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ORIGINAL REPORT

Late-Occurring Neurologic Sequelae in Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose
Children with acute lymphoblastic leukemia (ALL) are often cured, but the therapies they receive may be neurotoxic. Little is known about the incidence and severity of late-occurring neurologic sequelae in ALL survivors. Data were analyzed to determine the incidence of adverse long-term neurologic outcomes and treatment-related risk factors.

Patients and Methods
We analyzed adverse neurologic outcomes that occurred after diagnosis in 4,151 adult survivors of childhood ALL who participated in the Childhood Cancer Survivor Study (CCSS), a retrospective cohort of 5-year survivors of childhood cancer diagnosed between 1970 and 1986. A randomly selected cohort of the survivors' siblings served as a comparison group. Self-reported auditory-vestibular-visual sensory deficits, focal neurologic dysfunction, seizures, and serious headaches were assessed.

Results
The median age at outcome assessment was 20.2 years for survivors. The median follow-up time to death or last survey since ALL diagnosis was 14.1 years. Of the survivors, 64.5% received cranial radiation and 94% received intrathecal chemotherapy. Compared with the sibling cohort, survivors were at elevated risk for late-onset auditory-vestibular-visual sensory deficits (rate ratio [RR], 1.8; 95% CI, 1.5 to 2.2), coordination problems (RR, 4.1; 95% CI, 3.1 to 5.3), motor problems (RR, 5.0; 95% CI, 3.8 to 6.7), seizures (RR, 4.6; 95% CI, 3.4 to 6.2), and headaches (RR, 1.6; 95% CI, 1.4 to 1.7). In multivariable analysis, relapse was the most influential factor that increased risk of late neurologic complications.

Conclusion
Children treated with regimens that include cranial radiation for ALL and those who suffer a relapse are at increased risk for late-onset neurologic sequelae.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Current 5-year survival rates exceed 80%.[1] Significant advancements that improved survival occurred with the implementation of CNS-directed therapy.[2] Initially, cranial radiation was the mainstay of CNS-directed therapy, but this was associated with cognitive impairment.[3,4] Subsequently, most prophylactic treatment regimens substituted intensified intrathecal and systemic chemotherapy for cranial radiation. Radiation is still used in populations at high risk for CNS disease. Acute neurotoxicity has been reported in 8% to 18% of children with ALL[5-8] and occurs as a consequence of CNS leukemia, therapy-related damage, infection, or stroke. CNS-directed therapy can result in leukoencephalopathy, seizures, altered intellectual or psychomotor function, and neurosensory dysfunction.[9-12] The risk of late neurologic complications related to CNS-directed therapies has not been well established. Several factors may influence risk, including age at the time of treatment, sex, CNS involvement at diagnosis, radiation dose, chemotherapy used, and time from therapy.[3,13-19]

The goals of this analysis were to describe the incidence of adverse neurologic conditions occurring at least 5 years after diagnosis and to evaluate the effect of different treatment regimens on the risk of developing these neurologic events. The Childhood Cancer Survivor Study (CCSS) includes data on more than 4,000 survivors of childhood ALL, which

affords the opportunity to evaluate the long-term neurologic effects of childhood ALL.

PATIENTS AND METHODS

Inclusion Criteria

The CCSS is a retrospective cohort of survivors of childhood leukemias, brain tumors, lymphomas, Wilms tumor, neuroblastoma, sarcomas, and bone tumors diagnosed between 1970 and 1986 at one of 26 collaborating institutions (Appendix Table A1, online only).[20] Patients were eligible for the CCSS if they were younger than 21 years at diagnosis and had survived at least 5 years from diagnosis, independent of disease status.

Approval for the study was obtained from the human subjects committee at each collaborating institution. Consent was obtained from patients (or their proxy) to participate in the study and to allow abstraction of medical records. Additionally, the study recruited the nearest-age sibling of a random sample of participating patients to serve as a comparison group.

Collaborating institutions identified 20,691 5-year survivors who met eligibility criteria. Of these, 14,363 completed a questionnaire or telephone interview, 3,205 declined to participate, 3,058 were lost to follow-up, and 65 were unable to participate because of a language barrier. We previously compared demographic and cancer-related characteristics among participants, nonparticipants, and those lost to follow-up and found that these three groups were similar and not a likely source for bias.[21,22] There were 4,151 childhood ALL survivors. A group of 3,899 randomly selected siblings of childhood cancer survivors participated and served as the comparison group in this analysis.

