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REVIEW PAPER

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Primary intracranial neoplasms of infancy and early childhood

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Abstract We investigated the age-related location, gender distribution, and histology of 107 brain tumors in children under 4 years of age seen in our department between 1984 and 1997. The male-to-female ratio was 1.4 (62/45 cases) with a prevalence of supratentorial tumors (60/47=1.3); the main histological entity was astrocytoma (33.6%), followed by ependymoma (14.0%). In the 1st year of life 22 cerebral neoplasms became clinically apparent. A higher ratio for supratentorial tumors was revealed (17/5=3.4), but without gender preference, and primitive neuroectodermal tumors (PNET) were the most frequent (5/22). In the 2nd year 25 tumors were found. The male-to-female ratio was 1.5 (15/10) and the supratentorial-to-infratentorial ratio, 1.1 (13/12). The two most common entities were astrocytoma and ependymoma (6 cases each). In addition, a survey of previously published investigations into this subject was performed and a compilation of data on 1960, 545 and 1084 tumors in children below the age of 1, 2 and 4 years, respectively, was prepared, which makes it the most extensive review of brain tumors of infancy and early childhood yet undertaken.

Key words Childhood brain tumor · Congenital · Infancy · Epidemiology · Etiology

Introduction

Tumors of the central nervous system (CNS) are among the most common pediatric neoplasms, second in both number and mortality only to diseases of the lymphoid-hematopoietic system in childhood [12, 18, 31, 32, 37] and to neuroblastoma in infancy [2, 18, 49]. Intracranial tumors in children, once thought to be rare, have been discovered more frequently since the introduction of more sophisticated diagnostic tools, e.g. CT and MRI, and comprise approximately 20–23% of all childhood cancers [5, 42]. Brain tumors in infancy and early childhood differ in topographical distribution, biological behavior, clinical and therapeutic aspects and also in prognosis and outcome from those that present in later childhood and among adults, and are of particular interest with regard to their etiology, as exogenous factors can only have acted during the short intrauterine or postnatal period; they have an incidence of up to 3.6 per 100,000 newborns and account for between 0.04% and 0.18% of deaths in children under 1 year of age [27, 29]. According to a worldwide survey, the ten most common types of brain tumors in infancy are, in declining order of frequency, astrocytoma, medulloblastoma, ependymoma, choroid plexus papilloma, PNET, teratoma, sarcoma, meningioma, ganglioglioma, and neuroblastoma [14]. In the 1st year of life they account for up to 10%, and in the first 2 years for up to 18%, of the total incidence of pediatric brain tumors [3, 14, 29].

We present an epidemiological survey of primary intracranial tumors of the first 4 years of life seen in our department over a period of more than 13 years, with reference to their age-related location, gender distribution, and histology, and compare our findings with those of previous investigations.

Materials and methods

The primary intracranial neoplasms of this survey were seen as biopsy samples in our department between January 1984 and June 1997, and the patients concerned were all Caucasian children under 4 years of age at the time of diagnosis. The selected tumors originated in brain tissue and its coverings, including intradural sections of cranial nerves as well as the pituitary gland. Metastases (2 cases; hepatoblastoma, neuroblastoma), vascular malformations (2 angiomas) and spinal tumors (11 cases=9.3% of all CNS tumors of this age group; 3 neuroblastomas, 3 lipomas, 1 teratoma, dermoid cyst, ganglioneuroma, sarcoma, malignant histiocytosis) were excluded. Tissue sections were routinely stained with hematoxylin-eosin, Nissl stain (cresyl fast blue), and van Gieson. A minority were also stained with periodic-Schiff reagent (PAS) or were investigated by immunohistochemistry. Our findings were compared with the results of 35 other investigations of at least 10 cases each of CNS neoplasms of infancy and early childhood, listing the relative frequency of the six most common brain tumors of this period of life according to a survey by the International Society for Pediatric Neurosurgery [15].

