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Neurological hospitalisations in childhood cancer survivors treated before 2001: findings from the French Childhood Cancer Survivor Study cohort

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Abstract

Purpose Childhood cancer survivors (CCS) have an increased risk of developing late chronic diseases, which can be influenced by the cancer type and its treatment. These chronic diseases can be severe and disabling, typically emerging years to decades after treatment. These deficits negatively impact quality of life, intelligence quotient, and memory. This study investigated how much the cancer type and treatment could affect the neurological hospitalisations in the French Childhood Cancer Survivors Study (FCCSS).

Methods We included 5579 childhood cancer survivors (CCS), diagnosed with solid tumours or lymphoma between 1945 and 2000, treated before 2001 and below the age of 21 years at initial treatment. The follow-up period was from 2006 to 2018. Hospitalisation data were obtained by linkage with the National Health Data System. We calculated the relative hospitalisation rate (RHRs) and absolute excess rate (AERs). Multivariable analyses were conducted using a Generalized Linear Model (GLM) with a Poisson distribution to estimate the association between neurological hospitalisation and patient characteristics. The expected number of hospitalisations served as an offset to compare the risk for FCCSS survivors with that of the reference population. Risk estimates were reported as relative risk (RR) with 95% confidence intervals.

Results The hospitalisation rate for CCS was 114.2 per 10,000 person-years (PY), compared to 48.4 in the reference population. The highest hospitalisation rates were observed for epilepsy (AER = 27.1 per 10000 PY, 95%CI: 23.5–31.2 and RHR = 5.1, 95%CI 4.4–5.7). In multivariable analyses, central nervous system (CNS) tumours survivors had the highest relative risk (RR) of hospitalisation (RR = 9.4, 95%CI: 6.7–13.1) followed by neuroblastoma survivors (RR = 2.5, 95%CI: 1.7–3.7). In the whole population, survivors who received radiation to the head and neck had a significantly higher risk of hospitalisation (RR = 3.9, 95%CI: 3.3–4.7) compared to those who did not receive radiotherapy.

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Conclusions Head and neck irradiation was identified as a strong risk factor for hospitalisation. This underlines the importance of implementing specific neurologic surveillance programs for at-risk individuals.

Keywords Childhood cancer survivor, Risk factor, Hospitalisations, Neurological diseases

Background

Over recent decades, major progress has been made in the diagnostics, treatment and supportive care of paediatric cancers which has led to increasing 5-year survival rates which are now exceeding 80–85% for most cancer types [1–3]. Despite these improvements, childhood cancer survivors (CCS) are still at high risk of developing various late effects, including severe chronic diseases [4–6]. Patients who have been treated for malignant central nervous system (CNS) tumours are particularly prone to experience health problems [7].

These chronic diseases can include cancer and/or treatment-induced neurological deficits which can be severe and disabling conditions, and typically occur years to decades after treatment. Such deficits are known to affect negatively quality of life, intelligence quotient, and memory. Recent studies have increasingly identified pulmonary, auditory, endocrine-reproductive, cardiac, neurocognitive and others deficits [4, 8], although it is unclear whether they are influenced by demographics (age at diagnosis or sex), medical history or mainly by specific treatments received [9–11]. Cranial irradiation and surgery have been shown to be a leading cause of long-term neurocognitive deficits. The primary neurological manifestations reported in the literature include fatigue, vitality, sleep disturbances, and attention deficits. [12–15]. However, other studies have demonstrated that the prevalence rate of neurocognitive impairment was even higher among patients who did not receive such treatment but did receive chemotherapy [7, 16].

While neurological deficits in the CNS survivors have been extensively documented, neurological late effect among non-CNS childhood cancers are not understood. Indeed, many CCS are hospitalised at least once in their lifetime for a neurological condition, but the risk factors of such hospitalisations have not been investigated [17–19].

Few studies focussed the risk factors for neurological diseases in childhood cancer survivors [18, 19]. Therefore, we aimed to investigate whether the type of childhood cancer and characteristics of cancer treatment could affect the frequency of hospitalisations for neurological diseases in the French Childhood Cancer Survivor Study (FCCSS). According to a recent finding of hospitalisations for all FCCSS, the overall hospitalisation rate was 4012.1 per 10,000 person-years (PY) [16].

Materials and methods

Study population

The FCCSS cohort includes 7670 5-year survivors [20] diagnosed with solid tumours or lymphoma before the age of 21 years between 1945 and 2000. The methods for data collection and validation have been previously described in detail [21, 22]. The present analysis involved 5583 individuals who were identified in the National Health Data System (French acronym: Système National des Données de Santé - SNDS). As recording in the SNDS has started in France since 2006, individuals who died or were lost of follow-up before that date were not included.

The methods for linking the FCCSS data with the SNDS have been described previously [23]. A total of 72.8% (5583) of the survivors still alive in 2006 were linked to SNDS among the 7670 CCS. By eliminating the survivors with missing data, 5579 survivors (72.7%) linked with SNDS were included. A flow chart illustrating the selection of patients is depicted in supplementary Figure S1.

Database sources

The SNDS is the national healthcare claims database, which covers more than 98% of the French population. This database is composed of health insurance data from various health insurance schemes (Système National d'Information Inter-Régimes de l'Assurance Maladie - SNIIRAM), hospital data from public and private health institutions (Programme de Médicalisation des Systèmes d'Information - PMSI), which is divided into four components: medicine, surgery and obstetrics hospitalisations (MCO), in-home care (HAD), after-care and rehabilitation (SSR), and psychiatry (PSY), as well as the causes of death (Causes Médicales de Décès - CMDC) [24, 25]. For this study, we obtained all the information related to hospitalisation in neurological departements. We used data from hospitalisations in MCO as data on neurological hospitalisation for the FCCSS are only available in this component. The main diagnoses of diseases are coded according to the 10th revision of the International Classification of Diseases (ICD-10) [25].

