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Original Article

Medulloblastoma: A Common Pediatric Tumor: Experience of a Tertiary Care Cancer Center of Bangladesh.

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Abstract:

Background*: Medulloblastoma is a common malignancy in the paediatric population, accounting for 25% of all childhood brain tumors. The increasing magnitude of childhood cancer has become a threatening problem in developing countries like Bangladesh. But we have not enough data regarding the diseases of the children of Bangladesh. There is no literature available to shed light on Clinico-pathological types, diagnostic facilities and treatment patterns of this childhood cancer in our population. So this study is an opportunity to have experience about pediatric medulloblastoma of Bangladesh.*

Methods*: The study conducted from January 2014 to December 2018 at National Institute of Cancer Research and Hospital (NICRH). Data are collected from admitted children aged under 18 years in the department of Pa ediatric Hematology and Oncology (PHO) and confirmed by histopathology and/or immunohistochemistry after collection of tissues from pathological lab. The data were obtained from statistical analysis by PSPP software*

Results*: During 2014 to 2018 total diagnosed cases of childhood meduloblastoma were 57 but data were analyzed from only 52 patients. Male female ratio was 1.9:1. Median age of our patients was 6.12 years. Most common clinical features at pre-operative assessment were vomiting, headache, fever, convulsion, eye/vision involvement. Hydrocephalus was Present in 48 (92%) cases. Radiologically distal metastasis were found in 2 (3.85%) cases.*

Tumor resection was performed in all patients and total removal in 56.80% (N-25), gross total removal 25% (N-11), and partial removal 18.20% (N-8) and in 8 cases resection type were not elicited. Pathological grading were recorded in 52 patients , where all were Grade-IV (100 %).Within 22 months of follow up time absconded patients were 44.4%, partially treated cases are 9.6% with high death rate (23%). Regular treated cases with good outcome were 23%.

Conclusions: *Medulloblastoma is a challenging condition for neurosurgeon, radiotherapist and oncologists of Bangladesh. We have to reduce the abandon cases; review the risk stratification by using molecular profile and enhance the support service to improve the survival rate.*

RT- radiotherapy, CT-Chemotherapy, UB-Urinary Bladder.

All patients underwent preoperative Computed tomography (CT) or Magnetic resonance imaging (MRI) of head (Fig.1) But 90.4% (N-47) MRI/CT reports were able to given a proposed diagnosis like medulloblastoma or ependymoma, 5.7% (N-3) diagnosed as space occupying lesion (SOL) and 2 (3.9%) case didn't make any remarks regarding the brain lesion (Table-3).Tumors arise from midline (Vermis) were 71.15% (N-37) and from hemisphere were 28.85% (N-15).

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Introduction:

Medulloblastoma is a common malignancy in the paediatric population, accounting for 25% of all childhood brain tumors.[1] and accounts for approximately 30-40% of childhood posterior fossa tumors.[2,3] It is an embryonal tumor, located almost exclusively in the cerebellum, with an inherent tendency to metastasize via cerebrospinal fluid (CSF) pathways. While some genetic disorders (i.e.Gorlin syndrome, Turcot syndrome, Li—Fraumeni syndrome) are associated with an increased risk of medulloblastoma, for most patients the etiology is unknown.[4]

Medulloblastoma is referred to now as a primitive neuro-ectodermal tumor. The median age of diagnosis is 5 years, with 80% of cases being diagnosed in the first 15 years. But in Bangladesh, we have no population-based cancer registry which is necessary for determine the cancer burden of paediatric population and till now there are no study on paediatric medulloblastoma in our country. More over we have not enough knowledge about the presentations of the tumor, staging, surgical intervention, diagnostic accuracy and present treatment options available in Bangladesh of this feared disease.

Currently, risk stratification for patients is based on clinical features including age, degree of surgical resection and presence or absence of metastasis.[5] Standard of care treatment for children ³3 years entails surgical resection, craniospinal irradiation (CSI) and chemotherapy that has resulted in an overall cure rate of ~ 70 — 75%.[5,6] However, most survivors are left with long-term disabilities secondary to the disease and treatment.[7] In recent years, there has been progress in understanding the heterogeneity of medulloblastoma, which has led to further refinements of risk stratification and prognosis .[8.9]

Internationally the incidence of medulloblastoma is estimated to be 0.7 per 100 000 children[10] But lack of population-base cancer registry, we have no data regarding the burden of the diseases of Bangladesh.

