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CLINICAL STUDY - PATIENT STUDY

Clinical epidemiology for childhood primary central nervous system tumors

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Abstract This work was conducted by the French Brain Tumor Data Bank (FBTDB) and aims to prospectively record all primary central nervous system tumors (PCNST), in France, for which histological diagnosis is available. Results concerning children are presented. This study analyzes the childhood cases (0–19 years) of newly diagnosed and histologically confirmed PCNST (during the years 2004–2006) which have been recorded by the FBTDB. All French neuropathology and neurosurgery departments participated in this program. Neurosurgeons and neuropathologists completed a data file containing socio-demographic, clinical, radiologic and anatomopathologic information. The Tumor Registry from Herault was authorized to compile the data files with personal identifiers. About 1,017 cases (533 boys and 484 girls) of newly diagnosed childhood PCNST have been recorded (gliomas: 52%, all other neuroepithelial tumors: 31%, craniopharyngioma: 5%, germ cell tumors, meningioma and neurinoma: approximately 3% each, all histological subtypes have been detailed). Tumor resections were performed in 83.3%, and biopsies in 16.7%. The distributions by histology, cryopreservation of the samples, age, sex, tumor site and surgery have been detailed. To our knowledge, this work is the first databank in Europe dedicated to PCNST that includes the collection of clinical, radiological and histological data (including cryopreservation of the specimen). The long term goals of the FBTDB are to create

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a national registry and a network to perform epidemiological studies, to implement clinical and basic research protocols, and to evaluate and harmonize the healthcare of children and adult patients affected by PCNST.

Keywords Brain tumor · Database · Epidemiology · Neuropathology · Neurosurgery · Pediatric oncology

Introduction

Primary central nervous system tumors (PCNST) represent a complex heterogeneous group of pathologic entities which may be benign, malignant or of unpredictable evolution [1–6]. PCNST are the second most common childhood neoplasia after leukemia, and the most common form of solid tumor in children. PCNST are the leading cause of death from solid tumors in children [7–9]. The incidence of the PCNST in childhood varies between countries, age of inclusion, type and location of tumors recorded [10–18]. In the USA, it is estimated that about 8% of the tumors reported to the Central Brain Tumor Registry of United States (CBTRUS) occurred in persons under the age of 20 years; the incidence is 4.53/100,000 children-years for the children under 20 years old, and 4.61 for children under 15 years old [10]. In Europe, the incidence of childhood PCNST is 2.99/100,000 children-years (for children under 15 years old) [19]. Some data are available in France [19–23], but do not detail the histological subtypes as it is done in the CBTRUS [10] or in the German registry [13]. Furthermore, in order to develop research protocols and to evaluate therapeutic management it is important to detail and record clinical, radiological, histological data and follow-up.

The French neurosurgeons, neuropathologists and neurooncologists, in collaboration with epidemiologists and biostatisticians, have recently established the French Brain Tumor Data Bank (FBTDB) [24]. The main objective of this project is to prospectively record all PCNST in France for which histological diagnosis is available. The long term goals of the FBTDB are to create a national registry and a network to (1) perform epidemiological studies, (2) implement a new database and use it for setting up both clinical and basic research protocols, and (3) allow the evaluation of the medical practices of an area or of the entire country to harmonize the healthcare of patients affected by PCNST.

In collaboration with the French Society for Pediatric Neurosurgery (Société Française de Neurochirurgie Pédiatrique), the first results of our investigation of the childhood population (0–19 years old), during the years 2004–2006, are presented.

Material and methods

Childhood cases (0–19 years) of newly diagnosed and histologically confirmed PCNST, 2004–2006 recorded by the FBTDB were analyzed. Children under 15 years old and teenagers (15–19 years) have been studied separately to enable the comparison between these subgroups, as is recorded in the CBTRUS Statistical Report [10]. The data presented include age, sex, histological diagnosis according to the ICD-0-3 (WHO 2000) classification and SNOMED codes from Kleihues and Cavenee [2] and French nomenclature ADICAP [25] (a list of includes codes is presented in Table 1), clinical signs and symptoms, site of the tumor (supratentorial, infratentorial and spinal cord or cauda equina), radiology (contrast enhancement) and surgery (biopsy/resection). The 2007 WHO classification of tumors of the central nervous system [3] was not used because the histological diagnosis was made from 2004 to 2006.