Reference sample

For this study, we obtained our reference population from the General Sample of Beneficiaries (EGB). The EGB is a permanent random anonymized sample, representing 1/97th of the entire population included in the SNDS ($n \approx 830000$ in 2021) and has been shown to be representative of the general French population [24]. A total of 385,780 reference individuals were included in

this study. The selection of the reference sample was done by matching with sex, year of birth, and region (French administrative area) of residence and randomly assigned to each FCCSS survivor with the same characteristics. All healthcare data, as well as PMSI hospitalisation data, are available in the EGB except for hospitalisations in rehabilitation and psychiatric facilities.

Hospitalisation measures

For both the FCCSS and the reference sample, we obtained numbers of inpatient admissions to conventional hospital units from January 2006 until December 2018 or death, whichever came first, for each individual. Our outcome of interest was the total number of hospitalisations, which corresponds to the number of stays spent in the hospital with at least one night of hospitalisation, we also considered day hospitalisation as a stay spent in the hospital. We were interested in the main diagnoses related to hospitalisation for neurological diseases. (Chapter VI of ICD-10, coded as G00-G99).

Statistical analysis

The characteristics of the patients and the details of hospitalisations (number of CCS hospitalised, number of hospitalisation, hospitalisation rate, relative hospitalisation rate, excess of hospitalisation) were described according to hospitalisation-related diagnoses (defined as ICD-10 categories), and patient's characteristics (sex, age at cancer diagnosis, calendar time at cancer diagnosis, cancer type according to the International Classification of Childhood Cancer, Third edition (ICCC-3), time of follow-up, type of treatment, radiation therapy field position).

By dividing the total number of hospitalisations by the total of person-years, we obtained the hospitalisation rate for the FCCSS and for the reference population, expressed as a rate per 10,000 person-years. Relative Hospitalisation Rate (RHR) was calculated as the observed number of hospitalisations for the FCCSS divided by the expected number of hospitalisations for the reference population. Absolute Excess Rate (AERs) per 10,000 person-years between hospitalisations of the FCCSS and reference population were calculated as the observed number of hospitalisations minus the expected number of hospitalisations, divided by person-years at risk and multiplied by 10,000. The AER can be interpreted as the number of excess hospitalisations observed beyond that expected from the reference population per 10,000 persons-year. The 95% confidence intervals (CIs) were calculated using Fieller's theorem and assuming that the observed number of hospitalisations followed a Poisson distribution [26].

Multivariable analyses were conducted to estimate the association between neurological hospitalisation and patient's characteristics, specific type of treatment, radiation field received by the patient, according to the number of hospitalisations. Generalized Linear Model (GLM) was used to model the number of hospitalisations experienced by each patient, which followed a Poisson distribution. We used the expected number of hospitalisations as an offset to study the risk for FCCSS survivors relative to that for the reference population. In each model, we included sex, age at diagnosis of primary cancer (categorical variable), and the year of diagnosis (categorical variable). We reported risk estimates as relative risk (RR) and its 95% confidence intervals. We executed separate models for each ICD main group of neurological diseases to evaluate risk factors in the different types of hospitalisations. Two-sided p-values were reported, and those with $p<.05$ were considered statistically significant. Analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

Total numbers of hospitalisations

Among the 5579 CCS included, 854 (15.3%) were diagnosed with renal tumors, 773 (13.9%) with neuroblastoma, 720 (12.9%) with CNS tumors, and 634 (11.4%) with soft tissue and other extraosseous sarcomas (Table 1). Of these patients, 2790 (50%) were diagnosed before the age of 4 years, 1198 (21.5%) between the ages of 5 and 9 years, 1133 (20.3%) between the ages of 10 and 14 years, and 458 (8.2%) were diagnosed at 15 years of age or older. (Table 1). The average time between childhood cancer treatment and 2006 was 19.8 years (median: 19.0, interquartile range 12–26).

We observed 806 hospitalisations for neurological diseases among the FCCSS and 23,407 hospitalisations in the matched reference population. The hospitalisation rate was 114.2 per 10,000 PY for the FCCSS, compared to 48.4 in the matched reference population (AER=65.7 per 10000 PY, 95%CI: 60.0-71.9). CCS were hospitalised twice as often as the matched reference population (RHR=2.4, 95%CI: 2.2–2.5) (Table 1). During the 13-year follow-up period, 418 (7.5%) of the CCS were hospitalised at least once for neurological diseases, while 15,317 (3.9%) of the reference population were hospitalised at least once for the same diseases (Table 1).

Hospitalisations by main diagnostic groups

Compared to the reference population, CCS were more frequently hospitalised, for all categories of neurological diagnoses considered, except for the "nerve, nerve root, and plexus disorders" one. The highest number of hospitalisations per individual and per diseases were for "episodic and paroxysmal disorders" (AER=35.8 per 10000 PY, 95%CI: 31.7–40.5] (Supplementary Figure S3); RHR=3.7, 95%CI: 3.3–4.1) (Supplementary Figure S2). In

Table 1 Relative hospitalisation ratios by patient's characteristics (univariable analysis)

