ORIGINAL ARTICLE

Clinical Presentation of Supratentorial and Infratentorial Pediatric Brain Tumors in a Tertiary Care Hospital of Bangladesh

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Abstract

Introduction: *Intracranial tumors are the second most common malignancy in childhood and the most common solid tumors in children. They are the most frequent cause of morbidity and mortality associated with cancer in this age but there is no epidemiological study of pediatric brain tumors in Bangladesh. The objective of this study was to determine the clinical presentation of supratentorial and infratentorial intracranial pediatric tumors among children of Bangladesh.*

Methods: *A descriptive cross-sectional study was conducted in the Department of Paediatric Haematology and Oncology, National Institute of Cancer Research and Hospital from 2014 to 2018 in which clinical manifestations of 129 pediatric patients with intracranial tumors were recorded.*

Results: *Total 129 patients were analyzed. Tumor location was supratentorial in 62 patients (48.06%) and in infratentorial 67 (51.94%) patients. Total cerebellar syndrome occurred in 47 patients (36.43%). The supratentorial tumors with cerebellar syndrome were nine (6.98 %) patients and infratentorial tumors were 38(29.45%) patients. Cranial nerve palsy was significantly more common (N-24,18.6%) in patients with infratentorial tumors than supratentorial (N-16, 12.40%) tumors. Time needed from symptoms start to diagnosis/start of treatment in supratentorial tumors was more than infratentorial tumors and it was statistically significant.*

Conclusions: *Cerebellar syndrome and cranial nerve palsy were more common in patients with infratentorial tumors and statistically significant when compared with patients with supratentorial tumors. The interval between onset of symptoms and diagnosis or start of treatment of intracranial tumors were longer in supratentorial tumors, which was statistically significantly.*

Keywords: *Tumor, Intracranial tumour, Supratentorial tumour, Infratentorial tumour*

Journal of Green Life Med. Col. 2021; 6(1): 15-21

Introduction:

Intracranial tumors are relatively common in infants and young children.[1] An estimated 160,000 new cases of children below 15 years of age are diagnosed with cancer each year worldwide, with 90,000 deaths attributed to cancer.[2] Intracranial tumors are the second most common neoplasm in childhood; they account for 16.6 to 21% of all malignant neoplasms in children[3] but is still at a very nascent stage in the developing countries with only a few reports on the multidisciplinary approach.[4] In USA its annual incidence is 2.5 cases per 100,000.[5] In addition, they are the most common solid tumors at pediatric age and the most frequent cause of cancer-related morbidity and mortality in this group of patients[6,7] but there are not many studies in Bangladesh which have looked into the clinical presentations, pathological types, sides of involvement of pediatric brain tumors.

Little is known about the causes of brain tumors in children. Children with one of several genetic disorders including tuberous sclerosis and Li-Fraumeni syndrome are at increased risk, as are children who have received therapeutic irradiation to their head. The evidence that frequent cured meat consumption by the mother during pregnancy increases the risk is suggestive but not conclusive. For other potential risk factors, the evidence is limited and/or conflicting. These exposures and characteristics include pesticides, carcinogen metabolizing genes, and polyoma viruses.[8]

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Received: 11.10.2020 **Accepted:** 26.12.2020

Intracranial tumors location differs considerably in percentage according to the studied population: infratentorial (IT) tumors range from 21 to 67%; supratentorial (ST) tumors, from 30 to 64%, and those invading both spaces, from 2 to 15%, according to conducted studies.[9] Most of the study found that the ST tumors are less than IT tumors and Albright at al reported 30% to 40% of tumors are supratentorial in origin.[10] YU J et al reported 43.8% were suptratentorial[11] in a hospital of Fudan University , China.

