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Original Article

P53 and Ki-67 Expression in Primary Pediatric Brain Tumors: Does it Correlate with Presentation, Histological Grade, and Outcome?

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Abstract

Context: Pediatric brain tumors are a vexing problem for the neurosurgeon due to the fragile patient cohort. We attempt to find parameters which can help us to treat and prognosticate these patients in a better way. **Aims:** This study aims to correlate clinical presentation, outcome, and histological grade with P53 and Ki-67 expression in primary pediatric brain tumors. **Setting Design:** This was a prospective, observational study. **Patients and Methods:** Forty-seven patients with primary brain tumors in the age group 0–18 years were included in this study. Clinical presentation was noted. Patients were operated, and specimen was sent for histopathological and immunohistochemistry examination for p53 and Ki-67. The WHO classification of 2007 was used to grade the tumors. Follow-up was done at 3 and 6 months with Glasgow outcome score. Expression of p53 and Ki-67 in different tumors was correlated with clinical presentation, tumor grade and outcome. **Analysis Method:** Statistical Package for Social Science version 17. $P < 0.05$ was considered statistically significant. **Results:** There was statistically significant correlation between high tumor grade and high Ki-67 levels ($P = 0.000$). On *post hoc* analysis, there was a significant difference between p53 levels in Grade 1 and Grade 4 tumors. There was statistically significant correlation between neurological deficit and higher p53 levels ($P = 0.040$). There was statistically significant correlation between poor outcome and higher p53 ($P = 0.034$) and Ki-67 ($P = 0.000$) levels at 3 months follow-up which continued at 6 months. **Conclusions:** From this study, we conclude that p53 and Ki-67 expression in pediatric brain tumors is associated with poor outcome and correlates with tumor grade. Moreover, p53 expression correlates with neurological deficit.

Keywords: *Ki-67, p53, pediatric brain tumors, WHO grade*

Introduction

Malignant brain tumors are the most common solid tumors in childhood. They are the leading cause of cancer-related death in this age group and account for 20%–30% of all childhood cancers.[1] The common pediatric brain tumors are gliomas, pineal tumors, craniopharyngiomas, teratomas, granulomas, and primitive neuroectodermal tumors (PNETs, primarily and medulloblastoma).[2] In children, around 60% of brain tumors occur below the tentorium, whereas, in adults, majority of tumors occur in the supratentorial compartment.[3] The clinical presentation of patients with brain tumors depends on tumor location, tumor type, and the age of the patient. Surgery with complete resection, if feasible, is the foundation of treatment along with radiation therapy and chemotherapy based on the diagnosis and other factors. P53 and Ki-67 have been widely used as markers to predict outcome in various malignancies. Studies regarding pediatric brain tumors in India are few, and different studies have given different results regarding the role of p53 and Ki-67 in pediatric brain tumors. This study analyzed the clinical presentation, histological grade, and outcome in primary pediatric brain tumors and correlated it with p53 and Ki-67 levels.

Patients and Methods

This prospective observational study was conducted in the Departments of Neurosurgery and Pathology in a tertiary care teaching institute from November 2014 to April 2016. It was approved by the Ethics and Scientific Committee of the Institute. 47 newly diagnosed patients with primary brain tumors in the age group 0–18 years were included in this study. Informed consent was taken from the patients, and their approval was taken for scientific publication of the data.

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Patients who had taken chemotherapy or radiotherapy before the surgery were excluded from the study. All patients were evaluated by history, clinical examination, laboratory and radiological investigations. The clinical presentation in terms of good (13–15) or poor (3–12) Glasgow, score (GCS) was noted. The presence or absence of neurodeficit and papilledema was noted. Patients were operated by craniotomy or craniectomy depending on the location of the tumor, and excision/decompression was done. If hydrocephalus was present, then patient was first operated for cerebrospinal fluid (CSF) diversion (shunt or endoscopic) followed by definitive surgery. The specimen was sent for histopathological and immunohistochemistry examination. Grading of tumor was done according to the WHO criteria 2007.[4,5] Ki-67 and p53 expression was calculated as percentage positivity.[6-8] Patients were followed up after discharge with Glasgow outcome score (GOS) at three and 6 months (as possible).Good recovery was quantified by GOS (4 and 5), fair recovery by GOS (3), and poor recovery with GOS (1 and 2). The difference in expression of p53 and Ki-67 in various tumors in correlation with clinical presentation, outcome, and histological grade was evaluated using Statistical Package for Social Science software (SPSS) version 17 (SPSS Inc, Chicago, USA). A Chi-square test was performed for categorical data, and mean and standard deviation was calculated for continuous data. Independent *t*-test was performed for comparison between two groups. Analysis of variance was used for more than two group comparison for parametric data using SPSS version 17. *P* values were calculated using Chi-square test for the estimation of outcome with type of tumor. $P < 0.05$ was considered statistically significant.

