ABSTRACT

Background: Brainstem tumors account for 10 to 20% of all intracranial tumors in children. The clinical profile and outcomes of these tumors differ around the world. The aim of this study is to describe clinical characteristics, treatment, and outcome of brainstem tumor at the National Cancer Institute in Sudan.

Material and Methods: This is a retrospective study of children diagnosed with brainstem tumors and treated between January 1998 and December 2015 at National Cancer Institute, Sudan.

Results: A total of 15 children were diagnosed to have brainstem tumor. The mean age was seven ± 3.2 years. Female were mostly affected (60%) than male (40%) with a female to male ratio of 0.67. Diffuse brainstem gliomas were the most frequent tumor type with 14 cases (93%). Cranial nerves palsies were the most frequent presenting clinical feature (80%). The mean pre-diagnostic symptomatic interval was two months. Eleven (73%) patients received external beam radiotherapy. The abandonment rate was 13%. Overall survival rate at one and two years were 13% and 7% respectively.

Conclusion: Overall this study draws attention to the situation of pediatric brain tumors in Sudan. The prognosis of brainstem tumors in our setting is dismal. Late diagnosis in addition to limited resources contributes to poor outcome in these patients.

Keywords: pediatric, tumor, radiotherapy, gliomas, brainstem

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Tumours arising in the brainstem (midbrain, pons, and medulla oblongata) account for 10 to 20 percent of all intracranial tumors in children1,2. They considered as a heterogeneous group of tumours that have differences in biologic behavior. Their peak age in paediatric population is 7–9 years, with no gender predilection2-4. The signs and symptoms of Brainstem tumors (BST) are highly variable and nonspecific. This is due to the variability in size, location, and histopathological features and growth pattern of the tumors. Among the common clinical findings include cerebellar signs (e.g., ataxia, dysmetria, and dysarthria), long tract signs (e.g., motor deficit, increased tone, hyperreflexia, etc.), behavioral changes, and cranial nerve palsies (unilateral or bilateral)5,6. The Sixth and the Seventh cranial nerves are commonly involved6. Neuroimaging is the standard method to diagnose and classify brainstem tumour (BST). Classification of BST depends primarily on location and characteristics of these tumours on brain magnetic resonance imaging (MRI)2,7. Many of these tumours appear isointense in brain computed tomography (CT). Therefore CT is not the imaging modality of choice. The majority of childhood BST, as determined using MRI, is diffuse intrinsic pontinegliomas (DIPGs), which accounts for 80% of all BST8. Other types are generally defined as focal, dorsal exophytic or
cervicomedullary\textsuperscript{9,10}. From a histopathological standpoint, BST can be classified simply as low-grade or high-grade gliomas. High-grade gliomas represent the majority of DIPGs\textsuperscript{11}, whereas exophytic tumors are mostly graded low-grade astrocytoma\textsuperscript{4}.

Pretreatment biopsies are not routinely performed because of the significant morbidity associated with the biopsy procedure. Furthermore, histopathology results do not affect the management strategy or outcome for these tumors\textsuperscript{12}. However, the usefulness and safety of stereotactic brainstem biopsy have been reported in several studies\textsuperscript{13-17}. In fact, stereotactic biopsy may be indicated for BST that are focal or atypical, especially when surgical excision is possible.

Since diffuse brainstem gliomas are inaccessible to neurosurgical resection\textsuperscript{18}, the standard radical treatment consists of conventional external-beam radiation (EBRT), with local field radiation for a total dose of 54 to 60 Gray (Gy) delivered in 30 fractions (1.8 to 2 Gy per fraction per day) over a period of six weeks\textsuperscript{19}. Despite the use of EBRT, the prognosis of these tumors remains poor, and 90\% of children die within two years of diagnosis\textsuperscript{2,19}. In contrast, exophytic and cervicomedullary types of BST are amenable to curative surgical resection with five years survival of 90\%\textsuperscript{20}. It is worth mentioning that Hargrave et al conducted a systematic review of publications reporting on BSG in children and found that 1-year survival rates range from 25\% to 53\%, whereas 2-year survival rates range from 5\% to 23\%\textsuperscript{19}. The roles of chemotherapeutic and biological agents in the treatment of BSG remain unclear\textsuperscript{21,22}.

