RESEARCH COMMUNICATION

Pediatric Brain Tumours at a Tertiary Care Hospital in Karachi

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Abstract

The objectives of this study were to determine the epidemiology of brain tumors during infancy and childhood and to define and segregate childhood brain tumors vis-à-vis their morphological characteristics. The present study includes pediatric brain tumors, ICD-10 category C71 encountered during 10 years (January 1989 through December 1998) at a tertiary care hospital in Karachi. Eighty one cases were included, 58 (71.6%) in males and 23 (28.4%) in females with a male to female ratio of 2.5:1. The cases were divided into 3 age groups each covering five years of life (0-4, 5-9, 10-14 years), with the greatest number in the second age group i.e. 5-9 years followed by the third age group and the 0-4 year age group. The mean age for all cases, both genders was 8.8 years (95% CI 7.9; 9.6) with a marginal variation for cases occurring in the cerebrum and cerebellum. The malignancies occurred at a younger age in the males for each subcategory by site and morphology. The morphological distribution of cases was astrocytoma (28 cases, 34.6%), primitive neuroectodermal tumor or PNET (40 cases; 49.4%), ependymoma (8 cases, 10%), mixed glioma (4 cases; 5%) and a case of oligodendroglioma. The 81 malignancies included in this study were further categorized by site into two groups, supratentorial (27 cases; 33.3%) and infratentorial (54 cases; 66.7%). The morphological categorization of supratentorial tumors was astrocytoma (17 cases; 63%), ependymoma (5 cases; 18.5%), mixed glioma (2 cases; 7.4%). PNET with rhabdoid differentiation, oligodendroglioma and pinealoblastoma comprised 1 case (3.7%) each. The 17 supratentorial astrocytoma were sub-categorized as follows - pilocytic astrocytoma (5 cases; 29.4%), grade II astrocytoma (6 cases; 35.3%); grade III astrocytoma (2 cases; 11.8%), anaplastic astrocytoma (1 case; 5.9%) and glioblastoma multiforme (3 cases; 17.7%). The morphological categorization of infratentorial tumors was astrocytoma (11 cases; 20.4%), medulloblastoma (38 cases; 70.4%), ependymoma (3 cases; 5.6%) and mixed glioma - astroependymoma (2 cases, 3.7%). The morphological sub-categorization of infratentorial astrocytoma was pilocytic astrocytoma (7 cases, 63.6%), with gemistocytic astrocytoma, grade II, grade III and anaplastic astrocytoma comprising 1 (9.1%) case each. The morphological categorization of medulloblastoma was classical medulloblastoma (15 cases; 39.5%), desmoplastic medulloblastoma (8 cases; 21.1%), medulloblastoma with astrocytic differentiation (12 cases; 31.5%), medulloblastoma with neural differentiation (2 cases; 5.3%), and neuroblastic medulloblastoma (1 case; 2.6%). The pediatric brain tumors in Karachi reflect a developing country scenario, with a strong male predisposition and a late presentation with a peak in the 5-9 year age group. There is a predominance of medulloblastoma and a paucity of astrocytomas. The current study is a single institution study and needs cautious interpretation. Population-based studies are required to determine the cancer burden due to pediatric malignancies of the brain in this population and for the morphological categorization of brain tumors in Karachi.

Key Words: Brain tumours - pedriatric - morphology - Karachi, Pakistan

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Introduction

Childhood neoplasms are the second most common cause of death after trauma, the commonest cause beyond the neonatal age group (Fernbach and Vietti, 1991). Intracranial tumors in children, once thought to be rare, have been discovered more frequently since the introduction of sophisticated diagnostic tools viz. CT and MRI (Birch et al., 1990) and have overtaken acute lymphoblastic leukemia as the most common neoplasm in childhood. Intracranial childhood tumors affect 33 per 100,000 children annually (Tomita, 1998) and comprise about 20 – 23 % of all pediatric cancers (Preston-Martin, 1993). Approximately 1100 new cases are diagnosed in the United States each year (Robison et al., 1991). A 20 year survey of pediatric CNS tumors in patients below 20 years of age revealed an incidence of 31.0 and 25.9 per million in boys and girls respectively (Staneczek and Janish, 1997; Rickert et al., 1997). The overall male to female ratio ranges from 1.1 to 1.6 (Kurland et al., 1982;

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Mosso et al., 1992; Kallio et al., 1993; Preston-Martin et al., 1993).

