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Pediatric brainstem glioma: a rare childhood cancer - clinical profile, treatment, and challenges of management - a single-center experience from a developing country

Abstract

Introduction: Brainstem gliomas (BSGs) occur in the brainstem, located at the base of the brain. BSGs account for 10-20% of all primary CNS tumors. In a hospital-based study conducted at NICRH, BSGs constituted 7.69% of all childhood brain tumors.

Objective: To determine the clinical profiles of childhood BSGs and assess the outcomes of pediatric BSGs while addressing the challenges of management.

Methodology: It was a cross-sectional prospective study with a sample size of 44. We included all children during the study period and analyzed their data.The children were under 18 years of age. The study period was January 2020 and October 2022 at the Department of Pediatric Hematology and Oncology at the National Institute of Cancer Research and Hospital (NICRH), Bangladesh.

Results: There were 44 patients, comprising 29 males and 15 females. The mean age of onset was 7 years. The majority (43.2%) of children fell within the 5-9 years age group. The most common symptoms were limb weakness, ataxia, and vision defects. The duration of symptoms varied from 10 days to 2 years. Sixteen of the patients experienced intracranial hypertension, which led to the development of hydrocephalus. The lesions were pontine in 18 cases, involving the entire brainstem in 13 cases, both pons and medulla in 7 cases, and medulla in 3 cases.

Six patients underwent surgical intervention with histological evaluation, revealing astrocytoma (9.1%), oligodendroglioma (2.3%), and ependymoma (2.3%). Twenty-four (54.5%) patients received treatment, while others were unable to do so. The follow-up period extended to 12 months from the last enrollment. Only 8 patients completed both chemotherapy and radiotherapy treatments; other children discontinued or abandoned treatment due to financial constraints or the unavailability of 3D radiotherapy.

Out of 44 children, a total of 41 patients passed away, with a mean survival period of 3.9 months. This is due to the high treatment cost in the private sector and disorganized government medical services for children with cancer.

Conclusion: Most of the tumors in this series were located in the pons and demonstrated aggressive characteristics. The majority of our patients did not have access to radiotherapy due to their poor economic condition and the inadequate management of our government health system.

Keywords: brain stem glioma, childhood brain tumors

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Introduction

Brain stem gliomas are a rare and challenging type of brain tumor. It arise in the brain stem—the critical area of the brain responsible for controlling essential life functions such as breathing, heart rate, and motor control.

Brain stem gliomas encompass a diverse group of tumors with varying histology and prognosis. Using the term "brain stem gliomas" as a unifying classification can be misleading, as these tumors exhibit significant heterogeneity in terms of their biology, clinical presentation, treatment approaches, and outcomes. It is important to recognize the heterogeneity of brain stem gliomas as it has implications for prognosis, treatment strategies, and clinical management. Brain stem gliomas account for 10-20% of all primary CNS tumors in childhood and adolescence.[1,2]

Due to the absence of population-based cancer epidemiology data, the cancer burden among children and adolescents in Bangladesh is largely unknown.[3] Consequently, the specific incidence of pediatric brainstem gliomas in Bangladesh remains beyond estimate. Nonetheless, an analysis within our department [Department of Paediatric Haematology and Oncology, National Institute of Cancer Research and Hospital (NICRH)], utilizing a hospital-based dataset, revealed that childhood brainstem gliomas constituted approximately 7.69% of cases (20 out of 260).

The diagnosis process usually starts with a thorough clinical evaluation by a pediatric neurologist or oncologist. Imaging techniques like CT scans or MRI are crucial for identifying brain stem gliomas. Biopsy is not always possible, but when it can be done, it is important for confirming the diagnosis and determining the tumor's type and grade.

Managing children with brain tumors requires a multidisciplinary approach. These children are best treated at pediatric hospitals with the necessary resources and personnel. A team should include a pediatric neurosurgeon, oncologist, neuropathologist, neuroradiologist, radiation oncologist, endocrinologist, and physical rehabilitation services.