Characteristics	*N.* CCS (%)	*N.* CCS hospitalized	Observed	Expected	Hospitalisation rate per 10,000 PY	Hospitalisation rate for reference population per 10,000 PY	RHR[b] [95% CI]	AER[c] [95% CI]
All	5579 (100)	418	806	342.0	114.2	48.4	2.4 [2.2–2.5]	65.7 [60.0-71.9]
Men	3048 (54.6)	216	367	159.1	95.3	41.3	2.3 [2.1–2.5]	53.9 [47.1–61.8]
Women	2531 (45.4)	202	439	178.6	136.8	55.7	2.5 [2.2–2.7]	81.2 [71.9–91.6]
Age at cancer diagnosis (years)								
≤ 4	2790 (50.0)	178	323	140.57	90.9	39.6	2.3 [2.0-2.5]	51.4 [44.4–59.4]
05–09	1198 (21.5)	122	261	74.6	173.9	49.7	3.5 [3.1–3.9]	124.3 [107.6-143.4]
10–14	1133 (20.3)	87	160	91.5	112.2	64.2	1.7 [1.5-2.0]	48.1 [37.9–60.9]
15–20	458 (8.2)	31	62	33.6	106.1	57.4	1.8 [1.4–2.3]	48.6 [33.7–70.3]
Calendar time at diagnosis								
1946–1960	72 (1.3)	7	11	8.1	125.0	91.6	1.4 [0.6–2.2]	33.3 [10.6-104.6]
1961–1970	340 (6.1)	41	75	34.8	183.3	84.9	2.2 [1.7–2.6]	98.4 [72.2-133.9]
1971–1980	1098 (19.7)	121	207	89.5	151.9	65.7	2.3 [2.0-2.6]	86.3 [72.0-103.4]
1981–1990	1882 (33.7)	156	319	97.2	133.8	40.8	3.3 [2.9–3.6]	93.1 [81.6-106.1]
1990–2000	2187 (39.2)	93	194	62.8	68.8	22.3	3.1 [2.6–3.5]	46.6 [39.2–55.3]
Age at start of follow-up								
< 20	1590 (28.5)	54	117	38.8	56.9	18.8	3.0 [2.5–3.6]	38.0 [30.4–47.4]
20–30	2115 (37.9)	161	301	89.2	112.1	33.2	3.4 [2.9–3.7]	78.9 [68.9–90.2]
31–40	1341 (24.0)	145	299	98.9	178.4	59.0	3.0 [2.7–3.4]	119.3 [103.9-137.1]
> 40	533 (9.5)	58	89	56.5	138.8	88.1	1.6 [1.2–1.9]	50.7 [35.9–71.5]
Time between diagnosis and start of follow-up (years)								
6–10	1168 (20.9)	39	71	31.3	47.1	20.7	2.3 [1.7–2.8]	26.3 [19.3–35.9]
11–20	1976 (35.4)	125	268	72.1	106.1	28.6	3.7 [3.3–4.4]	77.6 [67.4–89.2]
21–30	1632 (29.2)	170	331	114.6	161.6	55.9	2.9 [2.6–3.2]	105.6 [92.5-120.7]
> 30	803 (14.4)	84	136	79.1	139.0	80.8	1.7 [1.4-2.0]	58.2 [44.9–75.4]
Cancer type[a]								
Hodgkin lymphomas	322 (5.8)	19	31	24.7	76.6	61.1	1.2 [0.8–1.7]	15.5 [7.1–33.9]
Non-Hodgkin lymphomas	631 (11.3)	39	57	42.6	70.5	52.7	1.3 [0.9–1.7]	17.8 [10.6–29.9]
CNS and miscellaneous intracranial and intraspinal neoplasms	720 (12.9)	166	385	39.3	441.2	45.1	9.8 [8.8–10.8]	396.1 [356.5-440.2]
Ependymomas and choroid plexus tumor	111 (1.9)	21	41	4.9	297.7	35.7	8.3 [5.8–10.9]	262.0 [189.1-363.1]
Astrocytomas	239 (4.3)	65	178	15.2	612.9	52.3	11.7 [10.0-13.4]	560.7 [480.8-653.8]
Intracranial and intraspinal embryonal tumors	231 (4.1)	40	94	10.4	328.6	36.4	9.0 [7.2–10.9]	292.2 [235.8-362.1]
Other CNS tumors	139 (2.5)	40	72	8.6	454.5	54.2	8.4 [6.4–10.3]	400.4 [313.0-512.1]
Neuroblastoma and other peripheral nervous cell tumors	773 (13.9)	40	90	37.0	90.8	37.4	2.4 [1.9–2.9]	53.5 [40.9–70.0]
Retinoblastoma	477 (8.5)	16	26	15.6	42.4	25.5	1.7 [1.0-2.3]	16.9 [9.2–31.1]
Renal tumors	854 (15.3)	39	60	58.2	55.8	54.1	1.0 [0.8–1.3]	1.6 [0.4–7.2]
Hepatic tumors	58 (1.0)	3	3	2.8	40.9	38.3	1.1 [0-2.3]	2.6 [0.03–232.5]
Malignant bone tumors	481 (8.6)	21	32	36.2	52.2	59.0	0.9 [0.6–1.2]	-

Table 1 (continued)