In a study by Poretti et al, infratentorial tumors (IT) account for 45– 60% of all pediatric brain tumors, and the most common infratentorial tumors include juvenile pilocytic astrocytoma (JPA), medulloblastoma, ependymoma, and brainstem glioma.[12] The reason why pediatric brain tumors have a propensity to occur in the posterior fossa has not yet been elucidated.[13]

The diagnosis of a brain tumor is often difficult to establish in a child, because many of the signs and symptoms may mimic those of more common childhood illnesses. Brain tumors produce neurologic symptoms that vary depending on the size, location, and invasiveness of the tumor.[14] In a study by El-Gaidi et al from Egypt, in case of supratentorial tumors main presenting features were – headache, vomiting, macrocephaly, disturbed conscious level, diminution of vision, squint, opthalmoplegia, ataxia , weakness and convulsions. On the other hand clinical features of infratentorial tumors were - vomiting, headache, visual disturbances, ataxia, weakness, cranial nerve involvement.[15] The treatment of intracranial tumors depends on the size and type of tumor, as well as on the child's general health status. The goal of treatment is total resolution of the tumor, symptom cessation and function improvement. Surgical intervention is necessary in most tumors and some can be completely removed. Chemotherapy and radiotherapy can be used for certain tumors.[16,17]

The objective of this study was to obtain useful and applicable information to establish clinical diagnosis of patients affected by symptoms consistent with neurological involvement that drive to the suspicion of ST or IT tumors-related intracranial involvement, on any of their initial presentations, in order to help accelerating opportune diagnosis and treatment.

Methods:

This study was conducted in the Department of Pediatric Hematology and Oncology (PHO), National Institute of Cancer Research and Hospital (NICRH) during year 2014 to 2018. Pediatric patients of 0-17 years (less than 18 years) of age diagnosed with brain tumors were included in this study. Intracranial tumors were confirmed by histology and immunohistochemistry (if needed) except few mid brain tumors, which were leveled by radiological diagnosis. Medical records were collected regarding age and gender distribution, clinical presentation, location and pathological types using the most recent 2007 World Health Organization (WHO) Classification of tumors of the Central Nervous System (CNS). Patients with inadequate medical records were excluded from this study

Data were analyzed using SPSS software.

Results:

Total recorded patient of intracranial and spinal tumor at PHO during 2014-2018 were 260. Among them CNS tumor were 137 but during analysis we used data from 129 patients with intracranial tumors and 8 spinal Tumors were excluded from study. These 129 patients, diagnosed with intracranial tumors, with a mean age were 8.73 ± 4.18 years.. There were 40 patients (31.01%) of the female and 89 (68.99 %) of the male gender. Tumor location was infratentorial (IT) in 67 patients (51.94%) and supratentorial (ST) in 62 patients (48.06%). Average time elapsed for start of treatment 6.63±8 months (Range 15 days -48 months). Most of the patients came from Dhaka division (N-24,18.60%) and Chittagong division(N-23,17.83%). All most all children's family were poor (N-103, 79.84%), 18.6% (N-24) were middle income group and only 1.55 %(N-2) patients families were rich. Three patients (2.33%) have family history of cancer. 82.17% (N-106) patients lived in village, rest of the in town.

Table-1 depicted the clinical features of our study patients. Intracranial hypertension manifested mainly as headache and vomiting. Headache occurred in 107 patients (82.95%). Among 107 cases 54 children (41.86%) with IT tumors and 53(41.9%) children with ST tumors (p = 0.89). Vomiting were in 46 (35.65%) children with ST and 51(39.54%) cases with IT tumors.

Cerebellar syndrome in the form of ataxia, dysmetria, dysdiadochokinesia, nystagmus, intention tremor occurred in 9 patients (6.98%) with ST tumors and 38(29.45%) with IT tumors (p = 0.043; 95% confidence interval). Seizures occurred in 4 patients ((3.1 %) with ST tumors and 10 (7.75%) with IT tumors (p = 0.83). Visual disturbances were present in 34 patients (26.35%) with ST tumors and 22 (17.03 %) with IT tumors (p = 0.106). Cranial nerve palsies occurred in 16 patients (12.40%) with ST tumors and 24(18.6%) with IT tumors (p =. 026). Facial nerve was the most common involved nerve.

