

Cognitive, behavior and academic problems in adolescent survivors of childhood acute lymphoblastic leukemia (ALL): A report from the Childhood Cancer Survivor Study

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Introduction: Over the past 30 years, survival rates for childhood ALL have improved and neurotoxicity has been reduced by largely replacing cranial radiation therapy (CRT) with additional systemic and intrathecal therapy. However, survivors treated without CRT may still be at risk for long-term neurocognitive deficits and reduced quality of life. Neurobehavioral problems during adolescence are particularly problematic as increased environmental demands for self-direction and higher order cognition are expected. As existing studies of cognition and behavior in adolescent survivors are limited by small samples, single-site data collection, and short follow-up intervals, we examined the prevalence of and risk factors for cognitive, behavior, and academic problems in adolescent survivors of childhood ALL using the Childhood Cancer Survivors Study (CCSS) cohort.

Methods: Caregiver report data were analyzed for 1426 5+ year survivors of childhood ALL who were diagnosed between 1970 and 1999 and between 12 to 17 years of age at follow-up, and 609 sibling controls. Cognitive and behavior problems were measured with the Behavior Problem Inventory (BPI). Academic problems were defined as special education placement (yes/no). Chi-Square tests were used to compare the frequency of elevated BPI scores ($\geq 90^{\text{th}}$ percentile) and special education placement in survivors versus siblings. Multivariable logistic regression was used to examine the association between CRT and chemotherapy doses (Table 1) and cognitive, behavior, and academic problems, adjusting for sex and age at diagnosis (<5 years, ≥ 5 years). In a subset of 736 survivors for whom longitudinal data were available, associations were examined between cognitive/behavior problems and special education placement during adolescence and self-reported educational attainment as adults (mean [range] age = 28.0 [25.0–37.3]).

Results: Compared to siblings, survivors were more likely to have elevated symptoms of anxiety-depression, inattention-hyperactivity, headstrong behavior, and social withdrawal, as well as higher rates of special education placement (Table 2). Relative to no CRT, treatment that included CRT at a dose of <20 Gy increased the risk for anxiety-depression (OR=1.69, [95%CI, 1.25-2.30]), inattention-hyperactivity (OR=1.25, [1.16, 2.00]), and social withdrawal (OR=1.98, [1.51, 2.61]). Moreover, risk of special education placement was increased for survivors treated with <20 Gy CRT (OR=1.89, [1.47, 2.45]) and ≥ 20 Gy (OR=2.45, [1.93-3.91]). Among survivors treated without CRT, cumulative doses of intrathecal or intravenous methotrexate (MTX) were not associated with risk for cognitive, behavior, or learning problems. Survivors with cognitive or behavior problems, and those who participate in special education during adolescence were less likely to graduate from college as adults (Table 2*).

Conclusion: Adolescent survivors of childhood ALL, especially those treated with CRT, are at significantly increased risk for cognitive, behavior, and academic problems that adversely impact adult outcomes. Participation in special education did not remediate this risk, as survivors receiving services were less likely to graduate college as adults. Interventions designed to improve adolescent neurobehavioral functioning should be prioritized.

Table 1.

		%	Mean ± SD
Age at diagnosis	< 5 years	79	3.74±1.82
	≥ 5 years	21	
Sex - Male		54	
Seizures or strokes after diagnosis - Yes		7	
CRT	None	50	
	<20 Gy	31	
	≥ 20 Gy	12	
IT MTX	<230 mg	44	
	≥ 230 mg	56	
IV MTX	None	55	
	<4.3 g/m ²	21	
	≥ 4.3 g/m ²	24	
Cytarabine	None	29	
	Yes	71	
Anthracyclines	None	48	
	< 300 mg/m ²	39	
	≥ 300 mg/m ²	13	
Alkylating agents	None	41	5716.26 ± 5424.92
	Yes	59	
Dexamethasone	None	26	
	Yes	74	

Table 2.

	Survivors	Siblings	p	College Graduation*	
				OR	95% CI
<u>Cognitive and behavior problems</u>					
Antisocial	14%	11%	0.0800	2.28	1.34, 3.90
Anxiety-Depression	17%	11%	0.0003	1.55	1.02, 2.35
Headstrong	22%	14%	0.0002	1.52	1.03, 2.23
Inattention - Hyperactivity	24%	14%	<0.0001	3.04	2.04, 4.54
Social Withdrawal	25%	12%	<0.0001	1.31	0.92, 1.88
<u>Academic Problems</u>					
Special Education – Yes	34%	14%	<0.0001	4.29	2.95, 6.22