Data Collection

At the time of enrollment, a comprehensive baseline questionnaire was completed by the participant (if age 18 years or older) or his/her parent (if $<$ age 18 years). Surveys were distributed by mail or administered by phone with trained interviewers. The majority of questionnaires were collected between 1994 and 1996. Survey questions regarding neurologic conditions began with the phrase, "Have you ever been told by a doctor or other health care professional that you have or have had. . . ?" If a participant gave a "yes" response, they were then asked their age at first diagnosis.

Treatment information was abstracted from medical records at the participating institutions. Information on cancer therapy included initial therapy, treatment for any relapse, and any conditioning regimen for bone marrow transplant (BMT). Data regarding exposure to 42 chemotherapeutic agents (either "yes" or "no") were abstracted, and cumulative doses were calculated for selected agents. Surgeries performed for cancer treatment at any time from the date of diagnosis onward, site of any tumor(s), and fields and doses of radiation therapy were recorded. Radiation data were centrally reviewed at the Radiation Physics Center at M. D. Anderson Cancer Center. The baseline questionnaire and abstraction form are available at www.stjude.org/ccss.

Four types of neurologic outcomes were considered: auditory-vestibular-visual sensory deficits, focal neurologic dysfunction, seizure disorder, and headaches. Auditory-vestibular-visual sensory deficits included any hearing loss (defined as hearing loss requiring a hearing aid, deafness in one or both ears not corrected by a hearing aid, or complete deafness in either ear), tinnitus, persistent dizziness, legal blindness in one or both eyes, and double vision. Focal neurologic dysfunction included deficits related to balance, tremors or movement, weakness, or inability to move arm(s) or leg(s). An aggregate variable for "any coordination problem" was derived from balance problems or tremors. Similarly, a variable for "any motor problem" was derived from weakness or inability to move arms(s) or leg(s). Reported decreased sense of touch or feeling was included as focal dysfunction, along with pain or abnormal sensation. A seizure disorder was defined by a report of epilepsy, repeated seizures, convulsions, or blackouts. Headaches were defined as any report of serious headaches or migraines. A "yes" response to any component of an aggregated variable was considered a "yes" for that variable.

Statistical Analysis

Descriptive analyses of demographics and treatment characteristics of the 5-year ALL survivors were performed. Incidence rates of each neurologic outcome following the 5-year survival were estimated by dividing the observed count of the outcome (only first events were counted for the composite-event outcomes) by the person-years at risk. Patients were observed from the fifth anniversary of the original diagnosis and censored at the time of outcome evaluation or at death. The post-5-year rate ratio (RR) for developing each late neurologic outcome, comparing survivors with siblings, was estimated by Poisson regression adjusted for age at the time of the study, sex, and race. Potential within-family correlation was accounted for by the generalized estimating equation.[23] We considered the prevalence at the study entry for having developed each neurologic outcome in the first 5 years post diagnosis among the survivors. The same analysis of incidence rates as the post-5-year period is not applicable to the first 5 years because of the requirement of the 5-year survival for the CCSS cohort entry. The prevalence ratio at 5 years post ALL diagnosis was estimated by dividing the observed count of each outcome of the survivors by its expected count, assuming survivors had the same outcome rate as the age-sex-race-matched siblings. Siblings' hazard for developing each neurologic outcome was modeled by 5-year age groups, sex, and race, which provided the rates for age-sex-race-matched siblings. The statistical inference of prevalence ratio was based on bootstrap, sampling families to account for potential within-family correlation.[24]

To evaluate effects of various factors, including age at diagnosis, therapy factors, relapse of the original cancer, and BMT, univariate and multivariate regressions were performed for each neurologic outcome, adjusting for age at the time of the study and sex. Decisions regarding which factors to include in the multivariate model were based on a priori anticipated clinical relevance and included factors not identified on the univariate analysis (Appendix Table A2, online only). Relapse from the original cancer and BMT were treated as time-dependent variables. All treatment exposures within 5 years from original diagnosis of ALL are considered. Starting at 5 years, cumulative incidence curves were calculated individually for auditory-vestibular-visual sensory deficits, focal neurologic dysfunction, seizure disorder, headache, or at least one neurologic deficit.

