Pediatric Brain tumors in Southeast Nigeria; An 8-year prospective longitudinal cohort study

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Abstract

Background: Pediatric brain tumors (PBT's) from previous studies are associated with poor outcomes in our subregion.

Methods. An 8 -year single center prospective study. All cases investigated with neuroimaging and treated were enrolled. Data was analyzed with SPSS (Inc) Chicago IL, USA version 23. Chi Square test, One-way Anova and confidence limits were used to evaluate associations using the 95% level of significance. Patients were followed up for a range of 1 to 7.5 years with a mean of 4.9 ± 1.3 years. Ethical approval was obtained for our study.

Results: 95 patients were enrolled, 84 satisfied the study criteria. There were 45 males and 39 females, M:F=1.1. The mean age was 9.9 ± 2.7 years 95%CI with a range of 9 months to 16 years. The most common symptom was headache for supratentorial lesions (73%) and gait disturbance (80.2%) for infratentorial lesions. More tumors were supratentorial in location (45(54.2%), while 33(37.1%) were infratentorial. Craniopharyngiomas (n=19), medulloblastomas(n=17) and astrocytomas (n=11) were the most common tumors. Hemoglobin genotype(AA and AS) had some influence on tumor phenotype, Odds ratio 8.9 and 3.3 for medulloblastoma and craniopharyngioma. 69 cases were microsurgically resected while 14 patients were treated with radiotherapy alone. The 30-day mortality for operated cases is $7.9 \pm 1.3\%$. Overall 1-year and 5-year survival was 67.9% and 53.6 % respectively. Survival rates varied among treatment groups ($\chi^2=8.9$, $P=0.017$).

Conclusion: Survival profile in this series suggests some improvement in comparison to previous studies from our region.

Background

Pediatric brain tumors (PBT's) in general currently constitute a great challenge confronting pediatric oncology units in many countries. [4] They contribute a significant proportion to the

overall morbidity and mortality profile of pediatric tumors worldwide. [4]The poor outcome

associated with PBT in the developing world is the result of a complex interplay of pathobiological

factors and environment-dependent care constraints presenting a relentless clinical challenge. Our

previous study presented a retrospective analysis of the outcomes prior to establishment of

multidisciplinary oncology boards.² In our index study we have observed and analyzed the presentation and outcome of a prospective cohort of pediatric patients with brain tumors who

received multidisciplinary care with microneurosurgery as the dominant treatment paradigm.

Methods

An 8-year single institution prospective observational study of pediatric patients with brain tumors

who received multidisciplinary care and were followed up between January 2010 and

December 2017. Our unit is the apex referral neurosurgical center in Southeast Nigeria serving a

large catchment population of up to 60 million people. Consent was obtained from caregivers

before enrollment of patients. Ethical approval for the study was obtained from the IRB of our

hospital. Our pediatric brain tumor patients receive multidisciplinary care with microneurosurgery

and radiotherapy as the main treatment modalities. A multidisciplinary oncology board review is

a component of our current patient care plan. Those with neuroimaging confirmed brain stem

gliomas or marker positive ICGCT are treated by radiotherapy without microsurgical resection.

We currently do not have a hospital chemotherapy protocol for pediatric brain tumors.

Radiotherapy treatment plans are case based and discussed at oncology board reviews.

Inclusion criteria:

Patients aged 16 years or less with brain tumors evaluated clinically, verified by

neuroimaging and treated either with microneurosurgery or radiotherapy alone or in

combination. Microneurosurgical resection status was defined as total microneurosurgical resection (TMNR) for complete resection verified by post-operative MRI within 48 hours of surgery or subtotal microneurosurgical resection (SMNR) for incomplete resection which is >

90% tumor volume resection.

All patients with histopathological confirmation

All neuroimaging verified brainstem tumors or intracranial germ cell tumors (ICGCT) with tumor

marker seropositivity with or without histopathological proof.

Exclusion criteria.

All cases without histopathological confirmation except brainstem or ICGCT's.

