Case Report

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Molecular And Clinicohistopathological Characteristics Of Brainstem Gliomas In Paediatrics And Adults: A Retrospective Comparative Study

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1. Abstract

1.1. Background
In contrast to pediatric brainstem gliomas, adult brainstem gliomas are rare and tend to be less invasive. There are some notable differences between adult and pediatric brainstem gliomas which significantly affect their management and prognosis. The goal of this study was to analyze clinicohistopathological, neuroradiological and molecular markers differences between these two age groups in a small series of 25 histologically proven brainstem gliomas.

1.2. Method
Between 2020 and 2022, 38 patients with histologically proven brainstem gliomas were retrospectively analyzed. Data about clinical course of a disease, neuroradiological, molecular biomarkers and histopathological findings were analyzed.

1.3. Results
The age ranged from 2 to 60 years (median 30 years). The female to male ratio was 1.1:1 in children and 2.5:1 in adults. The commonest presenting symptom in children was ataxia (52.9%), and headache (52.4%) in adults. Ocular symptoms were commoner in adults than pediatrics ($p<0.067$). On the post-contrast T1 weighted MRI, a higher proportion of children had diffuse and hyperintense masses involving the pons (52.9% versus 17.4%). Histologically, 73.7% of the tumors were astrocytomas with astrocytoma grade III being the most common. BSGs MGMT promoter expression in adults was significantly higher than in pediatric ($p<0.003$). With the exception of only one patient who died before surgery, the gross total resection was achieved in 71.4% of adults unlike 41.2% in pediatric patients.

1.4. Conclusion
The existence of clinical, radiological and molecular differences between adult and pediatric brainstem gliomas may be attributed by the differences in the tumor biology. The histopathological examination showed no significant difference between the two groups and the majority of tumors were grade III astrocytomas. Diffuse tumors remained to be highly common infiltrative lesion in children. BSGs MGMT promoter expression in adults was significantly higher than in pediatric ($p<0.003$). For resectable tumors, we advise gross total resection as they are associated with favorable outcome.

2. Keywords:
Adults,brainstem, glioma, histopathology, molecular, pediatrics.

3. Introduction

Brainstem gliomas (BSGs) are primarily found in children and account for 10-30% of posterior fossa tumors in this patient population. In adults, these tumors are uncommon and constitute only 2% of all brainstem tumors.4,5 BSGs include low-grade focal brainstem gliomas (FBSGs), which are associated with favorable prognosis and high-grade diffuse intrinsic pontine gliomas (DIPGs), known for their relentless growth and bleak outcome. FBSGs which are usually WHO grade I-II tumors, have been reported to have overall survival time up to 7 years, unlike DIPGs which are almost always highly malignant with reported median survival time less than 1 year.6,7

4. Advances in Molecular Pathology

The initial knowledge of the underlying molecular biology came from studying associated genetic predisposition syndromes that can lead to a low glioma development. Disease conditions like Neurofibromatosis type 1 (NF-1)8,9, Tuberous sclerosis complex (TSC 1&2) 10,11, and

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Cowden's syndrome (specifically Lhermitte-Duclos disease) [12-14] are known for their associated mutations in their genome and subsequent molecular pathways that will lead into benign low-grade gliomas. A major paradigm shift occurred in 1998 with the reported association of deletions involving chromosome 1 and 19 indicating chemosensitivity and a better prognosis of anaplastic oligodendrogliomas. Other examples within the sphere of neuro-oncology include assessment of IN11 gene deletion/ mutation in atypical teratoid/rhabdoid tumors, MGMT gene silencing in GBM, coexpression of EGFR deletion mutant variant III (EGFRvIII) with the tumor suppressor protein PTEN in high-grade gliomas.15 In 2014, a meeting held in Haarlem, the Netherlands, under the auspices of the International Society of Neuropathology, established guidelines for how to incorporate molecular findings into brain tumor diagnoses, setting the stage for a major revision of the 2007 CNS WHO classification.16 This has improved morphologic diagnosis in tandem with the development of new treatment options such as gene therapy and targeted therapeutics. A recent literature search has revealed few studies that has examined and compared the differences in the molecular characteristics between adults and children. We report the findings of 38 histopathologically confirmed cases of BSGs.

