



Histomorphological and Immunohistochemical Analysis of Gliomas

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In the present study, important parameters like frequency distribution of Gliomas, age group of Glioma patients, common sex involved, commonest site of occurrence, clinical presentations, radiological histopathological correlation, p16INK4a expression of the glial tumors are compared with other similar studies. The aim is to find out common age group of Glioma occurrence and it includes higher grades of Astrocytomas. The present study focuses on common symptoms such as head ache, histopathological correlation and common tumor etc and to study the Histomorphology of Gliomas to evaluate p16INK4a expression in Gliomas to correlate the p16INK4a expression with the WHO grading of Gliomas. Various parameters like age, sex, site, clinical symptoms, radiological correlation and WHO Grading were analysed. p16 IHC was expressed as positive and negative according to its nuclear staining of >25% cells in 10 continuous fields in 40x and it was found that p16 expression was Positive in all Grade 1 Astrocytoma, 3 out of 5 Grade II Astrocytoma and only in one Grade IV Glioblastoma. p16 expression was negative in 2 Grade II Astrocytomas and in 17 Grade IV Glioblastomas and in 2 cases of Myxopapillary Ependymoma.

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1. INTRODUCTION

The central nervous system is made up of the brain, spinal cord and their coverings. Their ability to receive, store and transmit information is unique in nature. Central nervous system neoplasms represent an unique, heterogeneous population of neoplasms and include both benign and malignant tumours. The tumours of central nervous system are reported to be less than 2% of all malignancies [1]. In India, tumours of CNS constitute about 1.9% of all tumours [2]. Gliomas are most common type among primary intracranial tumours making 35 to 50% of the tumours [3]. Gliomas are tumors of neuroepithelial tissue and comprise a complex and heterogeneous group of tumors which may be benign or malignant and they arise from the neuroglial cells. Glial cells are the most abundant cell types in the central nervous system. They surround the neurons and provide support. The glial cells include astrocytes, oligodendroglial cells and ependymal cells.

The factors have so far been conclusively shown to cause Glioma are exposure to high doses of ionizing radiation, and inherited mutations of highly penetrant genes associated with rare syndromes [4]. Several familial cancer syndromes are associated with tumors of the nervous system like, the Li-Fraumeni syndrome (TP53 germline mutations), neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2) and Turcot syndrome (APC and hMLH1/hPSM2 germline mutations). [5] Identification of genetic, behavioural, environmental and developmental contributors to Glioma risk through epidemiological studies, will help in reducing the disease burden.

Astrocytomas are most common Gliomas which has a wide spectrum of clinical behaviour that can be expressed as a grade. The most commonly used WHO grading system, uses four grades with grade I being the least malignant and grade IV the most malignant. The tumor progression from WHO Grade II to IV is associated with the sequential acquisition of genetic alterations, including mutations in the p53 and homozygous deletions of the p16 genes [4]. The distinction between different forms of Astrocytomas is mainly based on morphological features, but IHC plays an important role in diagnosing as well as in knowing the prognosis.

Oligodendroglial tumors which include Oligodendrogliomas and Oligoastrocytomas, has its origin from oligodendrocyte precursor cells [6, 7]. These tumors can be low grade (Oligodendroglioma) or high grade (anaplastic oligoastrocytoma) and may be a part of mixed Gliomas. These tumors have recently been demonstrated to have a frequent occurrence of loss of heterozygosity for the short arm of chromosome 1 and the long arm of chromosome [8].

Ependymomas, as their name implies, are glial tumors that exhibit ependymal differentiation [9, 10]. These are the most common primary tumor of the spinal cord (especially in adults) and the third most common pediatric CNS tumor. A number of alterations have been found to be associated with more biologically aggressive ependymomas. For example, gain of chromosome 1q and deletion of CDKN2A are not only more frequently encountered in pediatric intracranial ependymomas, these alterations likewise tend to correlate with anaplastic histology, increased recurrence, and shortened survival [11–16].

In analysing the various molecular genetics of Gliomas, study of loss of expression of p16 protein by Immunohistochemistry has been chosen for this study. p16INK4 is a cell cycle regulator that specifically binds to and inactivates cyclin-dependent kinase 4 (CDK4). The p16/CDKN2 gene is located in chromosome 9p21 [17], a region with frequent loss of heterozygosity in malignant (grade III and grade IV) Gliomas [18,19]. Recently, several authors have studied large numbers of Glioma samples and shown that 27 to 34% of the clinical samples of malignant cases [20,21,22] and 68% of xenografts of Glioblastomas have homozygous deletion of p16/CDKN2 locus [23].

The diagnosis of Gliomas relies upon a combination of clinical, radiological and pathological methods [24,25]. The present study will evaluate the histomorphology and the expression of p16 in Gliomas using Immunohistochemistry to investigate the role of p16 in the Gliomas. The results of the present study may provide guidance with respect to the clinical diagnosis, assessment and treatment of Gliomas.

2. MATERIALS AND METHODS

2.1 Study Place

Department of Pathology, Sree Balaji Medical College and Hospital, Chennai.

2.2 Study Design

It was a prospective study for a period of two years, from October 2016 to September 2018.

2.3 Study Population

Formalin fixed Paraffin embedded sections which were histopathologically diagnosed as Gliomas. Relative clinical history obtained from the patient's requisition form.

2.4 Inclusion Criteria

All cases of Gliomas received in histopathology and diagnosed as Glioma.

2.5 Exclusion Criteria

- Biopsy specimen not received in formalin.
- Cases diagnosed as Gliomas but unavailability of blocks.

2.6 Material Used

1. Tissue sections prepared from formalin fixed paraffin embedded tissues
2. Haematoxylin and Eosin staining kit
3. p16(G175-405) mouse monoclonal antibody kit
4. Positive control-Carcinoma cervix specimen
5. Negative control- Lipoma specimen

2.7 Assessment of p16 Positivity

The expression of p16 was considered positive if there were >25% of cells in 10 continuous high power (x40) magnification showed presence of yellow or brown nucleus under microscope. When this criteria was not satisfied, the tumor was considered negative for p16 IHC [26].

