This trial was registered at clinicaltrials.gov as no. NCT00760656. (*Blood*. 2013;122(4):550-553)

Introduction

Long-term survivors of childhood acute lymphoblastic leukemia (ALL) are at risk for cognitive impairment after cranial radiation therapy (CRT).¹⁻⁴ Previous outcome studies that directly assess survivor intelligence have focused on function during the first 10 years after diagnosis, with relatively few reports extending follow-up into adulthood. During the first decade after treatment, declines in intelligence have been reported with 24 Gy or 18 Gy CRT.³ In addition, adult survivors of childhood cancer have been reported to demonstrate long-term functional deficits, including lower educational attainment⁵ and self-reported cognitive impairment.⁶

To our knowledge, no published reports have examined change in cognitive function of ALL survivors during extended intervals into adulthood. It is unknown whether the degree of cognitive impairment increases with time. Here, we report change in a measure of global verbal ability (ie, Verbal intelligence quotient [IQ]) for 2 testing points separated by a median interval of 28.5 years, beginning at least 1 year after completion of CRT for childhood ALL.

health outcomes in adult survivors of childhood cancer.⁷ Survivors enrolled in SJLIFE were previously treated at St. Jude Children's Research Hospital and are now at least 10 years from diagnosis and are at least 18 years old. From this large cohort, survivors who received CRT for childhood ALL and had previously undergone intelligence testing at St. Jude as part of the institution's standard of care were identified. Initial testing occurred when survivors were ≥ 1 and < 10 years posttherapy. Exclusion criteria included a history of craniotomy, ventriculoperitoneal shunt, subsequent central nervous system neoplasm, traumatic brain injury, genetic disorder associated with neurocognitive impairment (eg, Down syndrome), or active treatment of cancer. Of the 138 participants who met the eligibility criteria, 31 declined participation, 3 were medically unable to participate, and 2 withdrew after consent. This left 102 survivors (73.9%) who participated in follow-up testing. Compared with participants, nonparticipants included slightly more men, although no differences were noted in current age, age at diagnosis, time since diagnosis, or cranial radiation dose. Among participants, 33.3% underwent 18 Gy CRT and 66.7% underwent 24 Gy CRT. Among nonparticipants, 37.1% underwent 18 Gy CRT and 62.9% underwent 24 Gy CRT. Participants did not differ from eligible nonparticipants on initial IQ testing (all P values $> .10$; Table 1). The study protocol was approved by the St. Jude Children's Research Hospital Institutional Review Board, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Study design

Study population

Adult survivors of childhood leukemia were recruited from the St. Jude Lifetime Cohort (SJLIFE), an institutional protocol designed to examine

Procedures

Survivors completed follow-up neurocognitive testing during a 2-hour session in dedicated testing rooms. All testing was conducted by certified

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Table 1. Survivor demographic and treatment characteristics

Demographics	Participants		N	%
	N	%		
Participants				
N = 102				
Demographics				
Gender				
Female	56	54.9		
Male	46	45.1		
Race				
White	96	94.1		
Other	6	5.9		
Highest grade				
College graduate	32	31.4		
Noncollege graduate	70	68.6		
Current employment				
Full time	62	60.8		
Part time or unemployed	38	37.3		
	Mean	SD	Min	Max
Current age (y)	38.4	6.2	27	55
Treatment factors				
IT MTX (mL)	103.6	88.5	0	496
IV MTX (g/m ²)	2.22	2.90	0	21.8
Age (y)				
At diagnosis	5.0	3.2	0.8	15.3
At initial testing	11.0	3.8	4.3	23.1
At follow-up testing	38.5	6.2	26.6	54.7
End of therapy to initial testing (y)	3.4	2.3	1.0	9.3
Diagnosis to follow-up testing (y)	33.5	5.7	18.8	46.4
Initial to follow-up testing (y)	27.6	5.6	14.0	38.4
CRT dose (Gy)				
	N	%		
18	34	33.3		
24	68	66.7		
Neurocognitive assessment				
	Mean	SD		
Nonparticipants (n = 36)				
IQ at initial testing				
Verbal	92.7	14.6		
Performance	93.6	17.0		
Full Scale	92.4	15.4		
Participants (n = 102)				
IQ at initial testing				
Verbal	97.4	15.4		
Performance	95.3	16.5		
Full Scale	96.0	15.9		
IQ at follow-up testing				
Verbal	87.1	17.1		
Performance	95.7	16.8		
Full Scale	91.3	15.5		
Academic				
Reading	91.3	9.8		
Mathematics	85.8	17.48		
Attention: sustained	89.7	16.99		
Processing speed	89.5	27.45		
Memory				
Total recall	92.7	18.14		
Long-term	92.4	18.94		
Executive function				
Fluency	89.3	16.07		
Flexibility	77.6	32.01		