The treatment and prognosis of brain stem gliomas are significantly influenced by factors such as tumor morphology, type, and location.[4] Due to the challenging location within the brainstem, surgical resection is often not feasible,[5] and therefore, other treatment modalities are necessary. In general, surgical intervention is typically beneficial for dorsal exophytic tumors and cervicomedullary tumors, yielding positive outcomes. Because of their infiltrative nature and brainstem localization, diffuse intrinsic pontine gliomas (DIPGs) are not amendable to surgical resection. Standard treatment is fractionated radiotherapy in this codition. A few centers advised radiotherapy and chemotherapy.[6]

Understanding the biology, clinical presentation, and treatment options for brain stem gliomas is crucial for developing more effective therapeutic approaches. This article delves into the complexities of brain stem gliomas, exploring the latest research, diagnostic techniques, and emerging treatments aimed at improving the lives of those affected by this devastating disease.

Objectives:

1. To determine the clinical profiles of childhood brainstem gliomas (BSG).
2. To assess the outcomes of pediatric BSG treatment at our institute.
3. To address the challenges encountered during the management of BSG in Bangladesh.

Materials and methods

Inclusion criteria: We conducted a cross-sectional prospective study at the Department of Pediatric Hematology and Oncology, National Institute of Cancer Research and hospital [NICRH]. Data were collected from all patients under the age of 18 years treated in our unit for brainstem glioma between January 2020 and October 2022. We included all patients who fulfilled our criteria during the study period. Ethical approval for this study was obtained from the NICRH ethics committee. Patients were included if they met the following criteria:

1. The tumor was located in the brainstem (midbrain, pons, thalamus and medulla oblongata).
2. The diagnosis was based on histological confirmation or on clinical history with characteristic MRI appearance.
3. A complete medical record, including clinical data, imaging of brain, and detailed treatment data, operation records was available.

Exclusion criteria: Those cases were excluded if the tumors originating in the cerebellar peduncles or the cervical spinal cord.

Data collection: Our Department collected clinical data from pediatric brain stem glioma cases. The data included patient demographic information, details at the time of diagnosis such as age, sex, duration of symptoms, main symptoms and signs, tumor description on MRI, and pathological reports if available. We also recorded the treatment administered at diagnosis and during follow-up, including the clinical and radiological course, complications and death. All data were collected in electronic devices and transferred to SPSS software for further analysis.

Results

Patient demographics and presenting features

Our study sample, which was selected based on the inclusion criteria we previously mentioned, consisted of 44 patients. The average age of the patients in our cohort was 7.26 years, with ages ranging from 2.5 to 17 years.

The majority of our patients were male (65.9%) and belonged to the 5-9 year age group (43.2%) (Table 1).

Table 1 Patient demographic and presentation characteristics (n=44)

Sl.no.	Demographics/ presentation	Number (%)
1	Age- mean in year (range)	7.26 years (2.5–17)
2	**Age group**	
	0-4 years	11(25%)
	5-9 years	19 (43.2%)
	> 10 years	14 (31.8%)
3	**Sex**	
	Male	29 (65.9 %)
	Female	15 (34.1%)
4	Presentation [Duration of symptoms, median (range)]	2mon (2days–24 mon)
5	**Presenting symptoms**	
	Limb weakness	30 (68.2%)
	Ataxia	17 (38.6%)
	Vomiting	16 (36.4%)
	Visual problem	13(29.55%)
	Dysarthria	10 (22.7%)
	Headache	8 (18.2%)
	Drooling of saliva	6(13.6%)
	Facial weakness	4 (9.1%)
	Vertigo	4 (9.1%)
	Respiratory difficulties	2(4.5%)
	Seizures	1(2.3%)
	Neck control loss	1(2.3%)

The median duration of symptoms was 2 months, with a range of 2 days to 24 months. The most common symptoms reported by our patients included limb weakness, ataxia, vision problems (such as blurry vision and diplopia), headache, vomiting, seizures, facial weakness, drooling of saliva, dysarthria, and vertigo (Table 1). No children were associated with neurofibromatosis type 1 (NF1).

Diagnosis: For the diagnosis of cases, we utilized MRI (n=40, 90.9%) and CT scan (n=4, 9.1%), as well as pathological biopsy results where available. To simplify the classification of infiltrating tumors based on their anatomy, we defined their location according to the site of the tumor epicenter. Using this criterion, we found that 40.9% (n-18) of tumors were located in the pons, while 6.8% (n-3) were located in the medulla. Most of the tumors extended beyond their primary location and involved more than one side, as shown in Table 2.