Characteristics	*N.* CCS (%)	*N.* CCS hospitalized	Observed	Expected	Hospitalisation rate per 10,000 PY	Hospitalisation rate for reference population per 10,000 PY	RHR[b] [95% CI]	AER[c] [95% CI]
Soft tissue and other extraosseous sarcomas	634 (11.4)	33	46	42.6	56.8	52.5	1.1 [0.8–1.4]	4.2 [1.5–12.2]
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	363 (6.5)	18	37	23.6	79.4	50.7	1.6 [1.1–2.1]	28.7 [16.8–49.1]
Other malignant epithelial neoplasms and malignant melanomas	257 (4.6)	21	33	18.4	102.6	57.1	1.8 [1.2–2.4]	45.5 [27.2–75.9]
Other and unspecified malignant neoplasms	9 (0.2)	3	6	0.9	550.5	82.0	6.7 [1.3–12.1]	468.8 [196.9-1115.7]
Treatment								
Radiotherapy	2789 (49.9)	289	566	198.7	163.2	57.3	2.8 [2.6–3.1]	105.9 [95.6-117.3]
Chemotherapy	4141 (74.2)	251	466	235.5	88.7	44.8	1.9 [1.8–2.2]	43.9 [38.5–49.9]
Radiation therapy field position								
Head and Neck	1086 (19.5)	196	400	72.9	300.5	54.8	5.5 [4.9-6.0]	245.7 [220.5-273.8]
Thorax	915 (16.4)	95	177	68.8	156.5	60.8	2.6 [2.2–2.9]	95.7 [79.2-115.5]
Abdomen	853 (15.3)	72	124	66.9	117.8	63.6	1.8 [1.5–2.2]	54.2 [41.8–70.3]
Pelvis	187 (3.3)	11	18	14.8	77.2	63.3	1.2 [0.7–1.8]	13.9 [4.7–41.3]
Arm and hand	14 (0.2)	1	1	0.9	54.9	53.7	1.0 [0-3.3]	1.1 [0 - >999.9]
Leg and foot	111 (1.9)	9	14	10.4	99.7	74.1	1.3 [0.6-2.0]	25.6 [9.1–71.9]
Cancer predisposition syndrome								
Unidentified syndrome	5432 (97.4)	391	762	334.5	110.7	48.5	2.3 [2.1–2.4]	62.1 [56.5–68.3]
Neurofibromatosis type 1	67 (1.2)	17	29	4.1	373.7	52.8	7.1 [4.5–9.6]	320.9 [216.6-475.2]
Li-Fraumeni syndrome	33 (0.6)	5	7	1.2	172.8	30.7	5.6 [1.5–9.8]	142.2 [62.8-321.8]
Other syndrome	47 (0.8)	5	8	1.9	142.6	35.1	4.1 [1.2–6.9]	107.5 [48.4-238.8]

[a]According to the International Classification of Childhood Cancer, Third Edition based on ICD-O-3

For CNS tumour, only malignant tumours and tumours of unknown behaviour were included

[b]RHR = Relative Hospitalisation Ratio, 95% CI = 95% confidence interval

[c]AER = Absolute Excess Risks per 10,000 person-years, 95% CI = 95% confidence interval

this main diagnosis group, hospitalisation rates were significantly higher for epilepsy (RHR = 5.1, 95%CI, 4.4–5.7) (Table 2). Hospitalisations for "transient cerebral ischaemic attacks and vascular syndrome" showed a high relative rate (RHR = 3.3, 95%CI: 2.3–4.3). Furthermore, RHR for "headache" were also increased in CCS (RHR = 6.9, 95%CI: 4.3–9.5) (Table 2).

The hospitalisation rates for "paralytic syndromes" were found to be significantly higher (RHR = 7.6, 95%CI, 6.1–9.2) (Supplementary Figure S2) compared to the refererence population. Detailed analysis revealed that "hemiplegia" had a particularly high relative rate (RHR = 12.8, 95%CI: 9.4–16.2), as well as "paraplegia and tetraplegia" (RHR = 6.4, 95%CI, 4.1–8.7) (Table 2).

Regarding "hydrocephalus and other disorders of the nervous system", the RHR was high (RHR = 7.1, 95%CI: 5.6–8.5) (Table 2, Supplementary Figure S2). Of note, "hydrocephalus" had the highest relative rate in this group (RHR = 17.6, 95%CI: 12.0-23.1) (Table 2), then "other disorders of brain" (*including anoxic brain damage not elsewhere classified*, *benign intracranial hypertension*, *encephalopathy unspecified*, *compression of brain*, *cerebral oedema*, *other specified disorders of brain*) (RHR = 5.5, 95%CI: 3.2–7.7) (Table 2) compared to the reference population,

Furthermore, the analysis revealed significant results for "inflammatory diseases of CNS" (RHR = 3.6, 95%CI: 2.3–4.9) (Supplementary Figure S2) compared to the reference population. Notably, the highest relative rate

Table 2 Relative hospitalisation ratio by main diagnosis groups of neurologic pathologies according to the 10th revision of the International classification of diseases. (univariable analyses)

