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RESEARCH ARTICLE

Neurologic Morbidity in Survivors of Childhood Hodgkin Lymphoma Treated With Radiation

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ABSTRACT

Background: Hodgkin lymphoma is the most common cancer in adolescence and is treated with chemotherapy and/or radiation therapy. Little is known about neurologic symptoms, signs, and morbidity in long-term survivors of childhood Hodgkin lymphoma that were treated with radiation. The aim of this study was to identify neurologic symptoms, signs, and related morbidity in survivors of childhood Hodgkin lymphoma who received radiation therapy.

Methods: Long-term survivors (≥5 years from diagnosis, ≤25 years at diagnosis, and ≥18-years old at study enrollment) and community controls matched for age, sex, and ethnicity were recruited and provided written consent. Participants answered a questionnaire, followed by a face-to-face interview and examination by a neurologist. All survivors were treated with chemotherapy and thoracic/neck radiation therapy.

Results: The study questionnaire and face-to-face interview were completed by 197 survivors and 191 controls. Male-to-female ratio was 94:103 in survivors and 95:96 in controls. Median age at tumor diagnosis was 14.7 years (range: 3.0–22.6) and median time from tumor diagnosis was 20.9 years (range: 10.7–45.6 years). Headaches (43.2% vs. 32.8%), dizziness (38.1% vs. 19.9%), bladder and (15.8% vs. 9.4%) bowel problems (20.3% vs. 12.8%), and sensory neuropathy (22.1% vs. 5.8%) were more prevalent in survivors. Migraine headaches (32.0% vs. 22.9%) were more prevalent in female survivors but did not reach statistical significance. Neurologic morbidity and disability measures showed low associated morbidity.

Conclusion: While survivors of childhood Hodgkin lymphoma treated with radiation experienced more neurologic symptoms when compared to controls, their neurologic morbidity was low.

Trial Registration: NCT01820117

1 | Introduction

Hodgkin lymphoma, a neoplasm of the lymphoid tissue, is the most common cancer diagnosed in adolescence [1]. In addition to chemotherapy, involved-node radiation therapy is the mainstay of treatment [2]. With modern chemotherapy and/or radiation treatment, survival in children and adolescents with Hodgkin lymphoma now exceeds 90% at 5 years [3]. Besides neurocog-

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nitive impairment, reported chronic neurologic morbidities in childhood cancer survivors include cerebrovascular disease, sleep disorders, fatigue, balance problems, gait problems, headaches, and epilepsy [4, 5]. Long-term outcome studies of childhood Hodgkin lymphoma survivors have confirmed increased risk of stroke, accelerated atherosclerosis, fatigue, and sleep disorders, and risk of these complications is proportionately related to the radiation dose [6–9]. Most of these studies, however, were retrospective and based on self-report of outcomes. While prospective data on childhood Hodgkin lymphoma survivors are lacking, a study of survivors of acute lymphoblastic leukemia reported a higher prevalence of severe headaches, although the definition of severe headache was not specified, and no details were provided on the type of headache and related morbidity [4].

An earlier prospective questionnaire and interview-based study demonstrated increased prevalence of headache, peripheral neuropathy, and other neurologic symptoms in long-term survivors of childhood acute lymphoblastic leukemia [10]. In contrast, prospective studies comparing neurologic outcomes in childhood Hodgkin lymphoma survivors and community controls, including a survey of patient-reported outcomes, a face-to-face interview, and an examination by a neurologist, have not been reported. One aim of this prospective study was to determine the prevalence of neurologic symptoms and deficits in a large cohort of long-term childhood Hodgkin lymphoma survivors who were treated with radiation and compare those results with a matched community cohort. Assessment of neurocognitive function was one of the primary objectives of the study, and those findings are already published [11]. We included some outcomes that may not be traditionally considered neurologic, such as bladder, bowel, and sexual function, as well as sleep disturbance. We hypothesized that survivors would have a higher prevalence of these symptoms because of chemotherapy-induced neuropathy, cerebral dysfunction, and exposure of the spinal cord to radiation. Results describing greater sexual dysfunction in survivors have already been published [12].