Multiple imputations under the assumption of "missing at random"[25] were used to impute age at first occurrence of any neurologic outcome if a "yes" response was recorded without an age of first diagnosis.[26] We used the multiple-imputation methodology of Taylor et al[27] with slight modifications for event-time imputations. This method employs piece-wise exponential models to describe the rates of each neurologic outcome by age, age at diagnosis, sex, relapse occurrence, and treatments (cranial radiation and high-dose methotrexate). The model fitting used an expectation-maximization algorithm. The same multiple imputation strategy was used for handling siblings with missing age at first occurrence. This imputation was repeated 10 times creating 10 complete data sets without missing values of age. Each analysis was conducted 10 times using the 10 data sets, and the results were summarized by standard methods for combining multiple-imputation analyses.[28] By repeating the imputation and analysis 10 times, we properly represent uncertainties of missing values in between-imputation variability.

RESULTS

Study Population Characteristics

General demographic information for patients and siblings in addition to basic treatment information for patients are included in Table 1. The median age at outcome assessment was 20.2 years (range, 5.9 to 44.6 years) for survivors and 26.4 years (range, 1.8 to 56.2 years) for siblings. The median follow-up time from ALL diagnosis to death or last survey was 14.1 years (range, 5.0 to 29.7 years). Siblings were on

Table 1. Characteristics of Childhood Acute Lymphoblastic Leukemia Patients and the Sibling Comparison Group

Characteristic	Survivors (n = 4,151) No.	Survivors (n = 4,151) %	Siblings (n = 3,899) No.	Siblings (n = 3,899) %
Age at interview, years				
< 20	2,045	49.3	1,086	27.9
20-29	1,723	41.5	1,381	35.4
30-39	372	9.0	1,116	28.6
40+	11	0.3	316	8.1
Sex				
Male	2,212	53.3	1,875	48.1
Female	1,939	46.7	2,024	51.9
Race/ethnicity				
White, non-Hispanic	3,383	81.8	3,414	90.7
Black, non-Hispanic	167	4.0	103	2.7
Hispanic/Latino	260	6.3	138	3.7
Other	327	7.9	107	2.8
Vital status at time of interview				
Alive	3,820	92.0		
Dead	331	8.0		
Age at diagnosis, years				
< 1	56	1.3		
1-9	3,340	80.5		
10+	755	18.2		
CNS therapy*				
Cranial + IT	2,220	60.8		
Cranial XRT	135	3.7		
IT alone	1,209	33.1		
No cranial XRT or IT	87	2.4		
CNS therapy, Gy				
Cranial ≥ 20	1,281	35.1		
Cranial > 0 to < 20	1,074	29.4		
IT alone	1,209	33.1		
None	87	2.4		
MTX IV†				
MTX IV, high dose	422	11.5		
MTX IV, not high dose	956	26.1		
No MTX or no MTX IV	2,279	62.3		
MTX IV (high dose)†				
Yes	422	11.5		
No	3,235	88.5		
Recurrence				
Yes	846	20.4		
No	3,305	79.6		
Bone marrow transplant				
Yes	208	5.1		
No	3,908	94.9		

NOTE. Some variables had missing values (such as race and treatment data); the numbers and percentages are based on available data only.

Abbreviations: IT, intrathecal; XRT, external radiation therapy; MTX, methotrexate; IV, intravenous.

*Cranial radiation includes a small number of patients (n = 342) who were treated with craniospinal radiation. The vast majority of patients who were treated with cranial radiation were also treated with intrathecal therapy (only 136 of the patients treated with cranial radiation did not receive any intrathecal therapy).

†High-dose methotrexate (IV) is defined as any dose of more than 5,000 mg/m^2.