Table-I

Clinical Feature and scintigraphy of ST and IT tumors

Clinical Feature	Total (n-129)	ST tumors (%)	IT Tumors (%)	P-value
Headache	107(82.95%)	53 (41.09%)	54(41.86%)	0.89
Vomiting.	97(75.18%)	46(35.65%)	51(39.53%)	0.665
Cerbellar Syndrome	47(36.43%)	9(6.98%)	38(29.45%)	0.043
Visual disturbances	56(43.41%)	34(26.35%)	22(17.06%)	0.106
Cranial Nerve Palsy	40(31.0%)	16(12.40%)	24(18.6%)	.026
Seizures	14(10.85%)	4(3.1 %)	10(7.75%)	.83
Fever	18(13.95%	8(6.2%)	10(7.75 %)	.686
Nasal_Block	12(9.3%)	8(6.2%)	4(3.10 %)	.285
Neck pain	2(1.56%)	1(0.78%)	1(0.78%)	
CSF diversion	39 (30.24%)	9(6.98%)	30(23.25%)	0.223
Unconscious	1(0.78%)	00%	1 (0.78%)	
Macrocephaly	49(37.99%)	10(7.75 %)	39(30.24%)	.87
Time needed to diagnosis in months	6.63±8 (mean)	24.1±2.8	3.2±7.5	000
Hydrocephalus.	28 (21.7%)	8 (6.2%)	20 (15.5%)	0.223

Cerebellar Syndrome- Ataxia, Dysdiadokinasia, Dysmetria, Nystagmus, Intention tremor.

Other less common manifestations were: Fever in 8 patients (6.2%) with ST tumors and 10(7.75 %) with IT tumors. Nasal block were 8 patients (6.2%) with ST and 4(3.10 %) with IT tumors. Neck pain was in 1 patient (0.78%) with both ST and IT tumor. Unconscious was present in 1 patient only with IT. Cerebrospinal Fluid (CSF) diversion by shunt was 6.98% in ST and 23.25% in IT. Macrocephaly was found in 37.99% (N-49) cases and time needed for diagnosis i.e. from start of symptoms and start of treatment were means 6.63±8 months, where ST with 24.1±2.8 months and IT with 3.2±7.5 months. Hydrocephalus was detected in 8 patients (6.2%) with ST tumors and 20 (15.5%) with IT tumors.

All cases (N-129) were not possible to evaluate about the nature of tumor cells. Five Brain Stem SOL was diagnosed by radiologically and were not possible to take biopsy. Among 124 cases, benign tumors were 19.35% (N-24/124), malignant tumors were 80.65% (N-100/124). Brain stem tumors were 7 in number, 5 tumors were not possible to evaluate pathologically but other two were evaluated as glioma (malignant). Histological varieties of ST tumors (Table-II) were: Astrocytic tumours (23; 17.82%)), Ependymal tumours (20;15.50%), Craniopharyngioma (5,3.86%) Germinoma (4; 3.10%) Meningioma (4; 3.10%). Oligodendroglioma, Ganglioglioma, Malignant peripheral nerve sheath tumor (MPNST), papillary tumor of Pineal Gland, Astroblastoma, Giant Cell Tumor of Soft Tissue- each tumor was one (0.78%) in number. In ST tumors 15(12.10%) were benign and 47(37.90) were malignant tumors. Location of Supratentorial tumors are depicted in Table-III.

Table-II

Distribution of Supratentorial Tumors.

Sl.No	Diagnosis	Number (%)	Remarks
1.	Astrocytic tumours(Pilocytic,Glioblastoma multiformis, Anaplastic, Pleomorphic xanthoastrocytomas,Gient cell)	23(17.82%)	
2.	Ependymal tumours	20 (15.50%)	
3.	Craniopharyngioma	5 (3.86%)	
4.	Germinoma	4 (3.10 %)	
5.	Meningioma	4 (3.10%)	
6.	Oligodendroglioma	1 (.78%)	
6.	Ganlioglioma	1(.78%)	
7.	Malignant peripheral nerve sheath tumor (MPNST)	1(.78%)	
8.	Papillary tumor of Pineal Gland	1(.78%)	
9.	Astoblastoma (Neuroepithelial Tumor)	1(.78%)	
10.	Giant Cell Tumor of Soft Tissue	1(.78%)	
11.	Benign: Malignant	15:47	(Ratio-1: 1.33)
	Total	62 (48.06%)	