All neurosurgeons and neuropathologists in France participating in the French Brain Tumor Data Bank (FBTDB) were instructed to complete a data file card for each patient who had neurosurgery from 2004 to 2006. Histological diagnosis was always made by confirmed neuropathologists and more than 90% of them worked in public academic centers. The methodology for the FBTDB accrual has been described in detail previously [24]. In summary, the data file card is placed in all French operating rooms where surgery for PNCST is practiced and systematically is sent along with the sample to the pathology lab. The card contains socio-demographic, clinical, radiological, surgical and pathological data (including an optional question about cryopreservation of the samples) and is simple to complete. The first parts of the card (socio-demographic, clinical, radiological and surgical data) are completed by the neurosurgeon. The second part is completed by the pathologist. The card is then mailed to the Tumor Registry in Herault (TRH, Registre des Tumeurs de l'Hérault, Montpellier, France), which has extensive expertise in working with tumor data and has the required authorizations for recording data with personal identifiers. The TRH compiles all the PCNST cards and analyzes the data in collaboration with the University Institute of Clinical Research of Montpellier-Nîmes (IURC, Institut Universitaire de Recherche Clinique, Montpellier-Nîmes, France).

Statistical analysis

In this descriptive work, a limited statistical analysis was included. Signs and symptoms, site of the tumor and surgery were compared between two age groups (0–14 and 15–19 years old) using Chi-square test. Site of the tumor

Table 1 Distribution of childhood primary central nervous system tumors by histology using ICD-O-3 and SNOMED codes from Kleihues and Cavenee in 2000 [2] and French nomenclature ADICAP in 2003 [25], age group and sex ($N = 1{,}017$)

Histology	ICD-O SNOMED	ADICAP	0–4 years	5–9 years	10–14 years	15–19 years	Boys/Girls	Total	%
Gliomas			152	148	118	108	259/267	526	51.7
Glioma tumors NOS		N7R0	7	3	5	3	10/8	18	1.8
Astrocytomas			97	91	74	67	162/167	329	32.4
Astrocytic tumors NOS		N7S0	10	8	7	4	14/15	29	2.9
Fibrillary astrocytoma	9420/3*	N7S2	5	2	2	1	3/7	10	1.0
Gemistocytic astrocytoma	9411/3	N7S4	0	1	0	0	1/0	1	0.1
Anaplastic astrocytoma	9401/3	N7T6	2	1	4	4	3/8	11	1.1
Glioblastoma	9440/3	N7X0	7	4	7	6	13/11	24	2.4
Giant cell glioblastoma	9441/3	N7X2	0	1	0	2	3/0	3	0.3
Gliosarcoma	9442/3	N7X4	0	0	0	1	0/1	1	0.1
Pilocytic astrocytoma	9421/1	N0S8	70	68	51	46	116/119	235	23.1
Pleomorphic xanthoastrocytoma	9424/3	N7S9	1	1	0	1	2/1	3	0.3
Subependymal giant cell astrocytoma	9384/1	N0T2	0	1	0	2	3/0	3	0.3
Subependymal giant cell astrocytoma (Bourneville)	9384/1	N0T3	2	4	3	0	4/5	9	0.9
Oligodendrogliale tumors			15	16	15	21	31/36	67	6.6
Oligodendroglioma	9450/3	N7V0	10	8	9	14	20/21	41	4.0
Anaplastic oligodendroglioma	9451/3	N7V4	5	8	6	7	11/15	26	2.6
Mixed gliomas			3	10	6	7	10/16	26	2.6
Oligoastrocytoma	9382/3	N7V2	1	1	6	3	5/6	11	1.1
Anaplastic oligoastrocytoma	9382/3	N7V3	2	9	0	4	5/10	15	1.5
Ependymal tumors			30	28	18	10	46/40	86	8.5
Ependymoma	9391/3	N7W0	8	9	8	5	14/16	30	2.9
Cellular ependymoma	9391/3	N7W1	0	0	1	0	1/0	1	0.1
Papillary ependymoma	9393/3	N7W4	0	1	1	0	2/0	2	0.2
Clear cell ependymoma	9391/3	N7W5	0	0	0	1	1/0	1	0.1
Anaplastic ependymoma	9392/3	N7W8	22	15	5	2	22/22	44	4.3
Myxopapillary ependymoma	9394/1	N7W2	0	3	2	2	5/2	7	0.7
Subependymoma	9383/1	N0W6	0	0	1	0	1/0	1	0.1
Other neuroepithelial tumors			99	92	72	56	186/133	319	31.4
Choroid plexus tumors			19	5	4	1	17/12	29	2.9
Choroid plexus papilloma	9390/0	N0Z0	15	4	4	0	13/10	23	2.3
Choroid plexus carcinoma	9390/3	N7Z0	4	1	0	1	4/2	6	0.6
Neuronal and mixed neuronal–glial tumors			8	15	30	32	48/37	85	8.4
Gangliocytoma	9492/0	N0L0	0	0	0	2	1/1	2	0.2
Desmoplastic infantile astrocytoma/ganglioglioma	9412/1	N0N0	1	0	0	0	0/1	1	0.1