Little is known about childhood brain tumours in Sudan. So far, to our knowledge, there is no published data regarding BST in Sudan. Here, we review the clinical presentation, treatment, and outcomes of BST in children treated at a tertiary cancer referral center in Sudan (as African low-income country).

**MATERIAL AND METHODS:**
The National Cancer Institute-University of Gezira (NCI-UG) in the Gezira state is the only specialized center outside the capital, Khartoum, where children with cancer are referred for chemotherapy and radiotherapy. Children below 15 years of age who were diagnosed with BST at NCI-UG between January 1999 and December 2015 were retrospectively identified. The data extracted included demographics, clinical presentations, radiology reports, treatment modalities, and outcomes.

We presented statistical data as frequency and percentage for a categorical variable or as both mean +/- SD and median (range) for a continuous variable. The pre-diagnostic symptomatic interval was defined as the interval between the onset of symptoms and/or signs and the time of diagnosis by neuroimaging (MRI or CT). Statistical tests were performed using SPSS (version 19.0; SPSS Inc.). Details that might disclose the identity of the patients were omitted, and only coded data were used for analysis. Ethics approval was obtained from the relevant authority before commencement.

**RESULTS:**
A total of fifteen children with BST were diagnosed between January 1999 and December 2015. Six out of fifteen children were male, and nine were female given a female: male ratio of 0.67 (Table 1). The mean age at diagnosis was seven year [Standard deviation (SD) 3.2]. The mean age of male and female were 9.5 and 7-year-old respectively. One case was less than five, eight (45\%) were between five and nine and six (40\%) between 10 and 15 years of age. About 80\% of our study population were
from rural areas and 20% from urban areas.

The most common presenting symptoms and signs at the time of diagnosis are presented in Figure 1 and Table 2. Cranial neuropathies were the most common sign overall (figure 2). Multiple cranial nerves involvement were identified in 9/15 (60%) cases. The average pre-diagnostic symptomatic interval was two months. Hydrocephalus was diagnosed in four cases. Ventriculoperitoneal (VP) shunt was performed in all cases with hydrocephalus to reduce the raised intracranial pressure and relieve child’s symptoms.

In 93% of cases, the diagnosis was based on neuroimaging. Pretreatment MRI was performed for all patients. On T2-weighted images, lesions were classified into three types (diffuse intrinsic, focal and exophytic). Of the 15 tumors, 14 (93%) were classified as diffuse intrinsic and one (6%) as exophytic. Regarding tumor location of the 15 tumors, the pons was involved in 13 (81%) cases, and the medulla was involved in the remaining two (19%) cases. Open biopsy was performed in one case with an exophytic cervicomedullary lesion on MRI brain.

The majority of our cases (93%) are diffuse and infiltrative lesions that are not amenable to surgical resection. Only one case with exophytic BST underwent craniotomy and partial resection, and this child succumbed before adjuvant radiotherapy started. Eleven out of the fifteen (73%) children with BST received external radiation therapy from Cobalt 60 machines using the conventional lateral opposing technique; the remainder (4 cases) received no RT because death occurred soon after hospital admission (2 cases) or therapy was refused by parents (2 cases). 7/11 cases received a radical dose ranging between 50.4 to 54 Gy, while 4 cases received a palliative dose (36 Gy). Three cases younger than seven years were irradiated under intravenous sedation. One case received palliative chemotherapy (temozolomide) for disease progression post radical radiotherapy. Of the 11 patients received RT, 4 cases experienced tumor progression after RT.

