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Original Research Article

Correlation of Immunohistochemical Subtypes to Clinicopathological Parameters, Risk Stratification and Survival Analysis of Medulloblastoma in the First Decade of Life: A Hospital Based Study

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Abstract:

Background: Medulloblastoma (MB) is a heterogeneous disease that displays distinct genetic profiles depending on molecular subgroups. This study is aimed to correlate molecular subgrouping of childhood Medulloblastoma using surrogate immunohistochemical markers and associate molecular subgroups, histopathological types, and available clinicopathological parameters with overall survival (OS) and progression-free survival (PFS) . This study includes 30 children aged less than 10 years and immunohistochemical staining using β-catenin and GRB2-Associated Binding Protein 1 (GAB1) antibodies, was used to classify the cases into wingless signaling activated (WNT), sonic hedgehog (SHH), and non-WNT/SHH molecular subgroups. Nuclear morphometric analysis was for assessment of degree of anaplasia and Kaplan-Meier survival curves were done.

Results: The cases were classified into WNT (10%), SHH (30%), and non-WNT/SHH (60%) subgroups. Histopathological types varied significantly according to tumor location ($p< 0.001$), degree of anaplasia ($p = 0.014$), molecular subgroups ($p < 0.001$), and risk stratification ($p = 0.008$). Molecular subgroups varied significantly with respect to age distribution ($p = 0.031$), tumor location ($p< 0.001$), histopathological variants ($p < 0.001$), and risk stratification ($p < 0.001$). OS was 77.5% and 50% after 1 and 2 years, while PFS was 65% and 27.5% after 1 and 2 years, respectively. OS and PFS were associated with histopathological variants ($p < 0.001$ and 0.001), molecular subgroups ($p = 0.012$ and 0.005), and risk stratification ($p < 0.001$ and < 0.001), respectively.

Conclusions: Medulloblastoma classification based on molecular subgroups, together with clinicopathological indicators, mainly histopathological types accurately risk stratifies children with Medulloblastoma and predicts their survival.

Keywords: Medulloblastoma, Beta-Catenin, GAB-1, Overall Survival, Progression-Free Survival.

Introduction

Medulloblastoma (MB) being the most prevalent malignant pediatric brain tumor accounts for up to 10% of childhood brain cancers. Advances in genome-wide analysis and gene transcription have led to the discovery that medulloblastomas are in fact heterogeneous tumors, which consists of distinct molecular subgroups; each having a unique genomic profile. This molecular classification suggests variable driving mutations leading to different cellular origins. [1]

Incorporation of this molecular classification into routine pathologic MBs evaluation is a must owing to its great importance in clinical practice. Few studies have used more simple techniques such as fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) as surrogate methods for molecular subgrouping. Such techniques are easily applicable and provide reliable results on routinely processed formalin-fixed paraffin-embedded (FFPE) specimens. [1]

Classification MB into its three main molecular subgroups (WNT, SHH, and non-WNT/SHH) can be achieved by β-catenin and GAB1 antibody assays.[2] WNT/β-catenin signaling pathway regulates a wide range of vital cellular functions including cellular proliferation, differentiation, genetic stability, apoptosis, and tissue renewal. Aberrations in this pathway have been implicated in several human malignancies which include colonic carcinoma, breast carcinoma, adrenocortical tumor, melanoma, high-grade gliomas and MB. WNT subgroup of

medulloblastoma (10-15% of MB) comprises almost classic histology in around 95% of the cases and rarely large cell/anaplastic (LCA) phenotype. [3] GAB1 (GRB2-Associated Binding Protein 1) belongs to the class of Gab family. It is believed to be a unique marker of SHH medulloblastoma subgroup.[4] SHH medulloblastoma subgroup (28–30% of MB) includes mostly the desmoplastic nodular (D/N) histologic subtype, a minority of classic variant and rarely LCA phenotype. [5]

Non-WNT/SHH MB subgroup which is further sub-classified into group 3 and group 4 is molecularly defined by overexpression of MYC gene. Group 3 (25–28% of all MB) being the most aggressive MBs have a grave prognosis and a high metastatic rate at diagnosis. Classic and LCA are the only histological variants encountered. Group 4 (40-45% of all MB) displays a high incidence of chromosomal copy number variations. Classic histology is the most predominant, while LCA histology is less commonly encountered in group 4 MB. [6, 7]

The current study aims to validate MB molecular subgrouping using surrogate IHC, and study the correlation of these molecular subgroups, histopathological types, and avail-able clinicopathological parameters with overall survival (OS) and progression-free survival (PFS) of MB patients.

Materials and Methods

Study Setting and Design: This retrospective study was carried at Cardiothoracic and Neuroscience Centre, Gauhati Medical College and Hospital, Assam, India

Duration of the Study: This research encapsulated a duration of 2 years, providing a substantial timeframe to obtain complete clinical data including age at diagnosis, sex, tumor location, mass size obtained by performance of Magnetic Resonance Imaging (MRI), metastasis at diagnosis (M0 or M+), type of surgery, size of residual mass after surgery, whether the cases received postoperative radiation and/or chemotherapy and complete follow-up data including recurrence and/or death.

Sample Size: A total number of 30 cases of childhood medulloblastoma diagnosed and treated over 2 years at Department of Neurosurgery, Cardiothoracic and Neuroscience Centre, Gauhati Medical College and Hospital were selected.

Methodology

Histopathological examination: Based on histological characteristics medulloblastoma cases are classified into classic, desmoplastic/nodular (D/N), medulloblastoma with extensive nodularity (MBEN) and large cell/anaplastic (LCA) MBs, based on the 2016 WHO classification of tumors of the central nervous system (CNS). [5] Degree of anaplasia in MBs were graded into a four tier scheme: no, slight, moderate, or severe anaplasia, based on four features: (a) enlarged nuclear size; (b) increased mitotic figures; (c) numerous apoptotic bodies; and (d) high pleomorphism with conspicuous nucleoli (large cell type) or pleomorphic crowded cells with frequent molding (anaplastic type). LCA variants were identified according to the presence or absence of severe or even moderate anaplastic features even in a focal manner. [8]

Nuclear morphometric analysis for degree of anaplasia: Hematoxylin and eosin (H&E) stained sections were examined under a light microscope for histomorphometric analysis. Ten different non-overlapping randomly selected fields from each slide were examined at a magnification of × 400. The degree of anaplasia of MB cases was assessed by quantitative analysis of the histological photomicrographs for nuclear size which was measured by nuclear perimeter in microns. [9]

Immunohistochemical analysis: Immunohistochemical use of β-catenin, GAB1 antibodies were used to classify MBs into three molecular subgroups: WNT, SHH, and non-WNT/SHH.[2] Formalin-fixed paraffin-embedded tissue blocks were cut into 5-μm sections.

Following processing with xylene, graded ethanol solutions, and 3% H2O2 for 10 min, antigen retrieval was performed in 0.05 M. citrate buffer at a pH of 6.0 at 100 °C for 5–10 min followed by blocking in goat serum for 10 min. Deparaffinization followed by antigen retrieval were performed in a Dako PT Link unit. Both high and low pH EnVision TM FLEX Target Retrieval Solutions were used at 97 °C for 20 min.

For immunostaining using β-catenin antibody Dako automated immune-stainer (Link 48) was used, a mouse monoclonal antibody and GAB1 antibody, a mouse monoclonal antibody. The slides were incubated with primary antibodies for 20–30 minuntes following treatment with a peroxidase-blocking reagent for 5 min. Horseradish peroxidase (HRP) reagent was added for 20 min and diaminobenzidine (DAB) chromogen solution for 10 min. Meyer's hematoxylin was applied for counterstaining.

Assessment of β-catenin IHC results: Immunoreactivity of nuclear β-catenin in ≥ 5% of tumor cells was considered positive. Either nuclear β-catenin immunoreactivity in < 5% of tumor cells or cytoplasmic positivity were considered negative for β-catenin expression wherein entire β-catenin negativity is rare.[10] Positive control included specimens of normal colon and colonic carcinoma whereas negative control was performed by

replacing the primary antibody with phosphate-buffered saline (PBS).

Assessment of GAB1 IHC results: GAB1 positivity was detected as cytoplasmic staining in >30% of tumor cells whereas percentage of positive cells < 30% was regarded as negative. [11]

Synaptophysin, NeuN, and INI immunohistochemistry further confirmed the diagnosis of anaplastic MB with rhabdoid features. IHC revealed positive cytoplasmic and nuclear reactions for synaptophysin and NeuN, respectively, as well as intact nuclear expression of integrase interactor 1 (INI 1) to exclude atypical teratoid rhabdoid tumor [AT/RT].

Risk stratification: Patients were classified into standard and high-risk based on age at diagnosis i.e. > 3 or < 3 years), size of post-operative residual mass i.e. Maximum cross-sectional area <1.5 and > 1.5 cm2, histology, and presence or abscene of metastatic disease at diagnosis (M0 or M+).[12]

Statistical analysis: Statistical analysis was performed using the IBM SPSS software package version 20.0. Data were expressed as frequencies for categorical variables and continuous variables were expressed as mean ± SD or median and range. To verify the normality of distribution of variables the Kolmogorov-Smirnov test was used. Chi-square ($\chi 2$) and Monte Carlo (MC) tests were applied for comparing categorical variables,

Survival analyses [overall survival (OS) and progression-free survival (PFS)] were performed. OS was the time from date of diagnosis to death or the date of last follow-up whereas PFS was the time interval from date of surgery to the date of progression or relapse. Kaplan-Meier survival curves were done to determine the significance of relation with OS and PFS. A P value < 0.05 was considered statistically significant.

Results

Clinical characteristics: The current study included 30 MB patients. Their clinical data are summarized in Table 1.

Histopathological features, nuclear morphometric analysis for degree of anaplasia, and molecular subgroups: Based on microscopic evaluation of 30 MBs, 12 cases (40%) were of LCA histology, 10 cases of classic histology (33.3%), and 8 cases were D/N MB (26.67%).

Morphometric analysis for degree of anaplasia: Based on combined histopathological examination and image analysis, 14 cases (46.67%) showed severe anaplastic features, 11 cases (36.67%) showed moderate anaplasia, and 5 cases (16.67%) showed slight anaplasia. Mean nuclear perimeter for different histopathological types was as follows: 44.529 μm for D/N, 46.996 μm for classic, and 62.237 μm for LCA phenotype.

Molecular subgrouping: Based on IHC staining results, the WNT subgroup (nuclear β-catenin positivity, cytoplasmic GAB1 negativity) represented 10% of cases whereas SHH subgroup (nuclear β-catenin negativity, cytoplasmic GAB1 positivity) represented 30% of cases and non-WNT/SHH (both nuclear β-catenin, cytoplasmic GAB1 negativity) represented 60% of cases (Table 2).

Relation of histopathological types to clinicopathological parameter: The histopathological types differed significantly according to tumor location (p value < 0.001), degree of anaplasia (p value = 0.014), molecular subgroups (p value < 0.001) and risk stratification (p value = 0.008) (Table 3).

The majority of classic MBs and LCA were diagnosed at age between 1-4 years (80% and 75%, respectively); D/N MBs were distributed among all age groups. However, no significant relation was detected between histopathological types and age of the patients. Most of classic and LCA MBs were located at the midline (90% and 83.3%, respectively), whereas 87.5% of D/N cases were located at the cerebellar hemispheres.

50% of the classic histology showed moderate anaplasia. On the other hand 75% of LCA cases showed marked anaplasia. Regarding the molecular subtypes, 80% of classic histology was of non-WNT/SHH profile and 20% of WNT type. All of the D/N cases were of SHH type (100%).Most of the cases of LCA histology showed (81.3%) non-WNT/SHH profile.

Considering risk stratification, 50% of classic and 75% of D/N cases were of standard-risk group, respectively, whereas 83.3% of LCA cases were of high-risk group.

Relation of molecular subgroups to clinicopathological parameters: The molecular subgroups differed significantly in age distribution (p value = 0.031), tumor location (p value < 0.001), histopathological variants (p value < 0.001), as well as risk stratification (p value < 0.001). No significant relation, however was detected between the molecular subgroups and degree of anaplasia of the studied cases (Table 4).

Regarding WNT tumors, 67.67% of WNT tumors were detected among the patients in the age group of 1-4 years and were not seen in infants. They were all located in the midline and were mainly of classic histology (67.67%). All the cases of WNT subtype showed standard risk of stratification.

