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Research Paper

Polyneuropathy in Adolescent Childhood Cancer Survivors: The PACCS Study

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ABSTRACT

Background: Childhood cancer survivors (CCS) are at risk of polyneuropathy due to chemotherapy, but studies in young survivors are scarce and diagnosis is challenging. We aimed to study the presence of polyneuropathy and the possible effect of cumulative doses of chemotherapeutic agents in a representative group of adolescent survivors.
Methods: CCS aged nine to 18 years and age- and sex-matched controls were recruited from the cross-sectional Physical Activity and Fitness among Childhood Cancer Survivors (PACCS) study. CCS with various cancer diagnoses who had ended cancer treatment one year or more before study were included. Polyneuropathy was evaluated clinically and with nerve conduction studies (NCSs) in three motor and five sensory nerves. We used mixed-effects linear regression models to compare CCS and controls, and investigate possible associations between cumulative chemotherapy doses and NCS amplitudes.
Results: A total of 127 CCS and 87 controls were included, with 14% CCS having probable or confirmed polyneuropathy. NCS amplitudes were lower in survivors compared with controls in all nerves. The largest mean difference was 3.47 μV (95% confidence interval [CI], 2.18 to 4.75) in the tibial plantar medial sensory and 1.91 mV (95% CI, 0.78 to 3.04) in the tibial motor nerve. The cumulative dose of platinum derivatives was associated with lower tibial motor nerve amplitude (−0.20; 95% CI, −0.35 to −0.04 mV for 100 mg/m^2 dose increase) but not in other nerves. We found no significant associations between vinca alkaloids cumulative dose and amplitudes.
Conclusions: CCS without clinical signs or symptoms of polyneuropathy may have subtle nerve affection. The clinical long-term impact of this novel observation should be evaluated in larger, longitudinal studies.

Introduction

Cancer remains within the top five causes of death among children aged five to 14 years in Norway and other developed countries.[1] Norway is among the countries with the highest childhood cancer survival rates, reaching more than 80%.[2] However, childhood cancer survivors (CCS) are at risk of long-term consequences, including late adverse effects due to cancer treatment.[3-6]

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Some of these consequences may be insidious and not easily detected by current clinical approaches.

Polyneuropathy is a well-known side effect of chemotherapy[7-9] and has mainly been attributed to vinca alkaloids and platinum derivatives.[8] This side effect can manifest during the course of therapy and may remain after therapy has ended.[9] Although polyneuropathy is usually not life threatening, it can lead to several problems, such as pain, motor problems, and decreased sensation in the extremities.[10] These consequences can potentially disrupt the developmental process in childhood cancer survivors and complicate later life.[9] Furthermore, they can reduce the level of physical activity, and thereby aggravate late effects, and negatively affect quality of life.[9]

Polyneuropathy may be detected using clinical assessment and nerve conduction studies (NCSs). In the acute phase of chemotherapy, subjects often report symptoms of polyneuropathy without any abnormal NCS findings.[11-14] On the other hand, abnormal NCSs may be present without clinical symptoms (subclinical) and outlast the treatment period.[15] A combination of both clinical assessment and NCS to detect polyneuropathy is therefore recommended.[15] This method will identify a wider range of polyneuropathy, including subclinical polyneuropathy.

There is a tendency in the literature to report polyneuropathy in a dichotomized way. However, the neural effect of chemotherapy may be subtle and subclinical. In the absence of symptoms, subclinical polyneuropathy is usually not reported outside the context of research.[16] By identifying subtle affection of nerves after cancer treatment, we can detect physiological changes before clinical symptoms occur and intervene to prevent further decline.[17]

Several studies in CCS have reported subclinical polyneuropathy.[15,18-20] However, not all used an adequate control group, their NCSs were limited, or they only focused on a specific cancer subgroup. Thus, a study accounting for these limitations was needed.

In the current study, we aimed to describe the prevalence of polyneuropathy as well as subtle neural involvement in young CCS compared with healthy controls. In addition, we investigated the association between cumulative doses of chemotherapeutic agents and NCSs in CCS.

Methods

The Physical Activity and Fitness among Childhood Cancer Survivors (PACCS) Study

This study is part of the ongoing multicenter, cross-sectional, Physical Activity and Fitness among Childhood Cancer Survivors (PACCS) study. The PACCS study consists of four work packages (WPs), and the current study belongs to WP2,[21] which focuses on identifying various physiological determinants that can influence physical activity and fitness in CCS, including neurological function. The study participants who participated in PACCS WP1 were invited to participate in WP2. These participants were recruited from the university hospitals in Oslo and Bergen between January 2019 and December 2020.

In the current study, we included CCS aged nine to 18 years attending the Paediatric Oncology Outpatient clinic at Oslo University Hospital (OUH) or Haukeland University Hospital for routine consultations of any previous malignant disease and had ended cancer treatment at least one year before. We excluded survivors who did not receive chemotherapy, had known polyneuropathy of other causes (e.g. confirmed diagnosis of diabetes mellitus), did not consent to WP2, or had difficulties in understanding Norwegian language.