Diagnostic	ICD-10	*N.* CCS	Observed	Expected	RHR[a] [95% CI]	AER[b] [95% CI]
Inflammatory diseases of CNS	G00-G09	23	29	8.0	3.6 [2.3–4.9]	2.9 [1.9–4.5]
Meningitis	G00-G03	7	8	2.3	3.5 [1.1–5.9]	0.8 [0.4–1.8]
Encephalitis, myelitis and encephalomyelitis	G04-G05	6	6	2.9	2.0 [0.4–3.6]	0.4 [0.1–1.3]
Intracranial and intraspinal abscess and granuloma	G06	10	15	0.9	15.3 [7.6–23.1]	1.9 [1.2–3.3]
Systemic atrophies affecting CNS	G10-G13	5	5	1.9	2.5 [0.3–4.8]	0.4 [0.1–1.3]
Huntington disease	G10	1	1	0.3	3.4 [0-10.1]	0.1 [0.01-1.0]
Hereditary ataxia	G11	3	3	0.7	4.6 [0-9.7]	0.3 [0.1–1.2]
Spinal muscular atrophy and related syndromes	G12	1	1	0.8	1.2 [0-3.5]	0.02 [0-2.8]
Extrapyramidal and movement disorders	G20-G26	12	34	17.9	1.9 [1.3–2.5]	2.3 [1.4–3.7]
Secondary parkinsonism	G21	1	3	0.3	8.5 [0-18.2]	0.4 [0.1–1.2]
Dystonia	G24	8	28	13.8	2.0 [1.3–2.8]	2.0 [1.2–3.4]
Other extrapyramidal and movement disorders	G25	3	3	1.9	1.5 [0-3.3]	0.1 [0.02-1.0]
Degenerative diseases of the nervous system	G30-G32	4	5	1.9	2.6 [0.3–4.9]	0.4 [0.1–1.3]
Alzheimer disease	G30	1	1	0.4	2.4 [0-7.2]	0.1 [0.01–1.1]
Other degenerative diseases of nervous system	G31-G32	3	4	1.5	2.6 [0.05–5.2]	0.3 [0.1–1.2]
Demyelinating diseases of CNS	G35-G37	6	22	20.5	1.1 [0.6–1.5]	0.2 [0.04–1.1]
Multiple sclerosis and other acute dissemination demyelination	G35-G36	5	21	19.0	1.1 [0.6–1.6]	0.3 [0.1–1.1]
Other demyelinating diseases of CNS	G37	1	1	1.5	0.7 [0–2.0]	-
Episodic and paroxysmal disorders	G40-G47	197	345	92.0	3.7 [3.3–4.1]	35.8 [31.7–40.5]
Epilepsy	G40-G41	127	238	46.8	5.1 [4.4–5.7]	27.1 [23.5–31.2]
Migraine	G43	16	17	14.1	1.2 [0.6–1.8]	0.4 [0.1–1.3]
Headache	G44	8	27	3.9	6.9 [4.3–9.5]	3.3 [2.2–4.9]
Transient cerebral ischaemic attacks and vascular syndrome	G45-G46	34	41	12.3	3.3 [2.3–4.3]	4.1 [2.8–5.9]
Sleep disorders	G47	20	22	14.9	1.5 [0.9–2.1]	1.0 [0.5–2.1]
Nerve, nerve root and plexus disorders	G50-G59	104	151	163.3	0.9 [0.8–1.1]	-
Disorders of cranial nerves	G51-G52	12	29	7.2	4.0 [2.6–5.5]	3.1 [2.0-4.7]
Nerve root and plexus disorders	G54-G55	25	30	34.8	0.9 [0.5–1.2]	-
Mononeuropathies	G56-G58	71	92	119.5	0.8 [0.6–0.9]	-
Neuropathy, polyneuropathy and other disorders of peripheral nervous system	G60-G64	13	20	7.2	2.8 [1.6–3.9]	1.8 [1.0-3.1]
Neuropathy and polyneuropathy	G60-G63	12	19	7.1	2.7 [1.5–3.9]	1.7 [0.9–2.9]
Other disorders of peripheral nervous system	G64	1	1	0.1	9.8 [0-28.9]	0.1 [0.02-1.0]
Diseases of myoneural junction and muscle	G70-G73	6	9	3.8	2.3 [0.8–3.9]	0.7 [0.3–1.7]
Myasthenia gravis and myoneural disorders	G70	1	2	1.4	1.4 [0-3.3]	0.1 [0.01–1.1]
Primary disorders of muscles	G71	3	4	1.9	2.1 [0.04–4.2]	0.3 [0.1–1.1]
Other myopathies	G72	2	3	0.4	7.1 [0-15.1]	0.4 [0.1–1.2]
Paralytic syndromes	G80-G83	41	93	12.2	7.6 [6.1–9.2]	11.4 [9.2–14.2]
Cerebral palsy	G80	1	1	1.6	0.6 [0-1.9]	-
Hemiplegia	G81	23	54	4.2	12.8 [9.4–16.2]	7.0 [5.3–9.3]
Paraplegia and tetraplegia	G82	13	29	4.5	6.4 [4.1–8.7]	3.5 [2.3–5.1]
Other paralytic syndromes	G83	9	9	1.9	4.8 [1.7–7.9]	1.0 [0.5–2.1]
Hydrocephalus and other disorders of the nervous system	G90-G99	65	93	13.2	7.1 [5.6–8.5]	11.3 [9.1–14.1]
Disorders of autonomic nervous system	G90	1	1	0.4	2.3 [0-6.7]	0.1 [0.01–1.1]
Hydrocephalus	G91,G94	25	39	2.2	17.6 [12.0-23.1]	5.2 [3.8–7.2]
Toxic encephalopathy	G92	1	1	0.2	4.9 [0-14.5]	0.1 [0.01-1.0]
Other disorders of brain	G93	21	23	4.2	5.5 [3.2–7.7]	2.7 [1.7–4.2]
Cord compression and other specified diseases of spinal cord	G95	6	7	1.4	4.9 [1.3–8.7]	0.8 [0.3–1.8]
Cerebrospinal fluid leak and other specified disorders	G96	5	6	1.0	5.7 [1.1–10.3]	0.7 [0.3–1.7]
Postprocedural disorders of nervous system	G97	8	12	2.3	5.1 [2.2–7.9]	1.4 [0.7–2.6]
Autonomic neuropathy and myelopathy	G99	3	4	1.0	3.9 [0.1–7.6]	0.4 [0.1–1.3]

[a]RHR = Relative Hospitalisation Ratio, 95% CI = 95% confidence interval

[b]AER = Absolute Excess Risks per 10,000 person-years, 95% CI = 95% confidence interval

in this main diagnosis group was observed for "intracranial and intraspinal abscess and granuloma" (RHR=15.3, 95%CI: 7.6–23.1) compared to the reference population (Table 2).

An excess of hospitalisation for "neuropathy, polyneuropathy and other disorders of peripheral nervous system" (RHR=2.8, 95% CI: 1.6–3.9) (Supplementary Figure S2), as well as of hospitalisations for "extrapyramidal and movement disorders" was observed (RHR=1.9, 95%: CI 1.3–2.5) (Table 2, Supplementary Figure S2) compared to the reference population.

Hospitalisations and survivors' initial characteristics

Table 1 shown the results on hospitalisation rates for survivors of various types of malignant tumours. CNS tumour survivors had the highest relative rate (RHR=9.8, 95%CI: 8.8–10.8) (Supplementary Figure S4), and were the most frequently hospitalised group with 166 patients as compared to the others CCS survivors. Neuroblastoma survivors had an RHR of 2.4, 95%CI: 1.9–2.9 (Supplementary Figure S4). Renal and malignant bone tumour survivors were the least frequently hospitalised, (RHR=1.0, 95%CI: 0.8–1.3 and RHR=0.9, 95%CI: 0.6–1.2). For CNS tumour, astrocytomas survivors had the highest relative rate (RHR=11.7, 95%CI: 10.0-13.4, AER=560.7 per 10000 PY 95%CI: 480.8-653.8) (Table 1). For the whole cohort, 197 patients were hospitalised for "episodic and paroxysmal disorders" and 104 "patients for "nerve, nerve root, and plexus disorders" (Table 2).