2 | Methods

The data for this paper were gathered as a part of a previously published larger study of childhood Hodgkin lymphoma survivors [11]. The primary objectives of the parent study included evaluating brain integrity in adult survivors of childhood Hodgkin lymphoma treated with thoracic radiation, and identifying therapeutic factors associated with brain integrity. Neurologic morbidity data were collected as a secondary aim of this National Cancer Institute-funded study.

Participants were allowed to omit part or all of the neurology questionnaire. Methods for the parent study have been previously published [11]. In brief, survivors of childhood Hodgkin lymphoma were recruited from the St. Jude Lifetime Cohort Study (SJLIFE), a large retrospectively identified cohort of childhood cancer survivors with a longitudinal follow-up [13]. Community controls were recruited and matched for age, sex, and ethnicity. Eligibility criteria for childhood Hodgkin lymphoma included survival ≥5 years from diagnosis, age less than 25 years at diagnosis, age ≥18 years at the time of recruitment to the current study, and treatment with thoracic radiation. Both survivors and controls were excluded if there was a history of head trauma, a genetic condition that may cause cognitive impairment, congenital heart disease, or pregnancy.

All participants in the study were invited to respond to a questionnaire evaluating neurologic symptoms. This was followed by a face-to-face interview and examination by a board-certified neurologist (R.B.K.), which facilitated the collection of additional pertinent information to diagnose specific neurologic conditions, assess morbidity associated with neurologic symptoms and signs, and define neurologic deficits with a structured neurologic examination. Appropriate morbidity and/or disability scales were utilized to define the impact on function. Neurologic conditions' severity was graded according to a modified version of CTCAE, version 4.03 [14]. Presence and types of headaches were determined based on the International Headache Society criteria, version 2.0 [15], and headache-related disability was assessed by administering Migraine Disability Assessment Scale (MIDAS) [16]. A score of 5 or less suggests no headache-related disability, 6–10 as mild, 11–20 as moderate, and ≥21 as severe headache-related disability. Modified Rankin Scale was used to assess stroke-related disability. A score of zero suggests no disability, 3 is moderate disability requiring some help but can walk unassisted, and 5 is severe disability requiring nursing care [17].

2.1 | Ethical Approval

This study was approved by the St. Jude Children's Research Hospital's institutional review board (approval number Pro00003480) and conformed to national standards. Informed consent was obtained from all participating survivors and controls.

2.2 | Statistics

A two-sample *t*-test was used to compare age at survey assessment between survivors and controls, and Fisher's exact test was used to compare sex proportion between survivors and controls. Fisher's exact test was also used to compare the distribution of all categorical variables between the survivors and control groups to get *p*-values. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | Results

We identified 218 potentially eligible childhood Hodgkin lymphoma survivors and 208 community-matched controls. Of these, 204 survivors (93.6%) and 205 community controls (98.6%) enrolled in the main study. Comparison of age and sex, and information on chemotherapy and radiation therapy are provided in Table 1. There was no difference between survivors and controls in sex, race, age at assessment, smoking status, and body mass index [11]. Median age at childhood Hodgkin lymphoma diagnosis was 14.7 years (range: 3.0–22.6 years), and median time from childhood Hodgkin lymphoma diagnosis was 20.8 years (range: 10.7–45.6 years). Of the 204 enrolled survivors and 205 controls, 197 (96.6%) survivors and 191 (93.2%) controls completed the neurology questionnaire and face-to-face evaluation. The male-to-female ratio was 94:103 in survivors and 95:96 in controls.

TABLE 1 | Demographics and treatment variables.