Pediatric brain tumors operated in other facilities but referred to our center for radiotherapy (n=3)

All cases lost to follow up (n=8)

Data Acquisition and analysis

The age, sex and schooling profiles of the patients as well as the genotype, main

presenting symptoms and signs were recorded as well as the neuroimaging (brain MRI diagnosis),

serum tumor marker profiles, treatment modality received such as surgery, surgery with

radiotherapy or radiotherapy alone. All cases were followed up for a range of 1 to 7.5 years (mean

of 4.9 ± 1.3 years (95%CI) with brain MRI scan 6 monthly for 2 years and yearly afterwards.

30-day mortality, 1 -Year and 5-Year survival rates were also evaluated. Analysis of general and

subgroup outcomes among histopathological variants and treatment modalities was performed as

well. The influence of brain tumors and their treatment on schooling was evaluated and provided

an indirect assessment of the effect of PBT on cognitive function. All data were analyzed with

SPSS (Inc) Chicago IL, USA version 23. Confidence limits, Chi square test and One-way Anova

were used to evaluate associations between groups and subgroups at the 95% level of significance.

Results

95 patients were enrolled, while 84 satisfied the study criteria. Of 341 brain tumors treated in our center

during this period, pediatric tumors account for 24.6%. There were 45 males and 39 females, M: F=1.1.

Their ages ranged from 9 months to 16 years with a mean of 9.9 ± 2.7 years (95%CI). Case frequency per

year ranged from 5 to 19 with a mean of 10.5 ± 1.7 . Table 1 The most common symptom was headache for

supratentorial lesions (73%) and unsteadiness of gait (80.2%) for infratentorial lesions. Seizures was a

presenting symptom in 37(44%) patients. In 45(53.6%) patients, tumors were supratentorial in location,

while in 33(39.3%) and 6(7.1%) patients respectively, they were infratentorial and trans tentorial.

Craniopharyngiomas (n=19), medulloblastomas (n=17) and astrocytomas (n=11) were the most common

tumors. However when brain stem gliomas, a clinical group that are usually not biopsied (n=9) as well as

oligodendroglioma's (n=2) are added to the astrocytomas, gliomas (n=22, (26.2%) are the most common tumor

subgroup in our series. The most common tumors encountered among the age subgroupings is shown in

TABLE 1 and TABLE 2. Dysembryoplastic Neuroectodermal Tumors (DNETS) and low grade

astrocytomas were the only tumors seen in children below 2 years of age, ependymomas and

medulloblastomas were the most common tumor subtypes among age subgroups 3-5, 6-years respectively.

Craniopharyngiomas were the most common tumors among 9 to 11 and 12 to 14- year age group and also

was the most common tumor among surgically treated patients in this series. Low grade gliomas were the

dominant tumors among 15-16-year olds. 43 patients harbored WHO grade I tumor, while 3, 2 and 21

patients respectively harbored WHO grades II, III and IV tumors. Analysis of the variability between age

groups and tumor type showed was significant using one -way Anova ($F=6.4$ $DF_1=2$, $DF_2=12$, $P=0.013$).

70(83%) patients were of Hb AA Genotype, while 7(8.3%) had AS genotype, while 2(2.38%) had SS

genotype. In 5 patients Hb genotype was not determined. Among Hb AA patients, medulloblastoma was

the most common tumor ($n=15$, Odds ratio=8.9), Apart from medulloblastoma, the overall distribution of

other tumors among patients with Hb AA genotype was however did not vary significantly using one-way

Anova test. ($F=2.33$, $P=0.713$).

There was a preponderance of craniopharyngiomas among Hb AS subgroup ($n=5$, $X^2=9.7$, $P=0.002$, Odds ratio=3.3) and low grade astrocytomas among sicklers ($n=2$, $P=0.000$).
TABLE 1.