So this prospective study was carried out in our department (PHO) to study the clinical features, radiological interpretation, diagnostic challenge, type of surgical intervention in the posterior fossa, finally current and future treatment strategies of medulloblastoma.

Materials and Methods:

This study was conducted in the Department of Paediatric Hematology and Oncology (PHO), NICRH during year 2014 to 2018. Demographic variables, clinical variables, radiological findings with respect to age, sex, signs and symptoms, location of tumor, extent of surgical resection, histopathology type, follow-up period and outcomes were recorded. Clinical features were collected from statement of patients/ parents and records of general practitioner. Biopsy tissues were collected from respected pathological lab and confirmed by histology and/or immunohistochemistry.

In our department (PHO) treatment protocols are based on risk stratification (Table-1), which took into account age at presentation, residual disease [residual tumor at the primary site after surgery measured by postoperative gadolinium– enhanced magnetic resonance imaging (MRI)] or according to operation notes mentioned by neurosurgeons. Dissemination of disease at the time of diagnosis was evaluated by combination of full spine imaging and CSF (Lumbar cerebrospinal fluid) study.

Table-I

Risk classification of medulloblastoma.

Risk classification	Characteristics
Average-risk disease	> 3 years or 3 years of age, < 1.5 cm^2 postoperative residual tumor and the absence of metastatic disease
High-risk disease	< 3 years or 3 years of age, > 1.5 cm^2 postoperative residual tumor and/or the presence of metastatic disease

Results:

Total 2242 child with childhood cancer was admitted in the department of PHO during 2014 to 2018 and 260 (11.59%) were Central Nervous System (CNS) tumors. Among them diagnosed cases of childhood medulloblastoma were 57 and we have collected data from only 52 patients. Male female ratio was 1.9:1(M=34,F-18). Median Age of our patients was 6.12 years, range 2-14 years. Median duration of start of treatment after start of symptom was 7.1 months (Range 0.5 -60 months). Age of 7 patients were £3 years. Most common clinical features are listed in table-2.

Table-II

Common clinical features of 52 patients.

Signs and Symptoms	Results(N-52)	Remarks
Vomiting	45(86.54%)	
Headache	41(78.85%)	
Fever	21(40.38%)	
Convulsion	10(19.23%)	
Eye/vision involvement	21(40.38%)	Visual blurring and or diplopia
UB/Bowel involvement	2(3.85%)	
Gait abnormality /Limb paresis	a) Limb-21(40.38%) b) Facial - 01(1.92%)	
Unconsciousness	6 (11.54%)	
Tilting of Head	2(3.85%)	
Enlarge head size	12 (23%)	
Recurrence cases	3 (5.76%)	Patients done surgery previously but didn't take RT or CT

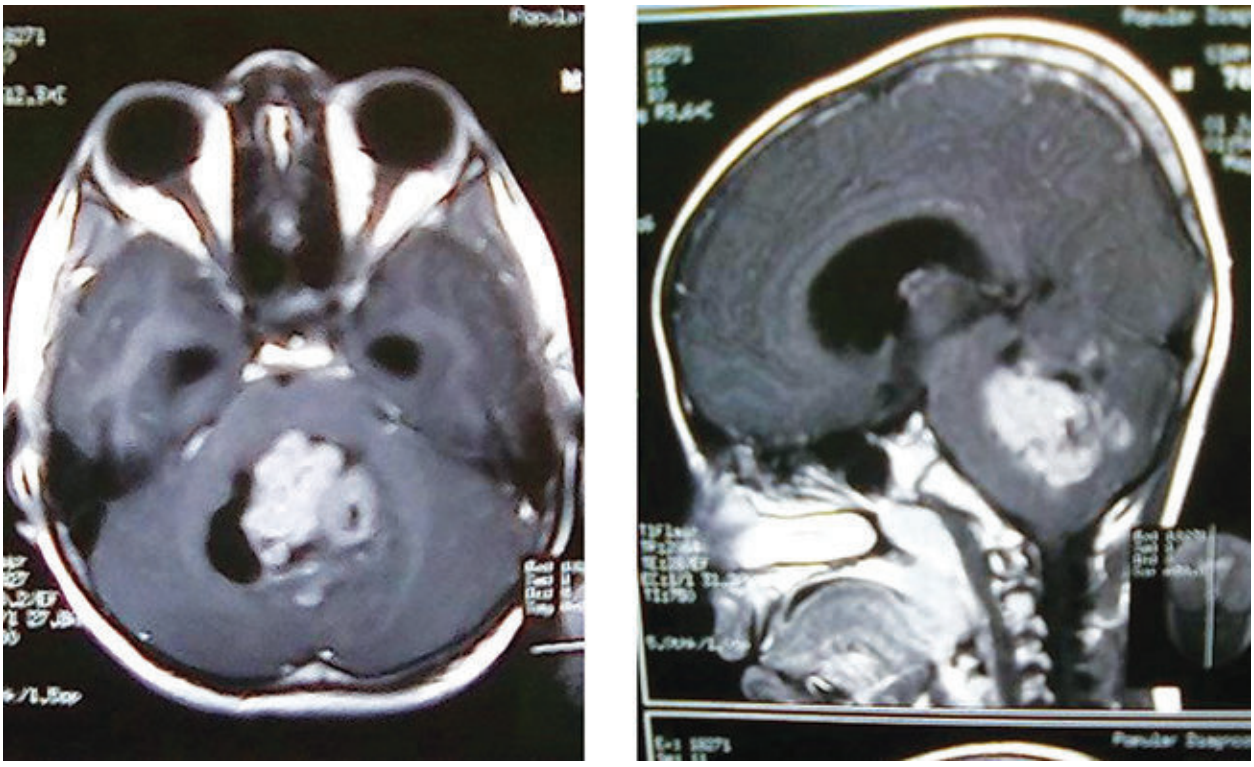

Fig.-1: *Brain magnetic resonance of Axial and sagittal images showing Medulloblastoma of a 8 years boy.*

Table-III
Investigations and its findings

Investigation	Results	Remarks
MRI/CT scan done	100%	
Radiological (MRI/CT Scan) evaluation:		
a). Proposed diagnosis (like Medulloblastoma,ependymoma)	a). 90.4% (N-47)	
b). Non specific diagnosis like space occupying lesion (SOL)	b). 5.7% (N-3)	
c). No comments	c). 3.9% (N-2)	
Hydrocephalus	a) Present 92% (N-48) b) Absent 8% (N-4)	
Radiologically metastasis	3.85% (N-2)	Liver and Spinal cord
Tumor location	Vermis 71.15% (N-37) Hemisphere 28.85%,(N-15)	

Tumor resection was performed in all patients but we were able to analyzed 44 cases where total removal were in 25 patients (N-44, 56.82%), gross total removal were in 11 patients (N-44, 25%), partial removal were in 8 patients (N-44,18.18%) but resection type could not elicited in 8 cases (15.38%,N-52) from operation notes or post operative MRI. (Fig 2)

Medulloblastomas are universally grade IV[11] because of their aggressive nature, with malignant cytologic features, rapid disease evolution, and a fatal outcome if not treated with multimodal therapies. These tumors show either classic histologic features or histologic features of one of the variant nonclassic subtypes: desmoplastic medulloblastoma, medulloblastoma with extensive nodularity, or large cell (LC) or anaplastic medulloblastoma.

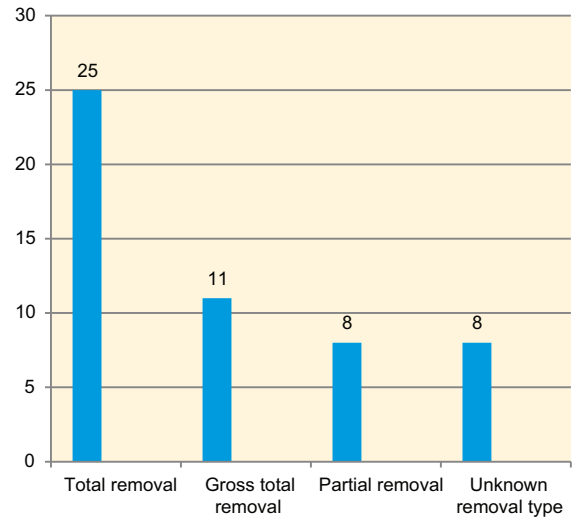

Fig.-2: *Types of removal of 52 Medulloblastoma*

In our study classical medulloblastoma (MB) in 51 cases (98%), Desmoplastic/Nodular MB -2 % (N-1), there was no large cell or anaplastic cell variant of Medulloblastoma. Provisional diagnosis of medulloblastoma by MRI/CT of 47 cases were evaluated by tissue biopsy and 38 (73%) cases were same as MRI/CT diagnosis. Only 9 patients were evaluated by immunohistochemistry (IHC) and all IHC reports correlated tissue biopsy reports. Cerebrospinal Fluid (CSF) was examined of 14 patients for malignant cells, only 5 cases (35.71%) were positive for malignant cells. Medulloblastoma were classified according to the risk stratification system into two groups (Table-4). In our study post surgical MRI were not done regularly or in timely. So for assessment of residual tumor, we have to rely on surgical note also, mentioned by neurosurgeon. In our study high-risk group and average-risk patients were 38 (73%) and 14 (27%) respectively.

Operative complications included gait unsteadiness in 32 cases (61.5%).

Table-IV

Common investigations and findings

Surgical and Pathological events	Result	Remarks
Tumor Removal	a) Total removal 56.82% (25/44) b) Gross Total Removal 25% (11/44) c) Partial Removal 18.18% (8/44) d) Not mentioned in 15.38% (8/52) pathological reports.	For result (d), % was calculated from total 52 cases
Pathological Grading	Grade-IV—52 (100%) .	
Pathological Types (Total number=52)	a) classical MB -98 % (N-51) b) Desmoplastic/Nodular MB -2 % (N-1) c)Anaplastic MB -0% d) Large cell MB -0 % e) MBEN -0%	MBEN-Medulloblastoma with extensive nodularity.
MRI/CT scan evaluation sensitivity	73% (N-38) correlated with tissue biopsy	
Tissue biopsy and IHC sensitivity.	100% ((N-9) IHC reports are same as biopsy reports.	
Shunt	32 (61.50 %)	
CSF study blast cell positive (N-14)	5 (35.71 %)	Total CSF study done in 14 cases
High-risk Average-risk	38 (73%) 14 (27%)	

Treatment and outcomes are described in Table 5. Our follow up (F/U) time is only 22 months. Due to various causes a large number of patients (44.4%) cannot afford treatment cost. Partially treated cases are significant in number (9.6%) with high death rate (23%).

Table-V

Treatment and outcome of Medulloblastoma

Sl.no	Follow-up status	Quantity	Remarks
	Life (32.6%)		
1.	1. Partially treated cases (9.6%)	i) Surgery with Homeopathy-1 ii) Surgery + only RT- 3 iii) Treated in PHO+ India-1	These patient do not come for regular F/U
	2. Fully Treated cases (Surgery+RT+CT)/ On Follow up (23%)	12 patients	
2.	Death (23%)	a) During RT/CT-4 b)After the end of treatment-3 c) recurrence cases-5	
3.	No Treatment/Abandoned (44.4%)	23 patients	
4.	Median Follow-up period	22 months	

Discussion:

Because of the lack of information on paediatric brain tumors in Bangladesh, especially on medulloblastoma, this study focused basically on clinical presentation, diagnostic tools, pathological types, surgical intervention and outcome of childood medulloblastoma.

Medulloblastomas(MB) are considered high-grade embryonal tumors based on histology and cell of origin. They can occur in both children and adults, although greater than 70% of cases are found in children less than 18 years old.[12] Our selected patients age were less than 18 years. From 2014 to 2018, total childhood CNS tumors treated in our department (PHO) were 260 and medulloblastoma were 57 (11.59%) in number but we collected data from 52 patients. Louis et al estimated that medulloblastoma is the accounts for 15—20 % of all CNS tumors and it is more frequent in male (~65%) and median age of onset is approximately 7 years.[13] Percentage of medulloblatoma in our study is a bit less (11.59%) than Louis et al but median age of onset (6.12 years) and sex ratio (M:F 1.9 :1) is nearer to other studies.

Patients of medulloblastoma often harbor a different type of embryonal tumor. Rorke et al mentioned that approximately 15% to 20% of infants who would previously have been diagnosed as having medulloblastoma, harbor a different embryonal tumor, the atypical teratoid/rhabdoid tumors[14] but none of our patients suffered from any different tumor.

Dorner et al maintioned average time from symptom onset to diagnosis ranges from 2 to 6 months.[15,16] but in our study, median duration from start of symptom to start of treatment/diagnosis was 7.1 months (Range 0.5 -60 months). This data more or less correlate with previous studies in our Institute.

Patients with medulloblastoma commonly present with signs and symptoms of cerebellar dysfunction and increased intracranial pressure (ICP). Common signs and symptoms of increased ICP such as headaches (worse on lying down and upon waking up in the morning), nausea, vomiting, gait changes, sixth cranial nerve palsy (caused by hydrocephalus and hence a false localizing sign), diplopia, nystagmus and papilledema. Medulloblastoma can also present acutely with a severe alteration in consciousness and even coma. This is usually due to hemorrhage into the tumor, and rapid tumor expansion with acute hydrocephalus and/or compression of the brainstem.[17] In our findings most common symptoms were vomiting (86.54 %), headache(78.85%), Eye/vision involvement i.e diplopia, nystagmus and papilledema (40.38%),Fever (40.38%),gait change (40.38%) , facial paralysis was in one patient, unconsciousness(11.54%) and macrocephaly (23%).This study more or less correlate with the findings of study of Estelles et al findings where vomiting 79.4 %, headaches 71.4%, gait change 36.5%.[18]

Due to its wide availability, computed tomography (CT) is often the first imaging study performed in children presenting neurological symptoms which suggest a brain tumor. Nevertheless, magnetic resonance imaging (MRI) is a superior method, due to its greater sensitivity compared to CT and the fact that it allows for a more precise assessment of the tumor's size, location and neoplastic subarachnoid spread.[19] Our cent percent patients were evaluated by CT scan or MRI at first. But in all cases, CT/MRI could not able to confirm the tumor type. Only 90.4% (N-47) MRI/CT reports were able to given a proposed diagnosis like Medulloblastoma, Ependymoma etc, 5.7% (N-3) diagnosed as non specific tumor i.e. space occupying lesion (SOL) and in 2 (3.9%) cases didn't make any remarks regarding the brain lesion. In the study Hydrocephalus were found in 92% (N-48) cases, which correlate with Koral et al. who said that as the lesions grow, there is anterior displacement and compression of the fourth ventricle, which often leads to obstructive hydrocephalus in approximately 90% of cases if uncompensated.[20] Subarachnoidal spreading occurs more frequently along the normal CSF flow, hence the most common location of metastases is along the posterior surface of the spinal cord.[21,22] We have identified metastasis in spinal cord for one patient, one in liver. Malignant cells for CSF were positive for 5 (35.71 %) cases. But Fouladi M et al maintioned, the tumor tends to metastasize through the subarachnoid space. Thirty-two percent of patients showed cerebrospinal fluid (CSF) dissemination at diagnosis.[23] In our series tumors arise from midline (Vermis) were in 37 children (71.15%) and from hemisphere were in 15 cases (28.85%).This data correlate with data of Nalita N et al study where tumors from vermis (midline) were 78.2% and from hemisphere were 21.8%.[24]

Radiological diagnosis of metastasis were only 3.85%,which is far different from Estelles et al [18] study

where Twenty-one Patients (32%) had dissemination at the time of diagnosis,which was detected by radiology.

In the management of medulloblastoma, complete resection should be performed if possible as several studies have correlated outcome with extent of resection and amount of residual tumor.[25] Kumar et al reported in their study gross total resection in 8 (15%) patients, near total resection in 34 (64%) patients and subtotal resection in 11 (21%) patients.[26] But in our study the data is a bit different ,that is total removal of tumor were in 25 patients (56.82%), gross total removal were in 11 patients (25%), partial removal were in 8 patients (18.18%) and reports about the extent of surgical removal of 8 patients (15.38%,N-52) were not mentioned in surgical notes or post surgical MRI.

Lee et al said most patients have resolution of hydrocephalus following tumor resection, but approximately 40% will require a ventriculoperitoneal shunt within 4 weeks of resection.[27] In our finding shunt requirement is more than Lee et al. In our series shunt requirement during tumor operation were 61.50%, which is nearer to the study of Kumar et al (60%).[26]

Medulloblastomas are undifferentiated embryonal neuroepithelial tumors of the cerebellum arising predominantly from the cerebellar vermis .The cell of origin and the exact histological classification of this highly malignant tumor are still controversial.[28] However Estelles et reported histologically classic MB is 71.4% and Nodular MB is 25.4% [18] But in our calculation the classical type of Grade-IV medulloblastoma were 98% (N- 51) , Desmoplastic/ Nodular MB -2 % (N-1), there was no large cell or anaplastic cell variant of medulloblastoma. Findings of Kumar et al (classical MB -90.3%,Desmoplastic medulloblastoma 3.2%) are more nearer to our data.[26]

We evaluate the sensitivity of CT/ MRI diagnosis of medulloblastoma. We considered 47 cases that were diagnosed as medulloblastoma by CT/MRI and followed the biopsy reports of those patients. Biopsy results yielded 73% (N-38) diagnosis were same as MRI/CT recommendation. Tissue from 9 patients that diagnosed as medulloblastoma by biopsy were done immunohistochemistry and found all IHC reports correlated tissue biopsy reports.

However, there is a disparity in survival rates in low to middle income countries—ranging from 33% to 73%.[29,30] Treatment refusal or abandonment (44.4%) is a major problem for our country. Partially treated cases are significant in number (9.6%) with high death rate (23% within 22 months of F/U). Our follow up time is only 22 months and only 23% patients are on follow up with expected health. Abandoned from child cancer treatment is a common problem in low income countries Most common reasons were financial difficulties. A study in Kenya found 54% children with cancer were abandoned from treatment.[31] Our experience (44.4%) is less in number than Kenya.

Future of Medulloblastoma Management

The current clinical risk stratification for children with medulloblastoma as listed in Table-1 fails to recognize the biologic heterogeneity of this disease and has not been useful in accurately predicting outcome with 20% of average-risk patients failing risk-adapted cytotoxic therapy and 50 — 70% of those with high-risk disease doing well with the same approach.[32] There are four medulloblastoma molecular groups —WNT-activated, SHH-activated, group 3, and group 4 and addressing these clinical and molecular features of medulloblastoma patients will get more benefit from the new risk-adapted therapeutic approach. Ongoing clinical trial after performing molecular analysis of tumors are started in developed countries like USA. The genomic era of medulloblastoma is fast ushering in a need for a more personalized approach to treating this disease by using molecular information from each patient's tumor and deciding on best combination of targeted therapies to produce sustained tumor control. It should be remembered that despite the rapid advances made in the last few years understanding the molecular landscape of medulloblastoma, surgery and cytotoxic therapy are still the mainstay of treatment for this aggressive tumor.

Conclusion.

Childhood medulloblastomas remain a challenging oncologic condition specially for Bangladesh where a large number of children cannot afford treatment expenses and abandoned from treatment. Cancer care in Bangladesh depends entirely on a patient's socioeconomic status. This situation should be change. In this moment our main goal is to improve the support of average-risk patients with current treatment regimens and maintain adequate survival. For patients with high-risk and recurrent disease, survival remains poor. But advances in understanding molecular profile and associated clinical outcome will eventually lead to better risk stratification and enable

oncologists to give better treatment plan for each individual patient. Therapy for childhood medulloblastoma requires a delicate balance between the need to intensify therapy and the desire to reduce toxicity to have a better quality of life.

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