Table 1 continued

Histology	ICD-O SNOMED	ADICAP	0–4 years	5–9 years	10–14 years	15–19 years	Boys/Girls	Total	%
Dysembryoplastic neuroepithelial tumor (DNET)	9413/0	N0N2	1	7	16	8	19/13	32	3.1
Ganglioglioma	9505/1	N7N0	6	7	13	21	26/21	47	4.6
Anaplastic ganglioglioma	9505/3	N7N1	0	1	1	0	1/1	2	0.2
Central neurocytoma	9506/1	N4L0	0	0	0	1	1/0	1	0.1
Pineal parenchymal tumors			2	5	2	2	5/6	11	1.1
Pineal parenchymal tumors NOS		P7P0	0	2	0	0	1/1	2	0.2
Pineocytoma	9361/1	P7P2	1	0	0	0	0/1	1	0.1
Pineoblastoma	9362/3	P7P4	1	3	2	2	4/4	8	0.8
Embryonal tumors			70	67	36	21	116/78	194	19.1
Medulloepithelioma	9501/3	N7Q0	2	0	0	0	0/2	2	0.2
Medulloblastoma	9470/3	N7P0	39	45	31	16	82/49	131	12.9
Desmoplastic medulloblastoma	9471/3	N7P2	10	7	3	1	14/7	21	2.1
Supratentorial PNET	9473/3	N7M2	9	10	1	2	8/14	22	2.2
Neuroblastoma	9500/3	N7M0	2	2	0	1	4/1	5	0.5
Ganglioneuroblastoma	9490/3	N7M1	1	0	0	1	0/2	2	0.2
Atypical teratoid/rhabdoid tumor	9508/3	X7R8	7	3	1	0	8/3	11	1.1
Tumors of peripheral nerves			1	4	5	19	13/16	29	2.9
Schwannoma			0	3	4	17	10/14	24	2.4
Schwannoma NOS	9560/0	N0A0	0	3	4	16	10/13	23	2.3
Plexiform schwannoma	9560/0	N0A6	0	0	0	1	0/1	1	0.1
Neurofibroma	9540/0	N0C0	1	1	1	2	3/2	5	0.5
Tumors of the meninges			5	3	10	16	13/21	34	3.3
Tumors of meningothelial cells			5	2	7	10	7/17	24	2.4
Meningioma NOS	9530/0	N0J0	2	1	3	1	3/4	7	0.7
Meningothelial meningioma	9531/0	N0K2	2	1	1	0	2/2	4	0.4
Fibrous (fibroblastic) meningioma	9532/0	N0J4	1	0	0	3	0/4	4	0.4
Transitional (mixed) meningioma	9537/0	N0K4	0	0	0	2	0/2	2	0.2
Psammomatous meningioma	9533/0	N0K8	0	0	1	1	0/2	2	0.2
Atypical meningioma	9539/1	N4J0	0	0	1	3	2/2	4	0.4
Anaplastic meningioma	9530/3	N7J0	0	0	1	0	0/1	1	0.1
Mesenchymal tumors									
Hemangiopericytoma	9150/1	V4K0	0	1	0	0	0/1	1	0.1
Tumors of uncertain histogenesis									
Hemangioblastoma	9161/1	V0G0	0	0	3	6	6/3	9	0.9
Lymphomas									
Malignant lymphomas	9590/3	K7G0	0	0	1	0	0/1	1	0.1

Table 1 continued

Histology	ICD-O SNOMED	ADICAP	0–4 years	5–9 years	10–14 years	15–19 years	Boys/Girls	Total	%
Germ Cell Tumors			4	8	15	9	24/12	36	3.5
Germinoma	9064/3	G7K0	1	5	13	6	18/7	25	2.5
Mature teratoma	9080/0	G0G0	2	0	1	1	2/2	4	0.4
Immature teratoma	9080/3	G7H1	1	2	1	2	4/2	6	0.6
Mixed germ cell tumors	9085/3	T7H0	0	1	0	0	0/1	1	0.1
Tumors of the sellar region									
Craniopharyngioma	9350/1	D0N2	5	21	18	10	28/26	54	5.3
Local extension from regional tumors									
Chordoma	9370/3	D4N4	0	1	1	4	3/3	6	0.6
Unclassified tumors			1	1	5	5	7/5	12	1.2
Total			267	278	245	227		1,017	100

* Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (SNOMED). Behavior is coded/0 for benign tumors, /1 for low or uncertain malignant potential or borderline malignancy, (/2 for in situ lesions) and/3 for malignant tumors

NOS not otherwise specified

(supratentorial, infratentorial, spinal cord or cauda equina and mixed) were also compared between the two surgical groups (biopsy and resection) using Chi-square test.

Results

During the years 2004–2006, 12,120 cases of newly diagnosed and histologically confirmed PCNST have been recorded by the TRH. This included 1,017 histologically confirmed childhood cases (<20 years) operated in 44 public or private neurosurgical departments. More than 95% ($n = 974$) of the children were operated in public academic centers. Of the 1,017 PCNST, 533 were boys (52.4%) and 484 were girls (47.6%). The median age at diagnosis for all childhood PCNST was 9 years.

The distribution by histology, age group and sex is shown in Table 1. Among neuroepithelial tumors gliomas were the most frequent, encompassing 50% of all childhood PCNST. About one-third of all childhood PCNST were other neuroepithelial tumors. Craniopharyngioma accounted for 5% and germ cell tumors, meningioma and neurinoma accounted for approximately 3% each. Pilocystic astrocytoma and medulloblastoma were the most common individual histologies. The median ages at diagnosis were as follow: gliomas: 8 years, other neuroepithelial tumors: 7 years, meningiomas: 13 years, tumors of peripheral nerves: 16 years old. Among the younger population, PCNST were slightly more common in boys, with neuroepithelial tumors slightly more common, and germ cell tumors twice as common in boys compared to girls. Approximately two-thirds of the choroid plexus tumors were diagnosed before 5 years old and three quarters of the neuronal and mixed neuronal–glial tumors were diagnosed after 10 years old.

Cryopreservation of the samples was reported on 254 (25%) of the 1,017 collected cases. The percentage of the cryopreserved tumors was almost the same in each age group. Table 2 details the number of cryopreserved tumors by main histological groups, and describes the radiological enhancement within these histological groups. Within the 1,017 PCNST collected in the database, the enhancement was positive on MRI and/or CT scan in 797 cases, negative on MRI and CT scan in 45 cases, doubtful in 28 cases, and not detailed in 147 cases.

Signs and symptoms in childhood PCNST were completely reported on 899 of the 1,017 collected cases (Table 3). Raised intracranial pressure was the most noted symptom and was present in more than the half cases in the children under 15 years old. Epilepsy was less than 13% among the younger population and present in about a quarter of the cases in the teenager's population.

Table 2 Number of cryopreserved childhood primary central nervous system tumors and contrast enhancement within the different groups of childhood primary central nervous system tumors ($N = 1{,}017$)

Histology	N	nb cryo T	Contrast enhancement				
			Yes	No	Doubt	Unknown	Yes/yes + no (%)
Pilocytic astrocytoma	235	56	201	3	1	30	98.5
All astrocytoma except pilocytic astrocytoma	94	19	72	5	4	13	93.5
Oligodendroglioma and mixed gliomas	93	20	61	16	6	10	79.2
Ependymal tumors	86	29	71	2	0	13	97.3
Choroid plexus tumors	29	9	24	0	0	5	100.0
Neuronal and MNG tumors	85	33	60	9	5	11	87.0
Pineal parenchymal tumors	11	2	10	1	0	0	90.9
Embryonal tumors	194	57	165	3	5	21	98.2
Tumors of peripheral nerves	29	7	16	0	0	13	100.0
Tumors of meninges except hemangioblastoma	25	6	20	0	1	4	100.0
Hemangioblastoma	9	1	8	0	0	1	100.0
Germ cell tumors	36	5	23	1	3	9	95.8
Craniopharyngioma	54	3	39	3	1	11	92.9
Other and unclassified tumors	37	7	27	2	2	6	93.1
Total	1,017	254	797	45	28	147	94.7