	Survivor (*N* = 197)	Controls (*N* = 191)	*p*-value
Age at survey assessment			
Mean (SD)	36.7 (8.0)	36.4 (9.1)	0.8
Median (Min, Max)	36 (23, 65)	35 (18, 66)	
Age at enrollment			
Mean (SD)	36.7 (7.9)	36.4(8.9)	0.8
Median (Min, Max)	35.4 (22.6, 64.6)	35.1 (18.3, 65.9)	
Sex			
Male	94 (47.7%)	95 (49.7%)	0.8
Female	103 (52.3%)	96 (50.3%)	
Race			
White	168 (85.3%)	164 (85.9%)	0.9
Other	29 (14.7%)	27 (14.1%)	
Smoking status			
Current	38 (19.2%)	28 (14.7%)	0.4
Former	35 (17.8%)	40 (20.9%)	
Never	124 (62.9%)	123 (64.4%)	
Body mass index			
Underweight	6 (3.05%)	3 (1.6%)	0.2
Normal weight	50 (25.4%)	58 (30.4%)	
Overweight	72 (36.5%)	54 (28.3%)	
Obese	69 (35.03%)	76 (39.8%)	
Age at diagnosis			
Mean (SD)	14.4(3.9)		
Median (Min, Max)	14.7 (3.0, 22.6)		
Time since diagnosis			
Mean (SD)	22.3 (8.2)		
Median (Min, Max)	20.8 (10.7, 45.6)		
Chemotherapy			
Anthracycline	150 (76.1%)		
Corticosteroid	134 (68.02%)		
Bleomycin	56 (28.4%)		
Cyclophosphamide	109 (55.3%)		
Vinca alkaloids	175 (88.8%)		
Radiation: Chest/Neck			
>30 Gy	43(21.8%)		
24–30 Gy	107 (54.3%)		
<24 Gy	47 (23.9%)		

3.1 | Headache

Repeated episodes of headache without attribution to a specific cause or illness and lasting at least an hour were reported by 85 (43.2%) survivors and 62 (32.8%) controls, $p = 0.046$. Amongst males, the frequency of headache in survivors and controls was not different, 26 (27.7%):23 (24.7%), $p = 0.7$. A greater proportion of female survivors reported headaches than controls, 59 (57.3%):39 (40.6%), $p = 0.02$ (Tables 2 and 3). Headache duration (<4 vs. ≥4 h) was not different among all participants and between males and females ($p = 0.8$). Of the 85 survivors with headaches, 41 (48.8%) had seen a family physician compared to 23 (38.3%) of 62 controls with a headache. Similarly, 21 (24.7%) of survivors with headaches had seen a neurologist for headaches compared to 16

TABLE 2 | Headache characteristics in survivors and controls.

Headaches	Survivors (197)	Controls (191)	*p*-value
Total	85 (43.1%)	62 (32.8%)	0.046
Gender			
Males	26 (27.7%)	23 (24.7%)	0.7
Females	59 (57.3%)	39 (40.6%)	0.02
Duration			0.8
<4 h	37 (45.7%)	24 (42.1%)	
>4 h	44 (54.3%)	33 (57.9%)	
Saw provider			
PCP	41 (48.8%)	23 (38.3%)	0.2
Neurologist	21 (24.7%)	16 (26.7%)	0.8
Headache type			
Migraine w/o aura	44 (22.3%)	34 (17.8%)	0.3
Migraine w/ aura	27 (13.7%)	20 (10.5%)	0.4
Episodic tension	33 (16.7%)	23 (12.0%)	0.2
Headache disability	114	136	0.2
None (<6)[a]	59 (71.1%)	40(72.7%)	
Mild (6–10)	8 (9.6%)	7 (12.7%)	
Moderate (11–20)	5 (6.0%)	6 (10.9%)	
Severe (>21)	11(13.2%)	2 (3.6%)	
Headaches per month	119	133	0.1
≥15	17 (21.8%)	6 (10.3%)	
<15	61 (78.2%)	52 (89.7%)	

Abbreviation: PCP, primary care physician.

[a]Headache disability as measured by Migraine Disability Assessment Scale.

(26.7%) controls. Family history of headaches was reported by 43 (47.3%) of the survivors and 27 (45.0%) of controls, $p = 0.9$.