SHH tumors were detected among all age groups; 44.44% of cases were detected among 1-4 years,

33.3% of cases were diagnosed in children between 5-10 years of age and 22.22% of cases were diagnosed in infants. Most SHH MBs were laterally located (88.89%). It included D/N (77.78%) as well as LCA (22.22%) phenotypes; 77.78% of SHH cases showed standard-risk.

Non-WNT/SHH MBs were predominantly diagnosed in the age group of 1-4 years (77.78%), 17 cases (94.44%) were located at midline; LCA and classic histology (55.5%, 44.4%, respectively) were seen in this subgroup. The majority of non-WNT/SHH MBs were high-risk tumors (83.33%).

Survival analysis: During the follow up period the OS was found to be77.5% and 50% after 1 and 2 years, respectively, with a mean of 19.1 months and median of 24 months (95% CI, 17.1-21.1). The PFS was found to be 65% and 27.5% after 1 and 2 years, respectively, with a mean of 15.83 months and median of 17 months (95% CI, 13.6-18.1) (Table 5).

Relations of OS and PFS to different clinicopathological parameters: Kaplan-Meier curves revealed that both OS and PFS are associated significantly with histopathological variants with p values of < 0.001 and 0.001 respectively; molecular subgroups with p value = 0.012 and 0.005 and risk stratification with p values of < 0.001 and < 0.001, respectively. MBs of LCA histology exhibited the worst OS and PFS (18.8% and 12.5%, respectively).

Among the molecular subgroups, WNT had the best outcome with excellent PFS (100%), whereas the non-WNT/SHH showed the worst OS (33.3%).

Both OS and PFS were poor with the high-risk group patients (22.7% and 9.1%, respectively). Also, PFS was associated significantly with the degree of cellular anaplasia, being worst with severe anaplasia (5.6%) (p value = 0.003) (Table 6).

Table 1 Clinical characteristics of the studied cases

	No.(%)
AGE IN YEARS	
<1	6 (20%)
1 to 4	20(66.67%)
5 to 10	4(13.3%)
Mean ± SD.	7.7 ± 6.2
Median (min.-max.)	5 (1.8-26)
SEX	
male	17(56.67%)
Female	13(43.3)%
LOCATION OF MASS	
Midline	20(66.67%)
Lateral	10(33.3%)
CT MASS SIZE	
< 3 cm	16(53.3%)
> 3 cm	14(46.67%)
TYPE OF SURGERY	
Gross-total resection	5 (16.67%)
Near-total resection	7(23.3%)
Sub-total resection	18(60%)
RSIDUAL TUMOR AFTER SURGERY	
< 1.5 cm2	14(46.67%)
> 1.5 cm2	16(53.3%)
METASTASIS AT DIAGNOSIS	
M0	16(53.3%)
M+	14(46.67%)
POST-OPERATIVE PROTOCOL	
No therapy	2 (6.67%)
Radiation therapy	10(33.3%)
Radiation plus chemotherapy	18(60%)
RISK STRATIFICATION	
Standard risk	14(46.67%)
High risk	16(53.3%)
RECURRENCE RATE	
No	8(26.67%)
Yes	22(73.3%)
DEATH	
Survival	15(50%)
Death	15(50%)

Table 2: Histopathological, IHC results, and molecular subgroups

	No. (%)	
Histopathological Types		
Classic medulloblastoma	10(33.3%)	
Desmoplastic/nodular medulloblastoma	8(26.67%)	
Large cell/anaplastic medulloblastoma	12(40%)	
Degree of Anaplasia		
Slight anaplasia	5(16.67%)	
Moderate anaplasia	11(36.67%)	
Severe anaplasia	14(46.67%)	
β-catenin EXPRESSION		
Positive nuclear expression	3(10%)	
Negative both nuclear and cytoplasmic expression	3(10%)	
Cytoplasmic expression	24(80%)	
GAB-1 Expression		
Negative	21(70%)	
Positive	9(30%)	
Molecular Subgroups		
WNT	3(10%)	
SHH	9(30%)	
Non-WNT/SHH	18(60%)	

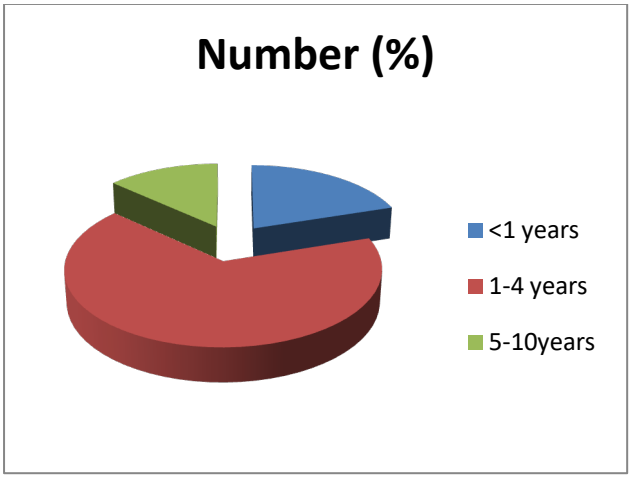

Figure 1: Pie diagram showing percentage distribution according to age

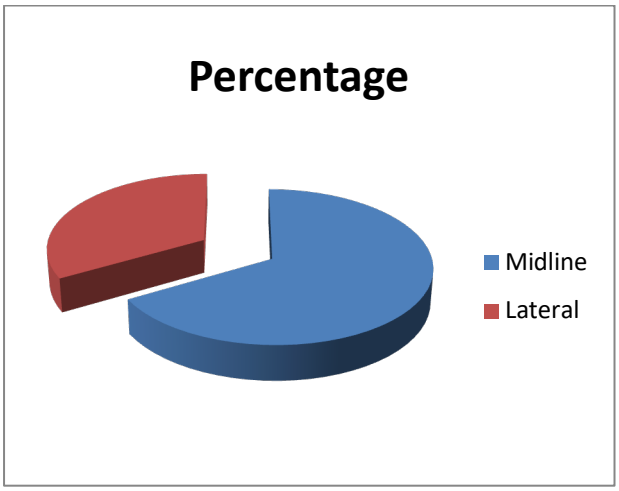

Figure 2: Pie diagram showing percentage distribution according to location of mass