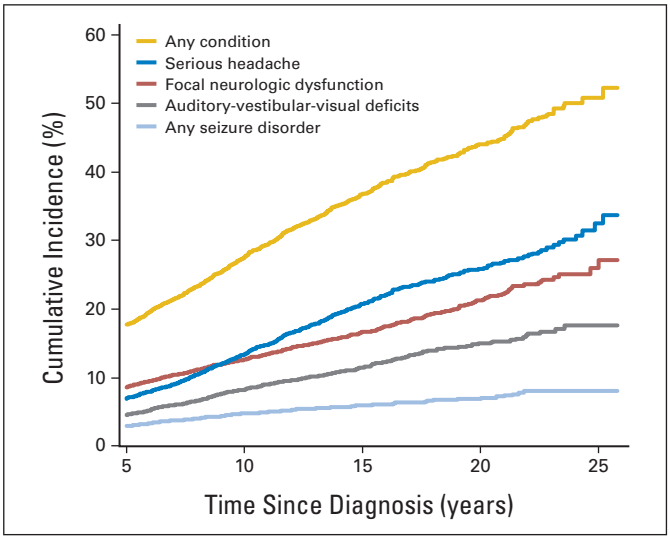

Fig 1. Cumulative incidence of selected chronic health conditions among 5-year survivors of acute lymphoblastic leukemia.

average older than patients at the time of interview. A higher percentage of patients in the study group were male compared with the sibling group. There were more self-reported non-white survivors (18.2%) compared with siblings (9.2%).

Approximately 80% of patients were between 1 and 9 years of age at diagnosis, and less than 2% were infants at diagnosis. The majority of patients (64.5%) were treated with cranial radiation (median, 23.8 Gy; range, 1.5 to 74.4 Gy). Of the patients who received cranial radiation, 67 received less than 17 Gy, 1,007 had between 17 Gy and 20 Gy, and 1,281 had more than 20 Gy. Nearly all patients (94%) received intrathecal therapy. Approximately 12% were treated with high-dose methotrexate (≥ 5,000 mg/m^2). Twenty percent reported at least one recurrence of their ALL, and 5% reported undergoing BMT. At the time of response, 92% of patients were alive and the other 8% had information reported by a proxy.

The overall cumulative incidence of any neurologic condition was 44.0% at 20 years (Fig 1). Serious headaches were most common, with a cumulative incidence of 25.8% at 20 years, followed by focal neurologic dysfunction (21.2% at 20 years) and auditory-vestibular-visual sensory deficits (15.1% at 20 years). Reports of seizures had the lowest cumulative incidence of 7.0% at 20 years. The cumulative incidence of late neurologic conditions by age at diagnosis, sex, and exposure to cranial radiation is shown in Figure 2.

Auditory-Vestibular-Visual Sensory Deficits: Hearing and Vision Problems

A total of 445 auditory-vestibular-visual sensory deficits were reported (Table 2) by 333 patients. Of those, 289 (64.9%) deficits developed late (at least 5 years after diagnosis). Late onset of persistent dizziness was more frequent (2.8 per 1,000 person-years) than other auditory-vestibular-visual sensory deficits. Relative to siblings, survivors were at elevated risk for all late-onset auditory-vestibular-visual sensory categories except any hearing impairment and legal blindness. Seventy-five survivors (26.5%) reported two or more auditory-vestibular-visual sensory deficits (Table 3).

Univariate analysis (Appendix Table A2) and multivariable analysis (Table 4) revealed several factors that influenced risk of auditory-vestibular-visual sensory deficits after 5 years from diagnosis. Children