A diagnosis of migraine without aura was established in 44 (22.3%) survivors and 34 (17.8%) of controls, $p = 0.3$. The prevalence was also not significantly different amongst males (11.7% vs. 12.6%, $p = 1.0$) and females (32.0% vs. 22.9%, $p = 0.2$). Migraines with aura were diagnosed in 27 (13.7%) of survivors versus 20 (10.5%) of controls ($p = 0.4$). We did not find a significant difference when comparing males and females separately, $p = 0.3$ and 0.7. Episodic tension-type headaches were diagnosed in 33 (16.8%) survivors compared to 23 (12.0%) controls, $p = 0.2$. There was no significant difference in episodic tension-type headache amongst male and female survivors and controls, $p = 0.2$ and 0.7. Chronic daily headaches (≥15 days of headache per month for the last 3 months) were present in 21.8% of survivors with headaches compared to 10.3% of controls with headaches ($p = 0.1$). Chronic daily headache was more prevalent in male survivors (28.6%) when compared to male controls (0%), $p = 0.02$. Amongst females, 19.3% of survivors had chronic daily headache versus 15.8% in controls ($p = 0.8$).

As assessed by MIDAS, there was no difference between survivors and controls, including no difference based on sex, and for any mild, moderate, or severe headache-related disability, $p = 0.2$ (Table 2).

TABLE 3 | Neurologic symptoms and signs in survivors and controls.

Symptoms	Survivors	Controls	*p*-value
Headaches	85 (43.2%)	62 (32.8%)	0.046
Males	26 (27.7%)	23 (24.7%)	0.7
Females	59 (57.3%)	39 (40.6%)	0.02
Dizziness	75 (38.1%)	38 (19.9%)	<0.01
Males	25 (26.6%)	14 (14.7%)	0.049
Females	50 (48.5%)	24 (25%)	<0.01
Falls	11 (5.6%)	3 (1.6%)	0.05
Stroke	4 (2.03%)	1 (0.5%)	0.4
Seizures	6 (3.1%)	7 (3.7%)	0.8
Excessive daytime sleepiness	110 (60.4%)	90 (49.7%) 39 (43.3%)	0.045 0.4
Males	45 (51.1%)	51 (56.0%)	0.07
Females	65 (69.2%)		
Nocturnal snoring	73 (40.3%)	77 (42.8%)	0.7
Urinary urgency	31 (15.8%)	18 (9.4%)	0.07
Males	6 (6.5%)	6 (6.3%)	1.0
Females	25 (24.3%)	12 (12.5%)	0.04
Urinary hesitancy	14 (7.2%)	5 (2.7%)	0.06
Urinary incontinence	16 (8.3%)	13 (6.9%)	0.7
Constipation	40 (20.3%)	24 (12.8%)	0.06
Diarrhea	56 (29.2%)	56 (30.0%)	0.9
Stool Incontinence	13 (6.8%)	2 (1.1%)	<0.01
Sensory neuropathy	43 (22.1%)	11 (5.8%)	<0.01
Males	19 (20.4%)	5 (5.3%)	<0.01
Females	24 (23.5%)	6 (6.3%)	<0.01
Motor	4 (2.03%)	1 (0.5%)	0.4
Autonomic	18 (9.1%)	1 (0.5%)	<0.01

3.2 | Dizziness

Of the 197 survivors and 191 controls, 75 (38.1%) survivors and 38 (19.9%) controls reported experiencing episodes of lightheadedness ($p < 0.01$; Table 3). Higher prevalence of dizziness was found both in male (26.6% vs. 14.7%, $p = 0.049$) and female survivors (48.5% vs. 25.0%, $p < 0.01$). More frequent (≥12/year) and daily episodes were also more common in survivors (12.7% vs. 5.8%, $p < 0.01$), both male and female (9.6% vs. 1.1%, $p = 0.02$, and 15.5% vs. 10.4%, $p < 0.01$). Based on CTCAE v4.03 criteria, there was no difference between survivors and controls in the prevalence of moderate to severe dizziness (5.1% vs. 2.6%, $p = 0.3$).

