Child's Nerv Syst (1998) 14:547–550

ORIGINAL PAPER

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Epidemiological features of brain tumors in the first 3 years of life

Received: 10 May 1998

Presented at the 8th International Symposium on Pediatric Neuro-oncology, Rome, 6–9 May 1998

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Abstract We investigated the age-related location, gender distribution, and histology of 75 brain tumors in children under 3 years of age seen in our department between 1984 and 1997. These were characterized by a higher overall incidence in boys (42/33 cases; ratio 1.3) and a prevalence for a supratentorial location (48/27 cases; ratio 1.7); the most common histological entities were astrocytoma (25.3%) and ependymoma (17.3%), followed by medulloblastoma (13.3%) and PNET (10.8%); 44% were high-grade tumors corresponding to WHO grades III and IV. In the 1st (22 cases), 2nd (25 cases) and 3rd (28 cases) years of life, the boy–girl ratios were 1.0, 1.5 and 1.3, respectively, while there was a decrease with age in the frequency of supratentorial (ratios 3.4, 1.1, and 1.2) and high-grade tumors (77.3%, 36.0%, and 32.1%). In the 1st year of life the most common neoplasms were PNETs (22.7%) and in the 2nd year both astrocytomas and ependymomas (24.0% each); astrocytomas (35.7%) prevailed in the 3rd year of life.

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

Introduction

Tumors of the central nervous system (CNS) have overtaken acute lymphoblastic leukemia as the most common neoplasm in childhood, affecting 33 children per million per year [26], and comprise ca. 20–23% of all pediatric cancers [2, 17]. Brain tumors in infancy and early childhood differ in topographical distribution, biological behavior, clinical and therapeutic aspects and in prognosis and outcome from those that present in later childhood and among adults. These pediatric tumors are of particular interest with regard to their etiology, as exogenous factors can only have acted during the short intrauterine or postnatal period. According to a worldwide survey, the six most common types of brain tumors in infancy are, in decreasing order, astrocytoma, medulloblastoma, ependymoma, choroid plexus papilloma, primitive neuroectodermal tumors (PNETs), and teratoma [7].

We present an epidemiological survey of primary intracranial tumors of the first 3 years of life with regard to their age-related location, gender distribution, and histology, and review the pertinent literature.

Materials and methods

The primary intracranial neoplasms reviewed in this survey were sent to us as routine biopsy samples from seven neurosurgical centers and were seen in our department between January 1984 and December 1997. The selected tumors originated in brain tissue and its coverings, including intradural sections of cranial nerves, and the pituitary gland. Metastases, vascular malformations and spinal tumors were excluded. Tissue sections were routinely stained with hematoxylin-eosin, Nissl stain (cresyl fast blue), and van Gieson. A minority of cases were also stained with periodic acid-Schiff reagent or examined by immunohistochemistry.

Table 1 Frequency of brain tumors in the first 3 years of life according to histological type

Histology	1st year	2nd year	3rd year	Total (%)
Astrocytoma (total)	3	6	10	19 (25.3)
I/II	–1	–6	–8	–15
Pilocytic	–1	–3	–3	–7
III/IV	–2	–	–2	–4
Ependymoma (total)	3	6	4	13 (17.3)
I/II	–	–5	–4	–9
Subependymoma	–	–5	–3	–8
III/IV	–3	–1	–	–4
Medulloblastoma	3	3	4	10 (13.3)
PNET	5[a]	–	3	8 (10.8)
Mixed glioma	2	4	1	7 (9.3)
Ganglioglioma	2	1	1	4 (5.3)
Dermoid cyst	–	1	2	3 (4.0)
Craniopharyngioma	–	1	1	2 (2.7)
Teratoma	1	–	–	1 (1.3)
Others	3	3	1	7 (9.3)
Total	22	25	28	75 (100)

[a] Including a case of melanotic progonoma [21]

Results

The findings recorded in our investigation are listed in Table 1. A total of 75 biopsy samples of brain tumors in children under 3 years of age were examined. We found the most common tumors in the 1st year of life to be PNETs (5 cases; 22.7%); in the 2nd year astrocytomas and ependymomas (6 cases each; 24.0%) were most common, while astrocytomas accounted for 10 cases in the 3rd year of life (35.7%). The overall incidence of high-grade tumors (WHO III/IV) was 44%; they were most frequent in the 1st year, with 77.3% of cases (17 out of 22) as opposed to 36.0% (9/25) in the 2nd year and 32.1% (9/28) in the 3rd year. The most common histological entities were astrocytomas (19 cases; 25.3%) and ependymomas (13 cases; 17.3%), followed by medulloblastomas (10 cases; 13.3%) and PNETs (8 cases; 10.8%). In the 1st (22 cases), 2nd (25 cases), and 3rd (28 cases) years of life, the boy-girl ratios were 1.0, 1.5, and 1.3, respectively (total ratio 1.3, 42/33 cases), while there was a decrease in the frequency of supratentorial tumors with age (ratios 3.4, 1.1 and 1.2; total ratio 1.7, 48/27 cases).

Discussion

Brain tumors in infancy and early childhood differ in topography and biological behavior as well as in therapy and prognosis from those in later life [9]. Because of the adaptability of the developing nervous system and the elasticity of the skull, clinical symptoms in this age group initially tend to be nonspecific before macrocrania and vomiting become apparent at a later stage [19]; as 75% of pediatric brain tumors occur in the midline [26] they are frequently associated with hydrocephalus, necessitating insertion of a shunting device and potentially giving rise to systemic spread [18]. Upon diagnosis these tumors are often very large and can reach grotesque proportions, particularly in fetal cases presenting as “tumor brains” [20].