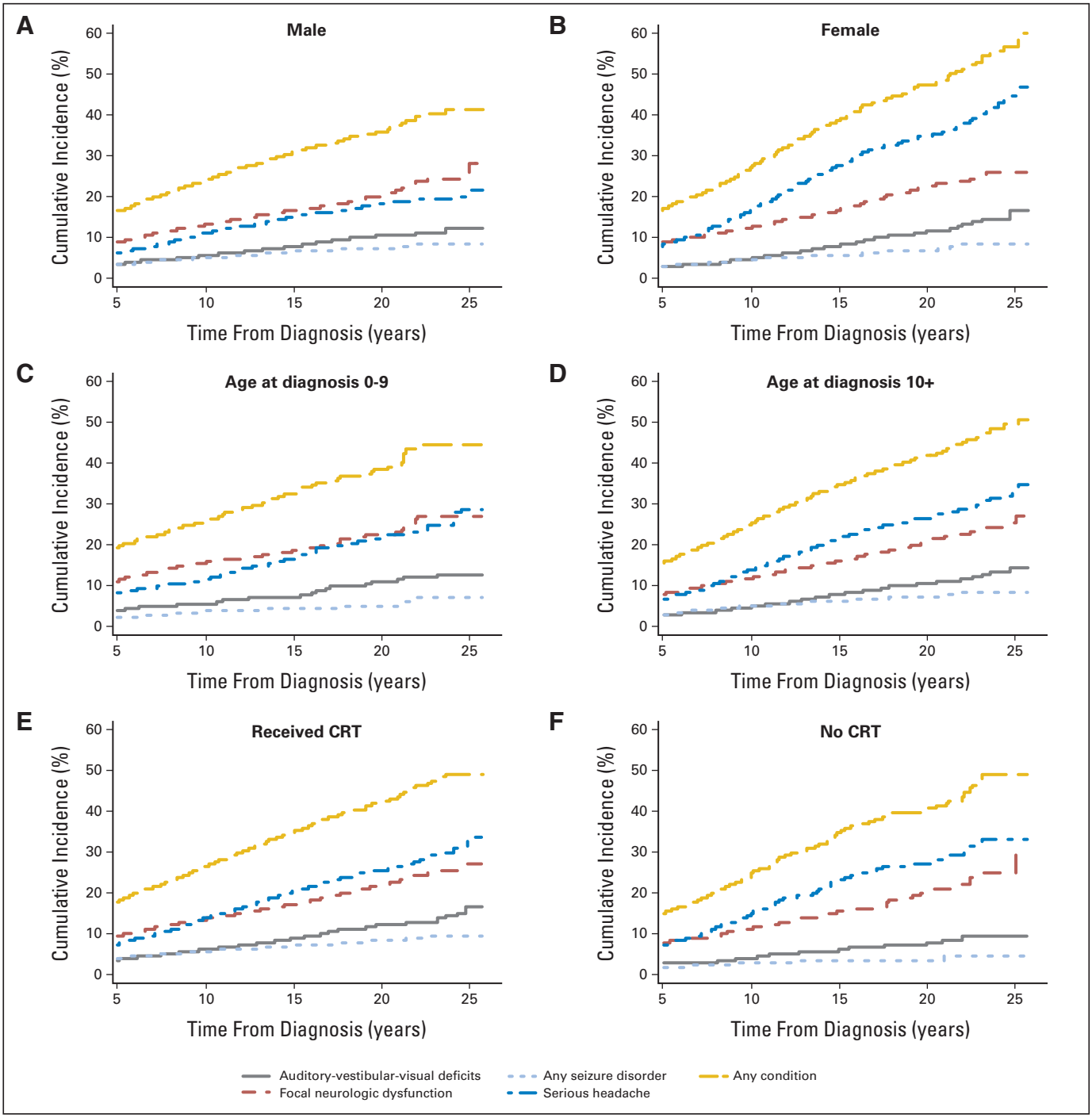

Fig 2. Cumulative incidence of selected neurologic conditions among 5-year survivors of acute lymphoblastic leukemia by sex, age at diagnosis, and by cranial radiation therapy (CRT).

treated at 10 years of age or older had slightly lower risk of auditory-vestibular-visual sensory deficit compared with children treated between 1 and 9 years of age. Patients who relapsed (RR, 2.0; $P < .001$) were at highest risk.

Focal Neurologic Dysfunction: Motor and Coordination Problems

Overall, 1,174 focal neurologic issues were reported (Table 2) by 696 patients. Of these, 626 (53%) developed late (> 5 years after diagnosis). Late coordination problems occurred at a rate of 4.1, motor problems at 3.3, decreased sensation at 3.0, and pain sensation at 6.1 per 1,000 patient-years. Relative to siblings, patients were at elevated risk for late-onset coordination problems (RR, 4.1; $P < .001$), motor problems (RR, 5.0; $P < .001$), decreased sensation (RR, 2.3; $P < .001$) and pain sensation (RR, 3.0; $P < .001$). Also, 151 survivors (30.2%) reported two or more focal neurologic conditions (Table 3). Patients who relapsed had increased risk for developing late focal neurologic problems (RR, 2.2; $P < .001$).