3.3 | Falls

Repeated falls, spontaneous or from tripping, were reported by 11 (5.6%) survivors and three (1.6%) controls ($p = 0.05$). Sex-based analysis was not performed due to small numbers.

3.4 | Stroke

Transient neurologic deficits lasting less than 24 h were reported by four female survivors. Modified Rankin score of 2 (slight disability, cannot do all prior activity but can manage own affairs) was reported by one survivor, and all the rest had a score of 0 (no symptoms). A stroke history without specifics was reported by one female control.

3.5 | Seizures

History of seizure was uncommon in survivors and controls (6 [3.1%] vs. 7 [3.7%], $p = 0.8$). Of all participants with a history of seizure, only one was still taking anti-seizure medication.

3.6 | Sleep

Participants (182 survivors and 181 controls) were asked if they experienced excessive daytime sleepiness. Excessive daytime sleepiness was reported by 110 (60.4%) survivors and 90 (49.7%) controls, $p = 0.045$. There was no difference among the males ($p = 0.4$) and females ($p = 0.07$). Nocturnal snoring was reported by 40.3% of survivors and 42.8% controls, $p = 0.7$. Symptoms suggestive of rapid eye movement sleep behavior disorder were more common in survivors, 18 (10.2%) versus 10 (6.0%). However, the difference was not significant, $p = 0.2$.

3.7 | Bladder and Bowel

Increased urinary urgency was reported by 31 (15.8%) of 197 survivors and 18 (9.4%) of 191 controls, $p = 0.07$. The difference in prevalence of this symptom was not significant in males, while 25 of 103 female survivors (24.3%) and 12 (12.5%) of 96 female controls reported urinary urgency, $p = 0.04$. Urinary hesitancy (delayed initiation) was reported by 7.2% survivors and 2.7% controls, $p = 0.06$. This was not different in males ($p = 0.3$) or females ($p = 0.1$). Reports of urinary incontinence were not significantly different amongst participants (8.3% vs. 6.9%, $p = 0.7$), males (3.3% vs. 2.1%, $p = 0.7$), and females (12.8% vs. 11.6%, $p = 0.8$). Only four female survivors and five female controls restricted their outside activities because of urinary control issues.

Constipation was reported by 40 (20.3%) of 197 survivors and 24 (12.8%) of 187 controls, $p = 0.06$. There was no difference between male and female survivors and controls, $p = 0.4$ and $p = 0.1$. Diarrhea was reported by 29.2% survivors and 30.0% controls, $p = 0.9$. Intermittent stool incontinence (soiling) was present in 6.8% survivors versus 1.1% controls, $p < 0.01$. This was significant for females ($p = 0.04$), but not for males ($p = 0.1$). Only eight survivors and nine controls were restricted from outside activities because of bowel symptoms ($p = 0.8$).

3.8 | Peripheral Neuropathy

Symptoms and/or signs of peripheral sensory neuropathy were present in 43 (22.1%) of 195 assessed survivors compared to 11 (5.8%) of 191 controls, $p < 0.01$. This difference was present in males, 20.4% versus 5.3% ($p < 0.01$), and females, 23.5% versus 6.3% ($p < 0.01$). Motor weakness was uncommon and was noted in only four survivors and one control, and the difference was not significant, $p = 0.4$. Autonomic dysfunction, as suggested by orthostatic blood pressure and heart rate response, was present in 18 (9.1%) survivors and one (0.5%) control, $p < 0.01$. This was present in both males and females, $p < 0.01$ and $p < 0.01$.

TABLE 4 | Abnormal neurologic findings on examination in survivors and controls.