5. Patients and Methods

5.1. Clinical Data Collection & Ethical considerations

We received approval from the Dalian hospital of DMU to collect data from the records of the patients in our study. No informed consent was required, as this was the retrospective study detailing the hospital courses of each patient, with no identifying information presented. Clinical data, including age at diagnosis, gender, preoperative signs and symptoms, time of last follow up, time of tumor recurrence and death, other co-existent malignancy or tumor-prone conditions, and pathologic diagnosis with cellular proliferation where collected when available. Inclusion criteria; all pediatric patients defined as those with age ≤14, and adult patients with the age of 14+ years; treated at our center from 2020 to 2022. All patients who underwent either surgical resection or biopsy. The pathology was determined by an experienced neuropathologist initially by using standard H&E stained sections. Immunohistochemistry (IHC) studies using Ki-67, glial fibrillary acidic protein (GFAP) and Olig2 were also performed. Likewise, the molecular markers including p[53], MGMT promoter and IDH1 were also determined whenever appropriate. Likewise, the imaging features were analyzed by a neuroradiologist. Primary tumor location was defined as the area in which the tumor mass was centered, with secondary sites representing surrounding areas with tumor infiltration. Multifocality represented the presence of multiple areas of enhancement in different brainstem regions. Lesions were characterized either as focal or diffuse, and T1 post-contrast appearance was defined as either enhancing or non-enhancing. Tumors were therefore characterized into four categories (diffuse enhancing, diffuse non-enhancing, focal enhancing, and focal non- enhancing) as previously described. Magnetic resonance imaging (MRI) scans and surgeons' intraoperative estimations were used to evaluate and derive the extent of surgical resection.

5.2. Evaluation of Recurrence and Progression

For patients with GTRs, recurrence is defined as evidence of new abnormal radiographic signals (T1 enhancement or T2 flair on MRI scans) compared with that of the immediate postoperative images. For patients who had residual tumor immediately after surgical treatment, progression is defined as enlargement of the previous lesion or appearance of new abnormal radiographic findings in other parts of the central nervous system. Follow-Up For patients who died, the time of death is recorded as the last follow-up. For patients who are still alive, the last available clinic notes or follow-up date recorded in the candidate file is recorded as the last follow-up.

5.3. Statistical analysis

The data were summarized using medians for quantitative variables, and counts and percentages for qualitative variables. Differences in quantitative variables were analyzed using the t- test while qualitative variables were evaluated using the Chi-square test. Values with $p< 0.05$ were considered statistically significant. All analyses were performed using IBM SPSS 22.0.

5.4. Limitation of the study

The current study has some important limitations that are worth mentioning. Firstly, the sample size was not determined statistically and was relatively small. This could due to under documentation of the cases. It was also difficult to follow up those alive patients after their discharge.

5.5. Delimitation of the study

I have used different biometric measures to let the study simulate a close reality.

6. Results

6.1. Demographic characteristics

Patient characteristics are given in Table 1. The age ranged from 2.7 to 61 years (median 32 years). The female to male ratio was 1.1:1 in children and 2.5:1 in adults.

Table 1:

	Children	Adults
	n=17(%)	n=21(%)
Sex		
Female	9(52.9)	15(71.4)
Male	8(47.1)	6(28.6)
Female to male ratio	1.1:1	2.5:1
Location		
Midbrain	0(0)	5(23.8)
Pons	9(52.9)	4(17.4)
Medulla	3(17.6)	3(14.3)
More than one location	5(29.4)	9(42.9)
Enhancement		

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Enhanced	9(52.9)	8(38.1)
Non-enhanced	8(47.1)	13(61.9)
Approach		
Infratentorial	16(94.1)	15(71.4)
Supratentorial	1(5.9)	6(28.6)
Resection		
GTR	7(41.2)	15(71.4)
STR	3(17.6)	4(19.0)
Biopsy	7(41.2)	2(9.5)

The WHO tumor grading and histological types were determined in 38 patients. Patients with high grade were more often younger (p = 0.203) than patients with lower grade tumors (Table 2).