Table (1): patient’s characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>7</td>
</tr>
<tr>
<td>Median age</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Urban</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Extent of surgery</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>0</td>
</tr>
<tr>
<td>Partial resection</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Gross total resection</td>
<td>0</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (73%)</td>
</tr>
<tr>
<td>No</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>No</td>
<td>14 (93%)</td>
</tr>
</tbody>
</table>

Table (2): Frequency of neurological signs at diagnosis

<table>
<thead>
<tr>
<th>neurological signs</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerves</td>
<td>12</td>
<td>80%</td>
</tr>
<tr>
<td>involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor deficit</td>
<td>10</td>
<td>67%</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>5</td>
<td>33%</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>4</td>
<td>27%</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

The median survival time for our study population was five months. Survivals at one and two years were 13% and 7% respectively. Out of the 11 patients who received radiation therapy, two cases died during treatment, with a sudden and severe deterioration in signs and symptoms. The seven patients finishing the planned course...
of radiotherapy had a transient clinical improvement ranging between 1-60 months. Parents of two cases decided to abandoned treatments.

DISCUSSION:
This study describes clinical profile and treatment outcome of BST among children referred for treatment at the NCI-UG, one of the only two oncology center in Sudan, between January 1999 to December 2015. Although brain tumours are the leading cause of cancer-related mortality in childhood, these tumour are rarely studied in developing countries. Among paediatric brain tumours, brainstem tumours constitute 10-15%\textsuperscript{2,10}. To our knowledge, our study is the first report on pediatric BST in Sudan. The present study attempted to describe the experience of treating paediatric BST at oncology institutes in a limited resource setting. In our study population, the mean age at diagnosis was seven years, concurring with other studies that reported mean age at diagnosis to be at 7 to 9 years among children with BST\textsuperscript{3,23-25}. Most previous studies reported equal gender distribution among children with BST\textsuperscript{2,10,26}. Gender analysis shows a female predominance in our cohort of children. However, these ratios may be biased by the small size of the cohort studied. The predominance of female patients has been previously reported\textsuperscript{27,28}. It is unclear
whether geographic or ethnic propensity can be attributed to the occurrence of BST. In fact, no specific risk factors have been described to be related to the incidence of BST.

In this study, children showed various signs and symptoms at diagnosis, usually, poly symptomatic. Cranial nerve deficits were the most frequent presenting feature followed by paresis. This trend is consistent with previous studies that reported cranial nerves involvement at a rate of 89%. In this cohort, the most commonly involved cranial nerves were the Sixth and the Seventh cranial nerves, similar to many reports in the literature.

In the current series, the rate of motor deficit was 67% and the cerebellar dysfunction was 33%. Cataltepe et al reported that the rate of cerebellar dysfunction and motor deficit were 51.6% and 50% respectively. In contrast, other authors reported abnormal gait and coordination to the most frequent sign. Hydrocephalus was described as a rare finding among children with BST despite all these neurological signs, except in cases of dorsal exophytic tumour which can grow dorsally into fourth ventricle and result in obstruction of normal cerebrospinal flow. Approximately 10% of DIPG patients have hydrocephalus at initial presentation. In this study, hydrocephalus was diagnosed in 3/15 (20%) cases.

In the current study, the average pre-diagnostic symptomatic interval was two months and this duration of symptoms was also reported in other studies. Nonspecific clinical features of these tumours can contribute to long symptoms duration before tumour discovery with neuroimaging. Furthermore, limited diagnostic facilities in our setting are another factor that contributes to delay diagnosis of BST. In Gezira State, there is only one CT scan in a government hospital and one MRI unit in a private practice; they may nonetheless be out of reach for many patients, who cannot afford the cost of these expensive services. Time to diagnosis was described by some authors as an indicator of tumour behaviors. High-grade BST invariably have a rapidly progressive course (weeks to months) while low-grade tumours have insidious course and a longer period (months to years) before diagnosis. Approximately 90% of BST are gliomas in origin.