Results

Forty-seven cases of pediatric brain tumors were analyzed in the study. The age of patients ranged from 10 months to 17 years. There were 32 male and 15 female patients. The clinical presentation of the patients is summarized in Table 1. Vomiting was the most common symptom present in 42 (89.4%) patients followed by headache in 41 (87.2%) and vision loss in 21 (44.7%) patients. 34 (72.3%) patients had papilledema, 35 (74.4%) had neurodeficit and 40 (85.1%) had good GCS (13–15) on presentation. Hydrocephalus was present in 33 (70%) patients, and CSF diversion was done in these patients. There were 31 (66%) infratentorial and 16 (34%) supratentorial tumors. The clinical features of the patients are summarized in Table 1.

Table 2 summarizes the histological distribution of the tumors. Medulloblastoma was the most common tumor constituting 17 (36.17%) of the patients. Pilocytic astrocytoma was the next most common tumor in our series constituting 7 (14.8%) of the cases. Other tumor types included glioblastoma multiforme (4), ependymomas (4), anaplastic ependymomas (4), and craniopharyngiomas (3). There were 2 cases each of pilomyxoid astrocytoma, subependymal giant cell astrocytoma, and supratentorial PNET. There was 1 case each of diffuse astrocytoma and oligoastrocytoma.

Table 1: Demographic and clinical profile of the study

Parameter	No. of patients
Age profile of study population	
Number of cases	47
Males	32
Female	15
Minimum age (months)	10
Maximum age (years)	17
Age groups (years), number of patients (%)	
0-5	11 (23.4)
6-10	20 (42.5)
11-15	11 (23.4)
16-18	5 (10.6)
Presenting symptom and signs, number of patients (%)	
Vomiting	42 (89.4)
Headache	41 (87.2)
Vision loss	21 (44.7)
Altered sensorium	17 (37.2)
Seizures	8 (17)
Diplopia	2 (4.3)
Papilledema	34 (72.3)
Optic atrophy	11 (23.4)
Cranial nerve palsy except 2nd nerve	15 (31.1)
Hemiparesis	7 (14.9)
Quadriparesis	1 (2.1)
Cerebellar signs	23 (48.9)
GCS	
3-12	7 (14.9)
13-15	40 (85.1)

GCS – Glasgow coma scale

Table 2: Histological distribution of tumors

Tumour type	No.of patients
Neuroectodermal tumors	19
Supratentorial PNET	2
Medulloblastoma	17
Gliomas	17
Pilocytic astrocytoma	7
Diffuse astrocytoma	1
Oligoastrocytoma	1
Pilomyxoid astrocytoma	2
GBM	4
SEGA	2
Ependymoma-	8
Grade 2 ependymoma	4
Grade 3 ependymoma	4
Craniopharyngioma	3

PNET – Primitive neuroectodermal tumor; GBM – Glioblastoma multiforme; SEGA – Subependymal giant cell astrocytoma

The clinical parameters (GCS, papilledema, and neurodeficit) were analyzed and correlated with p 53 and Ki-67 levels [Table 3]. The mean p 53 and Ki-67 levels were higher in patients with poor presenting GCS and papilledema. However, no statistically significant correlation was observed between these parameters and the p53 and Ki-67 levels. Patients with neurological deficit had more mean level of p53 and Ki-67, and there was statistically significant correlation between neurological deficit and high p53 levels with $P = 0.040$.

Although mean p53 and Ki-67 levels in low-grade tumors were lower than in high-grade tumors, there was no statistically significant correlation between the WHO grade of tumor and p53 ($P = 0.117$) levels. However, there was statistically significant correlation between higher WHO grade of tumor and higher Ki-67 levels with $P = 0.000$ [Table 4]. On *post hoc* analysis of the data, we found that the levels of p53 were significantly higher in Grade 4 tumors as compared to Grade 1 tumors with $P = 0.040$ [Table 4].