Cumulative doses listed for intrathecal (IT) and intravenous (IV) methotrexate (MTX). Initial testing denotes first testing ≥1 year and ≤10 years after CRT. Follow-up testing denotes current testing. All neurocognitive assessment scores presented in age-adjusted standard scores with an expected mean of 100 and an SD of 15. Participants did not differ from nonparticipants in initial Verbal IQ ($P = .12$), Performance IQ ($P = .60$), or Full Scale IQ ($P = .24$).

IT, intrathecal; IV, intravenous; Min-Max, minimum-maximum; MTX, methotrexate.

masters-level examiners, under the general supervision of a board-certified clinical neuropsychologist. Assessed domains included intelligence,⁸ academic skills,⁹ attention,¹⁰ processing speed,¹¹ memory,¹² and executive function

(ie, cognitive fluency and flexibility).¹³ Order of testing was standardized, and survivors' schedules were adjusted to limit the effect from fatigue and extraneous factors. Medical record abstraction was performed to capture previous IQ testing and exposure data including radiation treatment (whole-brain dose), and cumulative doses of intravenous and intrathecal methotrexate, as these chemotherapy agents have been associated with neurocognitive problems.¹⁴

Statistical analyses

Descriptive statistics for survivors are provided in Table 1, along with results of initial and follow-up testing conducted as part of SJLIFE. One-sample *t* tests were used to assess whether Full Scale, Verbal, or Performance IQ scores at both initial and follow-up time points differed from national norms (expected score, 100; standard deviation [SD], 15). One-sample *t* tests were used to assess whether differences between initial and follow-up Full Scale, Verbal, and Performance IQ scores were equal to zero. Differences in IQ scores (initial and follow-up testing) were modeled using predictors including gender, CRT dose, age at CRT exposure, cumulative intrathecal and intravenous methotrexate dose, years between diagnosis and initial testing, and years between initial testing and follow-up testing. Associations between difference in IQ scores and current neurocognitive performance were also examined.

Results and discussion

Compared with age-adjusted expectations from national norms, on the initial evaluation survivors demonstrated lower Performance IQ (mean [SD], 95.3 [16.5]; $P = .005$) and Full Scale IQ (mean [SD], 96.0 [15.9]; $P = .01$) but not Verbal IQ (mean [SD], 97.4 [15.44]; $P = .09$). Verbal IQ demonstrated a significant decline at follow-up (mean [SD] change, 10.31; $P < .0001$); no significant change in Performance IQ was apparent (change, -0.21 ; $P = .88$). Full Scale IQ also demonstrated a significant decline (change, 4.75; $P < .0001$), although, as this is a composite of Verbal and Performance IQs, change is driven by Verbal IQ. Figure 1 presents patterns of decline in Verbal IQ for all survivors as well as group averages for survivors who did and did not demonstrate a decline with time. Of note, 48.0% of survivors did not demonstrate a significant decline in Verbal IQ, suggesting potential protective factors or differential group vulnerability. Linear regression analyses revealed no statistically significant association between decline in Verbal IQ and gender (β , 0.80; $P = .73$), CRT dose (β , 0.51; $P = .15$), age at diagnosis (β , -0.51 ; $P = .14$), time between diagnosis and initial testing (β , -0.31 ; $P = .50$), or time between initial testing and follow-up testing (β , 0.08; $P = .66$). Decline in Verbal IQ was associated with current impairment on measures of sustained attention ($P = .002$) and reading ($P = .02$) but not processing speed, memory, or executive functions.

The current results indicate that CRT for childhood ALL is associated with an initial decline in performance abilities followed by a late decline in verbal abilities. The initial decline in Performance IQ is consistent with results of previous reports suggesting an earlier decline in nonlanguage reasoning abilities.^{15,16} The decline in Verbal IQ with time is a novel finding and suggests a progressive effect on brain function from CRT. Traditional variables associated with an early decline in cognitive abilities (eg, CRT dose,¹⁷ young age at diagnosis,³ and female gender),¹⁸ do not predict change in Verbal IQ during subsequent decades. Instead, a decline in Verbal IQ was associated with current attention and reading problems. Unfortunately, available data from initial testing were generally restricted to IQ scores, and measures of attention were not present in the medical records. Still, persistent problems in attention have been shown to