97 CNS tumour survivors were hospitalised for "episodic and paroxysmal disorders" and had the highest relative rate (RHR=16.9, 95%CI: 14.5–19.4) (Supplementary Table S3), compared to survivors of other types of malignant tumours (RHR=1.6, 95%CI: 1.2–1.9) (Supplementary Table S6). CNS tumour survivors were also more likely to be hospitalised for "paralytic syndromes" (RHR=53.3, 95%CI: 40.6–66.1) and "hydrocephalus and other disorders of the nervous system" (RHR=43.1, 95%CI: 32.3–53.8) (Supplementary Table S5). Compared to survivors of other types of malignant tumours, patients with neuroblastoma have a high relative rate for "episodic and paroxysmal disorders" (RHR=3.8, 95%CI: 2.6–4.9) (Supplementary Table S4).

In multivariable analysis, the risk of hospitalisation for CNS tumour survivors, was significantly higher (RR=9.4, 95%CI: 6.7–13.1, $p \leq .001$) compared to the reference population. The same result was observed for "episodic and paroxysmal disorders" (RR=12.9, 95%CI: 7.0–24.0, $p \leq .001$), and for "nerve, nerve root, and plexus disorders" (RR=2.8, 95%CI: 1.1–6.9, $p \leq .05$) (Table 3).

RHR for male survivors of childhood cancer were 2.3, 95%CI: 2.1–2.5 and 2.5, 95%CI: 2.2–2.7 for female survivors (Table 1). In a univariable analysis, the RHR was higher for survivors diagnosed with childhood cancer before the age of 9 and decreased for those diagnosed after the age of 9. In contrast, the RHR increased over time for survivors diagnosed with childhood cancer (Tabel 1). But in a multivariable analysis, the risk of hospitalisation has decreased over time (Table 3).

Role of treatments

Overall, survivors who treated with radiotherapy had a higher rate of hospitalisation (RHR=2.8, 95%CI: 2.6–3.1) compared to the reference population, while survivors treated with chemotherapy had a lower rate (RHR=1.9, 95%CI: 1.8–2.2) (Table 1). In multivariable analysis, the hospitalisation risk was associated to radiation therapy in survivors with other types of cancer (excluding CNS tumours, neuroblastoma, sarcoma) (RR=1.7, 95%CI: 1.2–2.3, $p \leq .01$) (Supplementary Table S11).

When considering all diagnostics of neurological diseases together, survivors who received radiation to the head and neck had the highest rate of hospitalisation (RHR=5.5, 95%CI: 4.9-6.0 and AER=245.7 per 10000 PY, 95%CI: 220.5-273.8) (Table 1), this finding being confirmed in a multivariable analysis, (RR=3.9; 95%CI: 3.3–4.7, $p \leq .001$) (Supplementary Figure S5), as compared to those who did not receive radiation therapy (Table 4). The result was significant for CNS tumour survivors (Supplementary Table S12), neuroblastoma survivors (Supplementary Table S13), and other type of cancer (Supplementary Table S15), excluding sarcoma (RR 1.8, 95%CI 1.1–2.9, $p \leq .05$, RR=2.4, 95%CI: 1.1–5.2, $p \leq .05$, RR=2.8, 95%CI: 1.9–3.9, $p \leq .001$) but not significant for sarcoma survivors (Supplementary Table S14).

In a more detailed multivariable analyses of neurological diseases for the whole cohort, this increase in risk was higher when considering only hospitalisations for "episodic and paroxysmal disorders" (RR=8.9, 95% CI: 6.1–13.0, $p \leq .001$), compared with patients hospitalised for the same condition but who did not receive head and neck radiation therapy (Table 4).

In a multivariable analysis, chemotherapy was not associated with an increase in relative risk (RR=0.5, 95%CI: 0.4–0.6) (Table 4). We consistently observed this trend in all of the other multivariable analyses performed. For survivors of neuroblastoma as shown in Supplementary Table S13, thoracic irradiation was associated with a significantly increased risk of hospitalisation (RR=2.8, 95%CI: 1.5-5.0, $p \leq .001$), whereas chemotherapy was associated with relative risk of 2.3, 95%CI: 1.3–4.3, $p \leq .01$. However, when we examined the effect of each type of therapeutic agent and each category of chemotherapy, including high-dose chemotherapy, we did not find any statistically significant association.

Additional analyses were conducted for the entire cohort, with results presented in Supplementary Table S1, S2, and S7. Separate multivariate analyses for

Table 3 Relative risk of hospitalisation by demographic and cancer type – age at start of follow up as continuous variable (multivariable analyses)