Table 2. Occurrence of Adverse Neurologic Outcomes by Time Period

	Auditory-Vestibular-Visual Sensory Deficits										Focal Neurologic Dysfunction											
	Any Hearing Impairment		Tinnitus		Persistent Dizziness		Legal Blindness in One or Both Eyes		Double Vision		Any Coordination Problem		Any Motor Problem		Decreased Touch or Feeling		Pain or Abnormal Sensation		Any Seizure Disorder		Any Headache	
Conditions	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Reported outcome																						
Yes*	56	1.4	136	3.3	141	3.4	46	1.1	66	1.6	306	7.5	268	6.5	215	5.2	385	9.4	249	6.1	848	20.8
No†	4,065	98.6	3,995	96.7	4,003	96.6	4,093	98.9	4,076	98.4	3,796	92.5	3,830	93.5	3,915	94.8	3,705	90.6	3,860	93.9	3,232	79.2
Diagnosis to 5 years																						
Yes	36		37		29		23		31		149		142		100		157		123		286	
PR‡	4.1		1.8		3.1		2.3		5.4		9.9		19.0		16.7		11.8		7.5		2.3	
95% CI	2.6 to 6.7		1.2 to 2.8		1.9 to 5.2		1.3 to 4.3		2.8 to 10.1		7.1 to 13.8		11.8 to 30.5		11.1 to 24.9		8.6 to 16.1		5.4 to 10.2		2.0 to 2.7	
P	< .001		.008		< .001		.006		< .001		< .001		< .001		< .001		< .001		< .001		< .001	
5 years after diagnosis																						
Yes*	20		99		112		23		35		157		126		115		228		126		562	
Rate§	0.5		2.5		2.8		0.6		0.9		4.1		3.3		3.0		6.1		3.3		16.2	
95% CI	0.5 to 0.6		2.4 to 2.7		2.8 to 2.9		0.5 to 0.6		0.8 to 1.0		3.9 to 4.3		3.1 to 3.5		2.8 to 3.1		5.9 to 6.3		3.1 to 3.4		15.8 to 16.6	
RR¶	1.9		1.6		2.7		1.6		2.5		4.1		5.0		2.3		3.0		4.6		1.6	
95% CI	1.1 to 3.3		1.2 to 2.1		2.1 to 3.6		0.9 to 2.8		1.5 to 4.0		3.1 to 5.3		3.8 to 6.7		1.8 to 2.9		2.5 to 3.7		3.4 to 6.2		1.4 to 1.7	
P	.026		< .001		< .001		.107		< .001		< .001		< .001		< .001		< .001		< .001		< .001	

Abbreviations: RR, rate ratio; PR, prevalence ratio.
*Excludes conditions prior to diagnosis.
†Includes "not sure" and missing responses.
‡PR at cohort entry (5 years since acute lymphoblastic leukemia diagnosis), adjusted for age, sex, and race; relative to siblings.
§Rate per 1,000 person-years.
¶RR, adjusted for age, sex, and race; relative to siblings; $P \leq .001$.

Seizures

A total of 249 patients (6.1%) reported a seizure disorder (Table 2). Seizures were a late-onset problem in 51% of patients. Survivors were at increased risk for developing a late seizure disorder when compared with siblings (RR, 4.6; $P < .001$). Patients who relapsed were also at higher risk for developing late-onset seizures (RR, 2.6; $P = .002$).

Headaches

Headaches were the most commonly reported neurologic issue, with a total of 848 (21%) survivors experiencing severe headaches. Most (66%) reported late onset. The risk of developing late-onset headaches was increased in the patient group compared with the sibling group (RR, 1.6; $P < .001$). Male survivors were at lower risk (RR, 0.4; $P < .001$) compared with female survivors. Older age at diagnosis (10 years of age or older) decreased the risk of late-onset headaches (RR, 0.6; $P < .001$).

Multiple Neurologic Conditions

To assess whether findings were driven by a smaller group of survivors with multiple abnormalities or a larger group with only one abnormality, we evaluated how many survivors reported two or more