Table 2:

	Children	**Adults**	**P**
	n=17(%)	n=21(%)	
Tumor size			
Diffuse	12 (70.6)	13 (61.9)	0.734
Focal	5 (29.4)	8 (38.1)	
Pathology			
GliomaI	1 (5.9)	3 (14.3)	0.613
Piloastrocytma	1 (5.9)	0 (0.0)	0.447
GliomaII	0 (0.0)	3 (14.3)	0.238
AstrocytomaII	5 (29.4)	7 (33.3)	1
AstrocytomaIII	9 (52.9)	6 (28.6)	0.185
GBM	1 (5.9)	2 (9.5)	1
WHO grade			
Low grade	7 (41.2)	13 (61.9)	0.328
High grade	10 (58.8)	8 (47.4)	

6.2. Clinical features

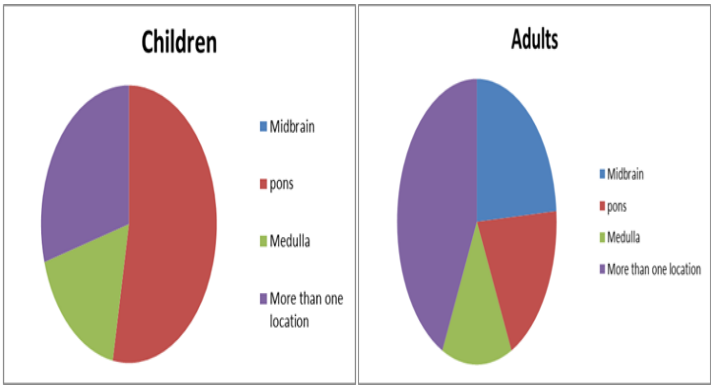
The clinical features are summarized in Table 3. The commonest presenting symptom in children was ataxia (52.9%), followed by headache (35.3%) and dysarthria in (23.5%). In adults, headache (52.4%) was the commonest symptom. Ocular symptoms were commoner in adults than pediatrics (p<0.067) and were the second commonest symptoms in this age group. Mixed signs of either cerebellar manifestations, cranial nerve palsies, neurologic deficits or signs of raised ICP occurred frequently in both age groups at an almost equal percentage (41.2% versus 42.9%).

	Children n=17(%)	**Adults n=21(%)**	**2**	**P**
			χ	
Signs Raised ICP			-	-
	2 (11.8)	3 (14.3)		
Cranial nerve palsy	2 (11.8)	3 (14.3)		
Cerebellar	4 (23.5)	5 (23.8)		
Neurological deficit	2 (11.8)	1 (4.8)		
Mixed or other	7 (41.2)	9 (42.9)		
Symptoms	6	11	1.109	0.292
Headache	-35.3	-52.4		
Ataxia	9	8	0.838	0.36
	-52.9	-38.1		
Ocular symptom	2	8	3.359	0.067
	-11.8	-38.1		
Dysarthria	4	3	0.534	0.465
	-23.5	-14.3		
Dysphagia	1 (5.9)	2 (9.5)	0.171	0.679
Vertigo	4(22.2)	4(19.0)	0.06	0.807
Hemiparesis/ Paraparesis	3	4	0.012	0.912
	-17.6	-19		
Quadriparesis	0 (0.0)	2 (9.5)	-	0.492
Vomit	6	5	0.602	0.438
	-35.3	-23.8		

Table 3:

6.3. Imaging features

The neuroradiological features are summarized in Histogram 1 and pie chart below. Pre-operative T1-gadolinium enhanced, T1- and T2-weighted images were available in all cases. Data about the location of the tumor was available in majority of patients. On the post-contrast T1 weighted MRI, a higher proportion of children had diffuse and hyperintense masses involving the pons (52.9% versus 17.4%). In contrast to the 23.8% of adult BSG which were solely located in the midbrain, no pediatric case was found to have BSG solely located in that location. The tumor was solely located in the medulla in 3 pediatric cases and 3 adult cases. Two parts of the brainstem were involved in 29.4% of pediatric against 42.9% of adult cases. The most common differential diagnosis was ependymoma (n=7) and cavernous hemangioma (n=4). Lymphoma, hemangioblastoma and ganglioma had occurred in a single case each.