Patient outcome after surgery and adjuvant therapy (if required) was assessed at 3 and 6 months on the basis of GOS. Out of the 47 patients, 8 (17%) had poor outcome (GOS 1 and 2), 16 (34%) had fair outcome (GOS 3), and 23 (48.9%) had good outcome (GOS 4 and 5) 3 months after surgery [Table 5]. It was observed that the values of both p 53 and Ki-67 were significantly higher in poor outcome group with $P = 0.034$ and 0.000, respectively. The trend continued at 6 months follow-up with a statistically significant correlation between poor outcome and high p53 and Ki-67 levels with $P = 0.012$ and 0.001, respectively. Six patients did not complete the follow-up period of 6 months, so they were not taken into the analysis at 6 months.

In addition to the above analysis, a subgroup analysis of the patient cohort was also done. There were 17 patients with a diagnosis of glioma which included 9 WHO grade 1

Table 3: Clinical parameters (Glasgow coma scale, papilledema, and neurodeficit) and p53 and Ki-67 levels

Clinical parameter	*n*	Mean		*P*	
		p53	Ki-67	p53	Ki-67
GCS (3-12)	7	9.000	21.21	0.769	0.132
GCS (13-15)	40	6.850	11.98		
Papilledema present	34	8.897	15.01	0.282	0.219
Papilledema absent	13	2.654	9.00		
Neurological deficit present	35	9.057	14.20	0.040	0.511
Neurological deficit absent	12	1.667	10.88		

GCS – Glasgow coma scale

Table 4: p53 and Ki-67 levels in different WHO grades of tumor and *post hoc* analysis for p53

	WHO grade	*n*	Mean	SD	ANOVA (*P*)	Dependent variable	*Post hoc* analysis				
							WHO grade (I)	WHO grade (J)	Mean difference (I-J)	SE	*P*
p53	1	12	0.54	0.7821	0.117	p53	1	2	0.1042	7.7665	0.989
	2	8	0.43	0.6232				3	−4.2083	9.8239	0.671
								4	−12.849	6.0593	0.040
	3	4	4.75	4.4253			2	1	−0.1042	7.7665	0.989
	4	23	13.39	23.723				3	−4.3125	10.4198	0.681
	Total	47	7.17	17.602				4	−12.953	6.9842	0.071
Ki-67	1	12	1.08	0.195	0.000		3	1	4.2083	9.8239	0.671
								2	4.3125	10.4198	0.681
	2	8	2.06	1.568				4	−8.6413	9.2179	0.354
	3	4	11.88	6.562			4	1	12.8496	6.0593	0.040
	4	23	23.93	14.546				2	12.9538	6.9842	0.071
	Total	47	13.35	14.900				3	8.6413	9.2179	0.354

n – Number of patients. ANOVA – Analysis of variance; SD – Standard deviation; SE – Standard error

Table 5: Comparison between outcome and p53 and Ki-67 levels at 3 and 6 months

	Outcome	*n* at 3 months	*n* at 6 months	Mean at 3 months	Mean at 6 months	*P*	
						3 months	6 months
p53	A	8	9	19.000	22.444	0.034	0.012
	B	16	12	9.750	8.417		
	C	23	20	1.261	0.700		
	Total	47	41	7.170	7.732		
Ki-67	A	8	9	17.81	21.39	0.000	0.001
	B	16	12	23.94	17.33		
	C	23	20	4.43	3.93		
	Total	47	41	13.35	11.68		

GOS 1, 2=A (poor); GOS 3=B (fair); GOS 4, 5=C (good) *n* is number of patients. GOS – Glasgow outcome score

tumors followed by 4 each of WHO grade 2 and 4. We found a statistically significant correlation between higher glioma grade and higher mean p53 and Ki-67 levels with $P = 0.001$ and <0.001, respectively [Table 6]. Similarly, there was statistically significant correlation between poor outcome and high mean values of p53 ($P = 0.007$) and Ki-67 ($P = 0.014$) at 3 months follow-up. At 6 months follow-up, the trend continued with $P = 0.011$ for p 53 and 0.021 for Ki-67, respectively [Table 7].

In neuroectodermal tumors, we found that there was statistically significant correlation between poor outcome and high mean Ki-67 level ($P = 0.047$), but not between outcome and p53 level ($P = 0.603$) at 3 months follow-up [Table 8]. At 6 months, 5 patients could not complete the follow-up period; hence, 14 patients out of 19 were analyzed. There was no statistically significant correlation between outcome and p53 ($P = 0.368$) and Ki-67 ($P = 0.165$) levels at 6 months [Table 8].