Table 3. Occurrence of Multiple Adverse Neurologic Outcomes

	Auditory-Vestibular-Visual Sensory Deficits				Focal Neurologic Dysfunction				All Adverse Neurological Outcomes			
	Any		Two or More		Any		Two or More		Any		Two or More	
Condition	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Reported outcome												
Yes*	333	8.2	93	2.3	696	17.4	290	7.2	1,395	35.7	448	11.6
No†	3,745	91.8	3,999	97.7	3,308	82.6	3,733	92.8	2,511	64.3	3,417	88.4
5 Years after diagnosis												
Yes*	208		75		348		151		919		190	
Rate‡	5.5		1.9		10.0		4.2		28.7		6.6	
95% CI	5.3 to 5.8		1.9 to 2.0		9.6 to 10.5		4.2 to 4.3		28.2 to 29.3		6.2 to 7.0	
RR§	1.8		8.0		2.9		4.9		2.4		1.9	
95% CI	1.5 to 2.2		5.1 to 12.7		2.5 to 3.3		3.7 to 6.5		2.2 to 2.6		1.6 to 2.3	

Abbreviation: RR, rate ratio.
*Excludes conditions prior to diagnosis.
†Includes "not sure" and missing responses.
‡Rate per 1,000 person-years.
§RR, adjusted for age, sex, and race; relative to siblings. $P \leq .001$.

Table 4. Late-Onset Neurologic Outcomes by Age, CNS Therapy, and Chemotherapy Exposures (multivariate analysis)

	Auditory-Vestibular-Visual Sensory Deficits			Focal Neurologic Dysfunction			Any Seizure Disorder			Any Headache		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Age at diagnosis, years												
< 1	0.5	0.1 to 3.7	.74	0.7	0.2 to 2.8	.63	0.9	0.1 to 6.9	.96	1.3	0.6 to 2.7	.45
10+	0.8	0.5 to 1.3	.38	1.0	0.7 to 1.4	.95	0.7	0.4 to 1.2	.19	0.6	0.4 to 0.8	< .001
1-9 (referent)	1.0			1.0			1.0			1.0		
Sex												
Male	0.8	0.6 to 1.1	.19	1.0	0.8 to 1.2	.76	1.2	0.8 to 1.8	.44	0.4	0.3 to 0.5	< .001
Female (referent)	1.0			1.0			1.0			1.0		
Cranial radiation												
≥ 20 Gy	1.4	0.9 to 2.2	.09	1.1	0.8 to 1.5	.40	1.3	0.8 to 2.2	.33	0.9	0.7 to 1.1	.31
< 20 Gy	1.5	0.9 to 2.4	.08	1.0	0.7 to 1.4	.81	0.9	0.5 to 1.7	.75	1.0	0.8 to 1.3	.97
None	0.5	0.1 to 2.4	.35	1.3	0.7 to 2.6	.43	0.5	0.1 to 3.4	.44	0.5	0.2 to 1.2	.13
IT alone (referent)	1.0			1.0			1.0			1.0		
MTX IV (high dose)												
Yes	1.5	0.9 to 2.7	.12	1.1	0.7 to 1.7	.75	0.9	0.4 to 2.0	.74	1.0	0.7 to 1.4	.88
No (referent)	1.0			1.0			1.0			1.0		
Recurrence												
Yes	2.0	1.4 to 2.9	< .001	2.2	1.7 to 3.0	< .001	2.5	1.5 to 4.2	< .001	1.2	0.9 to 1.6	.13
No (referent)	1.0			1.0			1.0			1.0		
Bone marrow transplant												
Yes	1.2	0.5 to 2.8	.69	1.1	0.6 to 2.2	.79	1.2	0.4 to 3.4	.76	0.6	0.3 to 1.4	.26
No (referent)	1.0			1.0			1.0			1.0		

Abbreviations: RR, rate ratio; IT, intrathecal; MTX, methotrexate; IV, intravenous.

neurologic conditions. The majority (82.9%) reported only one of the four neurologic problems (Table 3).

DISCUSSION

CNS-directed therapy is a key contributing factor to improving survival among children with ALL. When cranial radiation was linked to neurocognitive deficits, therapeutic regimens were modified to reduce or eliminate cranial radiation by substituting intensified intrathecal and systemic chemotherapy.[29,30] These CNS-directed therapies could also influence risk of late neurologic outcomes. We found that the risk of developing late neurologic complications is higher for survivors who received cranial radiation and/or suffered relapse of their leukemia.

Acute neurologic effects of direct leukemic CNS involvement and treatment-related complications are relatively well known.[31] CNS imaging changes on computed tomography and magnetic resonance imaging have been identified in ALL patients during and after therapy.[32,33] Whether systemic therapies and/or aggressive intrathecal therapies with known acute neurologic toxicities can lead to delayed neurologic consequences is unknown. In this cohort, systemic therapies and/or intrathecal therapies did not seem to influence risk of reported late neurologic complications.