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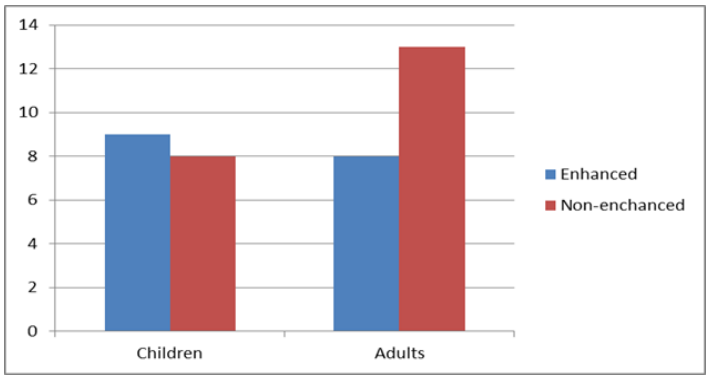
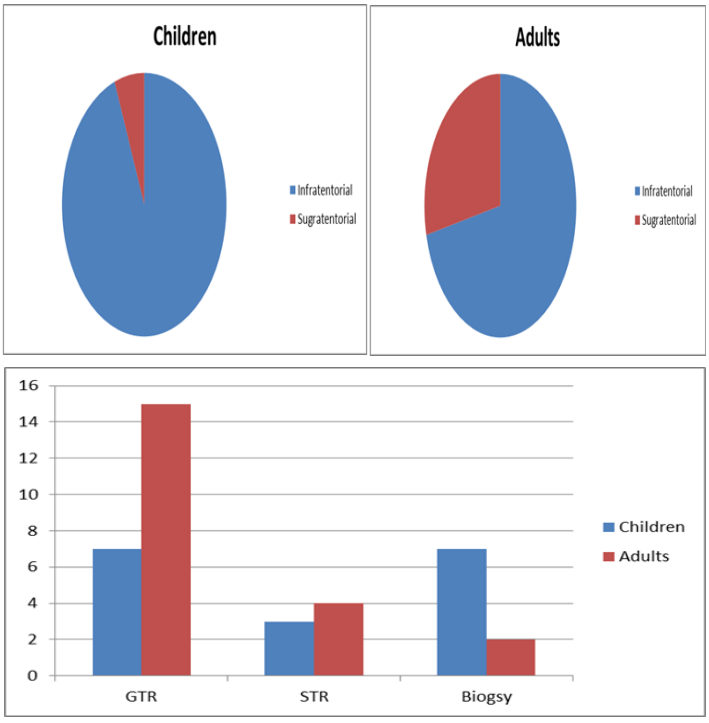


6.4. Surgical procedure

The majority of patients were operated by infratentorial approach (94.1% children versus 71.4%) which included the retrosigmoid and posterior midline approach. The other approaches like transcallosal, sub-occipital and sub-temporal were regarded as supratentorial approaches. The gross total resection was achieved in 71.4% of adults unlike 41.2% of pediatric patients Histogram 2). One patient died before the surgical procedure. The intraoperative complications included hemorrhage in only 1 patient and brainstem reflex in the other 2 patients.



6.5. Histopathological features

The WHO histopathology classification of the masses is summarized in Table 2. The Ki-67 expression ranged from 1-45% (median 9.79%) and results between tumors Ki-67 expression at <10% and >10% were statistically significant (p<0.019). A majority of tumors were astrocytoma grade III and it being the most frequent in children (52.9%) as opposed to 28.6% in adults although the result was statistically not significant (NS). Piloastrocytoma was only found in pediatric (5.9%). GBM accounted for 9.5% in adults in contrary to 5.9% in pediatric. Astrocytoma grade II occurred in 29.4% of pediatric while it accounted for 33.3% in adults. Histologically, 73.7% of the tumors were astrocytomas (Table 2).

6.6. Molecular features

The molecular markers are summarized in Table 4&5. Over 90% all the gliomas in both groups regardless of their WHO stage, expressed positively for GFAP and over 50% for Olig 2 glial markers.