An extensive review of brain tumors in infancy and early childhood was recently published in this journal, presenting data on 1960, 545 and 1084 tumors in children below the ages of 1, 2 and 4 years, respectively [19]. Compared with the overall results of this survey, our data show a higher incidence of supratentorial tumors and PNETs in all age groups and of ependymomas among under 2-year-olds, while teratomas are relatively rare and plexus tumors totally absent; however – apart from the lack of plexus papillomas – the overall ranking of the different histological entities according to frequency is similar to that given for infants by Di Rocco et al. [7]. As shown in previous reports, boys are more often affected than girls, while high-grade tumors are most commonly found in the 1st year of life (77.3% of cases, as against 36.0% and 32.1% in the 2nd and 3rd years). In accordance with most investigations, supratentorial tumors are particularly frequent within the 1st year and almost on a par with infratentorial tumors in the 2nd and 3rd years [19]. While ratios for gender distribution and location of tumors are fairly constant throughout an age group in most studies, the frequencies of separate histological entities vary considerably [19]. Apart from regional differences in incidence, this might be due to a bias in biopsy acquisition (routine material vs referred cases for consultation), low numbers of cases and thus statistically unsound results or historically varying and at times arbitrary classifications of tumors, e.g. dermoid cysts under germ cell tumors and PNETs – a fairly recent and controversial entity – under medulloblastomas [24] or vice versa. In the past, particularly the latter two tumors – among the most frequent and clinically important in pediatric neurooncology – have been inconsistently classified by researchers. Therefore, to get a fair idea of their frequency, they should either be seen as a single entity of primitive neuroectodermal tumors (regardless of location) or estimated from more substantial surveys that specifically distinguish between the two. In this way, the relative frequency of medulloblastomas and PNETs *together* is 15.9%, 20.8% and 20.4% in the first 1, 2 and 4 years of life [19]. In studies giving separate data on these two entities, the respective figures for medulloblastomas are 15.3%, 18.4%, and 13.5%, while PNETs account for 5.8%, 7.9% and 12.5% of brain tumors in the first 1, 2 and 4 years of life, based on 719, 266 and 304 cases [19].

Pediatric brain tumors, whose incidence seems to have risen in recent decades [6, 15, 24, 26], 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. Racial differences have been described in a number of studies [1, 16, 17] and a possibly genetic and/or environmental effect has to be considered for the seemingly more common teratomas and craniopharyngiomas in Japan [16] and Taiwan [27]; however, comparison of data from Japan/South East Asia and Europe on tumors of the 1st year of life shows that the respective frequencies for teratomas are rather similar, with 8.5% and 8.4%, while the corresponding figures for under 4-year-olds are 0.9%–2.9% in Germany but 5.1% in Mexico [19]. Pediatric brain tumors can be found more often among family members and siblings with cerebral neoplasms [13] or other diseases of the nervous system [2], while various congenital anomalies [12, 16], birth defects [10], genetic disorders [3, 12] and other kinds of cancer have been reported for a number of cases [8]. Familial tumor syndromes involving the CNS, for example, include both types of neurofibromatosis (association with neurofibroma, glioma and meningioma) and the Li-Fraumeni (astrocytoma, PNET), Cowden (gangliocytoma) and Turcot (medulloblastoma, glioblastoma) syndromes, while p53 tumor suppressor gene germline mutations are associated with the rise in the frequency of astrocytomas, medulloblastomas (frequently presenting with isochrome 17q and changes on chromosome 1) and, to a lesser extent, ependymomas (in 50% with loss of the short arm of chromosome 17); choroid plexus papillomas, on the other hand, tend to present with SV40-like elements, while germ cell tumors are more common in Klinefelter patients and seem to benefit from gonadotrophins [13].

Epidemiological investigations into pediatric CNS tumors have come up with a multitude of 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 account for only a few percent of cases [13, 17]. However, some tumors seem to be associated with the partly occupational (e.g. transportation and agriculture, i.e. maternal farm residence during pregnancy), partly dietary (e.g. cured meats, beer) 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 [4, 5, 14, 19, 23]. Findings for other suggested risk factors, such as head trauma, exposure to electromagnetic fields or infections during pregnancy, pesticides, smoking, and alcohol consumption, are at best inconclusive, especially given the small collectives in some studies, which limit the validity of results.

As to the notion of pediatric brain tumors being "congenital," it is generally assumed that CNS tumors in infancy must have developed during intrauterine life, as is evident in all tumors detected in utero [20] or within the neonatal period [11]. Some authors regard tumors present at birth or within the first 2 weeks as "definitely connatal," those in the 1st year as "probably connatal" and those first observed beyond that as "possibly connatal" when symptoms can be traced back to the first year of life [11]. Some tumors, though, do not follow this pattern and – depending on their postnatal growth – may not become symptomatic for some time after birth despite their presumed congenital origin: examples of such tumors are medulloblastomas, teratomas, hamartomas and craniopharyngiomas [22, 25]. However, further epidemiological, genetic and molecular-pathological data are necessary to clarify this aspect.

Acknowledgements This work was kindly supported by Hoechst Marion Roussel, Bad Soden am Taunus, Germany.

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