Childhood tumors are a biologically different entity from tumors of adult and later life. Brain tumors in infancy and childhood differ in topographical distribution, biologic behavior, clinical and therapeutic aspects, prognosis and outcome from those that present in later life (Giuffre, 1989). Some histological subtypes of tumors encountered in children are uncommon in adults. The common supratentorial brain tumors in children are astrocytoma, oligodendroglioma, primitive neuroectodermal tumor; ependymoma and teratoma whereas the common infratentorial pediatric brain tumors are astrocytoma, primitive neuroectodermal tumor, ependymoma and choroids plexus papilloma (Frank, 1988). The prognosis of histologically similar tumors is more favorable in children (Rickert et al., 1997). Although the mortality rate for pediatric brain tumors has historically been high. Recent diagnostic and therapeutic advances have allowed earlier detection and more effective treatment with a meaningful improvement in outcome (Pollack, 1999).

The overall age pattern of brain tumors includes a peak incidence below five years of age, which declines gradually till the age of 20 years. The age pattern varies by tumor type (Velema and Percy, 1987). The peak age for ependymoma and medulloblastoma is in the 0-4 year age group and peak for pilocytic astrocytoma is in the 5-9 year age group (Central brain tumor registry of United States; CBTRUS data for 1990-1993)

Pediatric neuro-oncology is a relatively new discipline in Pakistan and only a handful of studies are available for comparison. Khan et al (1983) conducted a study to determine the frequency of cancer in childhood (< 14 years of age) and concluded that the overall frequency of brain tumors at JPMC was 9%. Later in 1987, Malik reviewed 67 cases of pediatric brain tumors (total 245 cases) and determined that the frequency of childhood brain tumors is 27.3%. Akram (1995) conducted a retrospective study (1989 to 1995) on solid pediatric malignancies and estimated that the frequency of pediatric brain tumors at JPMC was 22.2%. Thus suggesting a rise in pediatric brain tumors over the years or an increased awareness or availability of better diagnostic facilities.

The objectives of the current study were to determine the frequency of brain tumors during infancy and childhood and to define and segregate childhood brain tumors vis-à-vis their histological characteristics.

Materials and Methods

The present study includes the epidemiological scrutiny of pediatric brain tumors, ICD-10 category C71 received during 10 years (January 1989 through December 1998) at the Department of Pathology Basic Medical Sciences Institute (BMSI) Karachi. Most of the cases were received from JPMC whilst a few cases were from private hospitals. We followed the Rorke et al (1985) criteria for diagnosis and classification but excluded meningeal tumors, paraganglioma and pituitary tumors from this study. The justification was that meningioma are derived from the covering of brain, paraganglioma are tumors of adjacent region infiltrating into brain and the pituitary tumors are tumors of neuroendocrine system.

The variables registered were surgical pathology number, age, sex, site of the tumor, hospital in-patient number and radiological findings. These were obtained from the surgical pathology registers, request cards and copies of surgical pathology reports. The reported epidemiological cancer data were rechecked. All surgical specimens were initially evaluated on Hematoxylin and Eosin (H&E) stained slides which were either retrieved from archived files of the Pathology Department or fresh

Table 1. Distribution of Brain Tumors by Morphological Subtypes by Gender and Age Groups

S. No	Morphological subtypes	Gender			Age Groups		
		Male	Female	M:F	1	2	3
1-	Astrocytomas						
	a) Pilocytic astrocytomas	9	3	3:1	1	8	3
	b) Gemistocytic astrocytomas	-	1	0:1	-	1	-
	c) Grade II	6	1	6:1	1	6	-
	d) Grade III	2	1	2:1	-	-	3
	e) Anaplastic astrocytomas	2	-	2:1	-	1	1
	f) Glioblastoma multiforme	2	1	2:1	-	1	2
2-	Oligodendroglioma	-	1	0:1	-	1	-
3-	Ependymoma	6	2	3:1	3	3	2
4-	rimitive neuroectodermal tumors						
	a) Medulloblastoma (classical)	10	5	2:1	3	6	6
	b) Medulloblastoma (desmoplastic)	5	3	2.7:1	2	4	2
	c) Medulloblastoma é astrocytic differentiation	11	1	11:1	2	7	3
	d) Medulloblastoma é neural differentiation	2	-	2:0	-	2	-
	e) PNET with rhabdoid differentiation	-	1	0:1	-	1	-
	f) Neuroblastic medulloblastoma	1	-	1:0	-	-	1
	g) Pineoblastoma	-	1	0:1	-	-	1
5-	Mixed gliomas						
	a) Oligoastrocytoma	1	1	1:1	-	2	-
	b) Astroependymomas	1	1	1:1	1	-	1
	Total	58	23		13	43	25

1= 0 - > 5 years, 2= > 5 - < 5 years, 3 = > 10 - < 15 years

sections cut from preserved paraffin blocks. Four sections, 3-4 micron were cut from each paraffin block, one was stained with H & E, one placed on a poly L-lysine coated slide for immunohistochemical staining (GFAP). The rest of the sections were kept for special staining as and when required. Special stains used were Phosphotungstic acid Hematoxylin (PTAH) stain, Cresyl fast violet (Nissl) stain, Reticulin stain, Periodic acid Schiffs (PAS) stain, Periodic acid Schiffs diastase (PASD) stain, and Trichrome stain. GFAP staining was performed on all cases by "Avidin Biotin Complex" (ABC) method using monoclonal mouse antihuman glial fibrillary acidic protein (DAKO @ code No. M0761) along with labeled strepavidin biotin (LSAB) kit (DAKO @ code No. K680).

All slides were reviewed under scanner (X10, X4), low power (X10, X10) and high power (X10, X40) lenses. While reviewing the slides the criteria and gradation defined by Paulus and Pieffer (1989) were followed but calcification, stromal background changes and giant cell formation were added to their gradation criteria. Mitosis was defined in number and grouped in a score of 1 to 3. Astrocytic tumors were graded following the St. Anne Mayo grading system. The results of immunohistochemical staining were evaluated by observing the whole area of neoplasm by sequentially examining lower power (X10) optical fields in the sections. The data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition) and computerized and analyzed using SPSS 13.

Results

The current cross sectional study is based on the epidemiological, histopathological and immuno-histochemical (GFAP) review of pediatric brain tumors (below 15 years age) received during 1989 – 1998 in the Department of Pathology, JPMC, Karachi.

A total of 74,590 surgical pathology specimens were received during the study period, out of which 1115 (1.49%) were neuropathology specimens. Six hundred and three cases (54.08%) out of the 1115 cases were intracranial while 509 (45.65%) were extracranial. Two hundred and eighty three (25.38%) neuropathology cases were of the pediatric age group (below 15 years age) and of these, 133 (47.0%) lesions were intracranial and included 83 neoplasms, 26 inflammatory lesions and 4 congenital malformations.

Eighty one cases out of the 83 pediatric neoplasms could be included in the study as the slides and blocks of two cases were not available. This included 58 (71.6%) cases in males and 23 (28.4%) in females with a male to female ratio of 2.5:1. A distinct male predominance was noted in all histological types as shown in table 1. The cases of the present study were divided into 3 age groups each covering five years of life (0-4, 5-9, 10-14 years) to highlight the sex distribution and age frequency amongst each age-group band. The maximum number of cases (43 cases - 33 males, 10 females) were observed in the second age group i.e. 5-9 years followed by 25 cases (17 males, 8 females) in the third age group i.e. 10-14 years and the least cases (13 cases - 8 males, 5 females) were observed in the youngest (0-4 years) age group. The youngest case was a 4 month male baby suffering from medulloblastoma. The mean age for all cases was 8.8 years (95% CI 7.9; 9.6) with a marginal variation for cases occurring in the cerebrum and cerebellum. On the whole the malignancies occurred at a younger age in the males for each subcategory by site and morphology (Table 2).

Table 2. Mean, Minimum and Maximum Age Range of Pediatric Tumors

	Both genders			
Ages in years	Mean Age (95% CI)	Minimum age	Maximum age	Age range
All cases	8.8 (7.9; 9.6)	0.4	15	14.6
Cerebral	8.6 (7.2; 10.1)	2.0	14	12
Cerebellum	8.9 (7.9; 9.9)	0.4	15	14.6

The morphological distribution of cases was astrocytoma (28 cases, 34.6%), primitive neuroectodermal tumor or PNET (40 cases; 49.4%), ependymoma (8 cases, 10%), mixed glioma (4 cases; 5%) and a case of oligodendroglioma. The 81 malignancies included in this study were further categorized by site into two groups, supratentorial (27 cases; 33.3%) and infratentorial (54 cases; 66.7%), the latter comprising of 2/3rd of the cases in the current study. The morphological categorization of supratentorial tumors was astrocytoma (17 cases; 63%), ependymoma (5 cases; 18.5%), mixed glioma (2 cases; 7.4%), PNET with rhabdoid differentiation, oligodendroglioma and pinealoblastoma comprised 1 case (3.7%) each. The supratentorial astrocytoma were graded as follows - pilocytic astrocytoma (5 cases; 29.4%), grade II astrocytoma (6 cases; 35.3%); grade III astrocytoma (2 cases; 11.8%), anaplastic astrocytoma (1 case; 5.9%) and glioblastoma multiforme (3 cases; 17.7%).

The morphological categorization of infratentorial tumors was astrocytoma (11 cases; 20.4%), medulloblastoma (38 cases; 70.4%), ependymoma (3 cases; 5.6%) and mixed glioma, astroependymoma (2 cases, 3.7%). The morphological categorization of infratentorial astrocytoma was pilocytic astrocytoma (7 cases, 63.6%) with gemistocytic astrocytoma, grade II astrocytoma, grade III astrocytoma, and anaplastic astrocytoma comprising 1 (9.1%) each. The morphological categorization of medulloblastoma was classical medulloblastoma (15 cases; 39.5%), desmoplastic medulloblastoma (8 cases; 21.1%), medulloblastoma with astrocytic differentiation (12 cases; 31.5%), medulloblastoma with neural differentiation (2 cases; 5.3%), and neuroblastic medulloblastoma (1 case; 2.6%).

Discussion

The current study was designed to segregate pediatric brain tumors from adult tumors and to determine the frequency, morphologic patterns and immuno-histochemical (GFAP) expression in these tumors. Brain tumors are the most common solid tumors that affect children of all ages, ethnicities and races, albeit with variations.

The number of cases in Karachi (81) registered over a

decade seem trivial for a tertiary care hospital and probably are a reflection of lack of accessibility and availibility of specialized health care systems. The other plausible reasons may be a lower occurrence of brain tumors either due to a diminished ethnic or racial predisposition and or a lower prevalence of risk factors. A racial proclivity was proposed by Froman and Lipsschitz in 1970. Their findings were supported by Annegers and Laleologos in 1994, when they reported a higher frequency of brain tumors in the white American population. The difference in race was also documented by Gurney et al in 2001, which clearly identifies that CNS tumors are more common in white children compared to black children, with an 18% higher rate between 1900 and 1995. The greatest difference was seen in white males at a 26% higher rate, compared to an 8% higher rate for white females.

It is not possible to calculate the incidence as this is a hospital based study. However the frequency of pediatric brain tumors in solid pediatric malignancies was 22.13%. In earlier studies, a lower frequency was reported. Grover and Hardas (1972) reported that the frequency of pediatric brain tumors in Bombay Cancer Registry was 8.2%. Khan et al (1983) reported that the frequency of childhood brain tumors in their institute was as low as 9%. Moreover, they emphasized that this low frequency was a result of environmental and regional differences. In contrast Akram et al (1995) conducted an epidemiological study covering 1989 through 1995 and according to them the frequency of pediatric brain tumors among solid pediatric malignancies was 22.2%, findings more in line with the present study. We feel that Khan et al (1983) may have made an erroneous judgment, and attributed the lower number of cases to racial protection rather than a hospital-based bias. The low frequency rates reported by Grover and Hardas (1972) and Khan et al (1983) could also be due to the non-availability of sophisticated radio-imaging techniques during that era. That era of developing countries also had limitations of histopathological diagnostic expertise and treatment options.

The tumor site and morphology of pediatric tumors has also remained a point of argument. Two thirds of the cases in the current study were infratentorial and the largest morphological subcategory was medulloblastoma. These findings compliment most published data on the subject, which also report a predominance of infratentorial tumors, though there are controversies. The controversies over the morphological hierarchy are more diverse with medulloblastoma and astrocytoma competing for the coveted highest frequency. These controversies arise probably because arbitrary definitions are used by individual scientists, whilst defining the studies, thus making them non-comparable. In the case of pediatric brain tumors the age limits used for certain developmental periods (e.g. the widely divergent ages of 12, 15 and 20 years for the upper limit of childhood) and the definition of age itself (meaning age at the time of first clinical symptoms or at diagnosis) and in the different approaches to histopathological diagnosis, as the terminology and classification of certain tumors have either changed or been handled arbitrarily over the years (Rickert et al., 1997).

The vast majority of published data, support medulloblastoma as the predominating pediatric brain tumor morphology (Packer at al, 1990, Mosso et al 1990). A preponderance of medulloblastoma was reported by Packer et al in 1990 with 74 (36%) PNET; 57 (28%) cerebellar astrocytoma and 18 (9%) ependymoma. Mosso et al in 1992 produced the results of childhood cancer registry of Torino (Italy) over a period of 20 years. In this series medulloblastoma were 56/293 (19.11%), astrocytoma 80/293 (27.3%), ependymoma 14/293 (4.78%) while a significant number of cases [80/293 (27.3%)] were labeled as "not otherwise specified". The findings of the various studies are tabulated in Table 3.

A few studies have also reported a preponderance of astrocytoma in their series. This is most often seen in studies where the upper limit of the pediatric age was 20 years. Farewell et al, in 1977 reported a series of 488 pediatric CNS tumors (467 intracranial) over a period of 39 years. In their study astrocytoma comprised 28%, medulloblastoma 25% and ependymal tumors 9% of the total. They considered glioblastoma multiforme as a separate entity which accounted for 9% of the intracranial tumors. Gurney et al in 1995 reporting data from the National Cancer Institute for the years 1974- to 1989 reported that astrocytoma and astroglioma comprise

Table 3. Morphological Distribution of Pediatric Brain Tumors, Comparison of Current Study and other Published Studies

Reference	Period of study	Total n=	Medullob lastoma %	Astrocyt-oma* %	Ependy moma %	Mixed Gliomas %	Oligoden droglioma%	Cerebellar Astrocyto mas %
Present study	1989-98	81	48.15	34.60	9.91	4.9	1.2	-
Farewell, et al (1977)	1935-73	467	25.0	28.0_	9.0	-	-	-
Humphrey (1982)	1950-75	451	24.19	12.64	8.0	1.11	-	24.61
Zaman (1990)	1988-89	20	40.0	-	10	-	-	40.0
Packer et al., (1990)	1975-85	207	36.0	-	9.0	4.0	-	28.0
Mosso et al., (1992)	1967-86	293	19.11	27.3	4.78	27.3	-	-
Gurney et al., (1995)	1974-89	2205	23.9	60.9	8.0	-	-	-
Khan et al (1983)	1993-95	30	46.7	40.0	13.3	-	-	-
Nazir (1995)	1991-95	20	-	65.0	5.0	-	-	-
Pollack (1999)	Based on several series	-	21	35.0	7.0	-	3.0	15.0

*= Astrocytomas excluding cerebellar astrocytomas except present study; _ = glioblastomas were considered a separate entity and accounted for 9%; _ =a All infratentorial tumors; _ = All supratentorial tumors;

60.9% of CNS tumors while PNET were 23.9% and ependymoma were 8.0%. Nazir (1995) studied 20 supratentorial brain tumors in children (below 16 years of age) through 1991- 1995 at PIMS. In his series 13/20 (65%) were astrocytoma while only 1 case (5%) was reported as ependymoma. Zaman in 1990 reported a series of 20 patients with 8 (40%) medulloblastoma and astrocytoma each and 2 (10%) ependymoma (table 3).
In children 70 % of brain tumors are infratentorial and 30% are supratentorial whereas it is vice versa in adults (Rosai, 1995). Posterior fossa tumors comprise a great number of childhood brain tumors (Robison et al, 1991). Pollack (1999) described statistics based on several studies and concluded that 48% of the pediatric brain tumors were infratentorial while 52% were supratentorial. Astroglial and mixed tumors in his results were 35%. The relative frequencies of PNET, ependymoma and oligodendroglioma were 21%, 7% and 3% respectively. He also subcategorized cerebellar astrocytoma and stated that this entity accounts for 15% of all pediatric brain tumors.

Compared to the previously published studies our series has a higher number of medulloblastoma. PNET are about half of the brain tumors; followed by astrocytoma and ependymoma. We followed the Rorke et at, (1985) theory and included the pineoblastoma under the heading of PNET. We did not segregate cerebellar astrocytoma since our study is a morphologic study but we have noticed that most of the astrocytoma located in the cerebellum had pilocytic morphology, which strictly cannot be included as malignant neoplasms. Not including them would further decrease the astrocytoma component of our series. Low frequency of astrocytoma could be due to smaller number of patients included in our study and may not reflect the overall incidence of the tumors. Oligodendroglioma are less frequent in childhood as is evident by various surveys including the present study. Ependymoma have a frequency of less than 10% in almost all surveys.

Data published by Gurney et al in 1995 also concluded that the majority of neoplasms that occur during the first two years of life are PNET. As the age advances there is a substantial increase in the gliomas of the brain. According to their results the incidence of childhood brain tumors is 27.6 per million children per year. This breakup of data further corroborated that there is extensive variation in rates of childhood brain tumors across individual years of age. The pattern is different for early childhood than that of the late childhood. Humphreys (1982) reported a series of 451 infratentorial brain tumors from Hospital for Sick Children (Toronto) during 1950 - 1975. In his series there were 125 (24.79%) PNET; 106 (24.61%) cerebellar astrocytoma and 36 (8%) ependymoma.

The frequency of intracranial childhood cancers as a component of all intracranial tumors irrespective of age varies in different studies. Wen-Qing et al, (1982) in a review of twelve large series of brain tumors highlighted that the below twenty years age group was 24.27%. This is a striking contrast of the age distribution of the cancer. According to Wen-Qing et al, (1982) the frequency of childhood brain tumor was 18.61 % they also admitted that frequency vary with different authors; Zulch and Mennel (8 %), Cushing (13.7 %), Katsura et al, (19 %), Dastur and Lalitha (16.8 %), Shuagshoti and Panyathanya (25.6 %). The mean age for all cases in Karachi was 8.8 years, with a marginal variation for malignancies arising in the cerebrum and cerebellum. This is higher then the mean or median age reported by other authors. The median age at diagnosis was 6 years with a male-to-female ratio of 1.3:1, in a study published by Farwell et al in 1977.
When divided into subgroups i.e. 0-5; >5 to<10 and >10 to <15 years of age; the tumors are more frequent in second age group i.e. 43/81 (53.1%). This finding is contrary to Velema and Percy (1987) who reported a peak incidence during first four years of life. However, results from Gurney et al, (1995) support our results. They reported a distinct increase in 4-8 and 5 – 10 years of age group for astroglial astrocytoma. Our findings are higher than the international literature while closer to the studies conducted in our region.

Conclusion

The current study is a single institution based cross sectional study and needs to be interpreted with care. Population-based studies are required to determine the precise cancer burden of our childhood population.

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