Variable	Survivor	Control	*p*-value
Language	0 (0.0%)	0 (0.0%)	NA
Mild dysarthria	2 (1.0%)	0 (0.0%)	0.5
Reading difficulty	3 (1.5%)	0 (0.0%)	0.5
Visual field deficit	1 (0.5%)	1 (0.5%)	0.7
Smooth pursuit eye	2 (1.0%)	2 (1.1%)	1.0
Saccadic eye	26 (13.2%)	27 (14.1%)	0.9
≥15% error rate on anti-saccades[A]	53 (26.9%)	23 (12.0%)	<0.01
Cranial nerve VII[b]	1 (0.5%)	0 (0.0%)	1.0
Cranial nerve VIII[c]	1 (0.5%)	1 (0.5%)	1.0
Cranial nerve XI	1 (0.5%)	0 (0.0%)	1.0
Left weakness[d]	1 (0.5%)	0 (0.0%)	1.0
Right weakness	1 (0.5%)	1 (0.5%)	1.0
Diminished/Absent muscle stretch reflexes	51 (25.9%)	15 (7.8%)	<0.01
Tremor	10 (5.1%)	6 (3.1%)	0.4
Impaired fast finger tapping	2 (1.02%)	0 (0.0%)	0.5
Finger-to-nose dysmetria	9 (4.6%)	0 (0.0%)	<0.01
Truncal ataxia	0 (0.0%)	1 (0.5%)	<0.01
Regular gait impairment	0 (0.0%)	0 (0.0%)	NA
Tandem gait impairment	10 (5.1%)	8 (4.2%)	0.5
Spinothalamic sensory changes	47 (25.3%)	13 (7.6%)	<0.01
Vibration/Proprioception	33 (16.84%)	4 (2.1%)	<0.01

Abbreviation: NA, not applicable.

[a]Measured by a bedside technique.

[b]Cranial nerves not mentioned in this table were normal.

[c]Assesses by finger rub bedside method.

[d]All proximal and distal muscles assessed, including finger and toe dorsiflexors and interossei. Present proximal and distal, 4/5 on Medical Research Council scale.

3.9 | Neurologic Examination

Neurologic deficits other than peripheral neuropathy and orthostasis were minor and identified in only a few survivors and controls. These non-neuropathy deficits included errors on anti-saccade testing (26.9% vs. 12.0%, $p < 0.01$), absent muscle stretch reflexes (25.9% vs. 7.8%, $p < 0.01$), and mild finger-to-nose dysmetria (4.6% vs. 0%, $p < 0.01$), and are provided in Table 4.

There was no difference in mild impairment of tandem gait (5.1% vs. 4.2%, $p = 0.5$).

4 | Discussion

While pulmonary, cognitive, and cardiovascular function have previously been reported, this is the first study of childhood Hodgkin lymphoma survivors that comprehensively assessed neurologic function by symptoms and physical examination [6, 8]. Neurologic abnormalities and symptoms may cause significant morbidity and affect quality of life. Small retrospective studies of neurologic long-term toxicity in survivors of non-Hodgkin lymphoma [18], and larger well-designed studies in acute lymphoblastic leukemia survivors [4, 10], mostly reported higher prevalence of neurologic symptoms and signs when compared to known norms or sibling controls. However, non-Hodgkin lymphoma and acute lymphoblastic leukemia patients receive much more neurotoxic chemotherapy (high-dose methotrexate, vincristine, and intrathecal chemotherapy). In contrast, those with Hodgkin lymphoma typically receive combination chemotherapy including bleomycin, alkylating agents, anthracyclines, and vinca alkaloids, with or without nodal radiation. We show that childhood Hodgkin lymphoma survivors treated with radiation are at increased risk of many neurologic symptoms. While we did not identify significant neurologic morbidity in survivors, some degree of dysfunction is present in many in this cohort. Low neurologic morbidity in survivors treated with thoracic radiation is an important finding, as many modern treatment regimens of childhood Hodgkin lymphoma avoid the use of radiation treatment and will likely have even lower morbidity. It is important for physicians involved in the care of these survivors to proactively ask about these symptoms and assess related disability, and to exclude non-cancer-related causes of these morbidities.

