EUROPEAN JOURNAL OF CANCER 45 (2009) 2552–2561

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Health and persistent functional late effects in adult survivors of childhood CNS tumours: A population-based cohort study

K.K. Boman[a,*], *E. Hovén*[a], *M. Anclair*[a], *B. Lannering*[b], *G. Gustafsson*[a]

[a]*Karolinska Institutet, Department of Women's and Children's Health, Childhood Cancer Research Unit, Astrid Lindgren Children's Hospital Q6:05, S-17176 Stockholm, Sweden*

[b]*University of Gothenburg, Department of Pediatrics, Pediatric Oncology, Queen Silvia's Children's Hospital, SU/Östra, S-416 85 Gothenburg, Sweden*

ARTICLE INFO

Article history:
Received 30 March 2009
Received in revised form 6 June 2009
Accepted 10 June 2009
Available online 16 July 2009

Keywords:
Childhood cancer
Central nervous system tumours
Adult survivors
Late effects
Disability
Long-term health
Population-based study
Health Utilities Index

ABSTRACT

Survivors of central nervous system (CNS) tumours are particularly vulnerable to tumour- and treatment-related disability. We present the incidence of specific and overall functional and health-related late effects in a national adult survivor cohort. Diagnostic subgroups at particular risk for persistent sequels are identified.

Data collection targeted 708 eligible >18 years old survivors, 708 parent proxies and 1000 general population controls. Functional disability including sensory and cognitive impairment, emotional status and pain was assessed using the Health Utilities Index™ Mark 2/3 (HUI2/3). Survivors and controls, and diagnostic subgroups were contrasted to identify the general and relative risk for late effects by sub-diagnosis.

Survivors had persistent late effects in sensation, mobility, self-care and cognition. Deficits in these domains indicated clinically important disability in overall health, although indices of emotion and pain were unaffected compared to controls. Late effects tended to aggravate with time, and female survivors had poorer health. Oligodendroglioma, mixed/unspecified glioma, intracranial germ cell tumour and medulloblastoma survivors had poorest overall health. Least late effects were found for other specified/unspecified CNS tumours (including meningeoma and nerve sheath tumours), and for astrocytoma. An impact on educational, vocational and family-related outcomes, and higher utilisation of social insurance or government subsidies validated health-related sequelae in adulthood.

Comparisons with controls confirm persistent disability in multiple functional domains in adult CNS tumour survivors. The heightened proportion of survivors presenting severe disability is a factor that specifically differentiates survivors from controls, although diagnostic subgroups differ significantly regarding the amount and severity of late effects.

1. Introduction

Central nervous system (CNS) tumours are the most common solid tumours of childhood, constituting ~28% of all paediatric malignancies in the Nordic countries.[1] Improved survival has resulted in a growing number of adult survivors after treatment for a childhood and adolescent CNS tumour (CCNST), i.e. patients diagnosed before their 19th birthday. The increase has prompted studies that address follow-up needs and late adverse effects of illness and treatment. These studies confirm that post-treatment morbidity and subsequent heightened risk of social disability are common after

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* *Corresponding author*: Tel.: +46 707883305 (mobile), +46 851774931 (office), +46 851772870 (secr.); fax: +46 8320274.
E-mail addresses: Krister.Boman@ki.se, kris3001@gmail.com (K.K. Boman).

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doi:10.1016/j.ejca.2009.06.008

otherwise successful treatment.[2–4] The range of late effects involves organ systems, tissue damage and neuro-cognitive and functional abilities that vary in aetiology, timing of onset, severity and complexity.[5–7] Recognition of potential late illness-related morbidity for CCNST survivors has been followed by recent research indicating that chronic disabilities can become apparent with time and interact unfavourably with normal ageing.[2,8,9] Based on the data from a large study sample, diagnosed in childhood and young adulthood (0–21 years), Oeffinger and colleagues[2] conclude that adult survivors of childhood cancer in general are a high-risk population for persistent adverse health conditions, with CCNST treatment being associated with the highest risk for chronic health conditions. Internationally, there are studies that involve smaller ($n \leqslant 44$), and younger groups of brain tumour survivors and that have used standardised assessment to address the consequences of morbidity in terms of health status and functional disability.[10,11]

When samples have covered mixed diagnoses, including the diagnosis of a CNS tumours ($n = 21$),[12] ($n = 133$),[13] the many survivors in their teens, adolescence or young adulthood were found to carry the burden of their illness and treatment, with generally poorest health outcomes for those diagnosed with a CNS tumour, retinoblastoma or bone tumour.[13]

Few large studies have specifically addressed health-related and functional late effects among adult CCNST survivors, using standardised assessments and multiple informants together with study-specific national population control data. Such an approach adds reliability to the evaluation of the range of late-occurring disabilities which are due to these patients being exposed to illness and treatment during a sensitive period in their growth and development. Detailed knowledge about incidence and severity of squealae that interfere with functioning provides necessary information about the need of preventive measures, rehabilitation and follow-up.

In this study, the aim was to determine the incidence and kinds of persistent health-related and functional late effects in a nation-wide cohort of adult survivors of CCNST together with community population comparison data (controls). We also wanted to identify diagnostic subgroups at particular risk.