MNG Mixed neuronal–glial, *N* Number, *nb cryo T* Number of cryopreserved tumors

Table 3 Signs and symptoms in childhood primary central nervous system tumors

Signs and symptoms	0–14 years ($n = 790$)		15–19 years ($n = 227$)		All ($n = 1{,}017$)		Comparison of the two age groups (0–14 and 15–19 years)
	Number	%	Number	%	Number	%	*P*
Epilepsy	91	12.8	45	23.8	136	15.1	0.0002
Headache	226	31.8	65	34.4	291	32.4	0.5037
Raise ICP	358	50.4	68	36.0	426	47.4	0.0004
MSD	99	13.9	10	5.3	109	12.1	0.0012
Deficit	183	25.8	52	27.5	235	26.1	0.6288
Other	162	22.8	26	13.8	188	20.9	0.0065
Asymptomatic	19	2.7	12	6.3	31	3.4	0.0139
Number reported	710		189		899		

Deficit Neurological deficit, *ICP* Intracranial pressure, *MSD* Mental status disorders

Among the children under the age of 15 years, the infratentorial site was the most frequent and accounted for approximately half of all cases. Tumors developing in two or three sites (mixed site) were not rare (6%). Among the teenagers, the supratentorial site accounted for more than half of the cases (Table 4).

Surgery (biopsy or resection) was reported on 918 of the 1,017 cases collected (Table 5). The proportion of resection (versus biopsy) was about the same in the younger population (<15 years) as in the teenagers (15–19 years) and account for more than 80%. Of the 872 cases for which the site of the tumor and the surgery were reported, a significant relation between the site of the tumor (supratentorial, infratentorial, spinal cord or cauda equina and mixed) and surgery (biopsy versus resection) with $P = 0.0013$ (Table 6) was evident. Table 7 shows the number of biopsies and resections for each main histological group and each tumor site.

Discussion

This work of the French Brain Tumor Data Bank (FBTDB) [24, 26] detailed all histological types and subtypes of primary central nervous system tumors (PCNST) for 1,017 children (included teenagers) with newly diagnosed and histologically confirmed PCNST in France from 2004 to 2006. Clinical and radiological data, site of the tumor,

Table 4 Distribution of childhood primary central nervous system tumors by site

Site of the tumor	0–14 years ($n = 790$)		15–19 years ($n = 227$)		All ($n = 1,017$)	
	Number	%	Number	%	Number	%
Supratentorial	309	44.3	106	54.4	415	46.5
Infratentorial	326	46.8	69	35.4	395	44.3
Spinal cord or cauda equina	20	2.9	17	8.7	37	4.2
Mixed	42	6.0	3	1.5	45	5.0
Number reported	697		195		892	

Comparison of the two age groups (0–14 and 15–19 years): $P < 0.0001$

Table 5 Surgery of childhood primary central nervous system tumors

Surgery	0–14 years ($n = 790$)		15–19 years ($n = 227$)		All ($n = 1,017$)	
	Number	%	Number	%	Number	%
Biopsy	124	17.4	29	14.2	153	16.7
Resection	590	82.6	175	85.8	765	83.3
Number reported	714		204		918	

Comparison of the two age groups (0–14 and 15–19 years): $P = 0.2868$

Table 6 Distribution of childhood primary central nervous system tumors by site and surgery

Site of the tumor	Surgery				Total
	Biopsy		Resection		
	%	Number	%	Number	
Mixed	23.81	10	76.19	32	42
Spinal cord or cauda equina	11.11	4	88.89	32	36
Infratentorial	11.63	45	88.37	342	387
Supratentorial	21.13	86	78.87	321	407
Total		145		727	872

Comparison of the two surgical groups: $P = 0.0016$

surgery (biopsy/resection) and cryopreservated cases were reported. The long term goals of the FBTDB are to create a national registry and an extensive data bank in order to support basic and clinical research and to evaluate the oncological management concerning the PCNST in the French population. However, this discussion is mainly focused on methodology, epidemiological data (incidence rate, sex, age, histology) and perspectives.