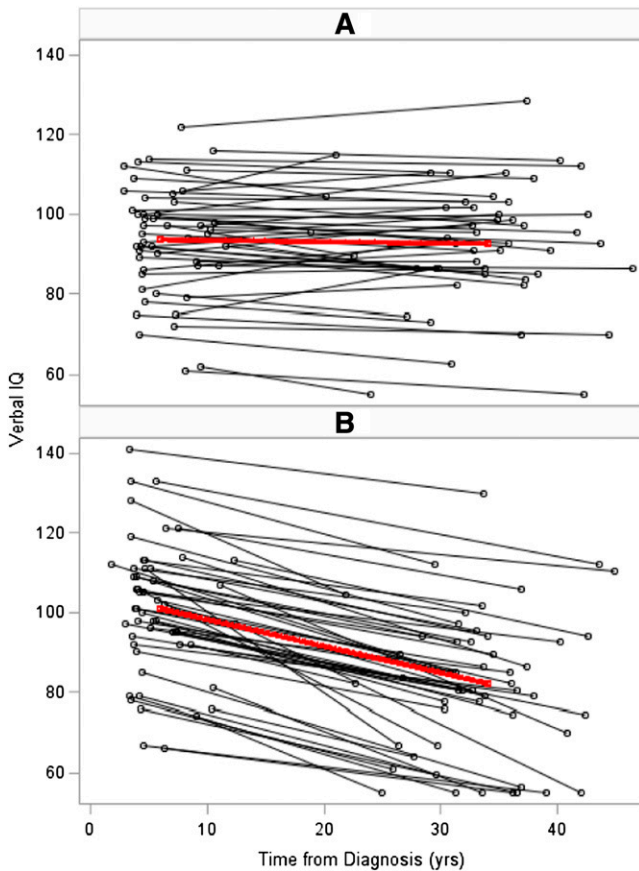


Figure 1. Change in Verbal IQ between initial testing and follow-up testing. The horizontal axis depicts testing intervals reflecting time from diagnosis to initial testing, first data point, and time from diagnosis to follow-up testing, second data point. The vertical axis depicts age-adjusted Verbal IQ scores (expected mean, 100; SD, 15), with age identified at time of respective testing. The top box (A) clusters the 49 survivors (black lines) and group average (red line) of those who did not demonstrate a decline in Verbal IQ from initial to follow-up testing, whereas the bottom graph (B) clusters the 53 survivors who demonstrated at least a 10-point decline in Verbal IQ between the 2 testing sessions. Of note, very few survivors demonstrated an increase in Verbal IQ from initial to follow-up testing (A).

affect verbal intellect during long periods,^{19,20} and it is certainly plausible that attention problems were present for many years. We have recently identified an association between increased risk for attention problems and increased time from diagnosis in a large cohort of adult survivors of childhood ALL (Krull KR, Brinkman TM, Li C, Armstrong GT, Ness KK, Srivastava DK, Gurney JG, Kimberg C, Krasin MJ, Pui CH, Robison LL, Hudson MM, manuscript submitted to *Journal of Clinical Oncology*). Thus, the interaction between

attention and verbal problems may continue to progress with time and age. Although the decline in Verbal IQ was not associated with current measures of memory, development of verbal abilities is heavily dependent on learning and long-term recall of new information with time.²¹ We recently demonstrated an increased risk for long-term memory problems in aging adult survivors of ALL treated with CRT,²² suggesting the need for further examination of the effect of memory problems on verbal intellectual abilities.

The findings from our study support several recommendations. These results provide additional evidence for the recommendation of avoiding CRT in the treatment of childhood ALL.²³ In addition, because verbal abilities are important to independent success in today's society, long-term adult survivors should continue to be monitored for declining verbal abilities, with appropriate interventions offered as needed. Ideally, current survivors would be educated and offered cognitive enrichment to prevent future decline in verbal abilities.

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Authorship

Contribution: K.R.K., D.K.S., M.M.H., L.L.R., and G.T.A. designed the study; K.R.K., A.S., M.M.H., L.L.R., and G.T.A. acquired the data; N.Z. and D.K.S. conducted data analysis; K.R.K., M.J.K., L.E.K., C.-H.P., M.M.H., L.L.R., and G.T.A. interpreted the data; K.R.K., N.Z., A.S., D.K.S., M.J.K., L.E.K., C.-H.P., M.M.H., L.L.R., and G.T.A. conducted manuscript drafts or revisions; K.R.K., N.Z., A.S., D.K.S., M.J.K., L.E.K., C.-H.P., M.M.H., L.L.R., and G.T.A. conducted final approval of the manuscript.

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