Headache was the most common symptom in our cohort and was much more prevalent in survivors than in controls. As previously reported in survivors of leukemia [10], this difference was mostly due to a higher prevalence in female survivors. Interestingly, we did not find a difference in migraine or tension-type headaches amongst survivors and controls. Although a larger proportion of female survivors had migraine headaches compared to controls, the difference was not statistically significant. Interestingly, chronic daily headaches, though infrequent, were more common in male survivors. Chronic daily headaches can be multifactorial, and their exact cause is unknown. Reassuringly, like previously reported in childhood leukemia survivors [10], headache-related morbidity was low in all participants.

Dizziness, described as lightheadedness and feeling off balance, and not as vertigo, was more prevalent in both male and female survivors when compared to controls. Almost 13% of survivors reported it as very prevalent, but only about 5% of survivors reported their symptoms as moderate or severe by CTCAE criteria. As with chronic daily headaches, symptoms of dizziness are likely multifactorial. It is quite likely that a higher prevalence of sensory neuropathy and autonomic dysfunction contributed to dizzy symptoms. Gait ataxia was uncommon and likely was not a major contributor to dizziness. Drugs used to treat Hodgkin lymphoma are not considered to have significant ototoxicity and are unlikely to lead to dizziness. The increased prevalence of dizziness is the same as reports on leukemia survivors [4]. One of the strengths of this study is that all participants underwent an interview and structured neurologic examination by an experienced neurologist. For the first time, we provide important data about physical neurologic issues in childhood Hodgkin survivors who were treated with radiation. We found a high prevalence of sensory impairment and neuropathy amongst survivors, both males and females. About 22% had sensory neuropathy, and approximately 9% had impaired orthostatic blood pressure and heart rate response, equally distributed amongst males and females. Diabetes was equally present in survivors and controls, and a greater prevalence of neuropathy in survivors may be due to vincristine use, as 138 of the 204 survivors were exposed it. Additional studies are needed to examine potential nutritional and metabolic etiologies for sensory impairment. Impaired baroreceptor reflex is well known in patients with head and neck cancer who are treated with neck radiation [19, 20]. This and the presence of peripheral sensory neuropathy likely explain the increased prevalence of orthostatic hypotension in our survivor cohort.

An important finding of this study is that except for findings consistent with peripheral neuropathy, other neurologic deficits were rare and very mild. Motor weakness, including in fingers and toes, was noted in a handful of participants. Even those with neuropathy had Grade 1 symptoms per CTCAE v4.03. Mild dysmetria and tandem gait abnormality were uncommon but more prevalent in survivors. Importantly, the effect on function and neurologic morbidity from these deficits was low in all affected survivors.

Abnormalities on anti-saccades (rapid production of eye movement exactly opposite to the presented target in the visual field) and rapid sequential hand movement (tapping a surface repetitively and sequentially with palm, edge of the hand, and fist) may correlate with neurocognitive function [21, 22]. We did find a higher prevalence of increased error rates when performing anti-saccades in survivors compared to adults. We intend to do further analyses of the data to see if these results are associated with neurocognitive findings.

The main weakness of this study is its cross-sectional nature and the lack of more sophisticated testing, such as electrophysiological studies, quantified gait and coordination analyses, and detailed investigations of neurologic morbidity. The strength of the study includes assessment of patient-reported symptoms among survivors and controls, followed by a face-to-face evaluation by the study neurologist, where follow-up questions were asked to ascertain underlying causes of the symptoms and signs.

In conclusion, we report that despite a higher prevalence of neurologic symptoms, neurologic morbidity is low in survivors of childhood Hodgkin lymphoma who were treated with radiation. As radiation treatment increases the risk of neurologic complications, it is likely that neurologic symptom burden and related morbidity are even lower in chemotherapy-only-treated childhood Hodgkin survivors. Neurologic symptoms and deficits did not affect day-to-day function in the survivors. However, care providers should actively seek these symptoms in survivors to alleviate discomfort and exclude alternative causes.

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Ethics Statement

This study was approved by the St. Jude Children's Research Hospital's institutional review board (approval number Pro00003480) and conformed to national standards. Informed consent was obtained from all participating survivors and controls.

Conflicts of Interest

The authors declare no conflicts of interest.

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