Subjects in the control group were excluded if they had chronic conditions that could influence physical performance, including heart, lung, or muscle disease or previous cancer. Controls were enrolled as part of the main PACCS study, and consisted of age- and sex-matched friends or siblings of the CCS, recruited by the survivors and their family. The exact number of subjects who were invited as controls are thus unknown. The suggested controls were screened by study personnel, and none were excluded based on the study exclusion criteria.

The present study is a substudy of the larger PACCS study, which was the basis for power calculation.[21] All participants gave written informed consent. The study was approved by the Regional Committees for Medical and Health Research Ethics with reference: 2018/739 and the data protection officers at the hospitals.

All participants underwent clinical neurological examination and NCSs by experienced neurologists or consultants in clinical neurophysiology at the two sites, OUH and Haukeland University Hospital. While performing the examinations, examiners were unaware of whether subjects belonged to the CCS or control group.

Outcome measures

Polyneuropathy in the current study was graded using Tesfaye criteria[16] (Table 1), a generic instrument to categorize polyneuropathy based on symptoms and signs in the neurological examination, in addition to NCSs. An abnormal neurological examination included positive symptoms and findings of neuropathy (pain, pricking sensation, numbness, weakness in the extremities, and ataxia), reduced/absent deep tendon reflexes in the lower extremities, or abnormal sensibility on the big toes for pinprick, temperature, light touch, vibration, or proprioception. These examinations screen for both small and large fiber involvement.

Three motor nerves (ulnar, peroneal, and tibial) and five sensory nerves (ulnar, radial, superficial peroneal, sural, and tibial medial), preferably on the right extremities, were examined. When performing the NCS, ideally supramaximal stimulations were used by increasing the intensity 20% above the maximum amplitude (in some children this was difficult due to the elicited pain). If temperatures measured in the lower extremities were below 30°C, the feet were heated.

To define abnormal NCS in this study, we used the amplitudes in the lower extremity. The nerves in the lower extremities, which are longer than those in the upper extremities, are therefore the first to be affected in length-dependent polyneuropathies. A minimum of two nerves with at least one sensory nerve with value below the amplitude threshold was defined as “abnormal NCS.” We focused on sensory amplitudes as the cytotoxic effect of cancer drugs are known to mainly affect sensory amplitudes.[22,23] Cutoffs for abnormal NCSs were set before analysis based on consensus among the experienced neurophysiologists on the basis of a combination of local laboratory reference values and available reference data on NCSs in children.[24,25] The amplitude thresholds were 2.5 mV for the peroneal motor nerve, 6 mV for the tibial motor nerve, 4 μV for the superficial peroneal and sural sensory nerves, and 3 μV for the medial tibial sensory nerve. Subclinical polyneuropathy was defined as having an abnormal NCS without the presence of clinical signs and symptoms.

In the Oslo study site, we also used quantitative sensory testing (QST) to test for small fiber neuropathy. We measured thermal thresholds for warmth, cold, and heat pain in three locations: thenar, thigh, and on the dorsal part of the foot, preferably testing the right extremities.

TABLE 1.
Tesfaye Clinical Grading

Tesfaye Clinical Grading	
Normal	• No signs or symptoms of polyneuropathy and • Normal NCS or validated measure of small fiber neuropathy
Subclinical polyneuropathy	No signs or symptoms of neuropathy with the presence of abnormal NCS *or* a validated measure of small fiber neuropathy
Possible polyneuropathy	The presence of symptoms *or* signs of polyneuropathy: • Symptoms Decreased sensation, positive neuropathic sensory symptoms (e.g., sleep numbness), prickling/stabbing, burning/aching pain, mainly in the toes, feet, or legs. • Signs Symmetric decrease of distal sensation or unequivocally decreased/absent ankle reflexes.
Probable polyneuropathy	Combination of symptoms and signs of neuropathy, including *minimum* 2 of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased/absent ankle reflexes
Confirmed polyneuropathy	• Abnormal NCS *and* a symptom(s) or a sign(s) of polyneuropathy • Normal NCS but positive finding from validated measure of small fiber neuropathy (thermal test, skin biopsy) *and* a symptom(s) or a sign(s) of polyneuropathy

Abbreviation:
NCS = Nerve conduction study

Covariates

Study participants' characteristics such as age, height, sex, and study site were assessed for both CCS and controls. In addition, we assessed age at cancer diagnosis, date of treatment completion, time since cancer diagnosis, type of cancer treatment, cumulative doses of chemotherapy, and cancer diagnoses for the CCS. Cancer diagnoses were classified according to the International Classification of Childhood Cancer 3rd edition.[26]

Cancer treatment was defined as surgery (yes/no), radiotherapy (yes/no), and stem cell transplantation (yes/no). Cumulative dose of vinca alkaloids (mg/m^2) was calculated depending on the approximate vincristine equivalent dose given for treating childhood cancers.[27] We added the individual doses of vincristine + (vinblastine dose divided by 3) + (vinorelbine dose divided by 15).[27] Cumulative dose of platinum derivatives (cisplatin equivalent dose, mg/m^2) was calculated by summing the cisplatin dose + (carboplatin dose divided by 4).[28,29]

Data analyses

Characteristics of the study participants in both patient and control groups are reported descriptively. We used numbers and proportions for categorical variables and means with S.D. for continuous variables. Alternatively, we report median and range for non-normally distributed continuous data. We checked the normality of our data visually by using histograms and Q-Q plots. We compared age, sex, time since diagnosis, and cancer diagnoses of CCS who participated in the current study compared with those who did not participate to investigate potential selection bias.

We used descriptive statistics (number and %) to present the Tesfaye clinical grade in survivors and controls. We used mixed-effect restricted maximum likelihood linear regression models with study site as random intercept to compare the amplitudes of all eight nerves of the upper and lower extremities between survivors and controls. The mixed-effect model is useful for data with more than one source of random variability and is quite robust in regard to distributional assumptions.[30] The models were adjusted for age, sex, and height. We report the marginal means with 95% confidence intervals (CIs) and *P* values extracted from the models. The models were performed in the following populations: (1) all survivors compared with controls and (2) only survivors classified as normal according to Tesfaye criteria compared with controls.

Furthermore, we analyzed the relationships between cumulative doses of vinca alkaloids and platinum derivatives, with the amplitudes for CCS using mixed-effect restricted maximum likelihood linear regression models. We transformed cumulative doses to have 10 mg/m^2 and 100 mg/m^2 increases for vinca alkaloids and platinum derivatives, respectively, to get a clinically meaningful effect estimate. We defined the study site as random intercept. The models were adjusted for age at diagnosis, time since diagnosis, sex, and height. We used Stata Multiprocessor version 16.1 for statistical analyses. A P value <0.05 was considered statistically significant.

Results

Characteristics of study participants

From a total of 270 CCS in WP1, 68 were excluded because they did not meet the inclusion criteria of the current study and 66 declined to participate in WP2 (Fig. 1). Subsequently, 136 CCS were eligible for neurological examination together with 88 matched controls. Nine of the CCS and one control subject could not follow the examination process due to various circumstances. Therefore, 127 CCS and 87 controls were included in the present study. There was no difference in age, time since diagnosis, and sex, but there were some slight differences in the distribution of cancer diagnoses between CCS who participated in the current study and those who dropped out after WP1 (Supplemental Table 1).

Mean age at study was approximately 13.5 years with equal distribution of males and females (Table 2). Survivors and controls did not differ regarding age, height, or sex. The majority of participants (148; 69%) were recruited at OUH. Mean age at cancer diagnosis was 5.1 (S.D. = 3.4) years, mean time since treatment completion 6.8 (S.D. = 3.6) years, and mean time since diagnosis 8.6 (S.D. = 3.7) years. The majority of survivors had been diagnosed with leukemia.

A total of 117 (92%) CCS received vinca alkaloids, with median cumulative dose of 32 mg/m^2 (range: 4.4 to 104 mg/m^2). Of all subjects who received vinca alkaloids, 115 (91%) received vincristine. The median cumulative dose for vincristine was 32 mg/m^2 (range: 4.4 to 64.5 mg/m^2). Twenty-seven (21%) CCS received platinum derivatives, with median cumulative dose of 725 mg/m^2 (range: 173 to 2338 mg/m^2). Of all subjects who received platinum derivatives, 14 (11%) received cisplatin with median cumulative dose of 236 mg/m^2 (range: 117 to 560 mg/m^2). Twenty-two (17%) subjects received both vinca alkaloids and platinum derivatives.

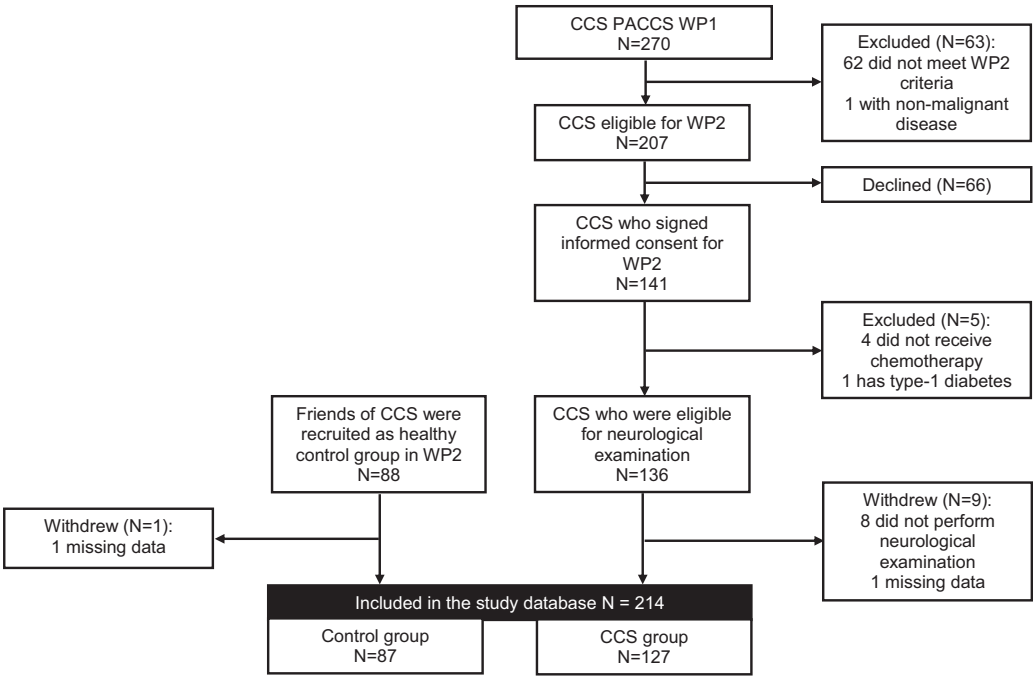

FIGURE 1. Flowchart of study participation.

Neurophysiological findings in CCS compared with controls

In our study, we found 17 individuals in the CCS group with signs, symptoms, and NCS findings suggestive of polyneuropathy (probable or confirmed), making a prevalence of 14% of patients with polyneuropathy (Table 2). Five of them (4%) were graded as having probable peripheral neuropathy and 12 (10%) as having a confirmed peripheral neuropathy according to Tesfaye clinical grading system.[16] Another 17 (13%) of CCS and two (2%) of controls had possible peripheral polyneuropathy. None of the participants in the control group had an abnormal NCS.

The prevalence of subclinical polyneuropathy among subjects in the CCS group was 2.4% (n = 3; Table 2). None of the study participants in the control group had subclinical polyneuropathy. There were seven study participants with positive finding on QST suggestive of small fiber polyneuropathy. Of those with positive QST, two were from the control group and five were from the CCS group. In the presence of signs or symptoms of polyneuropathy, an abnormal QST result is considered as confirmatory for polyneuropathy in line with Tesfaye et al.[16] This was the case for one subject in the CCS group, where confirmed polyneuropathy was determined based on an abnormal QST result without NCS abnormality.

We found that the average amplitudes were consistently lower for all survivors, even in survivors classified as normal according to Tesfaye criteria, compared with the control group (Fig. 2). Although most participants in the CCS group showed neither signs nor symptoms of polyneuropathy, we found significantly lower NCS amplitudes among CCS compared with the control group in all nerves (Table 3).

Effect of chemotherapeutic agents on polyneuropathy

We found that the cumulative platinum derivatives dose was associated with a lower amplitude in the tibial motor nerve. The effect was −0.20 (95% CI, −0.35 to −0.04) mV for every 100 mg/m^2 increase of cumulative platinum derivatives dose (Fig. 3 and Supplemental Table 2). No significant association was found in other nerves. Cumulative dose of vinca alkaloids was not significantly associated with amplitudes.

Discussion

We found that 14% of CCS had clinically probable or confirmed polyneuropathy. Moreover, when comparing CCS classified as normal according to Tesfaye criteria with healthy controls, the amplitudes for both motor and sensory nerves were also significantly lower in the CCS group compared with the control group. Thereby, the present study demonstrates that even CCS without any symptoms or signs indicative of polyneuropathy have subtle nerve affection.

The abnormalities in NCS do not always coexist with clinical symptoms and signs of polyneuropathy.[31-33] Abnormal sensory and motor amplitudes can be detected before clinical symptoms occur.[12,14] Even asymptomatic or subtle nerve affection reflect damage of the nerves, which may persist or increase long after the treatment period.[31] By comparing findings with those in a control group, we were able to observe subtle abnormalities that may otherwise have been overlooked. An early detection may benefit prevention programs to limit consequences of polyneuropathy in later life. For example, a sensorimotor training program and potentially endurance exercise can be included in the prevention programs as they have shown positive health outcomes related to polyneuropathy.[34]

The reported prevalence of polyneuropathy after chemotherapy has varied between studies,[15,18-20] ranging from 16% to 100%. In two studies, subclinical polyneuropathy was found in about 7% of those who underwent NCS.[19,20] Tay and colleagues[15] found that 53 of 101 CCS had electrophysiological polyneuropathy without symptoms or clinical findings. However, there were considerable differences in case definition, such as defining abnormal NCS by using only one peripheral nerve[20] instead of a set of criteria such as in our study. The number of cases is also highly dependent on the cutoffs for abnormal NCS. Normal values should ideally be based on local

TABLE 2.
Characteristics of Study Participants (N = 214)

Characteristics	CCS (N = 127)	Controls (N = 87)
Age at study (WP2), y, Mean (S.D.)	13.7 (2.6)	13.4 (2.8)
Height, cm, Mean (S.D.)	158.0 (13.8)	158.8 (14.9)
Age at cancer diagnosis, y, Mean (S.D.)	5.1 (3.4)	n.a.
Time since completion of treatment, y, Mean (S.D.)*	6.8 (3.6)	n.a.
Time since diagnosis, y, Mean (S.D.)	8.6 (3.7)	n.a.
Duration of chemotherapy, y, Median (range)*	1.8 (0.6-3.1)	n.a.
Sex, n (%)		
Male	66 (52)	43 (49)
Female	61 (48)	44 (51)
Study site, n (%)		
Oslo	83 (65)	65 (75)
Bergen	44 (35)	22 (25)
Type of malignancy (ICCC-3 main groups), n (%)		n.a.
I: Leukemia, myeloproliferative and myelodysplastic diseases	66 (52)	
II: Lymphoma, reticuloendothelial neoplasm	12 (9)	
III: CNS, intracranial, intraspinal neoplasm	12 (9)	
IV: Neuroblastoma and other peripheral nervous cell tumours	8 (6)	
V: Retinoblastoma	2 (2)	
VI: Renal tumours	14 (11)	
VII: Hepatic tumours	1 (1)	
VIII: Malignant bone tumours	6 (5)	
IX: Soft tissue and other extraosseous sarcomas	6 (5)	
Underwent surgery, n (%)†		n.a.
Yes	45 (36)	
No	80 (64)	
Stem cell transplantation, n (%)†		n.a.
Yes	13 (10)	
No	112 (90)	
Radiotherapy, n (%)*		n.a.
Yes	33 (26)	
No	93 (74)	
Type of chemotherapy, n (%)		n.a.
With vinca alkaloids	95 (75)	
Cumulative dose mg/m^2, median (range)†	32 (4.4-104)	
With platinum derivatives	5 (4)	
Cumulative dose mg/m^2, median (range)*	725 (173-2338)	
With both vinca alkaloids and platinum derivatives	22 (17)	
Without vinca alkaloids or platinum derivatives	5 (4)	
Tesfaye clinical grade, n (%)		
Normal	90 (71)	85 (98)
Subclinical polyneuropathy	3 (2)	0 (0)
Possible peripheral neuropathy	17 (13)	2 (2)
Probable peripheral neuropathy	5 (4)	0 (0)
Confirmed peripheral neuropathy	12 (10)	0 (0)

Abbreviations:
CCS = Childhood cancer survivors
CNS = Central nervous system
ICCC-3 = International Classification of Childhood Cancer, third version
N = number
n.a. = Not applicable
WP = Work package
Data reported as mean ± S.D., median (range), or number (%).
* 1 value was missing.
† 2 values were missing.

procedures and equipment, which is unachievable in most laboratories for pediatric cases. In the present study we defined cutoffs for abnormal NCSs based on a compromise between published normal values from other countries and local practice in the hospitals.

In this study, polyneuropathy is graded according to Tesfaye criteria.[16] Earlier studies have used different versions of Total Neuropathy Score (TNS)[35] to define polyneuropathy, with a common approach of TNS ≥1 as an abnormal finding.[15,18,19] Using a clinical scoring, experienced clinicians can identify polyneuropathy better than a self-reported assessment.[36] Nevertheless, by adding an objective measurement such as NCS, the diagnostic specificity becomes even higher. Different from these studies,[15,18-20] our approach resulted in a modest number of confirmed polyneuropathy cases (9.4%). The prevalence is also lower than in studies not using NCSs to confirm polyneuropathy.[37]

The reduced amplitudes obtained in the CCS group are in accordance with prior findings indicating the neurotoxic effect of chemotherapy.[15,18-20] It is suggested that neurotoxicity may depend on the cumulative dose of vinca alkaloids and platinum derivatives.[23,38] Of all eight nerves that we examined, we found that the cumulative dose of platinum derivatives was only associated with the motor amplitude in one nerve (tibial motor). No significant association was found for cumulative vinca alkaloids doses. The median cumulative dose of all vinca alkaloids in this study was 32 mg/m^2. Although neurotoxicity has been reported with cumulative doses as low as 4 mg/m^2, most symptomatic dose-dependent vincristine toxicities have been reported with a

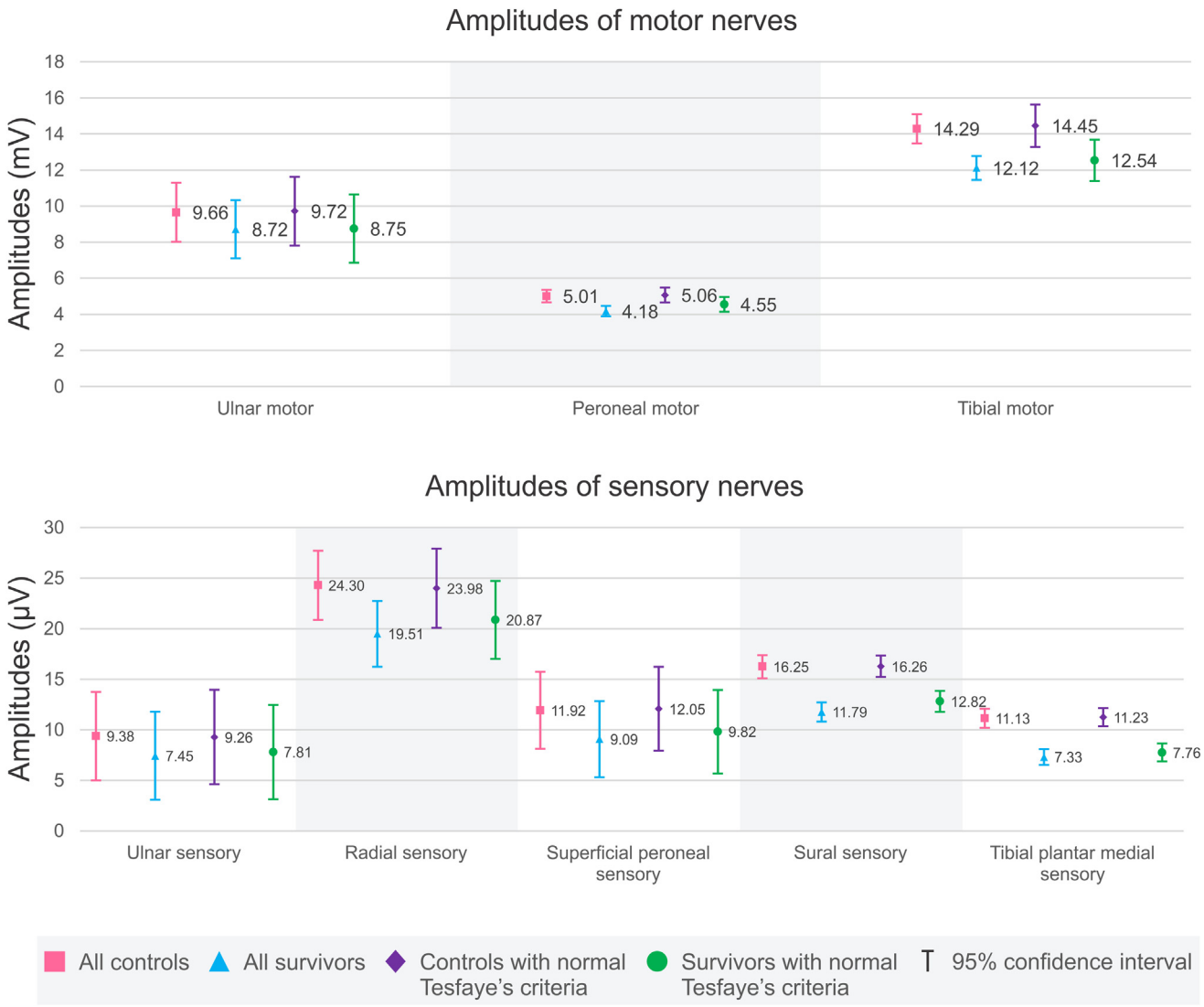

FIGURE 2. Mean amplitudes with 95% confidence interval of motor (in mV) and sensory (in μV) nerves in all survivors and controls, as well as in survivors and controls with normal Tesfaye criteria only. Figure 2 shows the predicted marginal mean amplitudes with 95% confidence interval of all nerves from mixed-effects linear model with study site as random intercept, adjusted for age, sex, and height from all controls (N = 85), all survivors (N = 124), controls with normal Tesfaye criteria (N = 84), and survivors with normal Tesfaye criteria (N = 88). *P* values for comparing marginal means between all controls and all survivors were $P = 0.001$ for the ulnar motor nerves and $P < 0.001$ for all the other nerves. *P* values for comparing marginal means between controls and survivors with normal Tesfaye criteria only were $P = 0.002$, $P = 0.040$, $P = 0.001$, $P = 0.009$, and $P = 0.010$ for the ulnar motor, peroneal motor, tibial motor, ulnar sensory, and radial sensory nerves, respectively; and $P < 0.001$ for all other nerves. The color version of this figure is available in the online edition.

TABLE 3.
Comparison of Amplitudes of Upper and Lower Extremities Between Survivors and Controls, Including Only Those With Normal Tesfaye Clinical Grading (N = 172)

Nerves	CCS (N = 88)	Controls (N = 84)	Mean Differences (control−CCS)	95% CI	*P* Value
Upper extremity					
Ulnar motor, mV	8.75	9.72	0.97	0.34-1.58	0.002
Ulnar sensory, μV	7.81	9.26	1.45	0.36-2.53	0.009
Radial sensory, μV	20.87	23.98	3.11	0.73-5.49	0.010
Lower extremity					
Peroneal motor, mV	4.55	5.06	0.51	0.02-0.99	0.040
Tibial motor, mV	12.54	14.45	1.91	0.78-3.04	0.001
Superficial peroneal sensory, μV	9.82	12.05	2.23	1.06-3.41	<0.001
Sural sensory, μV	12.82	16.26	3.44	1.95-4.94	<0.001
Tibial plantar medial sensory, μV	7.76	11.23	3.47	2.18-4.75	<0.001

Abbreviations:
CCS = Childhood cancer survivors
CI = Confidence interval
Marginal means and marginal mean differences with 95% CI from mixed-effects linear model with study site as random intercept, adjusted for age, sex, and height.

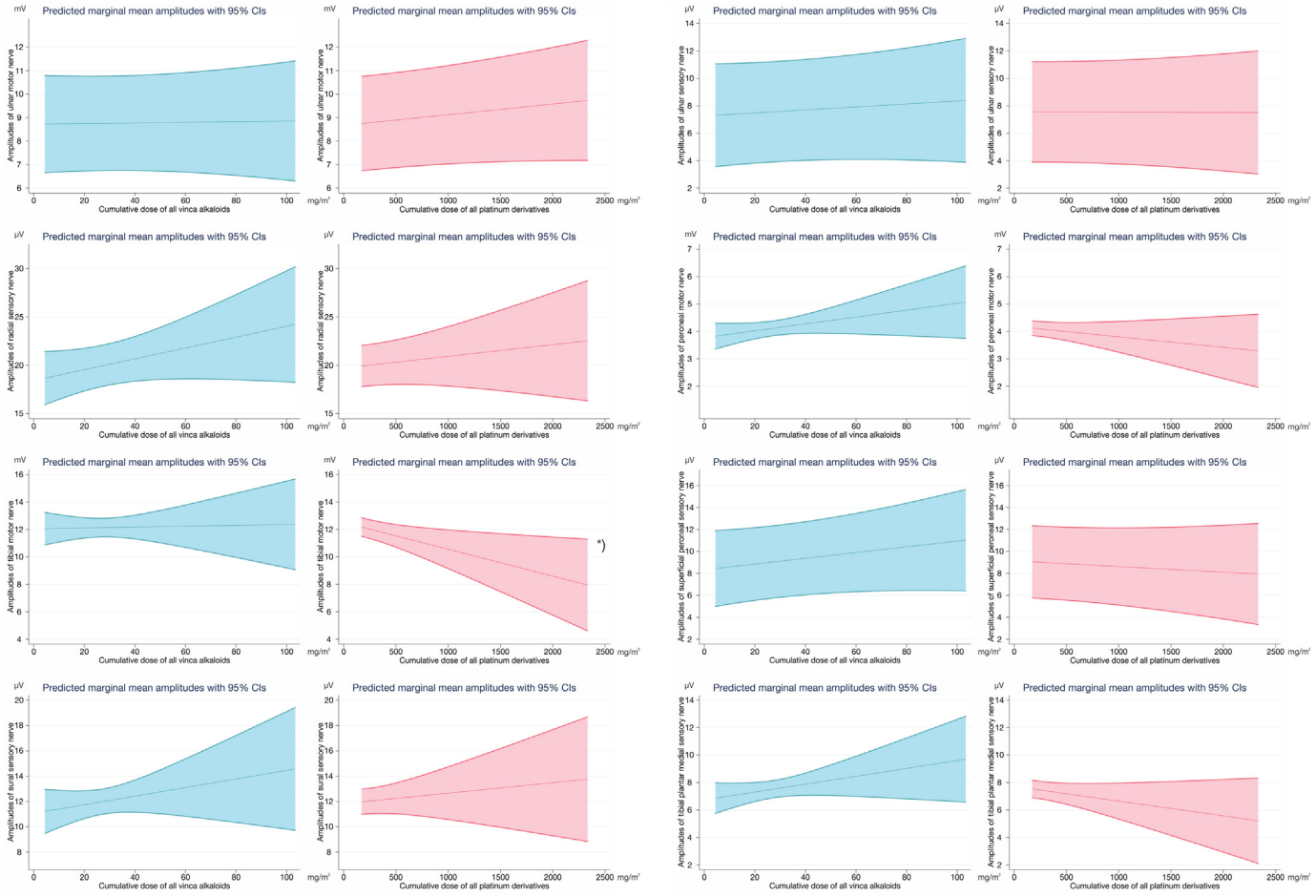

FIGURE 3. The effect of cumulative doses of vinca alkaloids and platinum derivatives on the amplitudes in childhood cancer survivors (CCS) (N = 124). Figure 3 shows the predicted marginal mean amplitudes in relation to cumulative vinca alkaloids and cumulative platinum derivative doses. Predictions are extracted from mixed-effect linear models with study site as random intercept, adjusted for age at diagnosis, follow-up time, sex, and height. Exact estimates are provided in Supplemental Table 2. *) Significant for $P < 0.05$. The color version of this figure is available in the online edition.

cumulative dose ranging from 30 to 50 mg/m^2.[22] A study by Kandula et.al.[20] also did not find correlation between vincristine dose and neurophysiological parameters. With cisplatin, symptomatic toxicity usually occurs after a patient has received 400 to 700 mg/m^2.[39] In our study, the median cumulative dose of all platinum derivatives was 725 mg/m^2. A decreased amplitude in tibial motor nerve associated with platinum derivatives might represent the effect of higher cumulative dose in this drug category. The tibial motor nerve is located in the distal part of the body, which is more prone to be affected in chemotherapy-induced polyneuropathy. However, only 21% of CCS in the present study have had platinum derivatives, which probably are too few to draw statistically firm conclusions. Genetic factors and the use of concomitant fungal treatment, which were not included in the current study analysis, may also affect the neurotoxicity of chemotherapy agents in CCS.[23,38,40]

Our findings are in accordance with previous studies on CCS that have shown a deleterious effect of cancer drugs on peripheral nerves.[15,18-20] Of 37 childhood acute lymphoblastic leukemia (ALL) survivors, Ramchandren et.al. found decreased amplitudes in the peroneal motor, median sensory, and/or median motor nerve in 11 survivors.[18] Tay et.al. reported abnormal NCSs involving sensory nerves (10.2%), motor nerves (18.8%), and both motor and sensory nerves (71%) in 69 of 101 childhood ALL survivors.[15] Jain et.al. found polyneuropathy involving the motor nerves in the common peroneal, tibial, and ulnar nerves in 22 of 80 childhood ALL survivors. In their study, no abnormality was found in sensory nerves.[19] In a more recent study, Kandula et.al. reported that 20 of 85 CCS had abnormal sural amplitude compared with normative data. They also found a small percentage of individuals with abnormal amplitudes in the tibial motor, peroneal motor, and median sensory nerves. However, a significant difference between the CCS and control group was observed only in the sural sensory nerve.[20] The participants in the study of Kandula et.al.[20] were older, whereas the other studies had participants within the same age group as in our study.[15,18,19]

Even though most (73%) CCS in the present study had no symptomatic polyneuropathy, they had overall lower amplitudes compared with the controls. This subtle nerve affection might not be clinically apparent during childhood and adolescence. Previous studies have included functional tests in this age group and found no difference between those with and without polyneuropathy.[15,18] However, a study that examined older cancer survivors aged seven to 47 years revealed some degree of functional decline[20]; this may indicate late manifestations of subtle nerve damage, possibly confounded with aging.[41] With a lower baseline in NCS compared with their peers, Survivors might be at a higher risk of developing overt polyneuropathy due to comorbidities such as diabetes mellitus and other metabolic syndromes.[20,42,43] These conditions may

affect their daily life functional ability in later life. A long-term impact of subtle nerve affection in CCS is beyond the scope of the present study.

The use of two different study centers may be considered a limitation; this could lead to interexaminer variations, particularly when performing NCS. We have accounted for this by using mixed-effect modeling with random intercept in our analyses. Moreover, we were unable to perform supramaximal stimulation in some of the study participants due to procedural pain. This is not uncommon in NCSs in children and may have affected our study findings, both in the CCS and control group. Most of the CCS had been treated with vinca alkaloids and only few of them with other drugs such as platinum derivatives. Therefore, one should be cautious to infer the study findings for cancer drugs other than vinca alkaloids. The results may also be biased toward CCS with leukemia, myeloproliferative, and myelodysplastic diseases. The lack of ethnic diversity (94% of study participants were Caucasian) means that our findings might not necessarily be pertinent to other populations. Included subjects were CCS that who eager to participate in a prospective study on physical activity, which might introduce some selection bias. However, we did not find any differences when comparing the participants and nonparticipants in the study.

The blinding of the examiners and the inclusion of a broad group of diagnoses and age- and sex-matched controls is a strength of our study. This strength has enabled us to compare the results from CCS with healthy individuals who belonged to the same sex and age group; this is particularly useful when essential information such as the normal values for NCSs in children are debatable. In previous studies,[15,18-20] only one study used matched controls for comparison between CCS and healthy individuals.[20] We used the Tesfaye scale, which was developed for diabetic neuropathy, but actually a generic scale composed of signs, symptoms, and objective measurements, applicable for any polyneuropathy. When compared with the symptoms-dominated scales, which will systematically underestimate subclinical polyneuropathy,[17] this might be considered a strength.

Conclusion

Cancer therapy affects both motor and sensory nerves. Importantly, this is true even for those who exhibit no signs or symptoms of polyneuropathy. The findings may have consequences for how we screen for adverse effects and the long-term follow-up of CSS. The clinical impact of the subtle nerve affection reported in the present study must be evaluated in longitudinal studies.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2022.11.012.

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