69 cases were microsurgically resected. Of 39 patients treated with surgery alone, 25 of them had

TMNR, while 14 had SMNR. 30 patients had SMNR with radiotherapy. In all, 41 resected tumors had

adjuvant radiotherapy, while 14 patients were treated with radiotherapy as primary treatment for

brainstem gliomas (9 cases) or marker positive intracranial germ cell tumors (ICGCT $n=5$)
TABLE 3. 37

cases of tumor associated hydrocephalus (TAH) received preoperative cerebrospinal fluid (CSF)

diversion with ventriculoperitoneal shunt (VPS), while 10 received endoscopic third ventriculostomy

(ETV), 4 patients had a temporary External Ventricular Drainage (EVD). Three EVDs were discontinued after tumor resection while one EVD was replaced with VPS. For craniopharyngiomas, 3 cases had Ommaya reservoir inserted for cyst aspiration following recurrence. For intracranial germ cell tumors, the presence a pineal region or suprasellar tumor with raised serum tumor markers (alpha fetoprotein and β -HCG) was diagnostic of malignant intracranial germ cell tumor (ICGCT) and this was seen in 5(6.0%) patients TABLE 2. We found a high CSF to blood gradient of α -fetoprotein and β -HCG in three patients. The CSF to blood gradient ranged from 2.7 ± 0.9 (95%CL) for alpha fetoprotein to 3.5 ± 0.3 (95%CL) for β -HCG among ICGCTs. The treatment complication rates as well as 30-day post-operative mortality is shown (Table 1). The mean complication rate is $13.9 \pm 3.7\%$, while the mean 30-day operative mortality rate is $7.9 \pm 1.3\%$, The long-term survival profiles are shown in TABLE 3. Survival rates varied both among treatment subgroups. $X^2=8.9$, $P=0.017$. Overall 1-year and 5-year survival generally was 67.9% and 53.6 % respectively. The influence of paediatric brain tumors and their treatment on school attendance and performance is shown in table 4. Only 15(18.5%) patients completed primary or secondary education and those who received surgical treatment only were more likely to complete their schooling $X^2=4.94$, $P=0.015$.

Discussion

From our study, the mean annual incidence of pediatric brain tumors receiving specialized care

in our center is 10.5 cases. Children accounted for 24.6% of all brain tumors treated in our center

during this period. Our hospital is a 1000- bed tertiary health facility; the largest multispecialty

hospital in the southeast region of our country endowed with a robust workforce in paediatric

neurosurgery. The annual incidence appears low; however, it may reflect constraints in accessing

care by patients generally and pediatric brain tumor patients specifically. Some of the constraints

have been studied extensively [23, 30]. At 9.9 ± 2.7 years, the mean age of occurrence of pediatric

brain tumors is similar to that from a previous study performed by the lead author of this paper

and other researchers from another region of our country [30]. as well as a recent retrospective

study from a center in our subregion with a smaller sample size [22]. In Morocco, a North African country, a large epidemiological study found a mean age of 9.3years [11]. A slight male preponderance found in our study is similar to some previous studies both from our country and elsewhere [4, 22, 23, 30]. Headache was the most common presenting features among supratentorial tumors while unsteadiness of gait occurred more frequently among infratentorial tumors. 53.6% of tumors in our index series occurred in the supratentorial compartment. Although the finding above is supported by another report from our sub region [4], it differed from reports from other regions in our country [1, 23,30] as well as previous studies in other parts of the world [4,11, 33]. This may suggest the existence of geographical variations in the topographical distribution of brain tumors which in the view of some authors may also be influenced by age [3, 15]. Craniopharyngioma (n=19) is the most common tumor among histopathologically confirmed cases in our series followed by medulloblastoma TABLE 2. However, when brain stem gliomas (n=9) and oligodendrogliomas (n=2) are included, gliomas (n=22) will represent the most common subgroup. Our previous study showed that medulloblastoma and astrocytomas were the most common tumors, while craniopharyngiomas were the third most common tumor subtype [30]. An epidemiological study from Morocco, a country in the North of Africa, reported medulloblastoma as the most common tumor followed by low grade astrocytoma, while

craniopharyngioma was the fifth most common tumor subtype [11]. We found a significant age group bias in the occurrence of brain tumors among our cohorts ($F=16.4$, $df_1=2$, $df_2=12$, $P=0.013$)

TABLE 1. Low grade Astrocytoma and DNETS were seen in patients below 2 years of age. Some previous studies have also found a preponderance of astrocytomas in under -2 children [6, 8]. Ependymomas were predominant among 3 to 5-year age group, while medulloblastomas were most common among age group 6 to 8 years respectively. Previous studies have also reported age group variability in the occurrence of ependymomas and medulloblastomas [5, 17, 20], as well as craniopharyngiomas which from our series is the most prevalent tumor between ages 9 and 14 years. A previous study found a higher incidence of craniopharyngiomas among black children in the United States of America [29]. The findings of our study seem to highlight as well this racial and geographical predisposition to pediatric brain tumors or may reflect a changing trend more so with the predominance of craniopharyngiomas in our series (22.6%) when compared to previous studies from other centers in our country [22, 23, 30], and elsewhere, some of which reported a higher frequency of occurrence of astrocytomas and medulloblastomas [3, 9, 10].