Characteristics	*N.* CSS	All hospitalisation (*N* = 418) *N.* CCS hospitalised, RR [95 CI]		Episodic and paroxysmal disorders (*N* = 197) *N.* CCS hospitalised, RR [95 CI]		Nerve, nerve root and plexus disorders (*N* = 104) *N.* CCS hospitalised, RR [95 CI]	
Sex							
Men	3048	216	0.9 [0.7-1.0]	103	0.8 [0.6-1.0]	49	1.1 [0.7–1.7]
Women	2531	202	1 [ref]	94	1 [ref]	55	1 [ref]
Age as at 2006 (mean)	26.2	30.1	0.9 [0.9-1.0] *	29.9	0.9 [0.9-1.0]	33.1	0.9 [0.9–1.1]
Age at cancer diagnosis (years)							
≤ 4	2790	178	1 [ref]	84	1 [ref]	44	1 [ref]
5–9	1198	122	1.3 [1.0-1.7] *	65	1.3 [0.8–2.2]	20	0.7 [0.3–1.4]
10–14	1133	87	1.0 [0.7–1.5]	40	0.8 [0.4–1.6]	24	0.6 [0.2–1.5]
15–20	458	31	1.6 [0.9–2.6]	8	1.2 [0.4–3.4]	16	1.3 [0.4–3.8]
p-trend			*0.8*		*0.9*		*0.7*
Calendar time at diagnosis							
1946–*1960*	72	7	2.4 [0.7–8.3]	4	2.8 [0.3–29.4]	2	1.8 [0.1–33.6]
1961–1970	340	41	2.5 [1.1–5.8] *	21	4.6 [0.9–23.6]	16	2.3 [0.3-18.15]
1971–1980	1098	121	2.2 [1.3–3.8] **	57	1.9 [0.6–5.6]	33	1.6 [0.4–6.6]
1981–1990	1882	156	1.6 [1.1–2.3] **	71	0.8 [0.4–1.7]	38	1.3 [0.5–3.5]
1990–2000	2187	93	1 [ref]	44	1 [ref]	15	1 [ref]
p-trend			*0.5*		*0.7*		*0.6*
Cancer type[a]							
Renal tumors	854	39	1 [ref]	21	1 [ref]	11	1 [ref]
Hodgkin lymphomas	322	19	1.6 [0.9–2.7]	4	0.8 [0.2–2.8]	8	3.6 [1.3–9.7] *
Non-Hodgkin lymphomas	631	39	1.3 [0.8–2.1]	15	1.1 [0.4–2.9]	13	2.2 [0.9–5.7]
CNS and miscellaneous intracranial and intraspinal neoplasms	720	166	9.4 [6.7–13.1] ***	97	12.9 [7.0–24.0] ***	12	2.8 [1.1–6.9] *
Neuroblastoma and other peripheral nervous cell tumors	773	40	2.5 [1.7–3.7] ***	16	3.3 [1.7–6.4] ***	14	1.9 [0.8–4.5]
Retinoblastoma	477	16	1.5 [0.9–2.5]	6	0.9 [0.3–2.7]	2	0.6 [0.1–4.7]
Hepatic tumors	58	3	1.3 [0.4–4.1]	1	-	1	2.9 [0.4–23.0]
Malignant bone tumors	481	21	0.9 [0.6–1.6]	7	0.6 [0.2–2.2]	11	1.5 [0.5–4.5]
Soft tissue and other extraosseous sarcomas	634	33	1.0 [0.6–1.6]	15	1.0 [0.4–2.6]	14	2.4 [0.9–5.8]
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	363	18	1.4 [0.9–2.4]	9	1.2 [0.4–3.9]	6	2.0 [0.7–5.8]
Other malignant epithelial neoplasms and malignant melanomas	257	21	1.8 [1.0–3.0] *	5	0.3 [0.04–2.7]	11	7.4 [3-18.4] ***
Other and unspecified malignant neoplasms	9	3	9.2 [2.7–30.9] ***	1	-	1	-

[a]According to the International Classification of Childhood Cancer, Third Edition based on ICD-O-3

*** $p \leq .001$, ** $p \leq .01$,* $p \leq .05$

radiotherapy and chemotherapy did not yield significant results for central nervous system tumors (Supplementary Table S8), neuroblastomas (Supplementary Table S9), and sarcomas (Supplementary Table S10)."

Childhood cancer predisposition syndrome

A total of 151 patients had a childhood cancer predisposition syndrome recorded in their medical records (67 neurofibromatosis, 33 Li-Fraumeni syndrome and 47 others syndromes). Excluding these patients, the results remained similar: no RHR or AER, either for all cancers or by type of cancer, varied by more than 5% (Supplementary Table S16 to Supplementary Table S30). Some of these predispositions have been associated with a number of neurological conditions, including epilepsy, Parkinson's disease, headaches, multiple sclerosis and sleep disorders.

Discussion

We evaluated 5579 patients who were 5-year survivors of childhood cancer and were followed during a period of 13 years. CCS treated between 1945 and 2000 in France

Table 4 Relative risk of hospitalisation by radiation field for the whole cohort (multivariable analyses)

Characteristics	*N.* CCS	All hospitalisation (*N* = 418) *N.* CCS hospitalised, RR [95 CI]		Episodic and paroxysmal disorders (*N* = 197) *N.* CCS hospitalised, RR [95 CI]		Nerve, nerve root and plexus disorders (*N* = 104) *N.* CCS hospitalised, RR [95 CI]	
Chemotherapy (ref no chemo)	4141	251	0.5 [0.4–0.6] ***	112	0.7 [0.5–0.9] *	66	0.7 [0.4–1.1]
Radiation field position							
Head and Neck	1086	196	3.9 [3.3–4.7] ***	113	8.9 [6.1–13.0] ***	23	0.9 [0.6–1.6]
Thorax	915	95	1.3 [1.0-1.6] *	41	0.7 [0.4–1.1]	15	0.9 [0.5–1.6]
Abdomen	853	72	0.9 [0.7–1.2]	29	1.4 [0.8–2.3]	15	0.8 [0.4–1.4]
Pelvis	187	11	0.8 [0.5–1.4]	6	0.3 [0.04–1.9]	1	0.2 [0.03–1.7]
Leg and foot	111	9	0.9 [0.5–1.8]	3	0.5 [0.1–1.9]	3	0.8 [0.2–2.5]
Arm and hand	14	1	-	1	-	-	-

Adjusted by sex, age as at 2006, age at diagnosis, calendar time at diagnosis

*** $p \leq .001$, ** $p \leq .01$,* $p \leq .05$

were hospitalised for neurological diseases more than twice as often as the general population during a follow-up period from 2006 to 2018. This higher rate of hospitalisation for neurological diseases was limited to survivors of CNS tumours and, to a lesser extent, to those of neuroblastoma. Among CNS tumour survivors, the hospitalisation rates were elevated for all ICD-10 groups of neurological diseases related to hospitalisations, though the RHR were the highest for hospitalisations related to "episodic and paroxysmal disorders", "paralytic syndromes, "hydrocephalus and other disorders of the nervous system", and "inflammatory diseases of CNS. Most of the excess hospitalisations were associated to radiation to the head and neck for childhood cancer expects for sarcoma survivors.