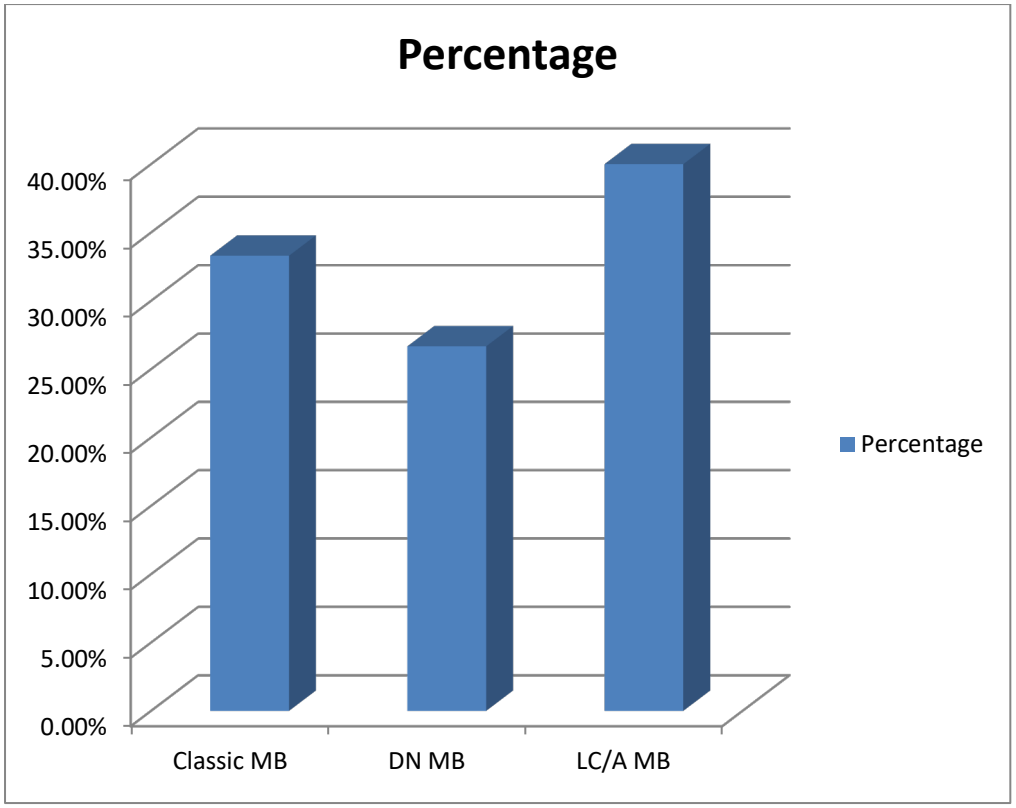

Figure 3: Graph showing percentage distribution according to histological subtype

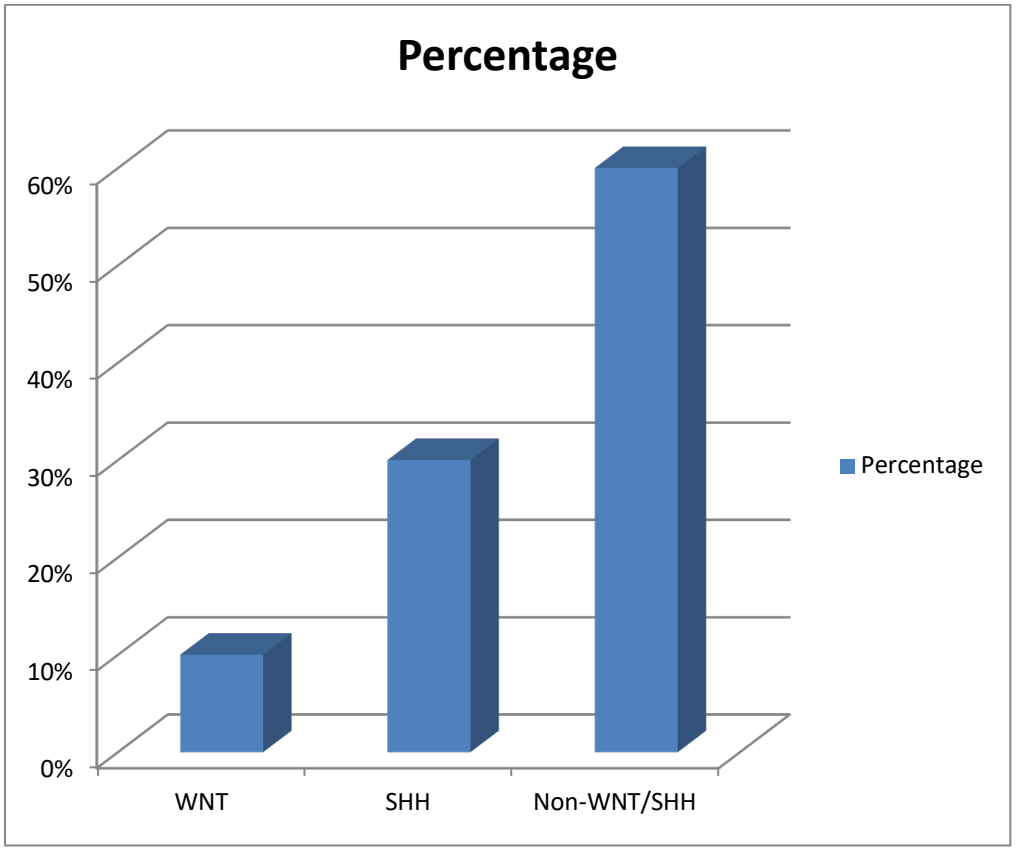

Figure 4: Graph showing percentage distribution according to molecular subgroup

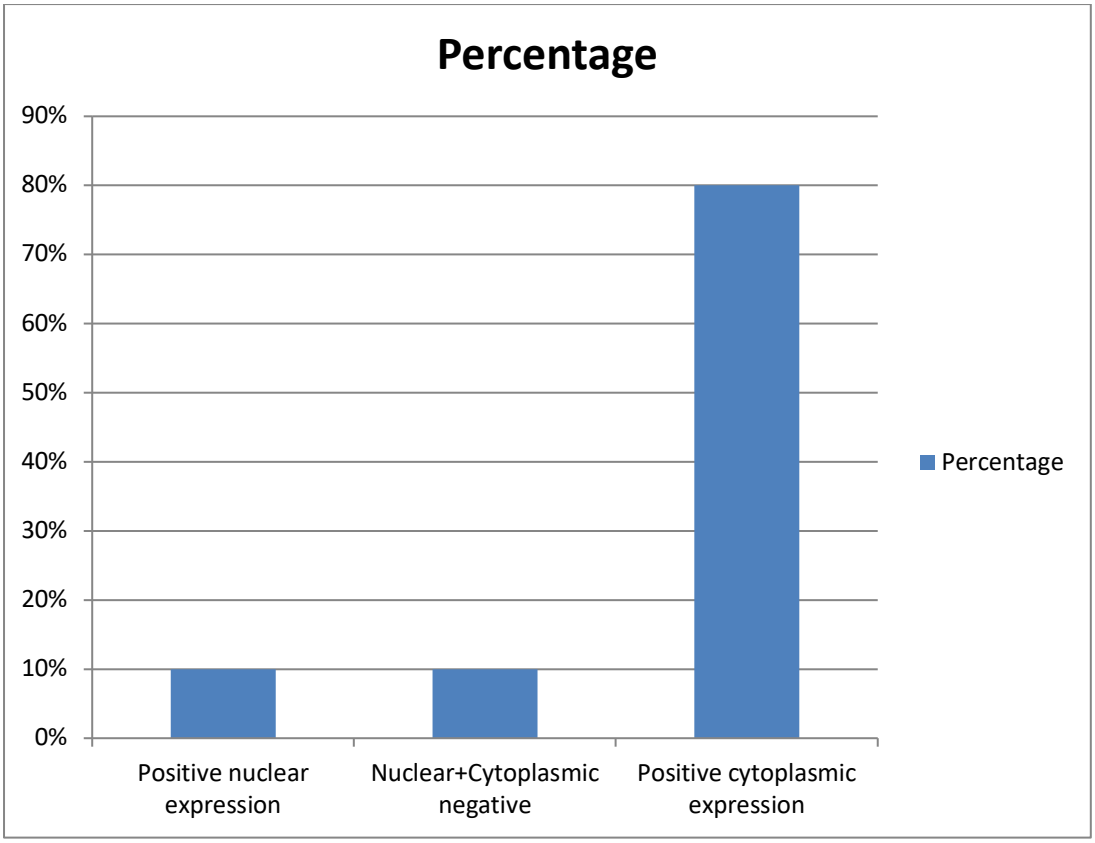

Figure 5: Graph showing type of beta-catenin expression in the Medulloblastoma cases

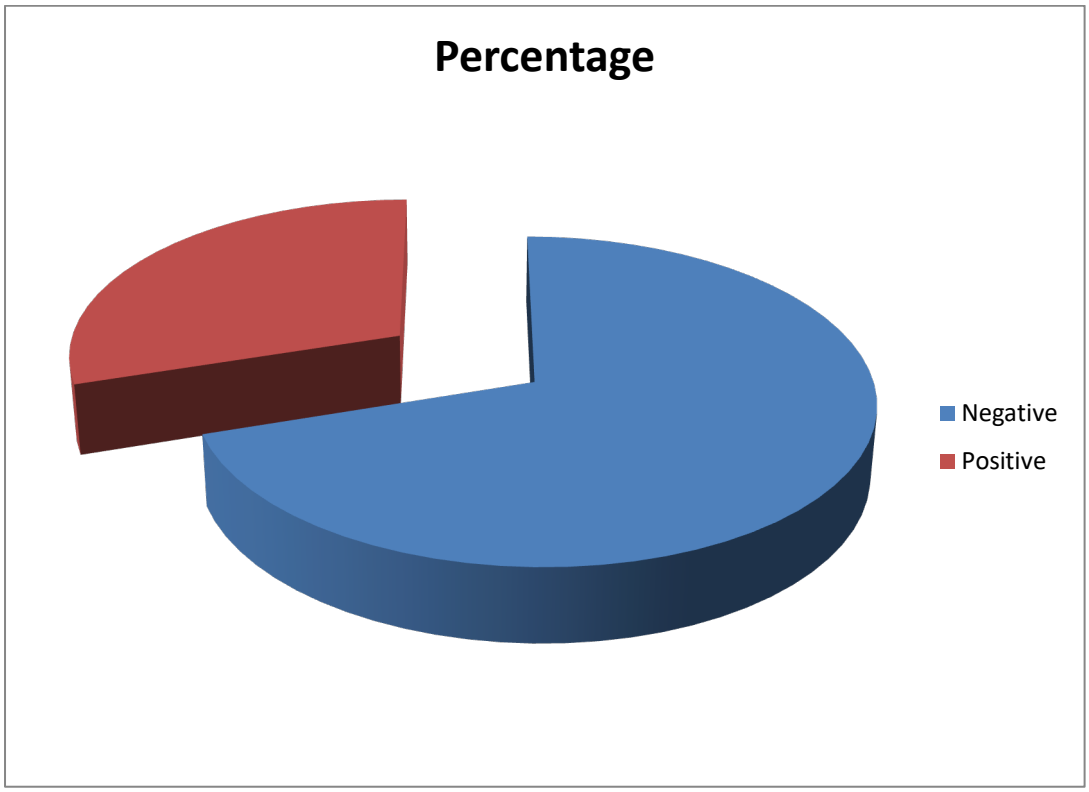

Figure 6: Pie diagram showing percentage of Medulloblastoma cases showing GAB-1 expression

Table 3 Relation of histopathological types to clinicopathological parameters

	HISTOPATHOLOGICAL TYPES			P VALUE
	Classic medulloblastoma (n = 10)	Desmoplastic /Nodular medulloblastoma (n = 8)	Large cell/anaplastic medulloblastoma (n = 12)	
AGE GROUP (years)				
< 1	2(20%)	2(25%)	2 (16.67%)	MC, p = 0.073
1 to 4	8 (80%)	3(37.5%)	9(75%)	
5 to10	0(0%)	3(37.5%)	1(8.33%)	
SEX				
Male	7(70%)	3(37.5%)	7(58.3%)	p = 0.495
Female	3(30%)	5(62.5%)	5(41.67%)	
LOCATION OF THE MASS				
Midline	9 (90%)	1(12.5%)	10 (83.3%)	MC, p < 0.001*
Lateral	1(10%)	7(87.5%)	2 (16.67%)	
DEGREE OF ANAPLASIA				
Slight	3(30%)	2(25%)	0 (0%)	MC, p = 0.014*
Moderate	5(50%)	3(37.5%)	3 (25%)	
Severe	2(20%)	3(37.5%)	9 (75%)	
MOLECULAR SUBGROUPS				
WNT	2(20%)	0(0%)	1 (8.33%)	MC, p < 0.01*
SHH	0(0%)	8 (100%)	2 (16.67%)	
Non-WNT/SHH	8 (80%)	0(0%)	9(75%)	
RISK STRATIFICATION				
Standard risk	5(50%)	6(75%)	2 (16.67%)	p < 0.008*
High risk	5(50%)	2(25%)	10 (83.33%)	