2. Patients and methods

2.1. *Participants*

We studied CCNST survivors and their parents from all six childhood cancer centres in Sweden, and a non-cancer comparison group (Table 1). Survivors were identified from the national childhood cancer registry (NCCR) that nationally covers patients diagnosed with a primary cancer diagnosis during childhood or adolescence, classified according to the International Classification for Childhood Cancer (ICCC-3).[14] Ninety-nine percent of NCCR registered patients are diagnostically specified, and morphologically verified at one of six university hospital paediatric cancer centres.[1] Survivors diagnosed with a primary CNS tumour 1982–2001 before their 19th birthday were eligible. Additional inclusion criteria were that patients at the time of the study were >18 years old, and that >5 years had elapsed from diagnosis. Of 5443 children diagnosed with cancer 1982–2001, 1535 had a CCNST. At the time of this study, 449 CCNST patients had died, and 708 fulfilled the inclusion criteria. Of the latter, 11 had died since last update of the NCCR, while 18 survivors and 22 parents could not be reached. Among the remaining 679 survivors, 531 (78.2%) completed study questionnaires. Table 2 presents medical characteristics of the survivor group. In addition to survivor-reported data, parent proxy ratings were collected from 556 parents (82.4%).

Responding ($n = 531$) and non-responding ($n = 148$) survivors were similar regarding time elapsed since diagnosis, age at invitation, sex and diagnosis, although they differed regarding age at diagnosis ($p = 0.023$). Non-responders were younger at time of diagnosis (mean: 9.52 years; SD: 4.97) compared to responders (mean: 10.56 years; SD: 4.43). The mean age at invitation of non-responders (90 males; 58 females) was 25.49 years (SD: 5.24). Table 2 shows medical characteristics of the survivor group for which outcome analyses were conducted. Comparison data were collected by sending study questionnaires to a randomly selected stratified (year of birth and sex) general population sample of 2500 subjects. Sixty of these were unreachable, and questionnaires were returned by 996 of the remaining (41%). Data were collected between June 2006 and December 2007, using a mail-back questionnaire. The study was approved by the Regional Research Ethics Committee and participants were included after having provided written informed consent.

2.2. *Outcomes*

Socio-demographic data and selected social background information were collected from survivors, proxy-respondents and controls using a self-report form. It covered family status, former need of remedial school training, academic attainment, employment, prior and present needs of medical-care services and utilisation of social insurance or governmental subsidies.

To assess the severity of late effects, we used the 15-item Health Utilities Index™ Mark 2/3 (HUI2/3).[15] The HUI2/3 was designated to collect sufficient information for classifying health status according to both the HUI Mark 2 (HUI2) and Mark 3 (HUI3), two complementary health classification systems.[16,17] The instrument can be used in a wide variety of clinical and general populations, including CCNST survivors.[16,18,19] The assessment allows for comparing findings with a growing base of data, while also being a standardised, reliable, valid and both theoretically and empirically well-founded measure.[16,17,20] Of the possible ways of evaluating HUI2/3 outcomes, we addressed nine single functional attributes, i.e. *vision*, *hearing*, *speech*, *cognition*, *pain*, *emotion*, *ambulation*, *dexterity* and *self-care*. We also used three compound multi-attribute outcome measures, i.e.: *sensation* (derived through a multiplicative function using weighted outcome scores for vision, hearing and speech), *mobility* (derived through a similar scoring algorithm based on ambulation and dexterity) and *overall health status* (calculated similarly, and based on vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain). The outcome measures of HUI2/3 are illustrated in Fig. 1.

Table 1 – Demographic characteristics of adult CNS tumour survivors and general population controls.

Characteristic	Survivors ($N = 603$)[a] N (%)	Control subjects ($N = 996$) N (%)	P
Sex			<0.0001
Male	321 (53.2)	377 (37.9)	
Female	282 (46.8)	619 (62.1)	
Age at assessment			<0.0001
<25	265 (43.9)	177 (18.5)	
25–30	213 (35.3)	378 (39.5)	
31–36	110 (18.2)	253 (26.4)	
>36	15 (2.5)	149 (15.6)	
Education			<0.0001[b]
Did not complete primary school	50 (8.3)	17 (1.7)	
Passed primary school	58 (9.6)	44 (4.4)	
Passed upper secondary school	203 (33.7)	223 (22.4)	
Entered university education	102 (16.9)	175 (17.6)	
Completed university education	188 (31.2)	537 (53.9)	
Data missing	2 (0.3)	–	
Need of extraordinary assistance in school			<0.0001[b]
Yes	228 (37.8)	115 (11.5)	
No	361 (59.9)	873 (87.7)	
Data missing	14 (2.3)	8 (0.8)	
Employment status			<0.0001[b]
Employed or studying	434 (72.0)	883 (88.7)	
Unemployed	157 (26.0)	108 (10.8)	
Data missing	12 (2.0)	5 (0.5)	
Social insurance or government subsidies			<0.0001[b]
Yes	199 (33.0)	195 (19.6)	
No	389 (64.5)	788 (79.1)	
Data missing	15 (2.5)	13 (1.3)	
Have own children			<0.0001[b]
Yes	78 (12.9)	402 (40.4)	
No	516 (85.6)	588 (59.0)	
Do not know	1 (0.2)	–	
Data missing	8 (1.3)	6 (0.6)	

a Including data from 72 parent proxy-reports.
b *p*-Values for survivor and control group comparisons, adjusted for sex and age at assessment.

The HUI2/3 provides both a descriptive categorical outcome measure, and an interval-scale measure of morbidity for each single-attribute and multi-attribute outcomes (utility scores). The descriptive measure ranges from no disability to severe disability.[21] HUI utility scores derive from general population preferences.[17,22] Single-attribute utility scores range from 0.00 (most severe impairment) to 1.00 (perfect health). The utility scoring for multi-attribute overall health is defined on a scale where perfect health = 1.00, and dead 0.00. Scores below 0.00 for overall health signify states considered worse than death.[17,21,22] HUI3 scores for mild disability states fall in the 0.89–0.99 range, moderate disability states fall into the range of 0.70–0.88, and severe disability states are indicated by scores <0.70.[15,16] Mean differences of $\geqslant 0.05$ for single-attribute utility scores and of $\geqslant 0.03$ for overall utility scores are regarded as clinically important.[15,21,23,24]

In this study we primarily used survivors' reports, but in the case of un-returned patient questionnaires, the proxy rating was used, if available (done in 72 cases).