For IT tumors (Table-IV), histological types were confirmed by biopsy or Immunohistochemistry except 5 cases, where biopsy were not possible and leveled by MRI report (Brain stem SOL). The Infratentorial tumors were the following: Medulloblastoma (N-38; 29.46%), Astrocytoma, (N-10; 7.75%) Ependymoma (N-10; 7.75%), brain stem SOL (N-7; 5.42%). Schwannoma and Meningioma both tumor was one (0.78%) in number. In IT compartment 9(7.25%) were benign and 53(42.75%) were malignant tumors. Five mid brain tumors were not possible to evaluate.

Table-III

Location of Supratentorial tumors

Sl.	Location of tumors	Number & Percentage
1.	Cerebelum (Frontal, Temporal Parietal, OccipitaL)	42(66.65%)
2.	Sella	11(17.46%)
3.	Thalamus	6(9.53%)
4.	Pineal Region	3(4.76%)
5.	Basal Ganglia	1(1.60%)
	Total	63 (62+1)

N.B: one tumor was both in Sella and Thalamus.

Histological grading of brain tumors (Table-V) were done according to the 2016 CNS WHO classification. Total 97 pathological reports were considered for evaluation as other biopsy reports (N-27) did not mentioned adequate information to do grading. Most common types were Grade-2 (N-36, 37.11%) then Grade-4(N-30, 30.93%), Grade-1(N-19, 19.59%) Grade-3 (N-12, 12.37%).

Table-IV

Distribution of Infratentorial Tumors.

	Diagnosis	Number (%)	Remarks
1.	Meduloblastoma	38(29.46%	
2.	Astrocytoma (Pilocytic, Glioblastoma multiformis, Anaplastic, Pleomorphic xanthoastrocytomas. Cerebellar Astrocytoma.	10 (7.75%)	
3.	Ependymoma	10(7.75%)	
4.	Brain stem Space occupying lesion (5 undiagnosed SOL+2 Glioma)	7 (5.42%)	
5.	Schwannoma	1 (0.78%)	
6.	Meningioma	1 (0.78%)	
7.	Benign: Malignant	9:53	Ratio- 1: 5.88
8.	Total	67 (51.94)	

NB: 5 tumors were not evaluated by biopsy

Table-V

Histological Grading of Brain Tumors (2016 CNS WHO)

	Grade	Frequency (%)	Remarks
1.	Grade-1	19 (19.59%)	Low-grade:56.70%
2.	Grade-2	36 (37.11%)	
3.	Grade-3	12 (12.37%)	High-grade:43.3%
4.	Grade-4	30 (30.93%)	
	Total	97 (100%)	

Surgery represents the initial treatment for the majority of pediatric brain tumors and in some cases it is the only treatment modalities.Table-VI delineated brain tumors removal types.

Table-VI

Tumors Removal

1.	Type of tumor removal	Frequency (%)
2.	Total removal	45 (34.88%)
3.	Gross Total	27 (20.93%)
4.	Partial removal	25 (19.38%)
5.	Only Biopsy	5 (3.88%)
6.	Not mentioned/Not operated	27(20.93%)

Treatment plan was represented in Table-VII.Therapeutic surgery was performed in 114 (88.37%) cases, and 121 patients (93.79 %) have got chemotherapy. Surgery and Radiotherapy without chemotherapy got 8 patients.