MC: Monte Carlo
*Statistically significant at $p \leq 0.05$

Table 4 Relation of molecular subgroups to clinicopathological parameters

	Molecular subgroups			P value
	WNT (n = 3)	SHH (n = 9)	Non-WNT/SHH (n = 18)	
AGE GROUP(YEARS)				
<1	0(0%)	2(22.22%)	4(22.22%)	MC, p = 0.031*
1 to 4	2(67.67%)	4(44.44%)	14(77.78%)	
5 to 10	1(33.33%)	3(33.33%)	0(0%)	
SEX				
Male	1(33.33%)	4(44.44%)	12(66.70%)	MC, p = 0.183
Female	2(67.67%)	5(55.55%)	6(33.30%)	
LOCATION OF THE MASS				
Midline	3(100%)	1(11.1%)	17(94.44%)	MC, p < 0.001*
Lateral	0(0%)	8 (88.89%%)	1(5.55%)	
HISTOPATHOLOGICAL TYPE				
Classic medulloblastoma	2(67.67%)	0(0%)	8(44.44%)	MC, p < 0.001*
Desmoplastic/nodular medulloblastoma	0(0%)	7(77.78%)	0(0%)	
Large cell/anaplastic medulloblastoma	1(33.33%)	2(22.22%)	10(55.55%)	
DEGREE OF ANAPLASIA				
Slight anaplasia	1(33.33%)	2(22.22%)	1(5.55%)	MC, p = 0.255
Moderate anaplasia	1(33.33%)	4(44.44%)	7(38.89%)	
Severe anaplasia	1(33.33%)	3(33.33%)	10(55.55%)	
RISK STRATIFICATION				
Standard risk	3(100%)	7 (77.78%)	3(16.67%)	MC, p < 0.001*
High risk	0(0%)	2(22.22%)	15(83.33%)	

MC Monte Carlo
*Statistically significant at $p \leq 0.05$

Table 5: Overall survival (OS) and progression-free survival (PFS) of the cases

	Mean (months)	95% CI	Median (months)	% 1 year	% 2 year (end of study)
Overall Survival	19.1	17.1-21.1	24	77.50%	50%
Progression Free Survival	15.83	13.6-18.1	17	65%	27.50%

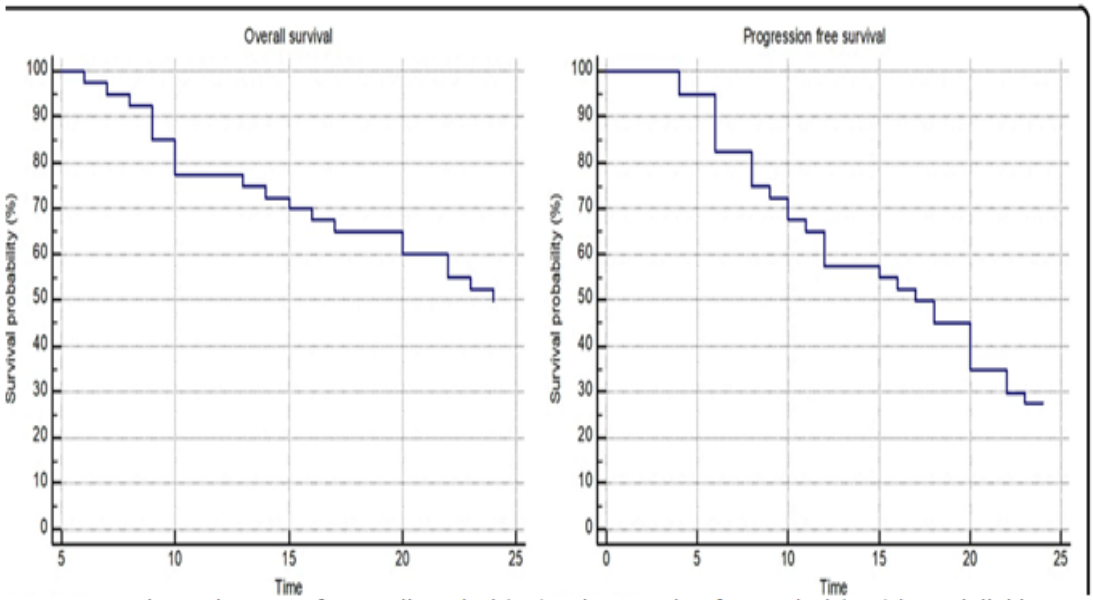

Figure 7: Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS) in medulloblastoma patients

Table 6 Relation of overall survival (OS) and progression-free survival (PFS) to different clinicopathological parameters

		Overall survival (OS)				Progression-free survival (PFS)			
		Mean	Median	% End of study	P value	Mean	Median	% End of study	P value
Age group (years)									
	< 1	18.38	20	50%	0.363	13.75	11	25%	0.182
	1 to 4	18.44	22	44.40%		15.15	17	22.20%	
	5 to 10	23.8		80%		22.8		60%	
Histopathological types									
	Classic medulloblastoma	21.93		71.40%	< 0.001*	20.5	22	42.90%	0.001*
	Desmoplastic/nodular medulloblastoma	23.1		70%		18.7	20	30%	
	Large cell/anaplastic medulloblastoma	14.13	10	18.80%		9.94	8	12.50%	
Degree of anaplasia									
	Slight anaplasia	22.86		71.40%	0.274	20.71		57.10%	0.003*
	Moderate anaplasia	19.53		53.30%		18	20	40%	
	Severe anaplasia	17.28	16	38.90%		12.11	11	5.60%	
Molecular Subgroups									
	WNT	24		100%	0.012*	24		100%	0.005*
	SHH	23.08		66.70%		18.92	20	33.30%	
	Non-WNT/SHH	16.29	15	33.30%		12.92	10	12.50%	
Risk stratification									
	Standard risk	23.61		83.30%	< 0.001*	21.61	23	50%	< 0.001*
	High risk	15.41	14	22.70%		11.09	9	9.10%	