Methodology

The primary difficulty in building a tumor registry is defining the type of tumor to be recorded. Particularly in neuro-oncology, the term brain tumor has been defined in numerous ways in the literature. Recent publications [4, 5, 10, 27, 28], the classification system of the World Health Organization [2, 3], and the European recommendations for coding tumors of the brain and central nervous system (CNS) [29] include all primary benign and malignant tumors located in the CNS, including the envelopes of the CNS and the origination of the nerves localized in the skull and the spine. Second, a registry has to record all cases of the defined tumors. The ascertainment system could influence the selection of tumor types to be included in the registry definition. As our registration system is based on the neurosurgical French network, we decided to record tumors that are always seen in neurosurgery. At the beginning of this work in 2004, we did not include pituitary tumors because we were not certain they are always seen by a neurosurgeon in France and the mesenchymal non-meningothelial tumors (excepted hemangiopericytoma) which were not considered as primary brain tumor by all the French community at this time. Except for these differences, we have selected the types of tumors that are included in the WHO 2000 [2] and CBTRUS classification schemes [10]. In addition, we use the French nomenclature [25] in combination with the WHO [2]. Since 2007, the FBTDB includes all the codes included in the WHO 2007 [3] and pituitary tumors.

Concerning the pediatric tumors, there is another scheme: the International Classification of Childhood Cancer (ICCC) [30] with the Third Edition (ICCC-3) [31]. This classification is currently used by the European childhood cancer registries [19, 32–34], by the French National Registry of Childhood Solid Tumors [21, 23] and by the FRANCIM network to study cancer incidence among adolescents in France [35, 36]. This scheme is based on the ICD-O 3 classification, and it is possible to do

Table 7 Distribution of childhood primary central nervous system tumors by surgery, site and main histology ($N = 872$)

Histology	Site								Total
	Mixed		SC and CE		Infratentorial		Supratentorial		
	B	R	B	R	B	R	B	R	
Pilocytic astrocytoma (PA)	1	7	0	6	11	106	13	55	199
All astrocytoma except PA	1	4	2	2	7	12	21	30	79
Oligo and mixed gliomas	1	2	0	0	10	15	18	40	86
Ependymal T	0	3	1	8	0	40	1	22	75
Choroid plexus T	0	2	0	0	0	7	2	13	24
Neuronal and MNG T	0	4	0	3	4	5	3	56	75
Pineal parenchymal T	2	1	0	0	0	2	3	2	10
Embryonal T	4	5	1	3	6	129	7	17	172
T of peripheral nerves	0	1	0	9	0	10	0	0	20
T of meninges except Hgb	0	0	0	1	0	2	0	18	21
Hemangioblastoma (Hgb)	0	1	0	0	0	6	0	2	9
Germ cell T	0	1	0	0	0	3	15	10	29
Craniopharyngioma	0	0	0	0	0	0	0	44	44
Other and unclassified T	1	1	0	0	7	5	3	12	29

B Biopsy, *MNG* Mixed neuronal–glial, *Oligo* Oligodendrogliomas, *R* Resection, *SC* and *CE* Spinal cord and/or cauda equina, *T* Tumor

the conversion between these two schemes (NCI–NIH–SEER website) [37]. The advantage of the ICCC-3 scheme is that it makes it possible to compare incidence of childhood PCNST in different countries. The inconvenience is that this scheme groups different kinds of histologies together and is not specific enough for detailed comparisons.

Childhood PCNST are heterogeneous tumors, so, in this descriptive work, we have detailed all histologies (using ICD-O 3) to facilitate the comparisons between the different series from the literature and because the clinical outcome of each kind of these tumors could be very different. Some recent reports (Table 8) are now available in different countries about detailed childhood PCNST histological distribution, for example in Denmark [12], Canada [14], Germany [13], Korea [11], Brazil [17], Taiwan [18], USA [10], but this was not available in France before this present work was completed. Furthermore, it is important to list the period of study, the population of study, the age at time of diagnosis, the percentage of histologically confirmed diagnosis, and so on, because all of these data may vary from study to study as it is illustrated in Table 8.

Incidence rate

The incidence rate of childhood PCNST continues to be controversial. It is very difficult to record all cases in a large area. The incidence rate may vary in the different countries and in different periods of time. In 2001, Kaatsch et al. [13] published compiled data from the International Agency for Research on Cancer (IARC). Age-standardized incidence rate (ASR) (per 100,000 children) of childhood PCNST (under 15 years old) range between 1.7 (in Hong-Kong) and 4.1 (in Sweden). The estimated ASR in France was 2.8. The data published in 2006 and 2008 showed: (1) the overall ASR of Childhood PCNST in Europe (1988–1997) was 2.99 (per 100,000 children, under 15 years old) [19], and (2) ASR in United States (2000–2004) was 4.61 per 100,000 children, under 15 years old and 4.53 for children under 20 years old [10].