Table 2 Location of brain stem glioma

Sl.	Side of tumor	Number (%)
1	Pons	18(40.0%)
2	Whole Brain stem	13(29.5%)
3	Pons and Medulla	7(15.9%)
4	Medulla	3(6.8%)
5	Midbrain and Pons	2(4.5%)
6	Thalamus and Midbrain	1(2-3%)
7	Hydrocephalus	16(36.4%)

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In our patient cohort, only 8 individuals underwent surgical intervention, and adequate tissue for pathological examination was obtained from 6 of them. Table 3 shows the variety of pathological types of gliomas (Figure 1).

Table 3 Surgical intervention and its outcome

Sl.	Surgery and biopsy findings	Number (%)
1	Surgical intervention	8 [18%]
2	Adequate tissue collection	6 [13.6%]
	Astrocytoma	4 [9.1%]
	Oligodendroglioma	1[2.3%]
	Ependymoma	1[2.3%]

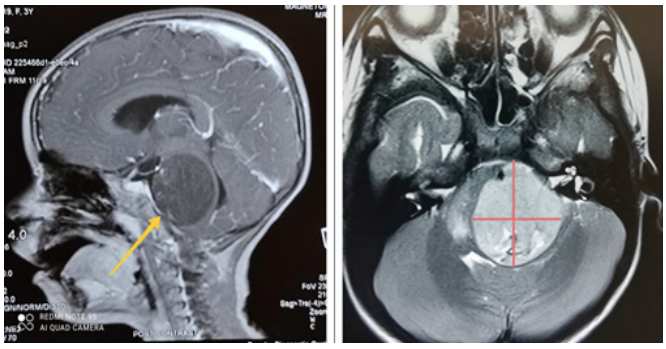

Figure 1 MRI findings show a fairly large (4cm x 4cm) expansile rounded lesion in the brainstem involving the pons and midbrain, with triventricular hydrocephalus.

Treatment: Surgical intervention is generally not a primary treatment option for brain stem gliomas (BSGs) but in certain cases, surgical biopsy may be performed to obtain a tissue sample for accurate diagnosis and to guide treatment decisions.

The choice of treatment for brain stem glioma varies according to factors like the tumor's type, size, location, the patient's age, and overall health. In our facility, we offered a range of treatment options, including radiation therapy, chemotherapy, targeted drug therapy such as Bevacizumab, and in some cases, surgical intervention has been conducted, as detailed in Table 4.

Table 4 The treatment options received by the studied patients

Sl.	Treatment history	Number (%)
1	The individual did not seek medical treatment	20 [44.5%]
	Treatment received [complete or incomplete]	24 [54.5%]
2	Only RT	12 [27.3%]
	Only CT	2 [4.5%]
	RT+CT	9 [20.5%]
	Surgery + RT	1 [2.3%]
3	Completed medical treatment	8 [18.2%]
4	Did not finish their medical treatment.	16 [36.4%]

Follow-up for our patients with brain stem gliomas typically involves regular monitoring and assessments to track tumor progression, evaluate treatment response, and manage any symptoms or side effects. Unfortunately, approximately half (44.5%) of the patients did not seek expensive radiotherapy treatment from private hospital.

We followed up with all patients [N-44] for 12 months, as described in Table 5 and Figure 2.

Table 5 After a 12-months follow-up period, the statistics are as follows

Sl.	Events	Number (%)
1	Total number of surviving patients:	3 [6.8%]
2	Patients who survived with completion of treatment:	2 [4.5%]
3	Patient who survived without receiving any treatment	1 [2.3%]
4	Total patient deaths:	41 [93.1%]
5	Deaths within the first month of diagnosis:	15 [34.05%]
6	Deaths within 6 months of diagnosis:	33 [74.91%]

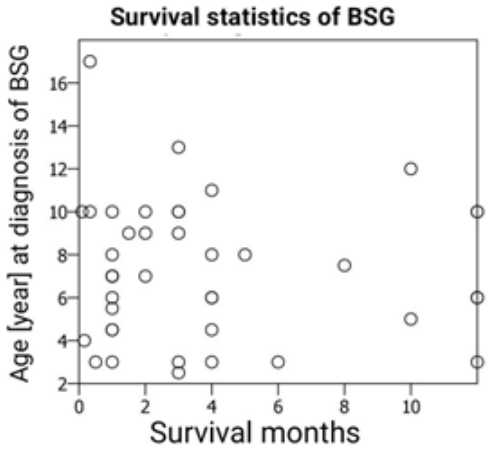

Figure 2 Scatterplots display the age of the patient and their survival time after diagnosis, measured in months.