3. RESULTS

The present study was determined to study the morphology and expression of p16INK4a in Gliomas. A total of 30 surgically resected, formalin fixed, paraffin embedded Glioma samples were collected during the study period. The clinical data were collected from the patient's requisition form and the details were recorded as per proforma. Out of various types of Gliomas, we received 4 cases of Pilocytic Astrocytoma, 5 cases of Diffuse Astrocytoma which included 1 case of its variant Gemistocytic Astrocytoma, 1 case of Anaplastic Astrocytoma, 18 cases of Glioblastoma and 2 cases of Myxopapillary ependymoma, giving a total of 30 cases of Gliomas. Analysis of the results were done using tables, pie charts and bar diagrams by obtaining results from the master chart.

3.1 Frequency Distribution of Gliomas

In our study the most common Glioma was Glioblastoma, which is a Grade IV tumor. Total number of Glioblastoma was 18 out of 30 Gliomas, i.e 60% of all the Gliomas received. The next common Glioma was Diffuse Astrocytoma which includes a case of Gemistocytic Astrocytoma (5 cases) followed by Pilocytic Astrocytoma (4 cases). We also had 2 cases of Myxopapillary Ependymoma and one case of Anaplastic Astrocytoma (Fig. 1).

Table 1. Distribution of Gliomas

S. no.	Glioma	No. of Cases	Percentage (%)
1.	Pilocytic Astrocytoma	04	13.33
2.	Diffuse Astrocytoma	04	16.7%
	Gemistocytic Astrocytoma	01	
3.	Anaplastic Astrocytoma	01	3.33
4.	Glioblastoma	18	60
5.	Myxopapillary ependymoma	02	6.7
Total		30	100

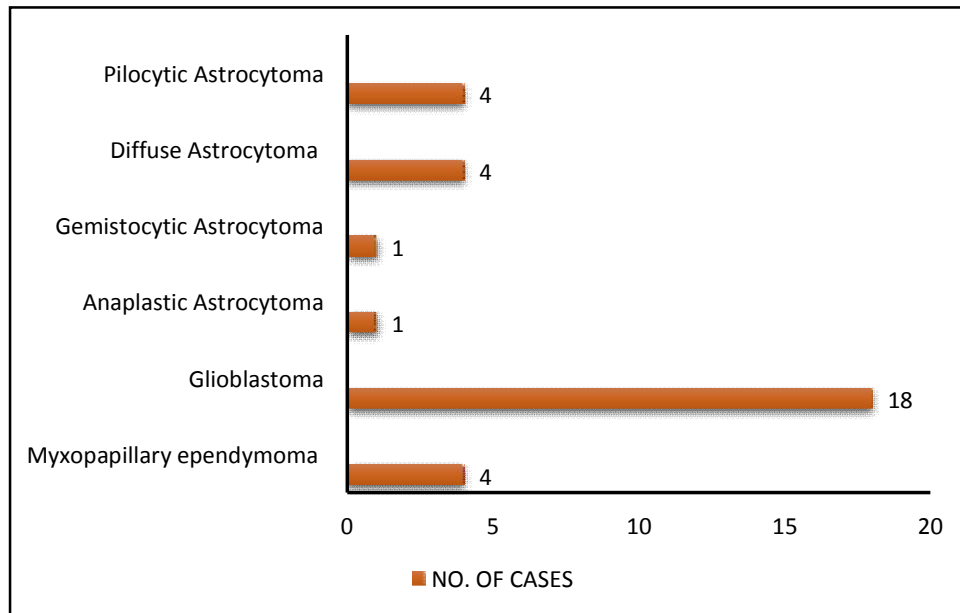


Fig. 1. Distribution of different types of Gliomas

Table 2. Distribution of WHO Grade of Glioma

S. No	WHO Grade	Glioma	No. of Cases	Total	%
1.	I	Myxopapillary ependymoma Pilocytic Astrocytoma	02 04	06	20
2.	II	Diffuse Astrocytoma Gemistocytic Astrocytoma	04 01	05	16.67
3.	III	Anaplastic Astrocytoma	01	01	3.33
4.	IV	Glioblastoma	18	18	60

Table 3. Age Wise Distribution of Gliomas

S. no	GLIOMA	0-10 yrs	11-20 yrs	21-30 yrs	31-40 yrs	41-50 yrs	51-60 yrs	61-70 yrs	>70 yrs
1.	Pilocytic Astrocytoma	1	2		1				
2.	Diffuse Astrocytoma				2	2			
3.	Gemistocytic Astrocytoma					1			
4.	Anaplastic Astrocytoma					1			
5.	Glioblastoma					1	6	8	3
6.	Myxopapillary ependymoma			1	1				
Total		01	02	01	04	05	06	08	03