In brainstem glioma, high morbidity and mortality rates are the rule and are independent of the extent of surgical resection or histology and grade. For this reason, surgical resection or pretreatment biopsies are not performed routinely. Therefore, clinical presentations and neuroimaging are essential for the diagnosis of BST. MRI brain is the diagnostic test of choice. Both T1- and T2-weighted axial and sagittal sequences should be obtained for the basic studies. The image quality of MRI scan is compromised easily by motion. Thus, sedation or anesthesia is required in most infants and younger children. CT brain is less accurate than MRI but can be used in emergency situations or when MRI is not available. Tissue biopsy should be reserved for indeterminate lesions on MRI accompanied with an unusual presentation. However, a survey conducted among paediatric neurosurgeons revealed that there was no consensus regarding what constitutes a typical BST on MRI. Cartmill et al. reviewed 18 BST patients who underwent CT-guided stereotactic biopsy and found that all patients had a histological diagnosis of glioma, five patients had developed a transient increase in their neurological deficits post-operatively (hemiparesis, increased eye movements, and VII nerve palsy), and no death was reported. Many non-neoplastic lesions may arise within the
brain stem include cavernous malformations, tuberculomas, and epidermoid cyst. Therefore Magnetic resonance spectroscopy (MRS) is very helpful when clinical and MRI presentations are atypical. Compared with benign lesions and low-grade tumours, high-grade tumours show increase choline/N-acetyl aspartate and choline/creatine ratios in MRS. Children with BST should be cared for by a multidisciplinary team including a paediatric oncologist, radiation oncologist, clinical radiologist, neurosurgeons and other therapists. Surgical resection is typically recommended early for cervicomedullary gliomas. Chemotherapy has a limited role in the management of these tumours; it is mainly used for high-grade tumours or at the late stages of the disease. Although many clinical trials have examined the concurrent temozolomide (TMZ) with RT for the treatment of BST in children, this combination did not alter the poor prognosis of BST in children. It is well-established that RT prolongs survival time and reliefs the neurological deficit. The majority of cases in this study treated with RT. Two cases succumbed during RT treatment with marked exacerbation of signs and symptoms. Nearly one-third of cases developed disease progression after a clinical response of a very short duration. In the current study, treatment abandonment and patients’ death before the start of treatment were the main reasons for patients not to be treated with RT. In this series, children with BST had symptoms for an average of two months before diagnosis and median survival of five months after diagnosis was confirmed. Survivals at one and two years were 13% and 7% respectively. This series illustrated that the prognosis of children with BST in our setting was considerably poor; this finding is worse than those of previous studies. In Cataltepe series, the two-year survival incidence was 25.6% and five-year survival incidence was 12.8%. It was reported in a previous series, the average survival time for patients with low grade astrocytoma (32.4 months) was better than those with high grade astrocytoma (6.4 months). The favorable clinical prognostic factors that were reported in previous studies include: young age at diagnosis (<3 years), prolonged interval between onset of symptoms and diagnosis (>6 months) and absence of cranial nerve palsies or long tract involvement at presentation.

The current study had clear limitations. It was based on a retrospective analysis of patients' records. Moreover, it was a single institution data, so we cannot make a conclusion on the status of paediatric BST in Sudan. Therefore, a prospective study with large number of patients is required for better standing of the clinical profile and treatment outcomes of BST in our limited resources setting.

CONCLUSION:
Overall this study draws attention to the situation of paediatric brain tumours in Sudan. Our findings are in concordance with international literature apart from the slight female predominance. In our limited resource setting, the prognosis of BST is dismal. Obstacles to a better outcome in our patients with this deadly tumour include late presentation, limited management resources, and a lack of a multidisciplinary approach to treatment with standardized adapted treatment protocols that outline the optimal approach to management of these patients in the context of Sudan’s medical capability. Therefore, early integration of supportive and palliative care in our set-up should be considered to improve the quality of life of these children and their families.
REFERENCES:


