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Hearing loss and quality of life in survivors of paediatric CNS tumours and other cancers

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Abstract

Hearing loss, a complication of cancer treatment, may reduce health-related quality of life (HRQoL), especially in childhood cancer survivors of central nervous system (CNS) tumours who often have multiple late effects. We examined the effect of hearing loss on HRQoL in young survivors of CNS and other childhood cancers.

Methods: Within the Swiss Childhood Cancer Survivor Study, we sent questionnaires about hearing loss and HRQoL (KIDSCREEN-27) to parents of survivors aged 8–15 years. We stratified the effect of hearing loss on HRQoL by cancer diagnosis, using multivariable logistic regression and adjusting for sociodemographic and clinical factors.

Results: Hearing loss was associated with impaired *physical well-being* [unadjusted estimated differences -4.6 (CI -9.2; -0.1); adjusted -4.0 (CI -7.6; -0.3)] and *peers & social support* [unadjusted -6.7 (CI -13.0; -0.3); adjusted -5.0 (CI -10.5; 0.9)] scores in survivors of CNS tumours (n=123), but not in children diagnosed with other tumours (all p-values > 0.20, n=577).

Conclusion: Clinicians should be alert to signs of reduced physical well-being and impaired relationships with peers. Especially survivors of CNS tumours may benefit most from strict audiological monitoring and timely intervention to mitigate secondary consequences of hearing loss on HRQoL.

Introduction

Hearing loss, especially in the high frequencies, is an adverse event of childhood cancer treatment, particularly after platinum chemotherapy or cranial radiation ≥ 30 Gray [1].

It is often irreversible and can be uni- or bilateral [1]. Hearing impaired children in the general population have lower health-related quality of life (HRQoL) in domains of school activities and social interactions, which are important for learning [2,3]. The only study on hearing loss and HRQoL in young childhood

cancer survivors is published more than 10 years ago [4], while cancer treatments constantly change. The study focused on patients diagnosed with neuroblastoma (1989-1995) without factoring in other comorbidities [4]. While hearing loss can pose difficulties for any child, survivors treated for central nervous system (CNS) tumours may suffer more from hearing loss since they often have multiple late effects which may reduce their social and educational skills [5]. Recently, oncologists have become more aware of ototoxicity [6-8]. Survivors should be carefully monitored for audiological problems and offered timely and targeted interventions to help them cope with hearing loss [9]. Audiological monitoring has not yet been fully implemented for survivors in follow-up care in Switzerland [8] and there is, currently, little data on the effects of hearing loss on childhood cancer survivors.

We thus undertook a nationwide, population-based study to examine the impact of hearing loss on HRQoL in children who were recently treated for childhood cancers (1995-2010) and focused on survivors of CNS tumours.

Materials and methods

Study population

The Swiss Childhood Cancer Survivor Study (SCCSS)

The SCCSS is a population-based cohort of all children registered in the Swiss Childhood Cancer Registry (SCCR), who were diagnosed since 1976, survived ≥ 5 years after initial diagnosis, and were alive at the time of the study [10]. The SCCR includes all patients diagnosed at age < 21 years in Switzerland with leukaemia, lymphoma, CNS tumours, malignant solid tumours or Langerhans cell histiocytosis [11]. Recent estimates indicate that the SCCR includes 95% of those diagnosed since 1995 in Switzerland.[12] We included survivors who were 8-15 years old at survey, and diagnosed between 1995-2010. We traced addresses and sent their parents a questionnaire in 2010-2016. Non-responders received a second copy and then were reminded by phone or postal mailing. Ethical approval was granted through the Ethics Committee of the Canton of Bern to the SCCR and the SCCSS (KEK-BE: 166/2014).

Measurements

SCCSS Questionnaire Survey

Hearing loss: Parents were asked if a doctor had told them that their child had hearing problems (**Supplemental Figure S1**). We coded missing answers (4%) as normal hearing.

HRQoL: We assessed HRQoL with the KIDSCREEN-27 questionnaire for parents [13], which groups 27 items into five dimensions of HRQoL: *Physical well-being*; *psychological well-being*; *autonomy*; *parents, peers & social support*; and, *school environment*. For each item, parents rated their child's HRQoL for the past week on a Likert Scale. For each dimension, we calculated a Rasch score between 0-100 and used international norms to convert them into T-scores (mean=50; SD=10). Higher scores indicate better HRQoL. This instrument has satisfactory psychometric properties [14-16] and has been used in childhood cancer survivors [5,15]. We used international norms as Swiss norm data were only available for the German-speaking regions [17] and 30% of our participants were from French- or Italian-speaking regions.

Sociodemographics and chronic health problems: The questionnaire also assessed sociodemographic data and chronic health problems (**Supplemental Table S1**). For each survivor, we created a sum score of cumulative disease burden by adding the numbers of identified health problems.

SCCR

Clinical information included age at diagnosis; age at survey; gender; cancer diagnosis; chemotherapy; radiotherapy; brain surgery; bone marrow transplant (BMT); and, relapse during follow-up time. We classified cancer diagnosis according to the International Classification of Childhood Cancer—3rd Edition [18].

Statistical analysis

We stratified our analyses for tumour types (CNS and non-CNS cancers) since we found previously that survivors of CNS tumour scored low on physical well-being [5], and interaction tests showed that hearing loss had greater effect on the HRQoL dimension *peers & social support* in survivors of CNS tumours ($p^{\text{interaction}}=0.005$).

We used t-tests to compare the mean scores of the five KIDSCREEN-27 dimensions of children with hearing loss to those of children with normal hearing and to norm values. We did

this separately for children with CNS tumours and those with other cancers. Among survivors of CNS tumours, those with hearing loss had worse HRQoL for *physical well-being* and *peers & social support*. For survivors of CNS tumours we then tested if the association might have been confounded by other factors, including sociodemographics, clinical characteristics, cancer treatment, or other chronic health problems (**Supplemental Table S2**) [19-21]. In multivariable linear regressions, we included *a priori* age at survey and gender, and all characteristics that had been significantly associated ($p<0.05$) with *physical well-being* and *peers & social support* in the univariable models. Likelihood ratio tests determined statistical significance. We performed a sensitivity analysis including those who completed hearing questions ($n=677$) only and obtained similar results. We used Stata (Version 13, Stata Corporation, Austin, Texas) to calculate Rasch- and T-Scores and to perform all other analysis.

Results

Characteristics of the study population

Of 976 parents contacted, 700 returned the questionnaire (72% response rate, **Supplemental Figure S2**). Survivors of CNS tumours ($n=123$) were older at diagnosis ($p<0.001$) and survey ($p=0.003$), and had more often platinum chemotherapy, cranial radiation, brain surgery, relapses, hearing loss, or more than one health problem (all $p<0.001$) than survivors of other cancers (**Tables 1, 2 and 3**).

Hearing loss and HRQoL

In survivors of CNS tumours, hearing loss was associated with poorer *physical well-being* (with hearing loss: T-score=44 vs. normal hearing: T-score=48, $p=0.047$) and *peers & social support* (with hearing loss T-score=40 vs. normal hearing: T-score=47, $p=0.040$; **Figure 1**). Differences remained after adjusting for sociodemographic and clinical characteristics and cumulative disease burden (estimated differences: *physical well-being* [unadjusted -4.6; adjusted -4.0]; *peers & social support* [unadjusted -6.7; adjusted -5.0], **Supplemental table S2**).

In contrast, survivors of other cancers had HRQoL comparable or higher than norm values in all dimensions, and there was no evidence

that hearing loss affected HRQoL (all $p<0.05$, **Figure 1**).

Discussion

Survivors of CNS tumours with hearing loss were more likely to feel physically worse and to have poorer relationships to peers than survivors with normal hearing or than the international norm. In survivors of non-CNS cancers hearing loss was not associated with HRQoL.

Our study had both limitations and strengths. Though we based our conclusion on parent-reported data [5,22-24,21], validity of self-reported hearing loss was good when compared to information from medical records [25,26]. We had no data on hearing aids, though these may affect HRQoL. A strength was the large population-based sample of young, recently diagnosed survivors treated according to the latest treatment protocols, and the comprehensive data available on cancer type, treatment and other chronic health problems.

The only other study that investigated effects of hearing loss on HRQoL in young survivors included 137 US neuroblastoma survivors (non-CNS cancer) [4], and found that survivors with hearing loss were less functional in school, and had lower psychosocial functioning and overall HRQoL. We found no effect of hearing loss in survivors of non-CNS cancers. The US study did not adjust for chronic health problems common in survivors of neuroblastoma, which may have confounded the association [6,7]. A US study in adult survivors ($n=406$) reported a negative impact of hearing loss on educational plans and social attainment in both survivors of CNS and non-CNS tumours.[27] It seems that the vulnerability to hearing loss change with increasing age as in our study survivors of CNS tumours only were vulnerable to hearing loss and other survivors could cope better with hearing loss. In our study, survivors of CNS tumours were treated more intensively and their burden of disabilities was higher than in those of non-CNS tumours. This might in return explain the low physical well-being in survivors of CNS tumours, which is consistent with previous studies.[28,5] The HRQoL dimension peers & social support was particularly affected in survivors of CNS tumours. It might be explained by the fact that they frequently suffer

from reduced neurocognitive functioning and sometimes have to repeat a year in school.[29]

Since audiological monitoring is only partly implemented for survivors in Switzerland [8], health professionals should pay careful attention to hearing problems and their effects in survivors of CNS tumours. Future studies should investigate if hearing aids or other interventions, including speech therapy, frequency modulation amplification systems or preferential classroom seating, help reducing problems with peers.