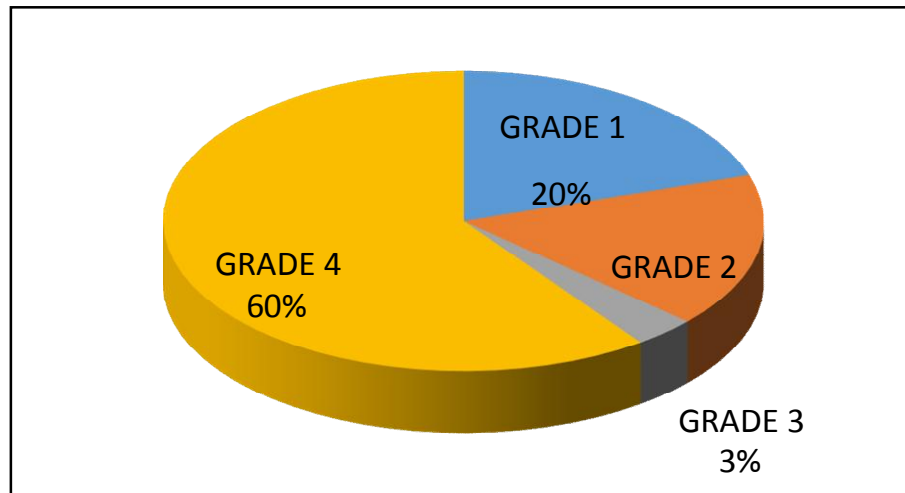


Fig. 2. Distribution of WHO Grade of Glioma

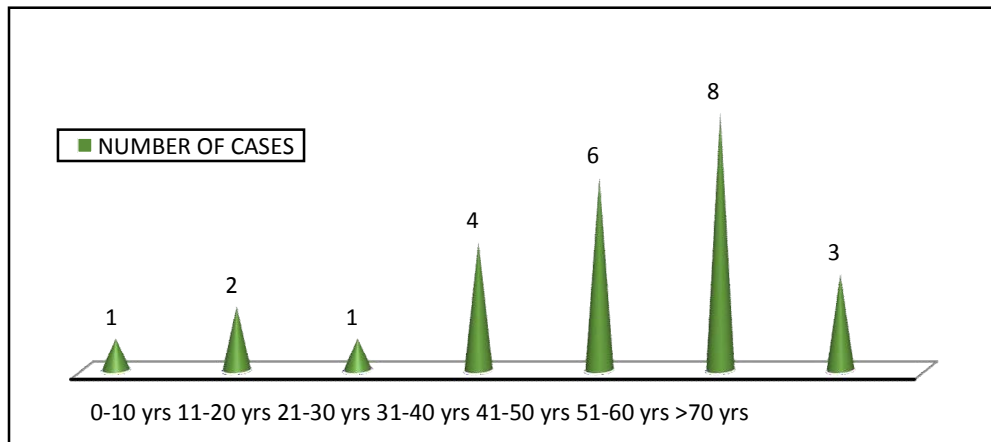


Fig. 3. Age Wise Distribution of Gliomas

3.2 Distribution of who Grade of Glioma

Grading of Glioma is an important aspect while reporting a Glioma. We had Gliomas of all 4 grades. The distribution of WHO Grade of Glioma is explained in table below (Fig. 2).

3.3 Age Wise Distribution of Gliomas

The Gliomas were categorised according to their age group. The age group ranged from 8 yrs to 77 yrs. The maximum incidence of Gliomas was in the 6th decade of life, followed by 5th decade. The mean age of Glioma incidence was 55 yrs (Fig. 3).

3.4 Gender Distribution of Gliomas

In all Gliomas predominantly incidence was common among males than females.

The male: female ratio was 2:1 in this study (Fig. 4).

3.5 Distribution of Different Clinical Symptoms / Signs Associated with the Tumours

The patients presented with various symptoms, often multiple. The most common symptom was Head ache (73.3%), followed by vomiting (70%) and convulsions (60%). The other symptoms included motor weakness, giddiness, neurological defects, visual disturbances, altered consciousness, lower back ache, speech defects and gait disturbances (Fig. 5). The result findings were summarized in figures (Figs. 6 - 19).

Table 4. Gender Distribution of Gliomas

S. No	Glioma	Male	Female
1.	Pilocytic Astrocytoma	02	02
2.	Diffuse Astrocytoma	03	01
3.	Gemistocytic Astrocytoma	01	00
4.	Anaplastic Astrocytoma	01	00
5.	Glioblastoma	12	06
7.	Myxopapillary ependymoma	01	01
Total		20	10

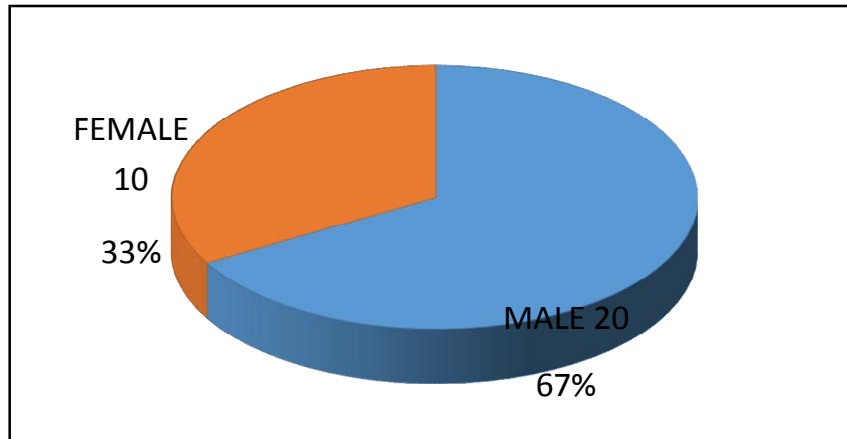


Fig. 4. Gender Distribution of Gliomas

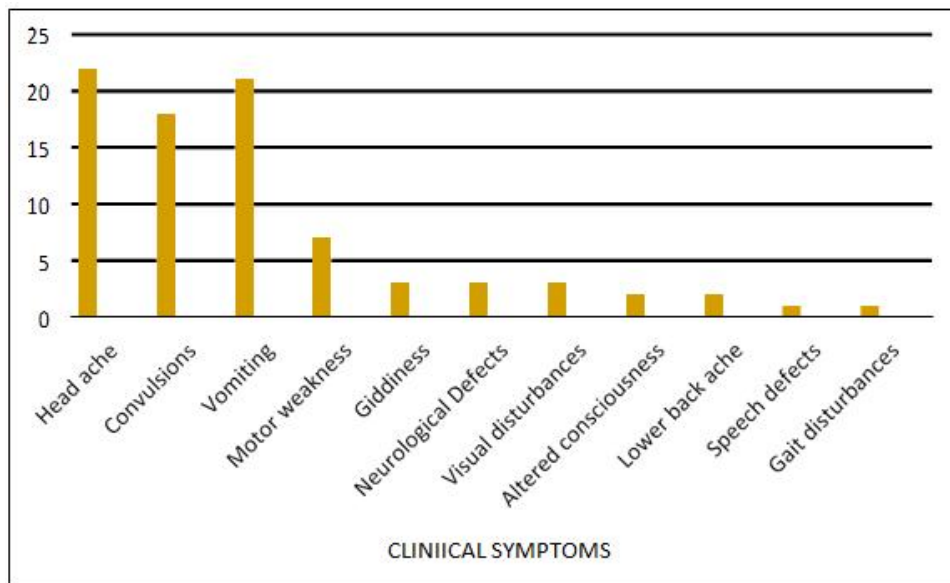


Fig. 5. Distribution of Different Clinical Symptoms / Signs Associated with the Gliomas