Low grade gliomas were predominant among adolescents between 15 and 16 years. We found an association between hemoglobin genotype and brain tumors. For instance, medulloblastomas

occurred more commonly among patients with HbAA (n=15, Odds ratio=8.9), while craniopharyngiomas occurred mostly in HbAS patients (Odds ratio=3.3, $\chi^2=9.7$, P=0.002). Moreover, both patients with Hb SS in our series had low grade astrocytomas, (n=2, P=0.000).

Our findings are supported by a previous study which reported 3 cases of astrocytoma among 47 sicklers with cancer [27]. To our knowledge, our study remains to date the largest

prospective study reporting an association between hemoglobin genotype and the predisposition

to specific brain tumor phenotypes. We do not know the extent to which our observations represent the salient relationship between hemoglobin genotype and brain tumor profiles in children. A multicenter study is necessary to further verify this association especially within sub-

Saharan countries which alongside the Indian subcontinent currently harbor over 90% of the

global burden of sickle cell disease [24]. Such a study may generate scientific evidence to suggest

a review of the current risk factor associations of PBT's.

We applied microneurosurgical resection to most cases (n= 69). Total microneurosurgical resection (TMNR) alone was the treatment modality in 52.5% of surgically treated cases. Of all

microsurgically resected tumors, 43 cases were WHO Grade I, 3 were Grade II, 2 were Grade III

and 21 were Grade IV tumors. Surgery provides a direct and effective treatment path for brain

tumors and the extent of resection correlates with overall outcome [12, 19, 33]. From our series,

those who received TMNR had the best survival profile Table 3 and also the best school

performance Table 4. However, majority of brain tumors in paediatric patients grow near functionally eloquent sites presenting a significant challenge to preserving them during surgery

[31]. Intraoperative neuronavigation and brain function mapping facilitate tumor resection and

help in preserving eloquent brain loci during surgery.²⁴ We currently do not have these parameters

in our unit and hence rely on microneurosurgical techniques. We believe the absence of neuronavigation and intraoperative brain mapping may be a significant limiting factor to performance of TMNR and may invariably play some role in lowering the survival profile of our

patients.

The role of radiotherapy in the treatment of pediatric brain tumors is well recognized [16, 25].

However, from our series, patients treated with radiotherapy had poorer overall survival (Table 3)

as well as school performance. Poor school outcomes with radiotherapy may partly reflect the

reality that more high-grade tumors with intrinsic propensity to poorer outcomes are treated with

this modality including brainstem gliomas. However, the long-term sequelae of radiation therapy

among paediatric brain tumor survivors especially its harmful effect on brain vasculature and

neurocognitive functions have been previously reported [2, 21]. Despite these sequelae, radiotherapy together with cerebrospinal fluid diversion remain the mainstay for treatment of brain

stem gliomas which constitute 10.6% of pediatric brain tumors in our series[32]. Radiation