Sex

Many previous studies have reported an obvious predominance of male patients with brain tumors with ratios ranging from 1.2 to 2.1 [11, 18, 38–41]. In our study (<20 years) the gender ratio is 1.10 and is close to the results of the Swedish Registry (ratio = 1.03) [42], Canadian work (ratio = 1.08) [14], Danish registry (ratio = 1.15) [12], and CBTRUS (ratio = 1.14) on 5,873 person under the age of 20 years [10]. On other hand, Rorke and Schut [43] explained that the male predominance of pediatric brain tumors merely reflected the gender distribution ratio in the normal childhood population. In France, the gender ratio (for the population <20 years) was 1.05 for the year 2005 [44]. However, there are some histological subtypes which are more frequent in boys (for example: embryonal tumors, gender ratio = 1.49, and germ cell tumors, gender ratio = 2) while other tumors are more frequent in girls (for example: meningioma, gender ratio = 0.44) in our series and that is comparable to the literature.

Table 8 Recent examples in different countries of reported studies that detail the histological distribution of childhood primary central nervous system tumors

Study and period	N	Country	Age at diagnosis	Population Study	Reference coding	Pathologically proven and particularity
Gjerris et al. 1998 [12] 1960–1984	911	Denmark	<15 years	Denmark area. Registry	–	Pathologically proven primary brain tumor in 94.6%
Keene et al. 1999 [14] 1975–1993	200	Canada	<18 years	Catchment area. Registry	–	Pathologically proven primary brain tumor, except for brainstem tumor
Kaatsch et al. 2001 [13] 1990–1999	3,268	Germany	<15 years	Germany area. Registry	ICD-O-2	All primary CNS tumors Germ cell tumors are treated separately
Cho et al. 2002 [11] 1959–2000	677	Korea	<16 years	Hospital series	ICD-O-2	Intra dural primary brain tumor Pathologic specimen only
Rosemberg and Fujiwara 2005 [17] 1974–2003	1,195	Brazil	<22 years	Hospital series	ICD-O-3	Primary CNS tumors Histologically confirmed
Wong et al. 2005 [18] 1975-2004	986	Taiwan	<18 years	Hospital series	ICD-O-3	Pathologically proven primary brain tumor in 85.4%
CBTRUS 2008 [10] 2000–2004	5,873	USA	<20 years	19 States of USA. Registry	ICD-O-3	All primary CNS tumors
Current study 2008, 2004–2006	1,017	France	<20 years	Hospital consortium	ICD-O-3	Primary CNS tumors Pathologic specimen only. Recording of the cryopreservation of the sample

Age

Some studies include teenage population in the childhood population [14, 17, 18], some others include children under 15 years old only [19, 41, 45]. In the present study, we have separated the children under 15 years old (790 cases) and teenagers (15–19 years old = 227 cases), as it is done in the CBTRUS [10], to make easy the comparison between series. In our series, the repartition of the number of cases for children (0–4 years old = 267 cases, 5–9 years old = 278 cases, 10–14 years old = 245 cases) is concordant (even if the age class are not always the same) with the data from Danish registry [12] and American registries [10], and some hospital series [18].

Histology

Mostly in agreement with the recent literature for all age groups, in the present work the most common childhood PCNST are astrocytomas (32.4%, included more than 2/3 of pilocytic astrocytomas), and embryonal tumors (19.1%, included more than 3/4 of medulloblastoma) followed by ependymomas (8.5%), neuronal and mixed neuronal–glial tumors (8.4%) and craniopharyngiomas (5.3%). The tumors of the meningothelial cells account for 3.3% and tumors of peripheral nerves for 2.9% only. Our study details the repartition of the histology subgroups as astrocytomas, ependymomas, neuronal and mixed neuronal–glial tumors, embryonal tumors, meningiomas (Table 1).