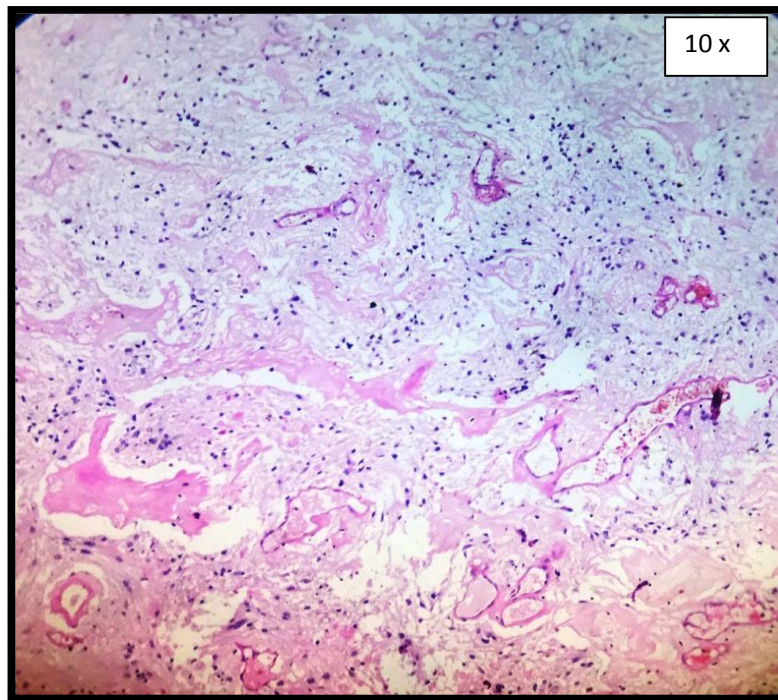


Fig. 6. H & E picture; 10 x magnification of PILOCYTIC ASTROCYTOMA - GRADE 1

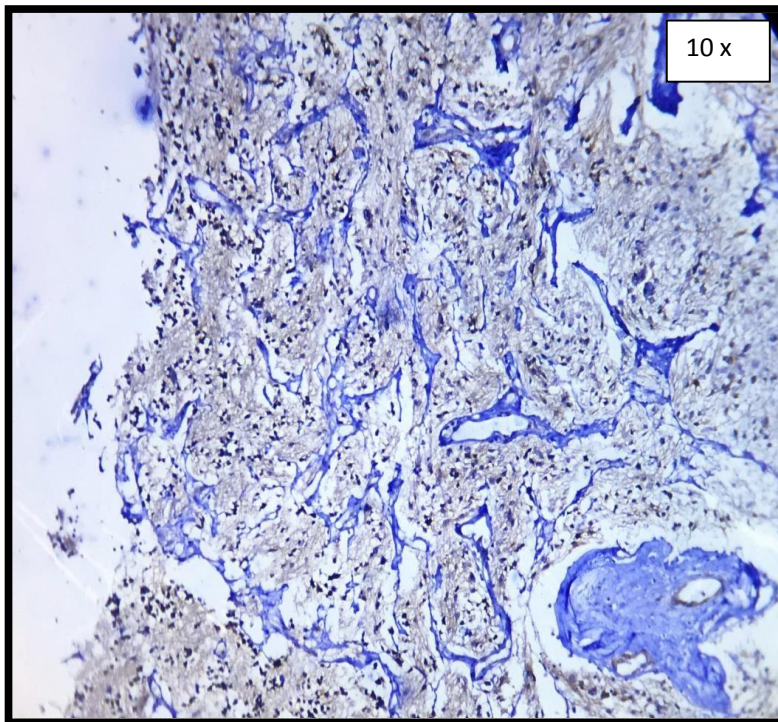


Fig. 7. IHC p16 picture; 10 x magnification of PILOCYTIC ASTROCYTOMA- p16 IMMUNOSTAINING POSITIVE

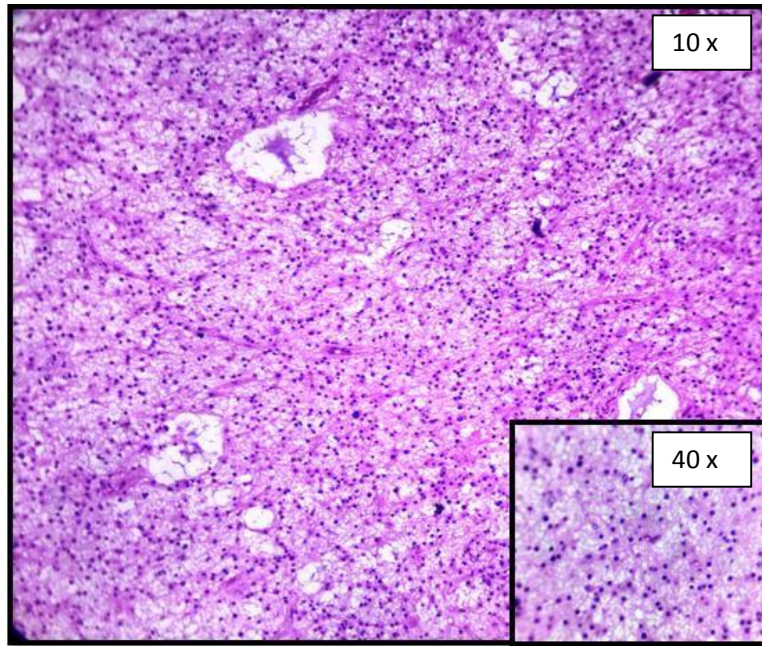


Fig. 8. H & E picture ; 10 x magnification of DIFFUSE ASTROCYTOMA - GRADE 2. Picture in the inset shows high magnification (40x) of DIFFUSE ASTROCYTOMA