Table-VII

Treatment of ST and IT tumors

Treatment Type	Frequency(%)
Surgery+RT+CT	105 (81.40%))
RT+CT	15 (11.63%)
Surgery+RT	8 (6.20%)
Surgery+CT	1 (.77 %)
Total	129 (100%)

Discussion:

Intracranial tumors are the second most common neoplasm in childhood. They are the most common solid tumors at pediatric age and the most frequent cause of cancer-related morbidity and mortality in this group of patients. [11,12,18]

Intracranial tumors location differs considerably in percentage according to the studied population, country and region. In Kuwait the frequency of childhood primary brain tumors is high with 43% ST and 57% IT. [19]

Consistent with the findings of other international pediatric brain tumor studies,[20]in this study supratentorial (ST) were 62 (45.06%) and infratentorial (IT) were 67 (51.94%). Most of the study stated infratentorial tumors are more than supratentorial tumors. Mean age of our patients were 8.73 ± 4.18 years, Male Female ratio was 2.22:1. Most international study reported male predominance. Rickert and Paulus et al [21] in their meta-analysis of 10,582 childhood brain tumors accumulated from 16 international surveys, reported that the M/F ratio was 1.29:1. Conversely, a few studies, albeit with smaller numbers of patients, have reported a slight female predominance.[22,23] Average time elapsed for start of treatment 6.63 months (Range 15 days - 48 months). But Boutahar FZ et al from Morocco found that the median time to diagnosis was 2 months (range, 0.25–20 months).The longest times to diagnosis occurred in children older than 5 years and in patients with supratentorial tumors or low-grade glioma.[24] About 79.84% of patients of this series were poor economically and it may be the causes of delayed diagnosis and start of treatment than other studies. Only 3 patients (2. 33%) have family history of cancer in our study, though, It is not clear if family history of cancer increases risk of cancer in children.[25] Benign tumors were 19.35 % (N-24/124), Malignant tumors were 80.65 % (N-100/124). It is perhaps difficult to calculate the share of over all intracranial benign and malignant tumors. In USA there is also huge variability in the reporting of tumors among U.S. states, with the percentage of nonmalignant tumors varying from 27% to 60% of overall (childhood) CNS tumors.[26]

Clinical signs and symptoms are usually not specific in childhood brain tumor, therefore causing diagnostic delay. Increase intracranial pressure like headache and vomiting were the most common presentation of brain tumors. In our series headache and Vomiting were more (41.86% and 39.54% respectively) in IT than ST (41.09%, 35.65% respectively) tumors. Headache in those cases is characteristically irresponsive to usual medications. There were two patients age below two years and in both the patients presented as inconsolable crying, vomiting and bulging anterior frontanelle. None of the symptoms were statistically significant (p-0.89 and p-0.66 respectively). Sánchez-Sánchez et al[27] found same result in headache and vomiting with ST tumors (42.1%, 63.6% respectively) but much higher figure in IT tumors (68.7%, 84%). The prevalence of intracranial hypertension in posterior fossa tumors coincides with the incidence of hydrocephalus. In our series hydrocephalus was found 15.50% and 6.2% in IT and ST tumors respectively but statistically is not significant (p-0.223). El-Gaidi et al reported from Cairo a much large figure of hydrocephalus (84.30% and 29.60% respectively) in IT and ST tumors.[14]

Cerebellar syndrome like ataxia, dysdiadokinasia, dysmetria,nystagmus,intention tremor were reported more common in IT than in ST tumors (29.45% vs. 6.98%). This data were statistically significant (p-0.043) and finding correlate with the findings of El-Gaidi et al[14] where ataxia in IT and in ST tumors were 33 % and 2.4% respectively.

Seizures were more frequent in IT than ST tumors ((7.75% vs 3.1%) in our study and no statistically significant difference was found. However, the percentages found in this case series are reverse to those reported by other authors, like Sánchez-Sánchez et al [27] who reported convulsion in IT and ST were 9.3% and 21% respectively. Cranial nerves involvement is usually more common in those patients with IT-located tumors. The study we carried out is consistent with these findings of IT and ST tumors were 18.60% and 6.98%, which is statistically significant (p-0.026). Less significant syndrome were visual disturbances (ST vs IT - 26.35% vs 17.03%), Fever (ST vs IT - 6.2% vs 7.75%), Nasal Block (ST vs IT - 6.2% vs 3.10%), Neck pain, (ST vs IT- 0.78% vs 0.78%), Unconscious (ST vs IT- 00 % vs 0.78%). All were statically insignificant.