treatment for brainstem gliomas in our series was associated with 40% and 0%, 1 -Year and 5-Year survival rates respectively which compares favorably with a report from a recent Asian Study[32]. We also treated serum marker positive ICGCT's with radiotherapy and the 1 year and 5-year survival rates for ICGCT from our series is 60% and 40% respectively which compares with some previously reported outcomes for non germinomatous germ cell tumors [13, 32]. From our index study, marker positive ICGCT constitutes 6% of all paediatric brain tumors. The use of generous radiation dose for tumor bed and ventricular space with or without craniospinal irradiation and chemotherapy is considered a vital component of the standard treatment protocol for germ cell tumors [18, 32]. Treatment complications and 30-day mortality rates varied with tumor phenotype. Medulloblastoma was associated with the highest rate of post-operative complications and 30-day mortality TABLE 1, while Ependymomas, craniopharyngiomas and low-grade gliomas were associated with lower rates. Patients overall survival (OS) also varied with tumor phenotype as well as treatment modality TABLE 1. Craniopharyngiomas, meningiomas, low grade gliomas, and ependymomas were associated with the best survival, while brainstem gliomas and medulloblastomas had the worst survival. Patients who received TMNR had the best survival of any treatment subgroup, while surgically treated patients survived better than those treated with radiation ($\chi^2=8.9$, $P=0.017$) TABLE 3. Although the overall 1-year and 5-year survival rates of 67% and 52%

respectively from our current study compare poorly to those from centers in the developed world [14, 26], they however represent an improvement when compared to our previous work as well as a recent study from our sub region [22, 30]. In our previous study, the 1-year and

5-Year survival rates were 53% and 47% respectively [30]. We believe this improvement is the

result of multiple factors, including the establishment of a multidisciplinary oncology center which

has an active radiotherapy unit equipped with a linear accelerator as well as increase in the number

of neurosurgeons with experience in paediatric neurosurgery. Furthermore, an increase in awareness and improved referral practices may partly account for the overall positive survival shift

in this study, which more so is significantly more experienced among those treated with TMNR.

From our study, PBT's negatively affect school attendance and performance, table 4

and the treatment modalities are also associated with variable influence on school performance.

Our findings are quite significant because PBT survivors are often excluded from studies evaluating childhood cancer survivors, due in part to concerns on the impact of cognitive limitations on the validity of assessment [26. 34].

To our knowledge, this is the first study evaluating school performance among survivors of PBT in our region and therefore provides the reference for further studies on this subject. More

clinical studies and collaborations are needed between centers treating PBT's within the sub-

Saharan region so as to further elucidate the variations in presentation, treatment practices, as well

as evaluate relevant potentially significant associations including hemoglobin genotype. This will

help us to summate the outcome of pediatric brain tumors within the region.

Limitation Of The Study

Our study reports a one- center experience. As a result, it is invariably exposed to the ‘tip of the

iceberg phenomenon’ that negatively profiles single center studies from tertiary referral centers.

We did not report an experience with chemotherapy for treatment of PBT’s due to a lack of protocol for PBT chemotherapy in our center

Conclusions

Craniopharyngiomas are among the most common tumors in our series of PBT’s.

Hemoglobin genotype may have an influence on PBT phenotype in our environment. TMNR is

associated with better overall survival and school performance profiles. Overall survival is improved in our study when compared to previous studies from our subregion. Multicenter collaborations are however required to better define the characteristics of PBT’s.

Declarations

Ethics approval: This Study was approved by the IRB of University of Nigeria Teaching Hospital

Enugu Nigeria with ethical reference number: NHREC/05/01/2008B-FWA00002458-

1RB00002323. Both verbal and written consent for participation was obtained from all caregivers.

Consent to Publish: Consent was also obtained from all the care givers for publication of the

study results.

Availability of data and materials: The data from this study are not sensitive and we do not require help with data management. The study materials are available for review if required.

Competing Interest Statement: We have no competing interest to declare

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Authors' Contributions: All the authors contributed significantly to the study and all have given

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Abbreviations

Abbreviations	
PBT's	Pediatric Brain Tumors
SPSS	Statistical Package for Social Sciences
ICGCT	Intracranial Germ Cell Tumors
IRB	Institutional Review Board
TNMR	Total Microneurosurgical Resection
SMNR	Subtotal Microneurosurgical Resection
MRI	Magnetic Resonance Imaging
DNETS	Dysembryoplastic Neuroectodermal Tumors
WHO	World Health Organization
Hb	Hemoglobin
TAH	Tumor Associated Hydrocephalus
CSF	Cerebrospinal Fluid
ETV	Endoscopic Third Ventriculostomy
EVD	External Ventricular Drainage
VPS	Ventriculoperitoneal Shunt
β-HCG	Beta-Human Chorionic Gonadotropin

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Tables

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