Discussion

Brainstem tumors in children represent 10% to 20% of all central nervous system tumors.[1,2] A population-based study in Morocco spanning from 2008 to 2012 found that pediatric brain tumors accounted for 16.7% of total brain tumor cases.[7] Incidence rates of primary brain and central nervous system tumors in children vary across regions and countries. However, due to the absence of population-based cancer epidemiology data, the specific incidence of pediatric brainstem gliomas in Bangladesh remains unknown. The hospital-based dataset, revealed that childhood BSG constituted approximately 7.69% of cases (20 out of 260). The low incidence of BSG in this hospital-based study, compared with international data, can be attributed to the following factors:

a. Not all patients are able to attend our hospital.

b. Some patients seek treatment at private hospitals, foreign facilities, or refrain from seeking treatment due to poor social conditions.

But during the study years, our department has faced the challenge of dealing with multiple cases of BSG in children on the same day as shown in Figure 3.

In our research, the average age of patients in our cohort was 7.26 years, spanning from 2.5 to 17 years. Predominantly, our patients were male (65.9%), with the 5-9 year age group (43.2%). A German study[8] revealed a median age at diagnosis of 5.6 years, also showcasing a clear male dominance (male to female ratio of 1.6:1), aligning closely with our own observations. Across various studies on pediatric brainstem gliomas, a consistent trend of male predominance has been noted.

When considering diagnostic delay (the duration between symptom onset and diagnosis), our research displayed a median duration of 2

months (ranging from 2 days to 24 months), similar to findings in developed nations such as New Zealand, where the duration was 2 months.[9] In an Indian study[10] the median symptom duration before diagnosis stood at 4 months (ranging from 1 week to 7 years).

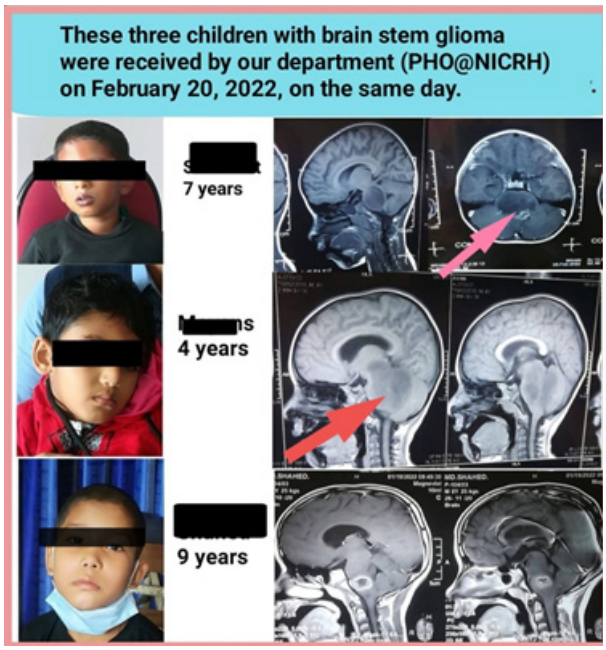

Figure 3 The burden of Brain Stem Glioma in an institute [NICRH] of Bangladesh where 3D conformal radiation therapy (3D-CRT) is not yet available.

A number of familial cancer syndromes have been associated with it, including neurofibromatosis type-1, Li-Fraumeni syndrome, and tuberous sclerosis, among others[11] but our patients showed no such syndrom.

The National Cancer Institute of USA[12] described the common signs and symptoms of pediatric brain and spinal cord tumors (BGG) as follows: trouble with eye movement, vision problems, Morning headache or headache that goes away after vomiting, nausea and vomiting, unusual sleepiness, paralysis of one side of the face or body, loss of balance, and trouble walking. Most of our findings were related to neurological deficiencies, including limb weakness, ataxia, vomiting, visual problems, dysarthria, headaches, drooling of saliva, facial weakness, vertigo, respiratory difficulties, seizures, and loss of neck control.

A study published in SpringerLink suggests that the incidence of hydrocephalus in children with brain stem glioma was approximately 22%.[13] However, the data revealed that hydrocephalus in our study was 36.4% (N=16) according to MRI findings.

Medical imaging has become invaluable in the diagnosis and management of brainstem gliomas; due to their location, getting a biopsy is almost impossible.[14,15] In this study for diagnosis of cases we used MRI (N-40, 90.9%),CT scan [N-4, 9.1%] and tissue biopsy (6, 13.6%).