2.3. *Statistical analysis*

We provide descriptive summary statistics for demographic characteristics of survivors and controls (Table 1), and groups were compared by sex and age at assessment using chi-square tests. Survivors and controls were compared regarding other demographic characteristics using ANOVAs with sex and age at assessment as covariates in a multivariate analysis.

Frequency distributions are presented for HUI2/3 categorical health/functional variables. Single-attribute and overall health status utility scores are presented with mean and SD estimates of central tendency. Differences in utility scores between survivors and controls, male and female survivors and diagnostic subgroups were analysed using ANOVA and *t*-test for independent groups. Sex and age at assessment were inserted as covariates in adjusted multivariate analysis comparing outcomes for survivors and controls. The clinical importance of statistical group differences was established according to recommendations.[15,21,23,24] Correlations (Pear-

Table 2 – Survivor medical characteristics.

Diagnosis	Survivors[a] N (%)	Age at diagnosis (years) Mean (SD)	Age at assessment (years) Mean (SD)	Time since diagnosis (years) Mean (SD)	Sex	
					Female – N (%)	Male – N (%)
IIIa Ependymoma	54 (9.0)	9.8 (5.0)	26.5 (5.4)	16.7 (4.9)	30 (55.6)	24 (44.4)
IIIb Astrocytoma	282 (46.8)	9.9 (4.4)	26.1 (4.9)	16.1 (5.0)	142 (50.4)	140 (49.6)
Low grade (I–II)	238 (39.5)	10.3 (4.3)	26.2 (4.9)	15.9 (5.2)	119 (50.0)	119 (50.0)
High grade (III–IV)	11 (1.8)	10.0 (4.7)	28.4 (5.0)	18.3 (3.8)	9 (81·8)	2 (18·2)
Optic glioma	33 (5.5)	7.1 (4.3)	24.1 (4.2)	17.0 (3.7)	14 (42.4)	19 (57.6)
IIIc Medulloblastoma/PNET	74 (12.3)	9.0 (4.9)	25.6 (4.5)	16.6 (4.8)	29 (39.2)	45 (60.8)
IIId1 Oligodendroglioma	25 (4.1)	9.3 (5.0)	26.6 (5.4)	17.2 (4.7)	10 (40.0)	15 (60.0)
IIId2 Mixed and unspecified glioma	14 (2.3)	10.0 (3.5)	24.1 (3.8)	14.0 (4.3)	5 (35.7)	9 (64.3)
Xa Germ cells – intracranial and intraspinal	25 (4.1)	13.3 (3.5)	28.9 (4.8)	15.5 (4.7)	9 (36.0)	16 (64.0)
IIIe2 Craniopharyngioma	49 (8.1)	10.3 (4.0)	26.0 (5.4)	15.6 (5.1)	26 (53.1)	23 (46.9)
IXb Nerve sheath tumours	10 (1.7)	13.2 (2.0)	25.8 (4.4)	12.6 (4.9)	4 (40.0)	6 (60.0)
XIIa Other specified	63 (10.4)	13.5 (3.1)	26.1 (5.0)	12.5 (5.2)	24 (38.1)	39 (61.9)
XIIb CNS-unspecified	7 (1.2)	14.4 (2.0)	27.1 (5.7)	12.7 (5.3)	29 (39.2)	45 (60.8)
Total	603 (100)	10.4 (4.5)	26.1 (5.0)	15.7 (5.1)	282 (46.8)	321 (53.2)

[a] Including those survivors for whom HUI outcome data from 72 parent proxies were used in analyses.

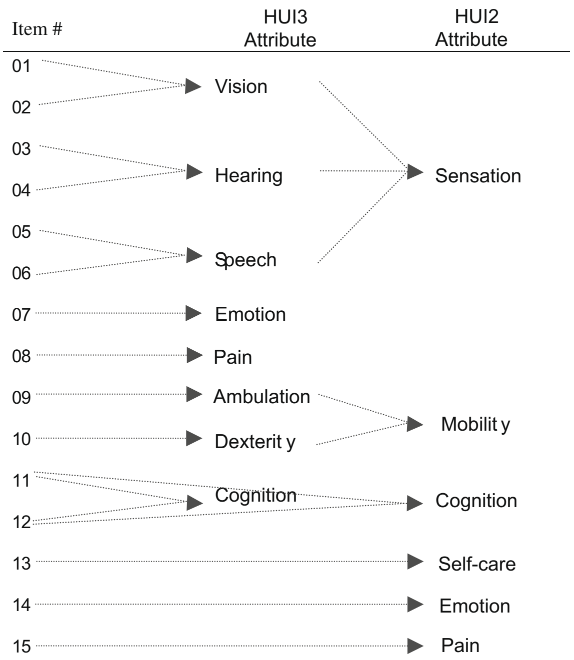

Fig. 1 – Items and item clusters corresponding to HUI3 and HUI2 single functional attributes, and multi-attribute outcome measures. The summary overall health status measure was based on HUI3 attributes. Figure reprinted with permission from Health Utilities Inc., Canada.

son's *r*) were calculated for associations between age at diagnosis, age at assessment, time since diagnosis and HUI2/3 utility measures. ANOVA and *t*-test for independent groups were used for the evaluation of the relationship between educational and social variables and overall health. Inter-rater agreement of the HUI2/3 outcomes of survivors and parent proxies was evaluated by calculating percent agreement, and one-way, single-measure, intra-class correlation (ICC).[25] Statistical significance alpha of 0.05 was applied, and analyses were carried out using the SPSS statistical package 15.0 for Windows (SPSS Inc., Chicago, Illinois).