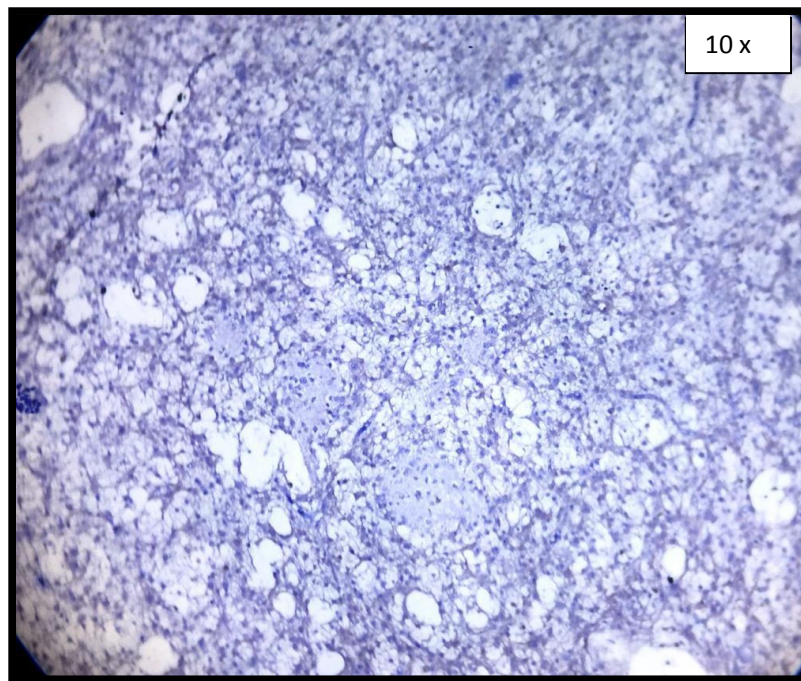


Fig. 9. IHC p16 picture; 10 x magnification of DIFFUSE ASTROCYTOMA - p16 IMMUNOSTAINING NEGATIVE

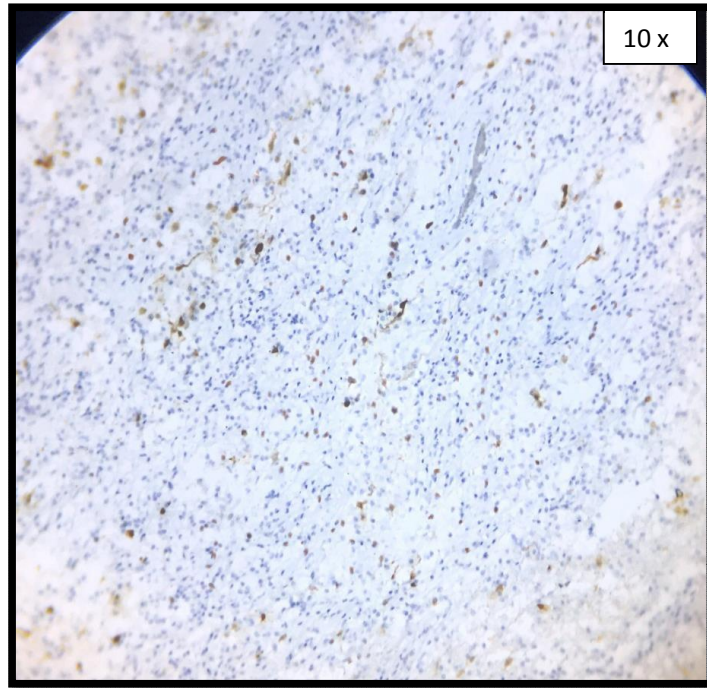


Fig. 10. IHC p16 picture; 10 x magnification of DIFFUSE ASTROCYTOMA - p16 IMMUNOSTAINING POSITIVE

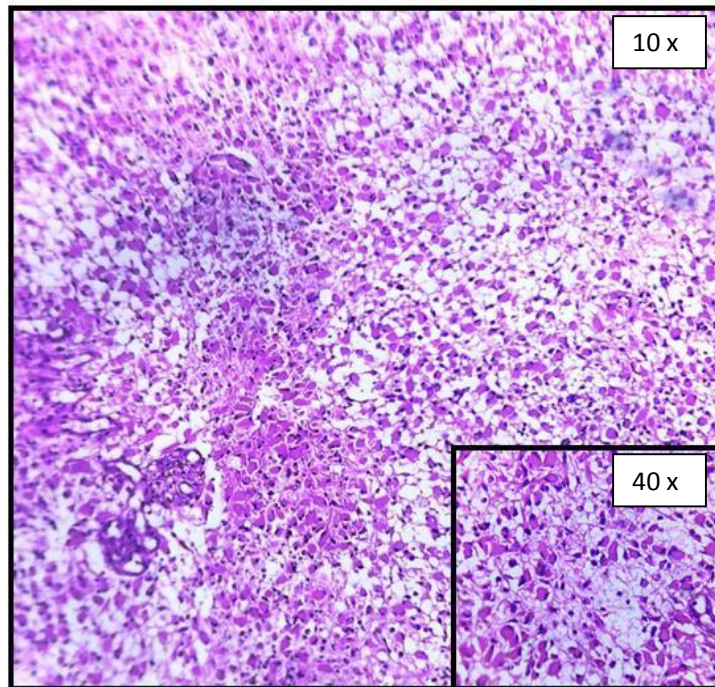


Fig. 11. H&E; 10 x magnification of GEMISTOCYTIC ASTROCYTOMA - GRADE 2. Inset: 40 x magnification showing gemistocytes