Tumor locations were identified through MRI imaging. In the USA, diffuse intrinsic pontine glioma (DIPG) constitutes around 75% to 80% of pediatric brain stem tumors.[16] In our study, tumor locations were predominantly in the pons (40%), followed by the total brain stem (29.5%) and combined involvement of the pons and medulla (15.9%), indicating an overall pons involvement of 85.4%.

In general, surgical intervention is not the first line of treatment for brain stem glioma due to the high risk of damage to the surrounding brain tissue.[17] Moreover, Bangladesh has a scarcity of pediatric neurosurgeons. In this scenario, only 8 patients underwent surgical intervention and adequate tissue for pathological examination was obtained from 6 of them. Most of the tumors were Astrocytomas (4/6), while the remaining two were Oligodendroglioma (1/6) and Ependymoma (1/6).

Managing brain stem glioma in developing countries presents challenges due to limited resources and expertise. Often, children with brain tumors in developing countries do not receive optimal care, resulting in suboptimal outcomes.[18] In Bangladesh, patients often face financial constraints as they come from impoverished backgrounds. Additionally, there is a severe scarcity of pediatric neurosurgical operation theaters in goverment hospitals and a lack of adequately skilled pediatric neurosurgeons. At our Institute, we offer various treatments, including conventional radiation therapy (2D-RT), chemotherapy (CT), and targeted drug therapy like Bevacizumab. These services (2D-RT, CT) are generally provided free of cost by the government. However, brain stem gliomas (BSG) require 3D-RT, which is not available until now in our hospital. Patients had to seek 3D-RT from private hospitals. Most patients were unable to afford these services and drugs from private sources.

Nearly half (44.5%) of the patients refrained from treatment due to the unavailability of free radiation therapy (3D-RT) at government hospitals. Throughout the data collection period, all of our hospital's radiotherapy machines (2D-RT) were out of order, resulting in patients being unable to access free radiation therapy. At private hospitals, the cost of radiotherapy for a child is too high. Many families cannot afford this, so most patients do not receive RT. Only a quarter of the patients sought radiation therapy from private hospitals. Eight patients completed the treatment, while 36.4% (16 patients) did not finish their course of treatment.

After completing treatment, children diagnosed with brain stem glioma requires lifelong follow-up care.[19] Our follow-up protocol involves routine physical examinations, medical tests, and periodic MRI scans.

An SEER database revealed that the median survival time for children with brain stem glioma is 24 months.[20]

Most children diagnosed with DIPG typically have a shorter life expectancy compared to other types of BSG. In our follow-up after 12 months, only 3 patients were alive. Like other developing countries, the prognosis of brainstem glioma in our country is poor. There are several reasons for this poorer outcome:

a. Limited access to healthcare for these patients,

b. A shortage of healthcare professionals trained to treat these rare cancers,

c. Economic constraints faced by patients,

d. A lack of research and clinical trials focused on rare childhood brain cancers,

e. International organizations exhibit an attention deficit toward this medical field.

Limitations of this study

The diagnosis process for brainstem gliomas typically begins with a thorough clinical evaluation by a pediatric neurologist or pediatric

oncologist, and it may involve specialists such as neurosurgeons, radiation oncologists, and radiologists in the diagnosis and treatment planning. However, it's important to note that at our center, not all types of consultants are available during the diagnosis phase. Many children with brain tumors come to us after evaluation by an adult neurosurgeon or following an operation performed by an adult neurosurgeon with inadequate operation notes. This situation poses challenges for staging and tailoring treatment.

Conclusion

Our study on pediatric brain stem glioma sheds light on the complexities and challenges associated with this rare and aggressive condition, especially in a country where medical services are disorganized. Through a comprehensive analysis of patient outcomes, treatment modalities, and prognostic factors, we have gained valuable insights into the current landscape of managing brain stem gliomas in children. Despite the formidable nature of this disease, advancements in medical research and innovative therapeutic approaches offer hope for improved outcomes in the future. Our findings emphasize the importance of continued research, collaboration among healthcare professionals, improvement of the medical service delivery system through planning, and the development of targeted therapies to enhance the overall prognosis and quality of life for children affected by brainstem disorders.

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Conflicts of interest

The authors have no potential conflicts of interest to disclose.

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