Results

The findings of our investigation are listed in Table 1. Data on 107 biopsy samples of brain tumors in children under 4 years of age were compiled; these represent 1.60% of all 6692 tumors diagnosed between January 1984 and June 1997, and 90.7% of all CNS neoplasms of this age group, while spinal tumors accounted for 9.3%. We found the most common tumors in the 1st year of life to be PNET (5 cases, Table 2) and in the first 2 years, astrocytomas and ependymomas (9 cases each, Table 3); astrocytomas alone made up a third of the brain tumors in the first 4 years of life and were by far the most frequent group (36 cases, Table 5), with 75% of them becoming clinically apparent in the 3rd and 4th years.

Malignancy was highest in the 1st year, with 77.3% of cases (17 out of 22), compared with 36.0% (9/25) in the 2nd year and 55.3% (26/47) for under 2-year-olds, compared with 45.0% (27/60) among 2- to 4-year-olds. The single most common histological entity was pilocytic astrocytoma (19 cases), followed by medulloblastoma (14 cases) and PNET (13 cases, Table 1), while no plexus tumors at all were observed. In all age groups there was a slight preponderance of male patients, which increased with age (between 1.0 and 1.5) and for a supratentorial location, which was most prevalent in the 1st year (3.4), followed by a decrease in the 2nd year (1.1) and a further rise toward the 4th year (1.3). The number of cases increased gradually with age: 22 in the 1st, 25 in the 2nd, 28 in the 3rd and 32 in the 4th year of life.

Table 1 Frequency of brain tumors according to histological type and in relation to age, gender and location, as seen in our department between 1984 and 1997 (*M* male, *F* female, *S* supratentorial, *I* infratentorial)

Histology	All cases (0–4 years)	Cases (0–1 years)	Cases (0–2 years)	M/F (0–4 years)	S/I (0–4 years)
Astrocytoma (total)	36	3	9	21/15	19/17
Benign	27	1	7	17/10	12/15
Pilocytic	19	1	4	12/7	6/13
Malignant	9	2	2	4/5	7/2
Ependymoma (total)	15	3	9	9/6	4/11
Benign	11	–	5	6/5	1/10
Subependymoma	9	–	5	5/4	–/9
Malignant	4	3	4	3/1	3/1
Medulloblastoma	14	3	6	9/5	–/14
PNET	13	5	5	7/6	13/–
Mixed glioma	9	2	6	7/2	7/2
Neuroblastoma	4	1	2	–/4	4/–
Ganglioglioma	4	2	3	1/3	4/–
Dermoid cyst	3	–	1	2/1	3/–
Meningioma	3	–	–	3/–	1/2
Sarcoma	2	1	2	1/1	1/1
Teratoma	1	1	1	1/–	1/–
Craniopharyngioma	1	–	1	–/1	1/–
Gliomatosis cerebri	1	–	1	–/1	1/–
Histiocytosis	1	1	1	1/–	1/–
	107	22	47	62/45	60/47

Table 2 Relative frequency, gender ratio and location of the most common pediatric brain tumors in the 1st year of life (*Astr* astrocytoma, *Med* medulloblastoma, *Epen* ependymoma, *Plex* plexus tumors, *Tera* teratoma, *nd* no data available)