Our results are consistent with those observed in other studies performed in the US, Nordic countries, and the Netherlands in which childhood cancer survivor's experienced higher rates of neurological hospitalisations compared to the general population. Generally, hospitalisation rates were higher in Europe, including the Netherlands [27] and Nordic countries (The ALiCSS is a population-based cohort of children and adolescents from the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) diagnosed with cancer during the period 1943 to 2008) [18, 28]. In US studies, hospitalisation rates were lower in both a small Utah cohort and the large US CCSS [29, 30]. Our findings demonstrated a comparable rate of hospitalisation for neurological diseases across all cancer types, expected a higher hospitalisation rate in CNS and neuroblastoma, as compared to other primary cancer types. Renal and malignant bone tumours hospitalisation rate was lower, consistent with research from Nordic countries [18, 19]. Almost half of the hospitalised patients were admitted due to episodic and paroxysmal disorders, and the hospitalisation rate was significantly elevated. Epilepsy was frequently experienced by survivors [31] and was the primary reason for hospitalisation, this finding has also been reported in prior studies conducted on the ALiCCS cohort [18, 19, 32, 33].

Among CCS, there exists a notable association between exposure to radiation therapy to the head and neck and an increased risk of hospitalisation for neurological diseases. This type of treatment is considered the primary contributor for neurological impairment due to its impact on a sensitive portion of the nervous system during radiation therapy [34]. In addition, an association was observed between thoracic irradiation administered to neuroblastoma survivors and increased hospitalisations for neurological disorders.

Contrary to earlier research [35, 36], our analyses did not reveal any significant associations between chemotherapy and neurological hospitalisations. Our analyses of each type of therapeutic agent, each category of chemotherapy, and high-dose chemotherapy did not yield any significant findings. Additional research is required to determine the underlying cause of this observation. In our study, we included patients who had been diagnosed over a period of more than three decades. Consequently, the therapeutic interventions implemented varied according to the temporal context of diagnostics. The advancement of radiation therapy and chemotherapy has substantially contributed to the mitigation of treatment-related late effects, leading to improved clinical outcomes for the survivors [37].

To the best of our knowledge, this is the first comprehensive and detail study of neurological diseases in long-term CCS compared to the general population in France and one of the first to describe the clinical diagnoses main with neurological hospitalisations and to study the risk factors linked to these events. We worked with a national administrative database, which provided comprehensive information on hospitalisations over a thirteen-year period for both CCS and their reference population. An advantage is that we included hospitalisations that occurred in day-hospital units. Among the cohorts of childhood cancer survivors in Europe, FCCSS contains very precise information about the treatments

administered, including radiation fields and dosimetry for radiotherapy and chemotherapy.

There are some limitations in our study that we need to acknowledge. We only analysed hospitalisations in conventional hospital units as information on rehabilitation and psychiatry institutions was not available in the EGB sample that we used as our reference. However, it is worth noting that conventional hospital units treat more than 90% of all hospitalised patients in France [38]. Furthermore, the EGB includes a population that does not consume any health care, and the data are stored for 20 years [25], which enables longitudinal studies of hospitalisations [39]. Significant gaps in hospital data exist for individuals who were diagnosed with cancer prior to 2001 and became five-year survivors by 2006, a time when hospital information became accessible. This likely explains the lower estimates compared to findings in other studies. It is very important to emphasize on the age at diagnostics in our study. Patients diagnosed before 1970 are older at the beginning of their follow-up, which may elevate the risk of neurological hospitalisations compared to patients diagnosed from 1990 onwards who are younger at the start of their follow-up period. Survivors from 2006, previously diagnosed with childhood cancer several decades ago, differ from those who were diagnosed at the same time but unfortunately did not survive until 2006 when hospital information was available. Our study underscores these distinctions, demonstrating that the decrease in RHR is influenced by the age at which follow-up was initiated and the duration between the initial diagnostics and the start of the follow-up period. Our analyses focused primarily on neurological hospitalisation data, collected several years after initial childhood cancer treatment. Therefore, pre-existing and pre-treatment neurological conditions in neuroblastoma survivors were not identified and not considered. Studies have shown that neuroblastoma can manifest itself through the development of neurological syndromes, such as paresis [40, 41], and opsoclonus-myoclonus syndromes [42, 43]. We were unable to explore the association between particular types of hospitalisations and surgery, and this will be the subject of a separate study.

In conclusion, our study has demonstrated that childhood cancer survivors in France experience hospitalisations for neurological disorders at a rate more than twice that of the general population. The data also indicates that there is an association between cancer treatment and various types of neurological hospitalisations. This suggests that it is important to focus on preventing long-term neurological complication, as CCS have a higher risk of developing such complications when compared to the general population [31], particularly in survivors of central nervous system tumours and neuroblastomas who have received head and neck irradiation.

Supplementary Information

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Supplementary Material 1

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

In accordance with French regulations, the study protocol was approved by a regional ethics committee of the INSERM and by the French Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés – CNIL* Authorization n°902287). Individual patient informed consent was not required for this study because we obtained a specific act in law from the French "Conseil d'Etat", the highest court in France (Order 2014-96 of 2014 February 3), that approved access to the SNDS for all survivors included in the FCCSS.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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