3. Results

Survivor and control groups differed in terms of the male/female ratio, apparently due to a tendency for female controls to respond more often than males (Table 1). Furthermore, age at assessment differentiated between groups (Table 1). Although within equal range, the upper age partition was somewhat smaller in the survivor group. Survivors had significantly more often received extraordinary assistance including remedial training in school, attained lower educational goals, and lower employment status, had made greater use of social insurance or governmental subsidies and had less frequently become parents (Table 1).

Overall agreement between survivor- and parent proxy ratings was good, but varied by attribute (Table 3).

3.1. *Disability compared to controls*

Survivors had a poorer health status than controls when compared regarding the proportions showing perfect health, on the one hand or mild, moderate or severe disability, on the other (Table 4). Compared to the general population controls, CCNST survivors indicated disability in all single-attribute functions except emotion and pain (Table 5). Most severe sub-normality was found in cognition, sensation and overall health.

Survivors and controls differed significantly in the *number* of affected functional attributes with 16.5% of survivors presenting disability in more than four attributes compared to 6.5% for controls (Table 6). Only 94 survivors (16.1%) and 166 control subjects (17.0%) reported no disability at all. Severity of the disability varied by functional attribute. Attribute utility

Table 3 – Survivor and parent proxy inter-rater agreement for participants with both sets of data (n = 482).

Attribute	HUI utility scores by means (SD)		Percent agreement	ICC[a]
	Survivors	Parents		
Vision	.9457 (.13)	.9483 (.13)	87.8	0.726
Hearing	.9726 (.14)	.9768 (.12)	95.5	0.563
Speech	.9691 (.10)	.9759 (.10)	90.1	0.601
Emotion	.9149 (.15)	.9291 (.13)	60.0	0.403
Pain	.9379 (.12)	.9396 (.15)	60.8	0.473
Ambulation	.9658 (.15)	.9624 (.16)	94.8	0.961
Dexterity	.9708 (.12)	.9694 (.11)	92.7	0.816
Cognition	.9232 (.18)	.9299 (.17)	68.4	0.582
Self-care	.9759 (.15)	.9756 (.14)	98.9	0.954
Sensation	.8761 (.17)	.8905 (.16)	81.6	0.692
Mobility	.9747 (.12)	.9762 (.11)	94.6	0.944
Overall health status (HUI3)	.7800 (.26)	.8023 (.27)	NA	0.678

NA = not applicable (calculated conclusive overall outcome variable).

[a] Intra-class correlation coefficient.

Table 4 – Health status based on the disability category for survivors and controls, and by sex.

Disability category (DC)	Survivors						Controls					
	All		Male		Female		All		Male		Female	
	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%[a]
Perfect health	94	16.1	57	18.3	37	13.6	166	17.0	64	17.3	102	16.7
Mild DC	178	30.5	107	34.4	71	26.1	360	36.8	142	38.5	218	35.7
Moderate DC	155	26.6	79	25.4	76	27.9	319	32.6	123	33.3	196	32.1
Severe DC	156	26.8	68	21.9	88	32.4	131	13.4	40	10.8	94	15.4
States < 0.0[b]	13	2.2	8	2.6	5	1.8	3	0.3	1	0.3	2	0.3
Total valid	583	100	311	100	272	100	979	100	369	100	610	100
Data missing	20		10		10		17		8		9	
Total group	603		319		284		996		377		619	

Note: Disability category comparisons: survivors and controls contrasted: $\chi^2 = 42.2$, df 3, $p < 0.0001$. Males and females contrasted in survivor group: $\chi^2 = 11.6$, df 3, $p = 0.009$, and in control group $\chi^2 = 4.1$, df 3, $p = 0.247$.

[a] Within entire group.

[b] Overall health utility score below 0, and part of the severe disability category.

Table 5 – Functional outcomes[a] by domain for survivors and general population controls.

Attribute variable	Functional domain	Mean (SD)		95% Confidence interval		t	df	p Value[b]
		Survivors ($N = 603$)	Controls ($N = 996$)	Lower	Upper			
Single-attribute utility function	Vision	0.9408 (0.15)	0.9767 (0.06)	–0.0483	–0.0235	–5.70	702	<0.0001
	Hearing	0.9754 (0.13)	0.9963 (0.05)	–0.0317	–0.0102	–3.83	691	<0.0001
	Speech	0.9707 (0.10)	0.9902 (0.05)	–0.0279	–0.0110	–4.50	755	<0.0001
	Emotion	0.9081 (0.15)	0.9148 (0.13)	–0.0206	0.0073	–0.94	1591	0.640
	Pain	0.9290 (0.15)	0.9240 (0.13)	–0.0088	0.0187	0.71	1589	0.651
	Ambulation	0.9569 (0.18)	0.9963 (0.04)	–0.0536	–0.0251	–5.41	633	<0.0001
	Dexterity	0.9675 (0.13)	0.9961 (0.04)	–0.0392	–0.0180	–5.29	669	<0.0001
	Cognition	0.9192 (0.18)	0.9723 (0.09)	–0.0689	–0.0373	–6.61	780	<0.0001
	Self-care	0.9707 (0.16)	0.9982 (0.03)	–0.0408	–0.0143	–4.08	627	<0.0001
Compound utility functions	Sensation	0.8788 (0.17)	0.9300 (0.10)	–0.0666	–0.0359	–6.56	855	<0.0001
	Mobility	0.9701 (0.13)	0.9975 (0.04)	–0.0382	–0.0166	–4.99	647	<0.0001
Multi-attribute utility function	Overall health status	0.7689 (0.27)	0.8537 (0.17)	–.01087	–0.0608	–6.95	857	<0.0001

[a] HUI2/3 single- and multi-attribute utility function scores.