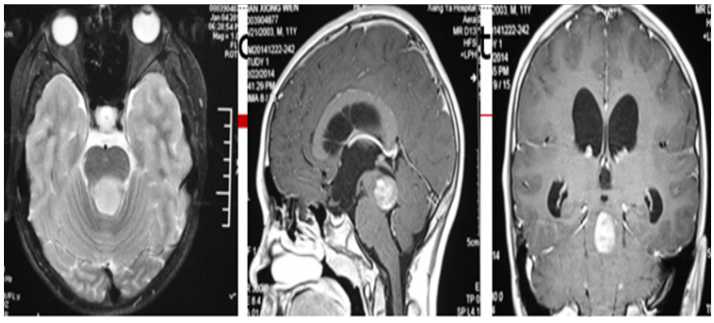
Table 4:

	Children	Adults	P
	n=17(%)	n=21(%)	
GFAP	17 (100.0)	19 (90.5)	0.492
Olig2	14 (82.4)	13 (61.9)	0.282
Ki67	6 (35.3)	17 (23.5)	0.708
P53	7(41.2)	13 (61.9)	0.328
MGMT	1(5.9)	9 (42.9)	0.012
IDH1	1(5.9)	4(19.0)	0.355

Table 5:

	Astrocytoma n=27(%)	Non-astrocytoma	P
		n=11(%)	
GFAP	25 (89.3)	11(100%)	0.545
Olig2	19 (70.4)	8 (72.7)	1
Ki67	14 (51.9)	9 (81.8)	0.145
P53	16(59.3)	4 (39.4)	0.288
MGMT	7(25.9)	20 (27.3)	1
IDH1	3(11.1)	2(18.2)	0.615

We found only 1 pediatric case and 2 adult cases of diffuse astrocytoma, IDH mutant. BSGs MGMT promoter expression in adults was significantly higher than in pediatric (p<0.012). Again p53 expression in adults was higher than in pediatric but the result was statistically NS.



Illustrative case 1: Left to right respectively; axial, sagittal and coronal MR images of the same patient showing the midbrain glioma which was resected through dorsal infratentorial supracerebellar approach.

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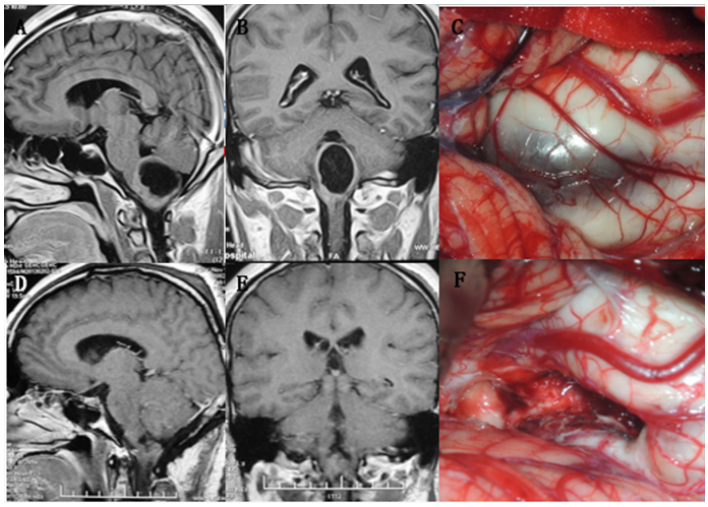

Illustrative case 2: A&B; Preoperative gadolinium enhanced T1 weighted sagittal and coronal MR images showing a medullary glioma that invaded the anterior wall of the 4th ventricle. D&E; Respective postoperative images after gross tumor resection C; Intraoperative images before and F after complete tumor removalthrough a posterior midline approach.

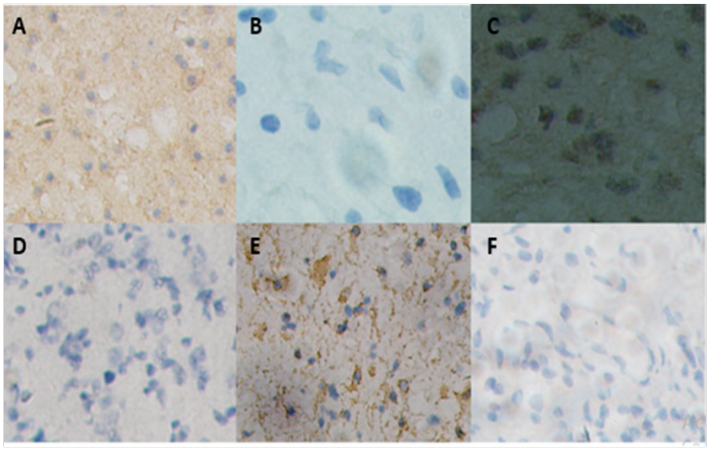

Figure 3: A-F; Immunohistochemical markers for diffuse astrocytoma showing expression of A; positive IDH, B; negative MGMT, C; positive P53, D; negative OLIG2, positive GFAPand Ki-67 counts.