*Statistically significant p-value <0.05

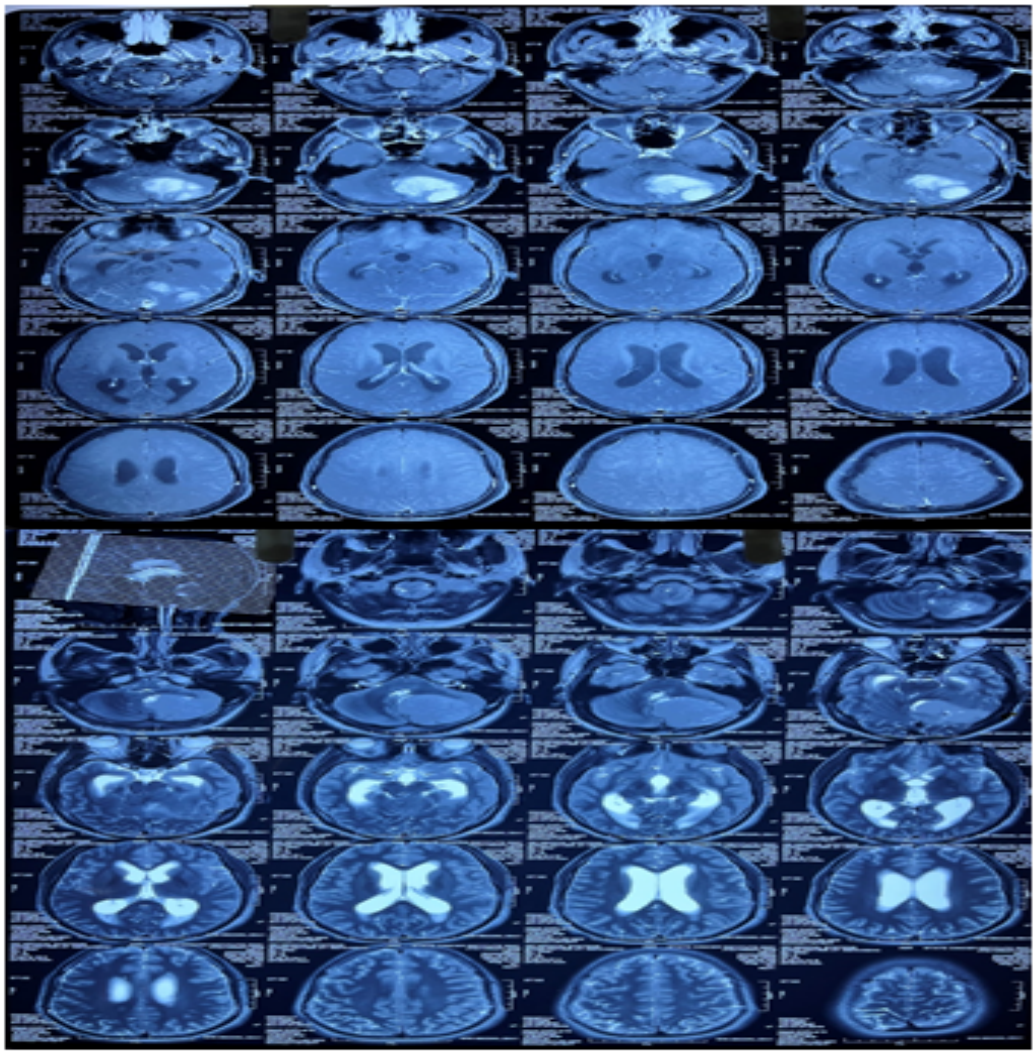

Figure 8: Magnetic Resonance Imaging of a patient of Medulloblastoma

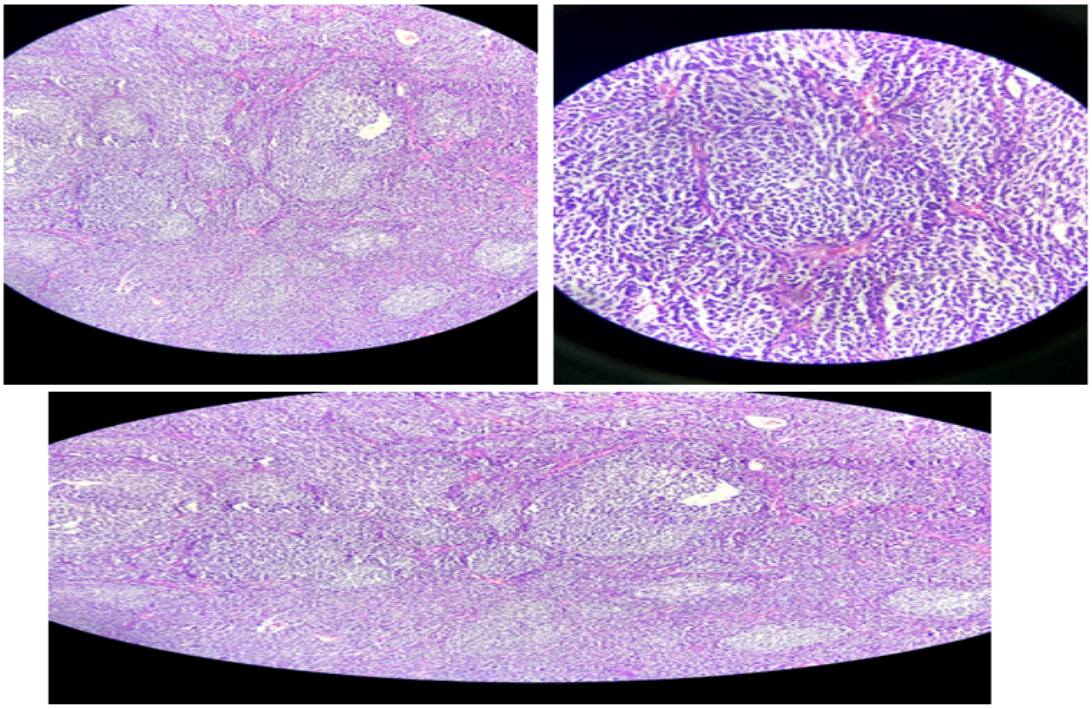

Figure 9: Histopathological features of various subtypes of Medulloblastomas

Discussion

The diagnosis of medulloblastoma requires a combination of routine histopathological evaluation with molecular features, to give an accurate integrated diagnosis, and to allow for a more refined risk stratification.[5]