[b] p-Values for survivor and control group comparisons, while simultaneously controlling for sex and age at assessment.

Table 6 – Proportions of survivors by number of affected functional attributes.

Number of affected functional attributes	Survivors, %		General population, %	
0	16.1		17.0	
1	27.4		31.5	
2	22.0		28.0	
3	17.8		17.1	
4	11.1	16.5	5.1	6.5
5	2.7		1.2	
6	1.5		0.2	
7	1.0		0	
8	0.2		0	

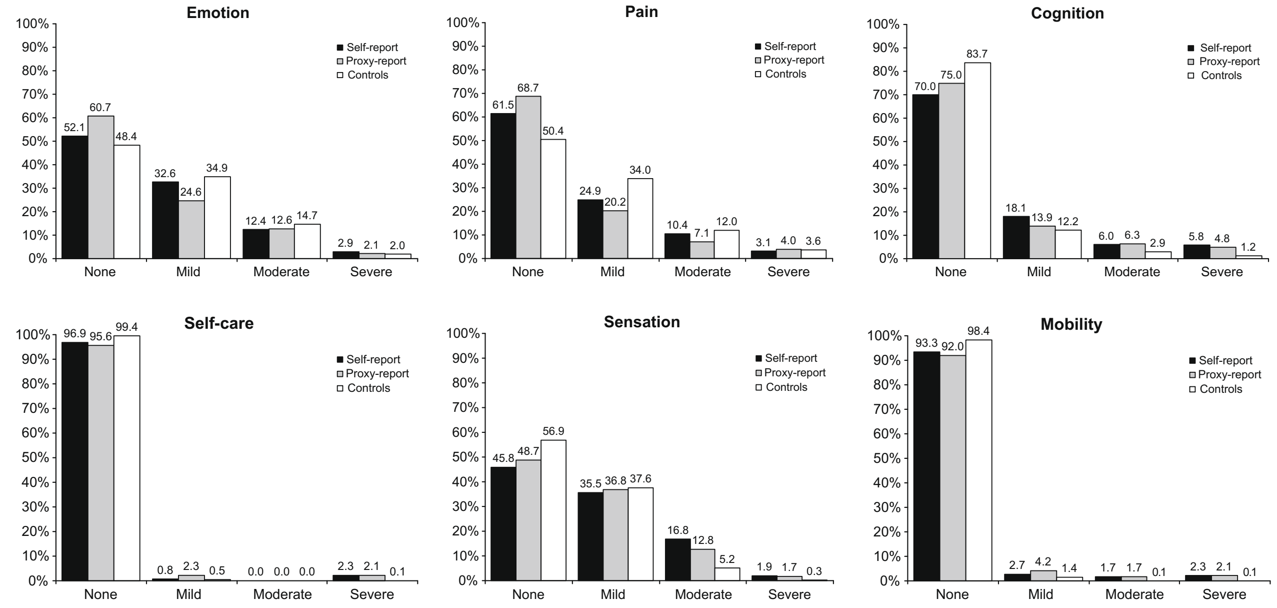

Fig. 2 – Health and functional outcomes by proportions (%) regarding severity of disability in survivors (self- and parent proxy-reported data for which both types of reports were available, $n = 482$), and general population comparisons (controls).

scores for survivors (self-reported) for whom proxy-reported data also were available indicated moderate to severe disability in 18.7% for sensation and in 4.0% for mobility, compared to 5.5% and 0.2% in controls (Fig. 2).

3.2. *Factors associated with late effects*

Compared to male survivors, outcomes for females indicated higher functional disability (health status in terms of the *categorical disability* measure, Table 4), and lower *utility scores* on overall health status (Table 7, $t_{581} = 2.50$; $p = 0.013$). Regarding *single attributes*, except hearing and dexterity, females presented a general pattern of lower scores than males, although differences were statistically significant only for pain (Table 7, $t_{495} = 3.28$; $p = 0.001$). Age at diagnosis was unrelated to health/disability. Age at assessment was negatively related to sensation (based on vision, hearing and speech; $r = -0.13$, $p = 0.001$), mobility (based on ambulation, and dexterity; $r = -0.09$, $p = 0.024$), pain ($r = -0.13$, $p = 0.002$) and overall health ($r = -0.10$, $p = 0.012$), while a similar pattern was not found for the controls. Time elapsed since diagnosis was negatively related to sensation ($r = -0.15$, $p = 0.0004$), mobility ($r = -0.08$, $p = 0.049$) and overall health ($r = -0.14$, $p = 0.001$). Survivors diagnosed during an earlier era had more of an adverse impact on sensation ($r = 0.15$, $p = 0.0003$), dexterity (r=0.10, $p = 0.011$) and overall health ($r = 0.14$, $p = 0.001$), than those diagnosed later.

A relationship was found for health- and functional status of survivors and educational and social outcomes. Survivors who had lower educational attainment ($F(4, 576) = 10.46$, df = 4; $p < 0.0001$), received more of remedial training in school ($t_{415} = -4.72$; $p<0.0001$), had lower employment status ($t_{217} = -3.59$; $p = 0.0004$), to a greater extent had utilised social insurance or governmental subsidies ($t_{267} = -8.99$; $p < 0.0001$), and who less frequently had become parents (t_{120}=2.53; $p = 0.013$) had poorer overall health in comparison to survivors with less pronounced educational and social sequelae.