There were 8 cases of ependymoma. There was statistically significant correlation between grade of ependymoma and Ki-67 level ($P = 0.017$) but not between grade of ependymoma and p53 level [Table 6]. There was no statistically significant correlation between ependymoma outcome and p53 and Ki-67 level at 3 and 6 months [Table 9].

There were three cases of craniopharyngioma. At 3 months, two patients had poor outcome, and one had good outcome. As the sample size was small, so no subgroup analysis with p53 and Ki-67 level could be done.

Table 6: p53 and ki-67 level in different WHO grades of glioma and ependymoma (subgroup analysis)

	For gliomas				For ependymomas			
	WHO grade	*n*	Mean	*P*	WHO grade	*n*	Mean	*P*
p53	1	9	0.500	0.001	2	4	0.625	0.158
	2	4	0.250					
	4	4	47.750		3	4	4.750	
	Total	17	11.559					
Ki-67	1	9	1.11	<0.001	2	4	1.13	0.017
	2	4	3.00					
	4	4	26.13		3	4	11.88	
	Total	17	7.44					

n – Number of patients

Discussion

Cancer is the most frequently diagnosed disease-related cause of death among children and adolescents. Among all childhood cancers, brain tumors are the most common solid pediatric tumors comprising 40%–50% of all tumors The p53 gene is a tumor suppressor gene located on chromosome 17 short arm (17p13) and is the single most common target for genetic alterations in human cancer. Disturbances in p53 function are strongly associated with carcinogenesis. Ki-67 is an established marker for proliferative index in cycling cells.[9] Ki-67 presence in a large proportion of cells suggests an aggressive neoplasm.

Table 7: Surgical outcome in different types of gliomas with respect to p53 and Ki-67 level at 3 and 6 months

	Outcome	*n* at 3 months	*n* at 6 months	Mean at 3 months	Mean at 6 months	*P*	
						3 months	6 months
p53	A	3	3	46.667	46.667	0.007	0.011
	B	2	2	25.000	25.000		
	C	12	11	0.542	0.500		
	Total	17	16	11.559	12.219		
Ki-67	A	3	3	24.00	24.00	0.014	0.021
	B	2	2	13.50	13.50		
	C	12	11	2.29	2.41		
	Total	17	16	7.44	7.84		

GOS 1, 2=A (poor); GOS 3=B (fair); GOS 4, 5=C (good); *n* – Number of patients. GOS – Glasgow outcome score

Table 8: Subgroup analysis for neuroectodermal tumors at 3 and 6 months

	Outcome	*n* at 3 months	*n* at 6 months	Mean at 3 months	Mean at 6 months	*P*	
						3 months	6 months
p53	A	3	4	3.667	15.250	0.603	0.386
	B	11	6	8.636	5.167		
	C	5	4	2.200	1.500		
	Total	19	14	6.158	7.000		
Ki-67	A	3	4	22.83	29.63	0.047	0.165
	B	11	6	29.45	22.75		
	C	5	4	10.70	10.88		
	Total	19	14	23.47	21.32		

GOS 1, 2=A (poor); GOS 3=B (fair); GOS 4, 5=C (good); *n* – Number of patients. GOS – Glasgow outcome score

Table 9: Subgroup analysis for ependymoma at 3 months

	Outcome	*n* at 3 months	*n* at 6 months	Mean at 3 months	Mean at 6 months	*P*	
						3 months	6 months
p53	B	3	4	3.667	5.000	0.599	0.067
	C	5	4	2.100	0.375		
	Total	8	8	2.688	2.688		
Ki-67	B	3	4	10.67	11.13	0.228	0.059
	C	5	4	4.00	1.88		
	Total	8	8	6.50	6.50		

GOS 1, 2=A (poor); GOS 3=B (fair); GOS 4, 5=C (good); *n* – Number of patients. GOS – Glasgow outcome score

P53 and Ki-67 have been widely used as markers to predict outcome in various malignancies.[10,11]

Majority of the patients in our study were males (68%) as compared to females (32%). Studies done by Rickert and Paulus[2] and by Nasir *et al*.[12] also found that the proportion of males was more than that of females. The most common presenting complaints were vomiting and headache which is common in pediatric brain tumors as seen in the studies by Wilne *et al*.[13] and Reulecke *et al*.[14]

Hydrocephalus was present in 33 (70%) patients. Raimondi and Tomita[15] in their study observed that the incidence of hydrocephalus in posterior fossa tumors was 83% whereas Wong *et al*.,[16] observed that the incidence of hydrocephalus was 56.7% in pediatric brain tumors.