Country	Reference	Cases	M/F	S/I	Astr	Med	Epen	Plex	PNET	Tera
Germany	This study	22	1.0	3.4	13.6	13.6	13.6	–	22.7	4.5
	[17]	12	0.7	1.0	8.3	33.3	–	–	–	–
	[27]	102	nd	nd	36.3	21.6	11.8	8.8	–	5.9
East Germany	[28]	722	1.0	nd	18.3	9.6	6.5	16.5	–	11.1
	[53]	130	1.3	nd	20.8	16.2	16.2	16.2	–	6.2
Austria	[29]	56	nd	nd	21.4	8.9	8.9	3.6	–	1.8
England	[31]	100	nd	1.5	31.0	20.0	18.0	13.0	3.0	3.0
France	[33]	29	1.6	2.5	24.1	17.2	24.1	3.4	–	1.3
	[34]	nd	1.1	1.5	27.0	14.0	25.0	9.0	9.0	5.0
Italy	[10]	14	1.3	1.8	21.4	21.4	21.4	–	–	7.1
	[21]	28	1.8	2.1	33.3	4.2	12.5	20.8	8.3	–
	[8]	39	nd	1.6	38.5	17.9	10.3	10.3	2.6	7.7
	[15]	51	1.2	1.4	36.1	25.5	10.6	8.5	–	4.3
Spain	[25]	29	nd	3.1	17.2	10.3	6.9	34.5	3.4	6.9
Canada	[57]	11	nd	4.5	45.5	–	–	9.1	9.1	9.1
	[2]	41	1.3	2.4	41.5	2.4	2.4	19.5	12.2	2.4
USA	[43]	39	1.3	1.8	30.8	23.1	2.6	15.4	2.6	7.7
	[26]	22	0.6	2.1	31.8	–	–	13.6	27.3	18.2
Mexico	[46]	32	1.0	2.6	25.0	3.1	15.6	3.1	9.4	9.4
	[12]	35	1.6	2.3	20.0	5.7	17.1	–	11.4	20.0
Argentina	[61]	40	0.8	4.0	44.7	13.2	5.3	13.2	10.5	2.6
Saudi Arabia	[38]	14	nd	1.0	28.6	35.7	14.3	7.1	14.3	–
Japan	[49]	10	0.4	9.0	30.0	–	10.0	10.0	–	20.0
	[56]	57	nd	2.0	29.8	21.1	5.3	17.5	1.8	1.8
	[47]	18	1.0	3.5	22.2	16.7	11.1	5.6	–	16.7
	[39]	218	1.0	2.3	24.2	16.5	11.3	12.4	2.1	9.3
Far East	[40]	307	1.1	2.1	23.3	17.2	11.1	10.7	4.2	8.4
Various	[14]	886	1.2	2.2	28.6	11.5	11.4	10.6	6.2	5.0
		1960[a]	1.09	2.06	24.1	13.3	9.8	13.1	2.6	7.9

[a] Two surveys [14, 39] have not been included as the latter is part of another study [40], while the former includes some of the investigations listed above

Discussion

Intracranial tumors in children, once thought to be rare, have been discovered more frequently since the introduction of more sophisticated diagnostic tools. A 20-year survey of pediatric CNS tumors in patients under 20 years of age [53] revealed an incidence of 31.0 and 25.9 per million in boys and girls, respectively; 93.6% were located intracranially, a similar figure to the 90.3% in our survey, with the remainder located in the spine. Brain tumors in infants and young children tend not to present until they are very large, because of the skull's elasticity and its ability to compensate intracranial hypertension, and can reach grotesque proportions, especially in fetal cases, where – as Giuffre [22] adequately put it – they can be regarded not so much as brain tumors but rather as 'tumor brains' [16, 41, 45, 58]. The adaptability of the developing nervous system allows for considerable tumor growth with scarce and mainly nonspecific clinical symptoms, the most common of which are macrocrania (in 64–82% of cases) and vomiting (39.2–56%) [31, 43, 47], often in association with hydrocephalus (78.6–90%) [21, 56, 61].

When dealing with the epidemiology of any kind of disease and trying to compare findings from different investigations, one has to be aware of the sometimes arbitrary definitions and requirements applied by individual scientists. In the case of pediatric brain tumors such problems lie for example in the age limits used for certain developmental periods (e.g., the widely divergent ages of 12 and 20 years for the end of 'childhood') [28], the definition of age itself (meaning age at time of first clinical symptoms or only at diagnosis) and in the different approaches to histopathological diagnosis, as the terminology and nosological classification of certain tumors have either changed or been handled arbitrarily over the years; Staneczek and Jänisch, for example, subsume dermoid cysts under germ cell tumors and PNET, a still controversial category of tu-

Table 3 Relative frequency, gender ratio and location of the most common pediatric brain tumors in the 2nd year of life