3.3. *Outcomes by tumour type*

In comparison to controls, all diagnostic subgroups presented sub-normal levels of overall health status (Table 8). Disability was most prominent in survivors of germ cell tumours, oligodendroglioma, ‘other gliomas’ (non-astrocytoma) and medulloblastoma, while survivors of other specified/unspecified CNS tumours and astrocytoma indicated the best health/

Table 7 – Single functional attribute utility scores for survivors by sex, and confidence intervals for mean differences.

Functional attribute	Mean (SD)		95% Confidence interval		*t*	df	*p* Value (2-tailed)
	Male (*N* = 321)	Female (*N* = 282)	Lower	Upper			
Vision	0.9478 (0.14)	0.9329 (0.16)	–0.0088	0.0388	1.24	598	0.217
Hearing	0.9743 (0.13)	0.9767 (0.12)	–0.0231	0.0183	–0.23	593	0.820
Speech	0.9751 (0.08)	0.9657 (0.12)	–0.0070	0.0257	1.12	495	0.262
Emotion	0.9147 (0.14)	0.9006 (0.16)	–0.0103	0.0384	1.14	597	0.257
Pain	0.9477 (0.12)	0.9076 (0.17)	0.0161	0.0642	3.28	495	0.001
Ambulation	0.9677 (0.15)	0.9446 (0.20)	–0.0056	0.0518	1.58	515	0.114
Dexterity	0.9677 (0.12)	0.9673 (0.14)	–0.0202	0.0211	0.04	596	0.969
Cognition	0.9288 (0.17)	0.9082 (0.19)	–0.0089	0.0500	1.37	595	0.171
Self-care	0.9798 (0.14)	0.9604 (0.19)	–0.0074	0.0462	1.42	500	0.155
Sensation	0.8875 (0.17)	0.8687 (0.17)	–0.0091	0.0466	1.32	591	0.186
Mobility	0.9770 (0.11)	0.9622 (0.15)	–0.0068	0.0363	1.34	512	0.179
Overall health status	0.7945 (0.26)	0.7396 (0.27)	0.0119	0.0980	2.50	581	0.013

functional ability. A significant main effect of diagnosis was demonstrated for six functional attributes (hearing, ambulation, dexterity, cognition, self-care and mobility) and for overall health (Table 8). Evaluation of the clinical significance of differences in health outcomes between diagnostic subgroups and controls indicated a clinically important heightened disability specifically among germ cell tumour, oligodendroglioma, mixed/unspecified glioma and medulloblastoma survivors.

4. Discussion

The adult CCNST survivors in this population-based cohort suffered from persistent deficits in cognition, sensory functions, mobility and self-care, whereas no emotional and pain sequelae were demonstrated. Overall health of survivors treated for intracranial germ cell CNS tumours, oligodendroglioma, other glioma (astrocytomas excluded) and medulloblastoma was most severely compromised. Lowest levels of disability was found for other specified/unspecified CCNST (incl. nerve sheath tumours and meningeoma), and astrocytoma. On a whole-group level, disability was in the mild to moderate range, although the more frequent occurrence of sequels in *multiple domains* was highly significant compared to controls. Survivors differed from controls in reported greater need of remedial training in school, lower educational status, greater reliance on governmental subsidies and regarding parenthood.

To our knowledge, this is the first large study of a population-based nation-wide cohort of CCNST survivors, using HUI2/3 for evaluation of late effects in adult life, and where outcomes are presented with study-specific comparison data together with guidance for interpretation of differences. To provide a benchmark for interpreting differences between groups in overall utility scores, it is essential to specify the magnitude of an important difference in utility scores within the HUI system. Differences greater than or equal to 0.03 in overall utility scores are associated with important variations in level of functioning within attributes,[26] and following the common recommendations, we interpreted a difference of 0.03 or more as being clinically important for compound HUI-measures, and 0.05 for single attributes.[21] In our presentation of findings we have related outcomes to these benchmarks.

Prior studies of health-related sequelae have typically addressed younger survivors, and involved smaller samples, and minor or no control groups.[12,27–29]Although HUI2/3 has not been used in studies that specifically address adult CCNST survivors, Alessi and colleagues[13] used HUI in addressing a large group of long-term survivors treated for different kinds of childhood cancer, including 133 brain tumour cases. Our findings parallel their findings in that cognition, vision, ambulation and dexterity were markedly affected. Thus, the most pronounced disabilities were by us found for *cognition*, *sensation* (vision, hearing and speech) and *overall health*. Here, differences between CCNST survivors and controls were indicated by both strong statistical significance, and clinically important disability among survivors. Furthermore, significant, although less pronounced impairment was indicated for *mobility* (dexterity and ambulation) and *self-care*. Our results also support those where chronic health conditions evaluated differently have been found to be particularly common among survivors of bone tumours and CCNSTs.[2]

Emotion and *pain* outcomes were similar for survivors and controls. In line with what has been indicated previously we can thus conclude that emotional sequels need not parallel functional disability, or be characteristic of these survivors.[4] On the other hand, emotional consequences have been established in studies of younger samples.[10–12] Together with previous findings, ours indicate that certain late effects may become more pronounced later in life (sensation, cognition and overall health status), while others may decrease or cease (emotion and pain). However, the interaction between time and severity disability areas is less informative when looking at the entire CCNST group, as our findings show that the pattern of illness-related disability differs for diagnostic subgroups.