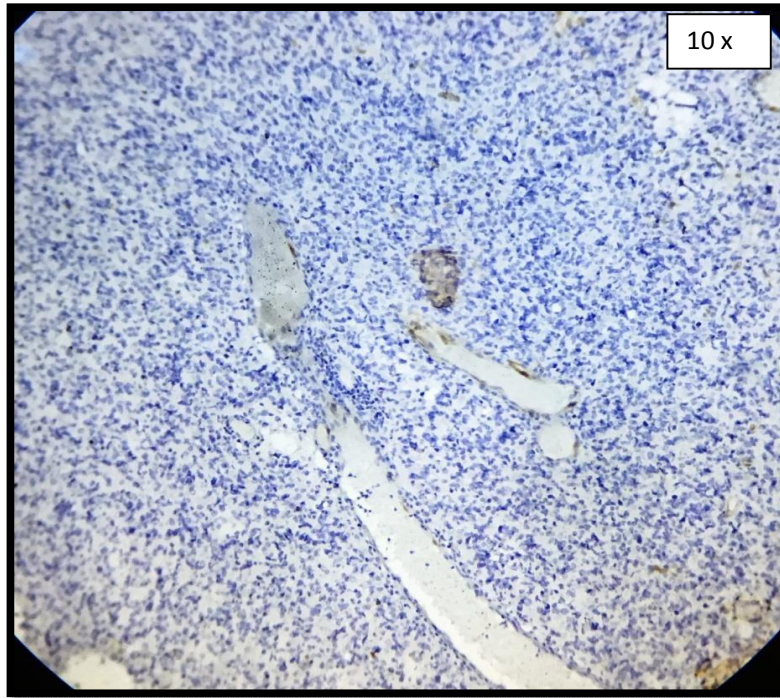


Fig. 12. IHC p16 picture; 10 x magnification of GEMISTOCYTIC ASTROCYTOMA - GRADE 2. - p16 IMMUNOSTAINING NEGATIVE

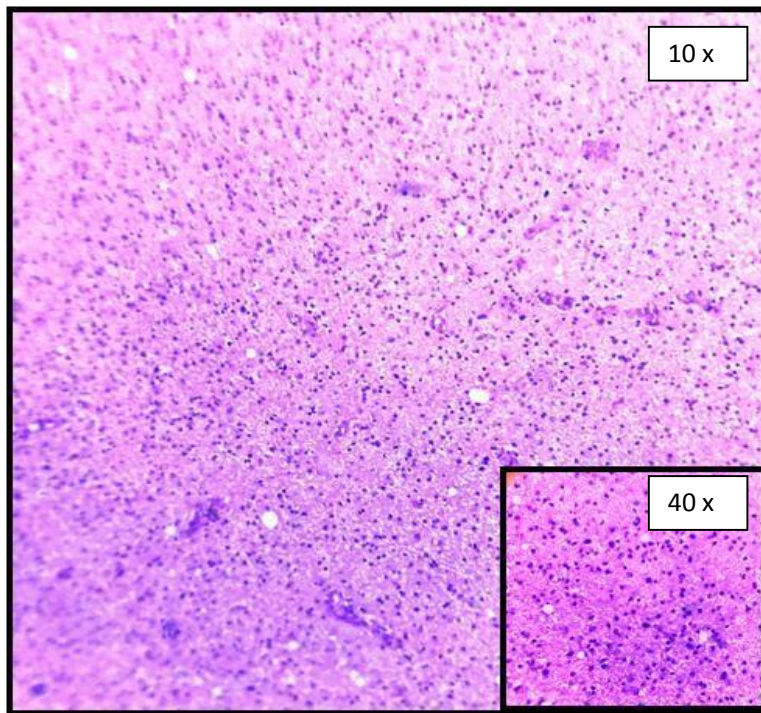


Fig. 13. H&E; 10 x magnification of ANAPLASTIC ASTROCYTOMA - GRADE 3. Inset: 40 x magnification showing anaplastic astrocytes

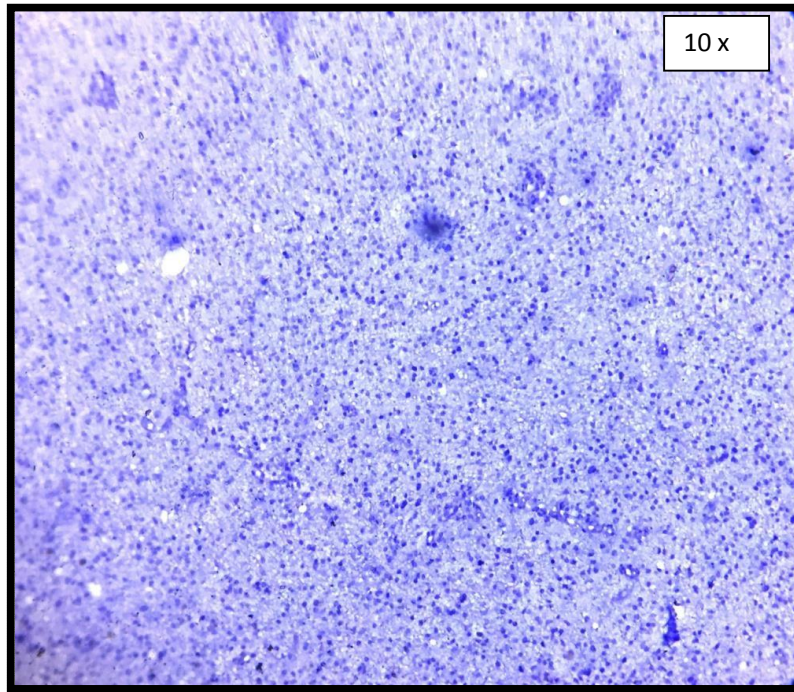


Fig. 14. IHC p16 picture; 10 x magnification of ANAPLASTIC ASTROCYTOMA - p16 IMMUNOSTAINING NEGATIVE

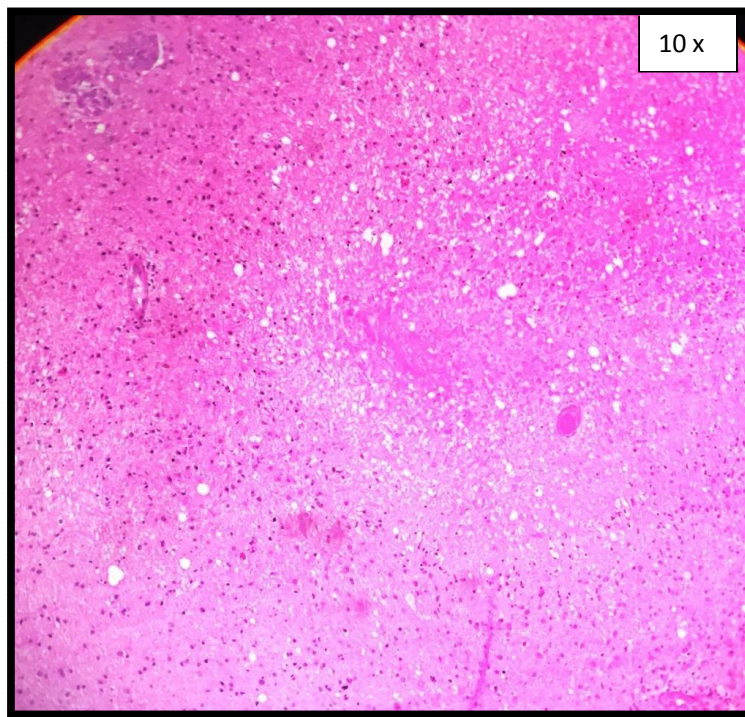


Fig. 15. H&E; 10 x magnification of GLIOBLASTOMA - GRADE 4.

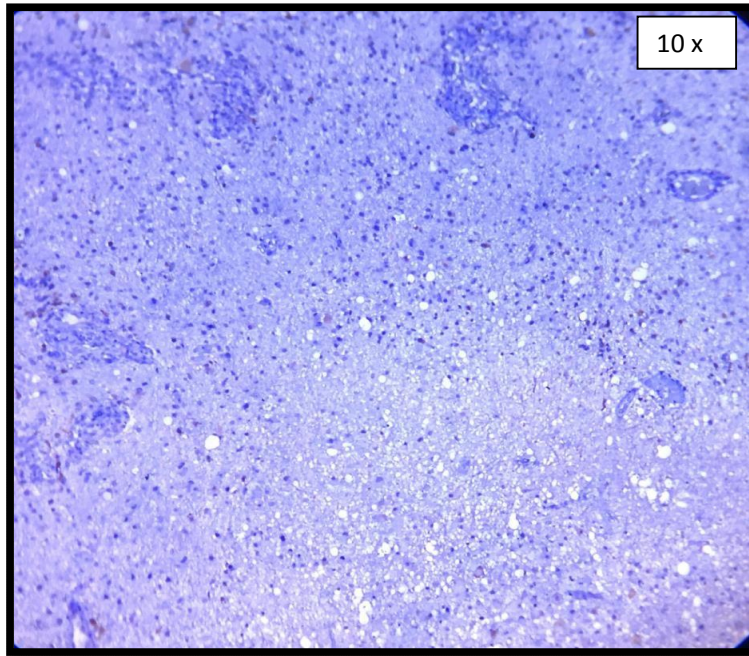


Fig. 16. IHC p16 picture; 10 x magnification of glioblastoma - p16 Immunostaining Negative

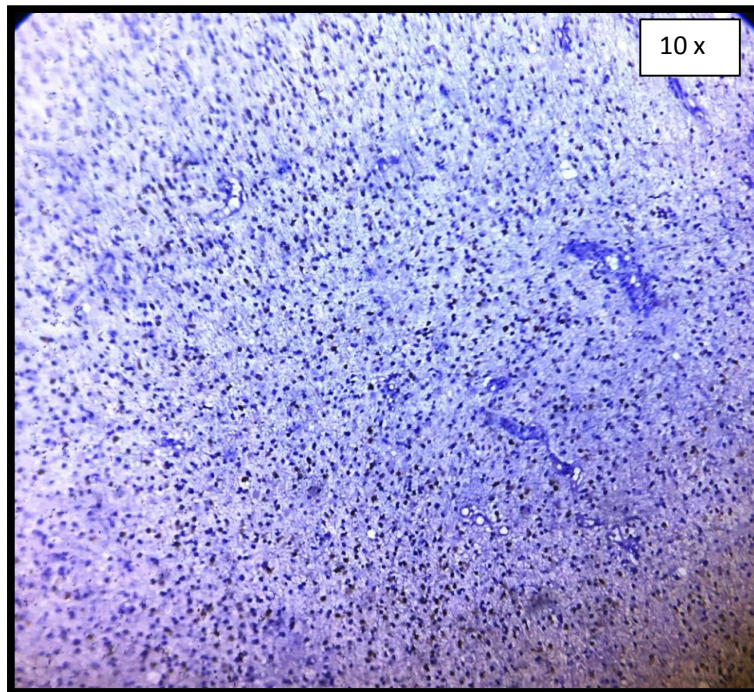


Fig. 17. IHC p16 picture; 10 x magnification of GLIOBLASTOMA - p16 immunostaining positive