Country	Reference	Cases	M/F	S/I	Astro	Med	Epen	Plex	PNET	Tera
Germany	This study	25	1.5	1.1	24.0	12.0	24.0	–	–	–
France	[33]	47	1.0	0.7	17.0	19.1	29.8	2.1	–	–
	[34]	nd	1.3	0.7	36.0	14.0	16.0	17.0	3.5	1.7
USA	[35]	15	nd	0.7	40.0	13.3	6.7	6.7	26.7	–
Saudi Arabia	[38]	20	nd	1.9	26.3	10.5	5.3	21.1	–	–
		107	1.20	0.93	23.6	15.1	20.8	5.7	3.8	0.8

Table 4 Relative frequency, gender ratio and location of the most common pediatric brain tumors in first 2 years

Country	Reference	Cases	M/F	S/I	Astr	Med	Epen	Plex	PNET	Tera
Germany	This study	47	1.2	1.8	19.1	12.8	19.1	–	10.6	2.1
England	[32][a]	93	nd	0.8	20.4	22.6	19.4	6.5	1.1	1.1
France	[20]	66	nd	1.5	31.3	15.6	21.9	9.4	–	–
	[33]	76	1.2	1.1	19.7	18.4	27.6	2.6	–	1.3
Italy	[3]	80	1.1	2.0	41.3	20.6	14.3	11.1	–	1.6
USA	[19][a]	54	1.0	0.6	25.9	29.6	16.7	5.6	–	9.3
	[35]	22	1.4	1.0	36.4	9.1	4.5	4.5	31.8	4.5
	[44]	40	nd	0.9	7.5	27.5	22.5	15.0	5.0	–
Saudi Arabia	[38]	34	2.4	1.4	27.3	21.2	9.1	15.2	6.1	–
Taiwan	[60]	33	nd	5.6	32.3	6.5	–	19.4	12.9	16.1
		545	1.24	1.22	20.7	16.9	14.5	6.6	3.9	2.8

[a] First 18 months of life

Table 5 Relative frequency, gender ratio and location of the most common pediatric brain tumors in first 4 years of life

Country	Reference	Cases	M/F	S/I	Astr	Med	Epen	Plex	PNET	Tera
Germany	This study	107	1.4	1.3	33.6	13.1	14.0	–	12.1	0.9
East Germany	[53]	736	1.3	nd	36.4	18.8	17.7	5.6	–	2.9
Austria	[52]	18	2.0	0.8	55.6	5.6	22.2	–	–	–
Mexico	[12]	196	nd	nd	27.0	13.8	16.3	3.1	12.8	5.1
Nigeria	[1][a]	27	nd	nd	66.7	11.1	–	–	–	7.4
		1084	1.30	1.19	35.5	16.9	16.7	4.3	3.5	3.1

[a] First 5 years of life

mors [50, 51], under medulloblastomas [53]. In addition, some studies have involved too few patients for viable statistic evaluation and include metastases, lymphomas and/or angiomas to varying extent.

Brain tumors in infancy and early childhood differ in topographical distribution, biological behavior, clinical and therapeutic aspects and prognosis and outcome from those that present in later childhood and among adults [22]. These tumors are of particular interest with regard to their etiology, as possible exogenous or genetic factors can only have acted during the short intrauterine or postnatal period. They are considered to be congenital, although, as in the case of tumors presenting some time after birth, the difficulty in estimating their postnatal growth renders the classification and definition of tumors as congenital rather problematic and obscure [43, 56].

It is generally assumed that intracranial tumors presenting in the 1st year of life have developed during intrauterine life. The prenatal origin is even more obvious in all tumors detected in utero [16, 41, 45] or within the neonatal period [29, 58]. Jellinger and Sunder-Plassmann proposed regarding tumors producing symptoms at birth or within the first 2 weeks of life as ‘definitely connatal’, those first seen in the 1st year as ‘probably connatal’ and

those seen in infants beyond 1 year of age as 'possibly connatal' when symptoms can be traced back to the 1st year of life [29], while others put the cut-off age at 18 months [19, 32]. However, the main problem lies in the different biological behavior of some tumors: even though they have developed in fetal life they may not be symptomatic within the 1st year of life. For example, medulloblastomas, teratomas, hamartomas and craniopharyngiomas are known to have a congenital origin but rarely manifest themselves at an early stage, suggesting that some pediatric neoplasms might be congenital in origin despite clinical manifestation later than in infancy [47, 54]. This point is also stressed by Jänisch, who reports that for at least half the astrocytomas in his investigation the interval between symptoms and diagnosis was more than 6 months [27]. These are the considerations that led us to extend the age limit of our investigation to 4 years.