In the present study, MB histopathological types included classic (33.3%), D/N (26.67%), and LC/A (40%) of MBs. These histopathological types were associated significantly with tumor location, degree of anaplasia, molecular subgrouping as well as risk stratification. Most of the classic and D/N cases in our results were of standard-risk group whereas most of LCA cases were of high-risk group. These results were in harmony with Ellison et al., who also reported that high-risk disease was associated with LCA phenotype. Furthermore, Jiang et al. also noted that LCA histology was an independent risk factor with a grave prognosis.[13] In the present study, all WNT medulloblastomas were located in the midline, which was in agreement with Pietsch et al., who also declared that WNT tumors were located mainly in the midline. This is probably due to the fact that their cell of origin derives from the lower rhombic lip.[15]

In our study, all WNT cases exhibited standard-risk stratification. Ellison et al. reported that some cases with high-risk features (including LCA morphology or M+) showed favorable outcomes, interestingly, when associated with WNT profile. [1] 30% of cases in the present study were SHH tumors. This was in accordance to a study conducted by Northcott et al. and Pietsch et al., where SHH subgroup represented 30% of their medulloblastoma cases. [5, 17] In the present study, most of the SHH medulloblastomas were located laterally. This is probably due to the fact that these tumors derived from the cerebellar granular precursor cells of the external granular layer (originated laterally from the cerebellar hemispheres) as reported by Gibson et al. [16]

All D/N MBs in the present study were of SHH type. This was in accordance to a study conducted by Pietsch et al. who also reported that D/N variant was almost exclusive for SHH-MB, followed by classic and LCA subtypes.[5] Ellison et al. further stated that all desmoplastic tumors were included in the SHH pathway.[1] Taylor et al. however reported that SHH medulloblastomas included both desmoplastic types and non desmoplastic/nodular types (up to 50%).[2]

Non-WNT/SHH MBs (60% of our cases), were predominantly located at the midline. Most of these cases were LCA and classic MBs and were high-risk tumors. Cho et al. and Tamayo et al., in their studies reported that non-WNT/SHH MB constituted the most common molecular subgroup and that the MBs of this group located in the midline filling the fourth ventricle.[6, 7] They also reported that non-WNT/SHH MBs were of high-risk group with dismal prognosis.

In the present study, the 2-year OS was 50% and the 2-year PFS was 27.5%; Tarbell et al. reported a higher 5-year OS (60%).[20] The OS and PFS in the present study was associated significantly with the histopathological types, molecular subgroups, and risk stratification. Classic and D/N histological types showed nearly similar OS (71.4% and 70%, respectively), with PFS of 42.9% and 30%, respectively whereas LCA histology exhibited the worst OS and PFS (18.8% and 12.5%, respectively). Similar results were obtained by a study conducted by Louis et al. who reported that D/N variant exhibited the best prognosis, whereas, LCA variant had a poor prognosis.[23] Nalita et al., in their study, however found no significant differences of survival rates between the histological variants.[22]

In the present study, patients with severe anaplasia showed significantly worse PFS (5.6%). Similar results were obtained by Giangaspero et al., who in their study also found that progression-free survival for MBs with severe anaplasia was significantly shorter than tumors with slight or moderate anaplastic features.[25]

In the present study, molecular subgroups were prognostically important, with significantly different survival rates. WNT tumors had the best outcome with excellent PFS, whereas non-WNT/SHH showed the worst and shortest OS (33.3%). SHH, on the other hand medulloblastomas had an intermediate (66.7%) OS. Ellison et al., Kool et al., Northcott et al. and Taylor et al. in their studies all reported the best outcome and a high 5-year OS (~ 95%) for the WNT subgroup, an intermediate (75–80%) OS for SHH MBs, while the worst and shortest survival for non-WNT/SHH subgroup.[1, 2, 17, 19] Similarly, Ramaswamy et al. also in his study confirmed that the WNT subtype had the best clinical outcome, with a 5-year OS >95%. [26]

In a study conducted by Thompson et al.,he found that the prognosis of WNT MB was excellent, even in the presence of poor outcome indicators such as somatic TP53 mutation, incomplete resection, and/or metastatic disease at presentation.[27] Many studies have attributed this good outcome of WNT subgro to the presence of WNT antagonistic secretions that modifies the permeability of blood-brain barrier; allowing high penetrance of chemotherapeutic agents into the tumor site.[28] This could allow for a less aggressive approach in treating WNT tumors.[3]

In addition to clinical and pathological outcome indicators, molecular markers are not only prognostically important but would also facilitate

the use of targeted therapies, such as GDC-0449, a novel SHH pathway inhibitor, particularly in infants.[1]

In the present study, both OS and PFS were poor with high-risk group patients (22.7% and 9.1%, respectively) whereas in the standard-risk group, the OS and PFS were 83.3% and 50%, respectively.

Nalita et al., in their study also reported 84.4% and 42.8% OS rates of standard-risk and high-risk groups, respectively.[22] Tarbell et al., Ramaswamy et al., and Ramaswamy et al., all reported in their studies higher 5-year survival rates (for high-risk MBs) reaching 60%.[20,26,29] Sirachainan et al. also reported OS rates of standard-risk and high-risk groups of 58–85% and 32–70%, respectively.[21] Thompson et al., in their study reported that patients with postsurgical residual tumor > 1.5 cm2 (an indicator of high-risk disease) had worse PFS and required aggressive treatment options. [27]

Clinical trials should therefore incorporate key molecular profiles which should include subgroup information, genetic, cytogenetic, and epigenetic changes, of this diverse disease entity that can suggest precise patients' outcomes and can allow for a more rational treatment strategy.[30] Medulloblastoma with extensive nodularity has been a limitation of this study owing to the rarity of this histological subtype. Larger studies with more sophisticated molecular markers as well as a prolonged duration of study is required for a better understanding of this entity.

Conclusion

Histopathological types, molecular sub-groups and risk stratification are important prognostic factors that are associated with overall and progression-free survival of children with Medulloblastoma. Patients with the same pathological type of Medulloblastoma may have distinct genetic backgrounds and therefore different prognoses. Therefore an advanced molecular testing scheme is recommended to yield better results, confirm the current data and further classify each molecular subgroup for better understanding of the disease so that a more focused management plan can be sorted out and better results can be obtained.

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