A notable finding was that female survivors were at higher risk for late effects in general by presenting with poorer health status in adult life. Here findings support what has been found for mixed groups of younger survivors in general,[13] and younger brain tumour patients,[5] although prior findings are somewhat inconclusive.[30] As in the survivor–control comparisons, the proportion of severely disabled survivors appeared to be a primary explanatory factor also for differences in health between men and women, e.g. 22% of males reported severe disability compared to 33% for females.

Our findings regarding overall health status in the general population sample suggest lower health/functional outcomes compared to what has been found in some other studies.[26,31] An explanation, in addition to differences because of cultural differences due the society/nation of study, could be that individuals with disability above the norm might be overrepresented in the partition that responded in our study. Such a response bias could be a result of that, among individuals of the general population, the willingness to respond to a health-related questionnaire might well be higher among those who suffer from some kind of extraordinary health conditions and/or disability. These individuals may find the questionnaire in a way more 'relevant', resulting in a higher motivation for responding, and subsequent overrepresentation compared to those for whom health is not an issue of particular significance. Such an explanation to our results is hardly complete, however, as inspection of sub-attributes indicates that the relatively low scores on emotion and pain are those that explain this difference while other single-attribute scores are similar, or only marginally low, compared to those found in other studies presenting general population outcomes.[26,31] Comparisons with other general population outcomes have to be done with caution, however, as studies are not consistent regarding key HUI assessment variables and groups' characteristics, mode of data collection, data analysis and presentation of findings.

We saw indications of that late effects of survivors increased with time. Furthermore, era of diagnosis was associated with reported late effects. Patients diagnosed later reported less disability than those diagnosed earlier, which is in line with prior studies of smaller samples indicating an increase with time persisting into adulthood.[9]

4.1. Late effect by kind of CNS tumour

The survivors in poorest health had suffered from intracranial germ cell tumours, followed by oligodendroglioma, mixed/unspecified glioma and medulloblastoma. Yet, the overall health measure only in part reflected the specific deficits survivors present with. Thus, survivors of, e.g. mixed/unspecified gliomas belonged to those with the poorest overall health, despite a good functional state in terms of many single attributes. This was due to their marked disabilities in motor functioning (dexterity and ambulation) and vision. Comparisons between diagnostic subgroups need also to consider that outcomes depend on diagnosis-specific differences in grade – or risk classification due to treatment consequences, but also that e.g. treatment may vary between patients within a specific diagnostic subgroup regardless of whether risk/grade classification is similar. However, factors related to tumour localisation and treatment may explain why survivors of oligodendroglioma (often temporally located), and germ cell tumours presented stronger indications of compromised health together with medulloblastoma survivors. On the other hand, the relatively favourable outcome for, e.g. the astrocytoma group reflects the fact that it comprised few high grade astrocytomas, where irradiation therapy is more likely to cause significant functional damage.

The finding that survivors of intracranial germ cell tumours were among those with relatively poorest outcomes

Table 8 – Functional disability in terms of attribute utility scores (mean, SD in brackets) by CNS tumour diagnosis, and matching outcomes for population controls.

Attribute	Astrocytoma ($N = 282$)	Oligodendroglioma ($N = 25$)	Mixed and unspecified glioma ($N = 14$)	Craniopharyngioma ($N = 49$)	Other specified and unspecified ($N = 80$)	Medulloblastoma/ PNET ($N = 74$)	Ependymoma ($N = 54$)	Germ cell – intracranial ($N = 25$)	Controls ($N = 996$)
Vision	.9456 (.15)***	.9004 (.23)*[b]	.8977 (.19)$^{\text{ns}}$[b]	.9251 (.16)**	.9600 (.11)$^{\text{ns}}$	.9350 (.13)$^{\text{ns}}$	.9568 (.12)$^{\text{ns}}$	.8996 (.20)**[b]	.9767 (.06)
Hearing[a]	.9832 (.12)$^{\text{ns}}$	.9725 (.11)$^{\text{ns}}$	1.0 (–)$^{\text{ns}}$	.9938 (0.4)$^{\text{ns}}$	.9774 (.07)$^{\text{ns}}$	.9294 (.21)**[b]	.9974 (.02)$^{\text{ns}}$	.9067 (.22)**[b]	.9963 (.05)
Speech	.9718 (.10)***	.9467 (.14)$^{\text{ns}}$	.9585 (.08)$^{\text{ns}}$	.9815 (.06)$^{\text{ns}}$	.9831 (.07)$^{\text{ns}}$	.9651 (.09)$^{\text{ns}}$	.9774 (.07)$^{\text{ns}}$	.9638 (.09)$^{\text{ns}}$	.9902 (.05)
Emotion	.9071 (.16)$^{\text{ns}}$	.8971 (.15)$^{\text{ns}}$	.9031 (.11)$^{\text{ns}}$	.8896 (.22)$^{\text{ns}}$	.9348 (.09)$^{\text{ns}}$	.9187 (.12)$^{\text{ns}}$	.9075 (.12)$^{\text{ns}}$	.9008 (.16)$^{\text{ns}}$	.9148 (.13)
Pain	.9092 (.16)$^{\text{ns}}$	.9521 (.11)$^{\text{ns}}$	.9577 (.07)$^{\text{ns}}$	.8966 (.18)$^{\text{ns}}$	.9371 (.11)$^{\text{ns}}$	.9710 (.06)$^{\text{ns}}$	.9345 (.16)$^{\text{ns}}$	.8933 (.10)$^{\text{ns}}$	.9240 (.13)
Ambulation[a]	.9417 (.16)***[b]	.9579 (.17)$^{\text{ns}}$	.8585 (.35)**[b]	.9828 (.10)$^{\text{ns}}$	.9646 (.16)$^{\text{ns}}$	.9516 (.17)**	.9526 (.19)$^{\text{ns}}$	.9579 (.17)$^{\text{ns}}$	.9963 (.04)
Dexterity[a]	.9703 (.12)***	.9408 (.13)$^{\text{ns}}$[b]	.8523 (.34)***[b]	.9974 (.02)$^{\text{ns}}$	.9731 (.13)$^{\text{ns}}$	.9678 (.12)$^{\text{ns}}$	.9604 (.14)$^{\text{ns}}$	.9721 (.11)$^{\text{ns}}$	.9961 (.04)
Cognition[a]	.9337 (.17)***	.8467 (.27)***[b]	.9831 (.04)$^{\text{ns}}$	.9506 (.12)$^{\text{ns}}$	.9535 (.11)$^{\text{ns}}$	.8747 (.21)***[b]	.9064 (.21)*[b]	.7908 (.32)***[b]	.9723 (.09)
Self-care[a]	.9756 (.15)*	.9521 (.21)$^{\text{ns}}$	.8462 (.38)***[b]	.9787 (.15)$^{\text{ns}}$	.9800 (.12)$^{\text{ns}}$	.9706 (.17)$^{\text{ns}}$	.9811 (.14)$^{\text{ns}}$	.9521 (.21)$^{\text{ns}}$	.9982 (.03)
Sensation	.8774 (.19)***[b]	.8329 (.23)*[b]	.8154 (.15)$^{\text{ns}}$ [b]	.8943 (.13)$^{\text{ns}}$	.9109 (.14)$^{\text{ns}}$	.8488 (.20)***[b]	.9047 (.12)$^{\text{ns}}$	.8600 (.15)$^{\text{ns}}$[b]	.9300 (.10)
Mobility[a]	.9733 (.12)***	.9692 (.14)$^{\text{ns}}$	.8723 (.32)***[b]	.9900 (.06)$^{\text{ns}}$	.9685 (.15)$^{\text{ns}}$	.9684 (.11)$^{\text{ns}}$	.9706 (.13)$^{\text{ns}}$	.9692 (.14)$^{\text{ns}}$	.9975 (.04)
Overall health status[a]	.7815 (.26)***[b]	.6927 (.31)**[b]	.6942 (.30)$^{\text{ns}}$[b]	.7762 (.25)$^{\text{ns}}$[b]	.8231 (.21)$^{\text{ns}}$[b]	.7386 (.27)***[b]	.7640 (.27)$^{\text{ns}}$[b]	.6407 (.38)***[b]	.8537 (.17)

$^{*-***}$p-Values in tests contrasting diagnostic subgroups to controls: $^{*}p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; ns, non-significant.

a Main effect of diagnosis found for the outcome variable.

b Indicative for clinically important difference in comparison to controls (see method section).

could not be foreseen. E.g. a prior study of childhood CNS germinoma survivors[32] using other outcome measures indicated good overall functional outcomes for this group. However, sample size was smaller, patients were considerably younger and had not reached adulthood, and outcomes were not systematically contrasted to other subgroups of CNS tumour survivors. Our study thus indicates a so far unknown fact – that adult survivors[32] of childhood intracranial germinoma are a risk group for relative functional disability in adulthood.

A possible limitation of this study concerns the self-report evaluation of disability, as subjective ratings may differ from other measures of morbidity. Response shift bias (RSB) may have influenced ratings, although reports about applicability, inter-rater agreement and principles for item construction indicate that the HUI is relatively robust against RSB.[11,16,19] According to the response shift theory, disabled populations may adopt a response pattern where difficulties are reported in a relativistic way, resulting in relatively favourable ratings of one's own health, and under-estimation of disability.[33,34] A potential bias relates to the lower proportion of survivors at the older end of the age range in this adult cohort, which might be explained by late deaths associated with the largest subgroup, astrocytomas.[1] Because of this potential bias, we reported outcomes based on analyses that were adjusted for age. Finally, outcomes are presented for diagnostic subgroups which are primarily established by use of histological verification only. This means a categorisation which does not optimally correspond with tumour – and treatment factors that are potentially important determinants of disability. Although such factors can seldom in full detail be established in large-scale studies from registers of adult survivors treated more than two decades ago, a next study will specifically address late effects related to tumour- and treatment factors in this adult survivor cohort.

In conclusion, adult survivors of childhood CNS tumours are at high risk for significant persistent functional, and health-related late effects, with female survivors being more vulnerable. An essential difference compared to general population controls is the large number of survivors presenting severe disability within multiple domains of functioning. Educational and social sequelae validate the significance of the established functional and health-related late effects. In view of the fact that survivors were compared with the general population with a customary incidence of morbidity, and because RSB may affect how survivors and parents evaluate health, the disability of survivors established in this study is more likely to be underestimated than overestimated. These findings highlight the importance of extended careful monitoring in adulthood of persistent late effects, as they may also aggravate over time.

Contributors

K.K.B. initiated the study, and with B.L. and G.G. elaborated conception and design. K.K.B. and G.G. provided study participants and patient data. K.K.B. and M.A. participated in developing assessment forms. K.K.B., M.A. and E.H. were responsible for collecting outcome data, and K.K.B. and E.H. conducted statistical analyses. All contributors were involved with the interpretation of the data, took part in writing the paper and read, revised and approved the final version.

Role of the funding source

The funding sources of this study had no role in study design; collection, analysis or interpretation of the data; or in the writing of the report. All authors had full access to the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Conflict of interest statement

None declared.

Acknowledgements

This study was granted by The Swedish Childhood Cancer Foundation and The Swedish Cancer and Traffic Injury Fund. Among the many people who made this study possible, our greatest appreciation goes to all participating survivors and parents.

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