In our study, the most common tumor group was that of neuroectodermal tumors (41%) followed by gliomas (36%). In studies by Jain *et al*.,[17] Baldwin and Preston-Martin[1] and Rickert and Paulus[2] astrocytomas were the most common CNS tumors of childhood. However, in studies by Nasir *et al*.[12] and Kumar,[18] medulloblastomas were the most common tumors.

There was statistically significant correlation between tumor grade and Ki-67 level (P = 0.000). A statistically significant correlation was also observed on *post hoc* analysis where the levels of p53 were significantly higher in Grade 4 tumors as compared to Grade 1 tumors with a P = 0.040. This can be due to the relatively less number of grade 2 and 3 tumors as the majority of tumors were of grade 1 (25.5%) and grade 4 (49%). Kim *et al*.[19] observed that P53 and Ki-67 expression was higher in malignant brain tumors, and that there was a close relationship between their expression and histological grade. Studies by Wakimoto *et al*.,[20] Rathi *et al*.,[21] and Chaloob *et al*.[22] demonstrated a significant relationship between tumor grade and Ki-67 levels in gliomas.

In our study, there was statistically significant correlation between outcome and p53 (P = 0.034) and Ki-67 (P = 0.000) level at three and 6 months follow-up. It was observed that the values of both p 53 and Ki-67 were significantly higher in the poor outcome group. Similar results were observed in studies done by Rickert,[23] Jaros *et al*.,[24] and Montine *et al*.[25]

In the subgroup analysis for gliomas, there was statistically significant correlation between grade and p53 (P = 0.001) and Ki-67 (P = 0.0001) levels. Studies done by Wakimoto *et al*.[20] and Rathi *et al*.[21] suggest similar results. In the same subgroup, there was statistically significant correlation between poor outcome and higher Ki-67 (P = 0.014) and p53 (P = 0.007) levels at 3 months which continued at 6 months follow up with P = 0.021 and 0.021, respectively. The previous studies by Bowers *et al*.[26] have suggested that Ki-67 has a role as prognostic factor in pediatric astrocytoma. However, Tibbetts *et al*.[27] and Horbinsk *et al*.[28] have not inferred that Ki-67 has a role as a marker of prognosis.

In neuroectodermal tumors, there was statistically significant correlation between poor outcome and higher Ki-67 level (P = 0.047) at 3 months follow-up, but there was no statistically significant correlation between surgical outcome and p53 level (P = 0.603). There was no statistically significant correlation between outcome and p53 (P = 0.368) and Ki-67 (P = 0.165) levels at 6 months. However, many previous studies done on neuroectodermal tumors by Jadali *et al*.,[29] Meurer *et al*.,[30] Ferrari *et al*.,[31] Nam *et al*.,[32] and Jaros *et al*.[7] have suggested the role of p53 and ki-67 as negative prognostic factors.

In ependymomas, there was statistically significant correlation between grades of ependymoma and Ki-67 level (P = 0.017) but not with p53 level (P = 0.158). Erten *et al*.[33] and Ridley *et al*.[34] found a significant relation between Ki-67 and histological grade. In a study of 30 pediatric ependymomas, Zamecnik *et al*.[35] concluded that p53 and Ki-67 positivity was an indicator of aggressive tumor behavior and poor outcome. Verstegen *et al*.[36] observed no significant relationship between the histological grade of ependymoma and p53 protein, but p53 positive cases had poor outcome. We did not find a significant correlation between outcome and p53 and Ki-67 level. This may be due to the small sample size and small follow-up time of 6 months.

In craniopharyngiomas, the sample size was small, and analysis with p53 and Ki-67 could not be done.

Conclusions

From this study, we conclude that p53 and ki-67 expression in pediatric brain tumors are associated with poor outcome

and correlates with tumor grade. Moreover, p53 expression correlates with neurological deficit. We recommend that p53 and Ki-67 analysis be done in all pediatric brain tumors for better characterization and prognostication. It may also have a role in planning adjuvant therapy in these tumors.

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Conflicts of interest

There are no conflicts of interest.

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