The percentage of the rare tumors such as pineal parenchymal tumors are 1.3% in the German and Korea series [11, 13], 0.9% in Taiwan [18], and 1.1% in our series; concerning the choroid plexus tumors, the Brazilian [17], Danish (for plexus papilloma) [12], Taiwan [18], German [13] studies describe 2.7, 2.4,1.9, 1.8%, respectively, and was 2.9% in our series. Atypical teratoid/rhabdoid tumor of the CNS, an extremely rare and aggressive tumor of early childhood [46] with a gender (M/F) ratio of 2.7 accounted for 1.1% of the all childhood PCNST in our series. Glioblastoma which is the most frequent glioma histology in all populations (composing approximately half the glioma cases) [10, 24], accounts for 2.8% in the German [13], 3% in the United States [10] childhood PCNST population and 2.4% in our study.

The present series has two unusual findings. First, the percentage of the neuronal and mixed neuronal–glial tumors (8.4%) is greater than in the literature (2.1% in the Taiwan [18], 2.5% in the German [13], 7.3% in CBTRUS [10] publications); secondly, the percentages of oligodendroglial tumors (6.6%) and mixed tumors (2.6%) are also greater than in the common literature. Two hypotheses could explain these differences: (1) the present study collected cases in recent years (2004–2006) and (2) French

pathologists are more influenced by the Sainte Anne classification [47] than other pathologists. In the Saint Anne classification, diffuse and anaplastic astrocytomas are considered as oligodendrogliomas or mixed gliomas and anaplastic oligodendrogliomas or anaplastic mixed gliomas, respectively. Of course, this fact could influence the French pathologists when they use the WHO classification. The goal of the present work is not to discuss the validity of the diagnosis made by pathologists but only to report the number of cases for each tumor. This could illustrate the difficulties to homogenize the histological diagnosis for some histological subtypes all over the world.

In this present work, childhood PCNST cases without histologic confirmation (for example: children with brainstem gliomas or children with positive cerebrospinal fluid tumor markers for CNS mixed malignant germ cell tumors) were not recorded. One of the goals of this work is to share our data with: (1) the French National Registry of Childhood Solid Tumors [23] and (2) the French pediatric neuro-oncology units, to collect all the French childhood PCNST cases, and then to participate to international studies with the Brain Tumor Epidemiology Consortium (BTEC) and the International Agency for Research on Cancer (IARC).

Clinical and radiological data, site of the tumor, surgery

The clinical data (Table 3) and radiological data (Table 2) are in agreement with that found in the literature [14, 48–51] and are partly linked to the topography of the tumor (Table 4). In this present work, tumors were only classified into three different sites (supratentorial, infratentorial, and spinal cord or cauda equina). The working group for the French record of PCNST has recently decided to modify the information Card to include the International Classification of Diseases for Oncology (ICDO-3) topography codes [52] for meninges (C70.0, C70.1, C70.9), brain (C71.0–C71.9), spinal cord and cranial nerves (C72.0–C72.5), pineal (C75.3) and to add pituitary (C75.1 and C75.2). It is not the goal of this work to discuss the neurosurgical practice (biopsy versus/resection) for each histological subtype and site of the childhood PCNST, but it would be interesting to have global information on pediatric neurosurgical practices concerning resection in other country (Table 7). We noted that neurinoma and meningioma are always resected no matter where the tumor is located. Pilocytic astrocytomas which are typically resected were biopsied in 19% of cases when located in the supratentorium. The data presented in Table 7 are important if we want to compare the median survival of one histological type or subtype of childhood PCNST between different countries.

A future goal of this work is to allow for the follow-up of patients to determine treatments, medical status and survivorship. For example, the FBTDB has recently completed a work entitle "Oncological patterns of care and outcome for patients with newly diagnosed and histologically confirmed glioblastoma in France in 2004, results on 952 cases" which was presented to the last American Society of Clinical Oncology meeting [53].

Virtual tumor bank

Recording cryopreservation of samples, to our knowledge, has not been reported previously and is original to our study. More than 250 identified childhood PCNST are cryopreserved. For these cryopreserved tumors we know the histological diagnosis and the main clinical and radiological features. This represents the first virtual tumor bank of childhood PCNST in Europe and holds great potential for future biological and clinical investigations.

Conclusion

To our knowledge, this work is the first European databank dedicated to PCNST that includes the collection of clinical, radiological and histological data (including cryopreservation of specimen), and which may have major clinical and research implications. Although, this large hospital-based series is not yet a study from a true population-based PCNST registry, it is representative of childhood PCNST in France. This work strongly suggests that the clinicians will need to work together with the registries in order to improve our knowledge of the epidemiology of childhood PCNST.

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