7. Discussion

The pathology and molecular biology of DIPG still remains poorly understood and small studies suggest they may have similarities but differ to both childhood and adult high grade glioma arising in other locations.17-21 It is likely that high grade gliomas in children and adults share common aberrant molecular pathways but the frequency and mechanisms involved probably will exhibit key differences. With increasing clinical trials on molecular biology of gliomas in recent years, the knowledge is starting to impact on drug development towards targeted therapies. However, selection for specific targeted therapy is unlikely to be based on, or restricted by, age but will require individual case by case testing for target presence in order to direct and maximize the efficacy of molecular therapy.19 We compare and discuss the differences in clinicohistopathological and molecular characterization between the two age groups.

7.1. Clinical presentation

Selvapandian et al have reported that in the pediatric age group, brainstem gliomas occurred commonly in the first decade and in adults in the third decade.22 Our findings appear to concur with their results in both age groups. However, in the adult age group some analysis has indicated the tumor commonality in the fourth decade. Furthermore, our results have shown that gait ataxia the most common presenting symptom in children. In adults, the most common presenting symptom was headache. Our results are quite different from those of Selvapandian et al[22], wherein palatal palsy was the most common presenting sign in both age groups. On the other hand, both age groups had patients who presented with mixed signs such as cerebellar signs like vertigo and ataxia, cranial nerve palsies sign like dysphagia, dysarthria and diplopia, neurologic deficits sign like hemiparesis and facial weakness/numbness and signs of raised ICP. Similar findings were also obtained by Selvapandian et al[22], who reported abducens and facial palsy, lower CN involvement and pyramidal and cerebellar dysfunctions being the commonest manifestations.

7.2. Imaging features

It has been reported in the literature that in the pediatric group, about 75% of brainstem gliomas are diffuse with around 80% to 85% of them predominantly arising from the pons[22], though they may extend to neighboring areas. These findings are in consistent with the findings in our series wherein about four-fifths of pediatric gliomas were located in the pons, and two-thirds of them being diffuse in nature. Surprisingly, 61.9% of adult BSG were also diffuse in nature. This could be explained by the fact that most of these tumors were large cysts arising from the floor of the fourth ventricle, which occupied more that 50% of the brainstem. Some authors have stated that in children the origin of brainstem gliomas is constant, in the floor of the fourth ventricle while in adults it could arise from anywhere.[22] This could be an explanation for higher prevalence of brainstem gliomas in pediatric and its associated poor prognosis.

7.3. Histopathology

Because of presence of various neuroradiological differential diagnoses, the need for confirming the brainstem gliomas by histopathological is essential. Gliomas are diagnosed using the morphological criteria according to WHO classification.23 Diffuse astrocytoma cells histologically represent stellate, spindle -shaped with fiber like processes, or plump with a large eosinophilic cytoplasmic mass. Anaplastic astrocytomas show more malignant cytological features-cellularity, anaplasia and mitoses. In addition to these features, glioblastomas show microvascular cellularity and necrosis microscopically. Oligodendrogliomas are traversed by a delicate capillary network and have a tendency to calcify, which is helpful in radiological and histological diagnoses.1 Rachinger et al found that in a series of 46 radiologically suspected brainstem gliomas histological examination confirmed a glioma in only 28 cases (61%) and revealed metastasis in 15% (n=7), lymphoma in 11% (n=5), inflammatory disease in

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4% (n=2), cavernoma in 2% (n=1) and gliosis in 6% (n=3).24 In our series, ependymoma was also the most common differential diagnosis (n=7) followed by cavernoma (n=4). Important to note in our series is that the pathology revealed almost half of the brainstem gliomas to be malignant WHO grade III astrocytoma. Of these, 70.6% were in the pediatric group. This is line with many articles in the literature.7,25-29 It is noteworthy that histopathology diagnosis is not only important in confirming the diagnosis, but also indicative in determining the therapeutic decisions.