Time needed for diagnosis for ST was 24.1±2.8 months and 3.2±7.5 months in IT tumors. Many of our patients suffered from symptoms for years without diagnosis of brain tumors by CT scan / MRI evaluation. Mainly these types of patients suffer from ST tumors. Ansell et al in a comparative study conducted between patients with intracranial tumors and patients with symptoms but without an intracranial tumor diagnosis, found an up to 60-month diagnostic delay, due to the atypical, heterogeneous and insidious presentation of some tumors.[28] In this case series, we found that patients with ST tumors took more time (24.1±2.8 months) from onset of symptoms to diagnosis/start of treatment than IT tumors and statistically significant difference was found.

A study from Mexico by Sánchez-Sánchez et al [27] reported that the most common histological variant were astrocytomas where found in 23.5% of patients, medulloblastomas in 11.7%, and gliomas of different lineages in 25.4%. But in our series most common

intracranial tumors were medulloblastomas in 29.46%, then astrocytomas were found in 17.82% of patients and gliomas of different lineages (Ependymoma, Oligodendro giloma, Ganlioglioma) in 17.06%, which is different from reports of the aforementioned author, this data correlate with study of American Association of Neurological Surgeons [29] , where most common types of pediatric tumors were medulloblastomas, low-grade astrocytomas (pilocytic), ependymomas, craniopharyngiomas and brainstem gliomas.

The grade refers to how aggressive the tumor cells appear to be. The higher the grade, the more aggressive the tumor. In this study Low-grade tumors (WHO I/II) were 56.70% and High-grade were 43.30%. This data correlate with study of El-Gaidi et al [14] where Low-grade tumors (WHO I/II) constituted 62.5% of all cases and high-grade tumors (WHO III/IV) 37.5%. Internationaly Low-grade gliomas comprise the most common type of brain tumor in children.

Surgical resection, as a first step in the multidisciplinary treatment, remains the mainstay of treatment.[30-34] In this study Total removal were 34.88%, Gross total were 20.93%, Partial removal were 19.38% and only biopsy were 3.88%. Reports of 20.93% patients were not available due to incomplete operation note by surgeons/not operated at all. In a study of Amsterdam by Neervoort et al[35] pediatric brain tumors surgical intervention reported 66% were total resections, 26% subtotal resections, and 8% partial resection. Total tumor removal in The Netherland was double than ours and a significant number of our study reports were incomplete. All these indicate the need of our neurosurgical service, especially in pediatric neurosurgical aspects.

Future of Pediatric Neuro-Oncology

The field of pediatric neuro-oncology is changing rapidly, especially in the field of molecular biology. Many common primary brain tumors now can be categorized according to molecular markers, which someday soon will serve as the basis of risk stratification in clinical trials. Our improved knowledge in the field of molecular neuro-oncology will lead to discover enormous number of molecular-targeted biologic agents. Some of them currently are being studied in clinical trials for recurrent or refractory disease. It is the hope that one day, more specific targeted biologic therapies will replace conventional chemotherapy or radiation in the treatment of childhood brain tumors. One of the great limitations in achieving success of biologic-based treatments is the ability of these drugs to cross the blood–brain barrier. To overcome this gatekeeper, a number of treatment strategies, including gene-based delivery systems, immunotherapies, and convection-based drug delivery, currently are being investigated.

Limitation:

This study has some obvious limitations. Most importantly, it is the relatively small sample size and lack of data from patients at the start of syndromes. Most of the patients attended our department after removal of tumor. So initial signs and syndromes were collected from patient's or parent's verbal history and prescriptions of General Practioners. Some base line investigation like endocrine abnormalities were not possible to collect.

Conclusions:

Cerebellar syndrome and cranial nerve pulsy are more frequently observed in patients with IT tumors, with a statistically significant when compared with patients with ST tumor. On the other hand the time elapsed between the onset of symptoms and diagnosis of intracranial tumor is significantly longer in children with ST tumors than IT, since symptoms have a more insidious onset and are confused with other benign conditions and it is also statistically significant in this study.

Financial support and sponsorship: Nil.

Conflicts of interest : There are no conflicts of interest.

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