Conclusion

Hearing loss reduces physical well-being and impairs relationships with peers in survivors of CNS tumours, but not in other survivors, so clinicians should be alert to these problems in this vulnerable group. They may benefit most from strict audiological monitoring and timely intervention to mitigate secondary consequences of hearing loss on HRQoL.

Ethical approval

All procedures performed in studies involving human participants accorded with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethics approval was granted by the Ethics Committee of the Canton of Bern to the SCCR and SCCSS (KEK-BE: 166/2014) and the SCCSS is registered at ClinicalTrials.gov (identifier: NCT03297034).

Informed consent

Informed consent was obtained from all participants (parents and survivors) for registration in the SCCR and participation in the SCCSS survey.

Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1 Sociodemographic characteristics of the study population

	Study participants		
	CNS tumours n=123	Non-CNS cancers n=577	p-value ^a
	mean (SD)	mean (SD)	
Age at survey, years	13 (2)	12 (2)	0.003
Sociodemographic characteristics	n (%^b)	n (%^b)	p-value^c
Gender			0.100
Female	62 (50)	244 (42)	
Migration background ^d			0.568
No	92 (75)	417 (72)	
Yes	31 (25)	160 (28)	
Language region of Switzerland			0.612
German speaking	90 (73)	400 (69)	
French speaking	29 (24)	149 (26)	
Italian speaking	4 (3)	28 (5)	
Parental education ^{e,f}			0.704
Primary	8 (7)	50 (9)	
Secondary	77 (63)	346 (60)	
Tertiary	34 (28)	163 (28)	
Child lives with/in			0.784
Both parents	103 (84)	464 (80)	
One parent and partner	7 (6)	38 (7)	
One parent	12 (10)	67 (12)	
Institution	1 (1)	2 (1)	
Siblings			0.237
No sibling	12 (10)	79 (15)	
Has sibling(s)	109 (90)	488 (85)	

Abbreviations: CNS, central nervous system, n, number; SD, standard deviation.

^aP-values calculated from t-tests comparing survivors of CNS to survivors of non-CNS tumours.

^bColumn percentages are given.

^cP-values calculated from chi-square tests comparing survivors of CNS to survivors of non-CNS tumours.

^dWe classified participants who were not Swiss citizens at birth, not born in Switzerland, or had at least one parent who was not a Swiss citizen as having a migration background.

^eWe classified parental education into three categories: primary education (compulsory schooling only [≤ 9 years]), secondary education (vocational training [10-13 years]), and tertiary education (higher vocational training, college, or university degree). If parents achieved different levels of education, we selected the parent with the highest education.

^fNumbers and percentages are based upon available data.

Table 2 Clinical characteristics of the study population

	Study participants		
	CNS tumours	Non-CNS cancers	p-value ^a
	n=123	n=577	
	mean (SD)	mean (SD)	
Age at diagnosis, years	5 (3)	3 (2)	<0.001
Sociodemographic characteristics	n (% ^b)	n (% ^b)	p-value ^c
Clinical characteristics			
Diagnosis (ICCC-3)			n.a.
I Leukaemias	-	273 (47)	
II Lymphomas	-	50 (9)	
III CNS tumours	123 (100)	0 (0)	
IV Neuroblastoma	-	61 (11)	
V Retinoblastoma	-	38 (7)	
VI Renal tumours	-	51 (9)	
VII Hepatic tumours	-	12 (2)	
VIII Bone tumours	-	12 (2)	
IX Soft tissue sarcomas	-	46 (8)	
X Germ cell tumours	-	11 (2)	
XI & XII Other rare tumours ^d	-	2 (1)	
Langerhans cell histiocytosis	-	21 (4)	
Treatments			
Chemotherapy			<0.001
Platinum	43 (35)	107 (19)	
No platinum	8 (7)	415 (72)	
Unknown platinum use	2 (2)	1 (1)	
No chemotherapy	70 (57)	54 (9)	
Cranial radiotherapy			<0.001
Yes, Gray ^e	32 (26)	46 (8)	
1-29	3 (9)	30 (65)	
≥ 30	27 (84)	13 (28)	
No	91 (74)	531 (92)	
Surgery			<0.001
Brain surgery	72 (59)	14 (2)	
CSF-shunt	6 (5)	0 (0)	
Both	26 (21)	0 (0)	
Bone marrow transplantation ^e			0.044
No	116 (97)	521 (92)	
Yes	3 (3)	43 (8)	
Relapse			<0.001
No	86 (70)	525 (91)	
Yes	37 (30)	52 (9)	

Abbreviations: CNS, central nervous system, ICC-3, International Classification of childhood cancer n, number; SD, standard deviation.

^aP-values calculated from t-tests comparing survivors of CNS to survivors of non-CNS tumours.

^bColumn percentages are given.

^cP-values calculated from chi-square tests comparing survivors of CNS to survivors of non-CNS tumours.

^dOther malignant epithelial neoplasms, malignant melanomas and other unspecified malignant neoplasms.

^eNumbers and percentages are based upon available data.

Table 3 Health outcomes of the study population

	Study participants		p-value ^b
	CNS tumours n=123	Non-CNS cancers n=577	
	n (% ^a)	n (% ^a)	
Hearing outcomes			<0.001
Normal hearing	98 (80)	533 (92)	
Hearing loss	25 (20)	44 (8)	
Severity of hearing loss			0.471
<i>Mild</i>	13 (52)	25 (57)	
<i>Moderate</i>	8 (32)	9 (20)	
<i>Severe (deaf)</i>	3 (12)	4 (9)	
<i>Unknown</i>	1 (4)	6 (13)	
Laterality of hearing loss			0.490
<i>Unilateral</i>	6 (24)	13 (30)	
<i>Bilateral</i>	17 (68)	24 (55)	
<i>Unknown</i>	2 (8)	7 (16)	
Chronic health problems/Cumulative disease burden			<0.001
0	32 (26)	331 (57)	
1	30 (24)	141 (24)	
2	28 (23)	70 (12)	
3 or more	33 (27)	35 (6)	

Abbreviations: CNS, central nervous system, n, number.

^aColumn percentages are given.

^bP-values calculated from chi-square tests comparing survivors of CNS to survivors of non-CNS tumours.

Fig. 1 Mean scores from KIDSCREEN-27 comparing survivors with hearing loss and normal hearing stratified by tumour type.

Higher scores indicate better HRQoL. International norms have a score of 50 ± 10 (SD). P-values calculated from t-tests comparing survivors with hearing loss and normal hearing.

Abbreviations: CI, confidence interval; CNS, central nervous system; p, p-value.

**Title: Hearing loss and quality of life in survivors of paediatric CNS tumours and other cancers,
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Have you been told by a doctor that your child have, or have had ...		If yes, when was it diagnosed the first time?	
No	Yes	Before cancer diagnosis	After cancer diagnosis
☐	☐	☐	☐
Problems with hearing			
If yes, which problems?			
☐	☐	☐	☐
Mild problems, not requiring hearing aids or completely corrected with hearing aid			
☐	☐	☐	☐
Moderate problems, not completely corrected by hearing aid			
☐	☐	☐	☐
Severe problems , not correctable by hearing aid (deaf)			
Are one or both ears affected?			
☐ One ear ☐ Both ears			

Supplementary Figure S1 Questions on hearing from the Swiss Childhood Cancer Survivors Study Questionnaire

Supplementary Figure S2 Response rate among parents of childhood cancer survivors in the Swiss Childhood Cancer Survivor Study

Supplementary Table S1 Classification of chronic health problems

Chronic health problems ^a	Symptoms/disease within each problem	n
Visual impairment n=123	▪ Eye motility dysfunction	23
	▪ Moderate to severe visual impairment or blindness in one or both eyes	64
	▪ Glaucoma	17
	▪ Strabismus	57
Speech difficulty n=58	▪ Stuttering, Loudness	58
Cardiac problem n=32	▪ Cardiac arrhythmia	14
	▪ Cardiac insufficiency	3
	▪ Deep vein thrombosis or lung embolism	4
	▪ Heart valve disease	11
	▪ Stroke	6
Pulmonary problem n=20	▪ Moderate or severe asthma	20
	▪ Recurrent pneumonia	14
Endocrine problem n=78	▪ Diabetes	15
	▪ Hypo- or hyperthyroidism	49
	▪ Growth hormone deficiency	61
Neurological problems n=144	▪ Weakness or paralysis of the arms or legs	56
	▪ Reduced sensitivity of the arms or legs	66
	▪ Balance disorders	99
Musculoskeletal problems n=152	▪ Reduced range of motion of joints	44
	▪ Chronic pain in bones or joints	81
	▪ Scoliosis	44
	▪ Shortening of the arms or legs	31

^a Survivors were classified as having had the respective chronic health problem if they reported at least one of the specific symptoms.

Missing information for visual impairment 7%, musculoskeletal problem 2%, neurological problem 1%, speech difficulty 1%, cardiac problem 2%, pulmonary problem 1%, and endocrine problem 1%.

Supplementary Table S2 Survivors of CNS tumours: Factors associated with physical well-being and peers & social support from the KidScreen-27, results from linear regression

	Physical well-being				Peers & social support			
	Univariable models		Multivariable model ^b		Univariable models		Multivariable model ^c	
	Coef (95% CI)	P ^a	Coef (95% CI)	P ^a	Coef (95% CI)	P ^a	Coef (95% CI)	P ^a
Hearing loss		0.047		0.026		0.040		0.091
No	Ref		Ref		Ref		Ref	
Yes	-4.6 (-9.2; -0.1)		-4.0 (-7.6; -0.3)		-6.7 (-13.0; -0.3)		-5.0 (-10.9; 0.9)	
Sociodemographics								
Age at survey per 5 years	-1.6 (-5.7; 2.6)	0.453	-3.9 (-7.2; -0.6)	0.015	5.0 (1.4; 8.6)	0.006	1.5 (-3.6; 6.6)	0.535
Gender		0.394		0.686		0.053		0.008
Male	Ref		Ref		Ref		Ref	
Female	-1.6 (-5.2; 2.1)		-0.6 (-3.4; 2.3)		4.8 (-0.1; 9.7)		6.0 (1.4; 10.5)	
Migration background		0.516				0.399		
No	Ref				Ref			
Yes	-1.4 (-5.6; 2.8)				2.5 (-3.3; 8.2)			
Language region		0.035		0.012		0.325		
German	Ref		Ref		Ref			
French	-2.9 (-7.0; 1.4)		-3.3 (-6.6; 0.1)		-2.2 (-8.0; 3.6)			
Italian	-11.9 (-21.9; -1.9)		-9.5 (-17.5; -1.4)		-9.4 (-23.2; 4.3)			
Parental education		0.252				0.403		
Primary	Ref				Ref			
Secondary	2.2 (-5.2; 9.7)				2.7 (-7.3; 12.7)			
Tertiary	5.2 (-2.7; 13.0)				5.9 (.4.7; 16.5)			
Having siblings		0.619				0.207		
No	Ref				Ref			
Yes	-1.7 (-8.3; 5.0)				-5.7 (-14.6; 3.2)			
Cumulative disease burden								
Number of additional health problems		<0.001		<0.001		<0.001		<0.001
0	Ref		Ref		Ref		Ref	
1	-5.4 (-9.6; -1.2)		-5.8 (-9.8; -1.7)		-7.3 (-13.6; -0.9)		-6.9 (-13.2; -0.7)	
2	-9.8 (-14.1; -5.5)		-9.0 (-13.2; -4.8)		-9.9 (-16.4; -3.4)		-10.7 (-17.2; -4.2)	
3 or more	-15.1 (-19.3; -10.9)		-14.7 (-18.7; -10.8)		-15.5 (-21.8; -9.2)		-14.9 (-21.1; -8.7)	
Clinical factor								
Age at diagnosis per 5years	-0.4 (-1.1; 0.3)	0.284			0.8 (-0.1; 1.8)	0.090		
Having relapse		0.001		0.005		0.267		
No	Ref		Ref		Ref			
Yes	-6.3 (-10.1; -2.5)		-4.4 (-7.6; -1.2)		-3.0 (-8.5; 2.4)			

Abbreviations: CNS, central nervous system; coef, coefficient; Ref, reference; CI, confidence interval.

^aP-values derived from likelihood ratio tests

^bAdjusted for gender, age at survey, language region, cumulative disease burden, and having had a relapse.

^cAdjusted for gender, age at survey, cumulative disease burden.

Selection of confounders: We tested age at diagnosis, cumulative disease burden, language region, migration background, parental education, having siblings and having had a relapse in univariable linear regression analysis. In multivariable regression models we included a priori gender and age at survey and confounders with $p < 0.05$ in univariable regressions.