7.5. Molecular characteristics

It is now appreciated that the genetic abnormalities associated with high grade gliomas in children are different from those in adults, which may contribute to the differences in brainstem glioma growth patterns.7 In adults, two major genome wide analysis studies have shown that no single mutated gene is responsible for GBM development but that 3 common pathways (receptor tyrosine kinase/RAS/p13/kinase, p53, and Retinoblastoma signaling are affected in over 80% of tumors.19,30 On the other hand, studies have confirmed that only p53 overexpression and mutation correlates with adverse outcome. The other two pathways need further studies.31,32 The Ki 67 antigen is a common and reliable IHC proliferating marker in brain tumors. It is an independent prognostic indicator, associated with poor survival in gliomas regardless of WHO grades.33 In astrocytomas, the expression of Ki 67 is upregulated and correlates with tumor grade and clinical prognosis.34 Likewise, we found that WHO grade II diffuse astrocytomas have a significantly lower Ki 67 than those in grade III astrocytomas. IDH which is a metabolic enzyme, may act as oncogene and it is postulated that IDH1 appears to act a tumor suppressor that when mutationally inactivated, contributes to tumorigenesis in part through induction of the HF-1 pathway.35 It has been reported that IDH 1/2 occur mainly in WHO grade II and III astrocytic and oligodendroglial tumors and in secondary GBMs, which develop from lower grade astrocytomas.1,36 IDH 1/2 mutations are rare in children but do occur in older adolescents and may more closely resemble adult low grade gliomas.36,37 In contrast to our study, no case in both groups tested positively for the IDH 1 mutation regardless of their WHO histopathological grade. IDH 1/2 mutational status is of notable diagnostic value, and particularly rare in primary GBM.38 Of note, IDH 1/2 commonly indicate a favorable diagnosis independent of WHO grades.39-41

The gene O-6 methylguanine-methyltransferase (MGMT) is involved in DNA repair. When MGMT promoter is methylated the gene becomes silenced and this means no MGMT enzyme will be produced, thus preventing the correction of DNA faults, including those produced by the chemotherapy agent Temozolomide/ (TMZ). MGMT promoter, a prognostic and predictive factor 42,43, correlates with benefit from alkylating agent chemotherapy in patients with IDH 1 wild type malignant gliomas of WHO grades III/ IV.44 In one study, it has been found to be one of the most important prognostic factor in adults GBM43, and also relevant in children glioma as well.45 In our analysis, MGMT expression in adults was significantly higher than in pediatrics ($p<0.003$). In our paper, we found p53 expression in adults to be higher than in pediatric but the result was statistically NS. Zhang et al 46, confirmed in their paper that H3F3A-TP53 co-mutation commonly occurs in both BSGs and thalamic gliomas. They suggested that somatic mutations in either PPM1D or TP53, are the genetic basis for dysfunction of the radiation-induced DNA damage response network in brainstem gliomas.

8. Conclusion

Brainstem gliomas still remains to be tumors known for their aggressiveness and relentless growth. The existence of clinical, radiological and molecular differences between adult and pediatric brainstem gliomas may be attributed by the differences in the tumor biology. The histopathological examination showed no significant difference between the two groups and the majority of tumors were grade III astrocytomas. Diffuse tumors remained to be highly common infiltrative lesion in children. BSGs MGMT promoter expression in adults was significantly higher than in pediatric ($p<0.012$). Diagnosis of diffuse astrocytoma, IDH1 mutant was made in one pediatric and two adult cases. We recommend BSGs to be classified based on their clinical behavior and expression of their molecular markers since the biology driving these tumors is different at different anatomical locations of the brainstem. A new era of molecular based therapies offers the promise of major benefits in the management of brainstem gliomas, and we recommend more researches to be done on this area so as to understand the biology that drives these tumors. For resectable tumors, we advise gross total resection as they are associated with favorable outcome.

9. Recommendations

1. Doctors should do more on documenting patients' history and physical examination findings.
2. Maximal resection of the tumor is advised whenever possible, otherwise a biopsy may be essential to determine the histology of the tumor.
3. Molecular biomarkers should be determined on routine basis to help in prognosticating the tumor.

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