Compared with previously published surveys, our cases showed a higher incidence of supratentorial tumors and PNET in all age groups and of ependymomas among children under 2 years of age, while teratomas were relatively rare and plexus tumors totally absent in our survey; in every age group there was a higher incidence in boys than in girls, and malignancy was highest in the 1st year, with 77.3% of cases, which corroborates the incidence of 85% reported by Kumar et al. [32]. As previously noted [12, 20, 37], supratentorial tumors were particularly frequent within the 1st year (Table 2); however, with the exception of one study [38] they were almost on a par with or slightly fewer than infratentorial tumors in the 2nd year (Table 3). On comparison of the results of past investigations it becomes apparent that, while ratios for gender distribution and localization of tumors are fairly constant throughout an age group, the frequency of separate histological entities varies greatly between individual studies, so that only a synopsis of all results can give a fair idea of their relative number. Our survey of 1960 brain tumors in the 1st year of life shows very similar results to the investigation of Oi et al. [40] (Table 2). These similarities are even more pronounced when all studies not featuring PNET as a separate entity are excluded [53]: the relative frequency of medulloblastomas increases from 13.3% to 15.3% and that of PNET, from 2.6% to 5.8%. When these data on tumors in the 1st year of life (Table 2) are compared with corresponding data collected in older age groups (Tables 3–5) a highly increased incidence of astrocytomas and ependymomas can be observed in older children, while the number of plexus tumors and teratomas drops dramatically after the 1st year; the overall incidence of medulloblastomas is virtually constant in the first 4 years of life.

Any consideration on the etiology of pediatric brain tumors has to take genetic and environmental aspects into account. While a higher incidence of Burkitt lymphoma in Africa is known to be associated with the Ebstein-Barr virus [1], a possible racial and/or environmental effect has to be considered as a reason for the higher prevalence of teratomas in Japan [39, 40] and Taiwan [60]; however, similar incidences are found in extensive surveys undertaken in Mexico [12] and East Germany [53], the latter of which ought to yield valuable epidemiological data, as post mortems were compulsary for stillborn children and deceased infants. Racial differences have been described in a number of studies [1, 12, 40, 42], and a higher incidence of pediatric brain tumors among family members and siblings with cerebral neoplasms (in 8.6% of families) [32] or other diseases of the nervous system [5, 23], various associated congenital anomalies [40], birth defects [24], genetic disorders [6, 9, 30] and malformative factors (in 15% of cases) [58] as well as other kinds of cancer have been reported in a number of cases [4, 18, 19].

It seems that the incidence of pediatric CNS tumors has gradually increased in recent decades [12, 13, 37, 53], averaging 1% annually worldwide and 6% in the United States [12]. An explanation for this could lie in improved diagnostic tools and higher awareness; however, one extensive study found a significant increase in tumor incidence particularly for males, which weakens this line of reasoning and points to a possible environmental influence [53]. Epidemiological investigations in this field have produced a plethora of – sometimes bizarre – potential risk factors with frequently contradictory results as to their impact on tumorigenesis. While heritable syndromes and ionizing radiation are widely regarded as the only two established causes of primary CNS tumors, each accounts for only a few percent of cases [42]. However, a higher incidence of pediatric brain tumors seems to be associated with the partly occupational (e.g. transportation and agriculture: maternal farm residence during pregnancy [7, 11, 23, 59]) and partly dietary (e.g., cured meats [36,48] or beer [7]) exposure of parents to nitrites and aromatic amino and nitroso compounds, while vitamins during pregnancy and childhood are correlated with a decreased incidence of pediatric brain tumors [11, 36, 48]. Findings relating to other suggested risk factors, such as head trauma, exposure to electromagnetic fields, infections during pregnancy, pesticides, smoking, and alcohol consumption are at best inconclusive, especially given the small collectives in some studies, thus limiting the validity of results.

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