Radiation to the CNS can injure the supportive tissues and neurogenic microenvironment of the nervous system and lead to neuronal loss or damage. Oxygen-free-radical damage and altered cytokine responses may influence the development of late delayed damage.[34] Glial and neuronal stem-cell damage may result in a progressive demyelination and/or neuronal cell loss. As patients age, endothelial damage may lead to vascular anomalies, including telangiectasias or malformations.[35] Radiation-induced genetic changes can lead to late development of second neoplasms.[36] Radiation can also increase the risk of stroke in this patient population but stroke usually occurs in patients who received 30 Gy or more of cranial radiation.[37] These late effects of cranial radiation may predispose patients to developing late neurologic consequences.

While neurocognitive, neuropathologic, and behavioral consequences of childhood cancer therapy have been well documented,[9] there are limited data on other neurologic complications, such as motor and coordination dysfunction, sensory loss, seizures, and headaches. In one study of 40 children with ALL, 23% were found to have neurologic signs at diagnosis, 30% developed gross motor disturbances and 18% developed fine motor dysfunction.[38] Motor dysfunction can persist for years after therapy, manifesting as difficulty with fine motor and handwriting skills.[39] Strength, balance, and agility can be reduced after ALL therapy compared with that in age-matched controls.[40] These findings are consistent with the reported 21.2% cumulative incidence of focal neurologic dysfunction in ALL survivors of the CCSS cohort.

There are fewer reports on auditory-vestibular-visual sensory complications and seizures after ALL therapy. Ocular morbidity and vision disturbance have rarely been reported in survivors of ALL.[41,42] Hearing loss occurs as a consequence of the leukemia, cancer therapy, or ototoxic supportive therapy. There are no long-term follow-up studies on hearing-related issues in ALL survivors. In one study,[43] reduced performance on simple alerted auditory reaction time was found in children, and it correlated with cortical atrophy and calcifications. Approximately 10% of patients will have a seizure during therapy.[11,44] We found the cumulative 20-year incidence of auditory-vestibular-visual sensory deficits to be 15.1% and 7% for seizures.

We identified serious headaches as the most common self-reported late neurologic condition. In both siblings and survivors, headaches were more common in females. Headaches were twice as common in both male and female survivors before age 20 but not different later in life (data not shown).

Patients who relapsed and/or those treated with BMT were at highest risk for neurologic sequelae. Relapse can occur in the CNS and increase the risk of neurologic complications. The data regarding site of relapse were not captured; thus, we are unable to determine the influence on risk of CNS involvement at relapse. Relapsed ALL generally requires more intensive therapy and consideration of BMT.

The large size of this cohort and the quality of the data are strengths of this study; however, certain limitations are recognized. First, CNS disease status at diagnosis was not recorded. Second, occurrence and time of onset of sequelae were obtained by self-report. There is a possibility that patients may report a deficit as a new problem 5 years after diagnosis and treatment when it was actually present earlier. We relied on the time at which the condition was diagnosed or confirmed by a physician. Third, self-reported events and response bias can lead to underestimation of problems by denial of difficulties in the survivor population.[45] Additionally, we do not have the ability to assess the validity of the various outcomes included in the analysis, irrespective of whether the respondent was the survivor or a proxy. While CCSS investigators have had excellent success in validating selected outcomes, such as second malignancies, our success in achieving medical record validation for other major outcomes has been limited.[46] Previous reports have demonstrated that survivors of stem-cell transplantation have the ability to recall many outcomes with a relatively good level of sensitivity and specificity,[47] but this does not address the issue of proxy reports or level of neurocognitive functioning that may apply to the childhood ALL population. Finally, it is possible that some reported late effects could be related to progressive disease because patients who were alive but had active disease at the 5-year follow-up points were eligible patients. Although this was likely a small number of patients, the methods of data capture do not allow separate analysis of disease state at time of entry.

While there is increased risk of late neurologic consequences in adult survivors of ALL, especially those treated with cranial radiation, many are free of reported problems. Substantial efforts to limit cranial radiation have been instituted since the era reflected in this study. It will be important to see if the risks of late neurologic consequences change as therapy continues to evolve.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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