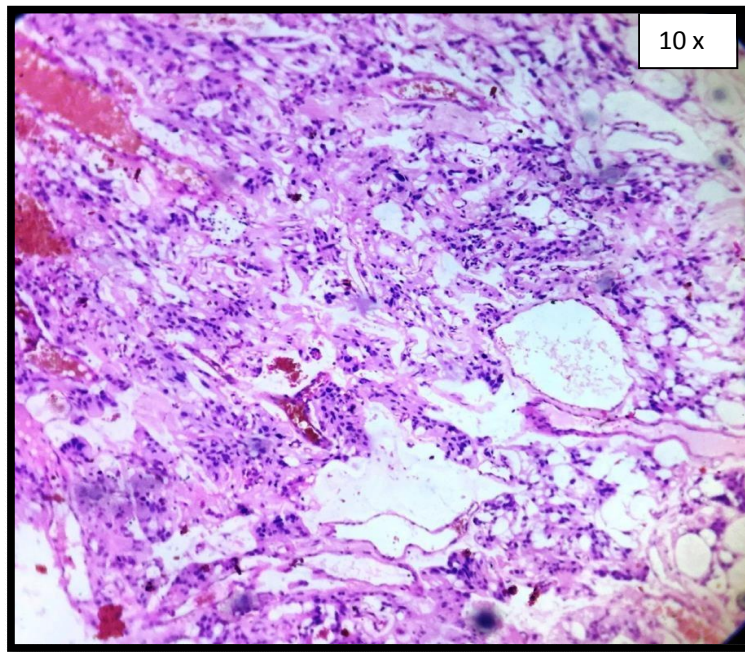


Fig. 18. H&E; 10 x magnification of MYXOPAPILARY EPENDYMOMA

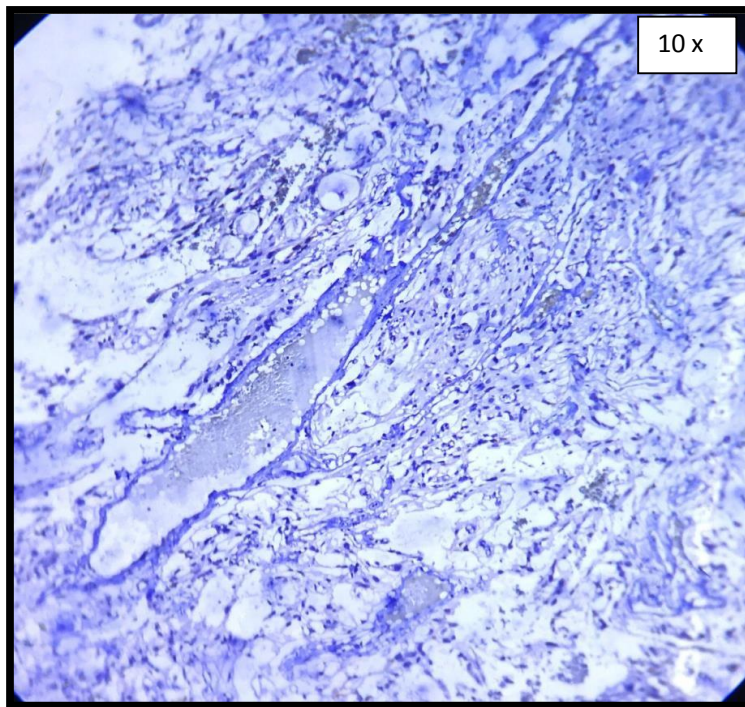


Fig. 19. IHC p16 picture; 10 x magnification of MYXOPAPILLARY EPENDYMOMA - p16 IMMUNOSTAINING NEGATIVE

Table 5. Distribution of different clinical symptoms / signs associated with the tumors

S. No	Symptom/ Sign	No. of cases	Percentage (%)
1.	Head ache	22	73.3
2.	Convulsions	18	60
3.	Vomiting	21	70
4.	Motor weakness	07	23.3
5.	Giddiness	03	10
6.	Neurological Defects	03	10
7.	Visual disturbances	03	10
8.	Altered consciousness	02	6.7
9.	Lower back ache	02	6.7
10.	Speech defects	01	3.3
11.	Gait disturbances	01	3.3

4. DISCUSSION

The present study was carried out on 30 Glioma specimens received at the Department of Pathology, Sree Balaji Medical College and Hospital, Chennai, during the period of 2 years from October 2016 to September 2018. Clinical details were obtained from the patients requisition forms and recorded. The received specimens were examined and analyzed for the histopathology and WHO grading. Immunohistochemical study using p16INK4a was also done once the histopathological confirmation of Glioma was made.

4.1 Frequency Distribution of Gliomas with WHO Grading

The common Glioma in our study was Glioblastoma (60%), followed by Diffuse

Astrocytoma (16.7%), Pilocytic Astrocytoma (13.3%). There were 2 cases of Myxopapillary Ependymoma, one case of Anaplastic Astrocytoma. A recent study in 2016 by Perry et al. [27] from Netherlands showed almost similar findings. The most common Glioma was Glioblastoma (52.9%) like in our study. The next common was Diffuse Astrocytoma (8.6%) which was also in concordance with our study. They also had other Gliomas like Anaplastic Astrocytomas 5.9%, Pilocytic Astrocytomas 5.0%, unique astrocytoma variants 1.0% Oligoastrocytic tumors 3.2%, Oligodendrogliomas 5.7%, Ependymal tumors 6.5% Malignant Gliomas, NOS 7.0%. The findings of other studied by Arpit Gohel et al. [28] and Guillamo et al. [29] are compared with the present study in the table below.

Table 6. Comparison of Frequency of Glioma with WHO Grading

S. No	Gliomas with WHO Grading	Arpit Gohel et al. [9]	Guillamo et al. [50]	Present study
1.	Pilocytic Astrocytoma (I)	10	1	4
2.	Diffuse Astrocytoma (II)	4	6	4
3.	Anaplastic Astrocytoma (III)	4	7	1
4.	Glioblastoma (IV)	13	4	18
5.	Oligoastrocytoma			
	Low grade (II)	0	4	1
	Anaplastic (III)	6	3	0
	Oligodendroglioma (II)	8	1	0
6.	Ependymoma (I)	2	0	0
	Myxopapillary Ependymoma	0	0	2
	Unspecified Glioma			
7.	Low grade	1	3	0
	High Grade	2	3	
Total		50	32	30

4.2 Comparison of Age Distribution of Gliomas

The mean age of Glioma incidence in our study was 30. The range was from 8 - 77. The most common age group involved is 6th decade of life. The age group differed for each Glioma type. Grade IV Glioma was common in 5th , 6th and 7th decades where as Grade III, II Gliomas were common in 4th decades of life. Grade I Astrocytomas were common among Pediatric age group in our study.

Histopathological study of Intracranial Gliomas by Arpit et al. [28] showed the common age group for incidence of Gliomas as 4th decade of life which was not in concordance with our study. In another study by Tirabosco et al. [30], the age ranged from 18 to 84 years, with 27 cases (34%) occurring during the seventh decade of life. This was in concordance with our study Schwartzbaum et al. [31] showed the findings which was more or less in concordance with our study. The mean age of each tumors as discussed: Glioblastoma - 64, Anaplastic Astrocytoma - 51, Astrocytoma NOS- 45, Oligodendroglioma - 41, Anaplastic Oligodendroglioma - 48 and Malignant Glioma NOS - 43.

4.3 Gender Distribution of Gliomas

In our study the common gender affected was male. The M: F ratio was 2:1 in our study. The below table shows comparison of Male: Female ratio of Gliomas with various studies.

Table 7. Shows comparison of gender distribution of Gliomas

S no	Study	M:F
1.	Present study	2 : 1
2.	Arpit Gohel et al. [28]	1.7 : 1
3.	Kleihues et al. [32]	1.25 : 1
4.	Tirabosco et al. [30]	1.15 : 1

All these studies shows male predominance like in our study but with a little variability in M: F ratio.

4.4 Site Distribution of Gliomas

In the present study, 25 cases out of 30 were in the cerebral hemisphere. 2 cases of Myxopapillary Ependymoma was in the spinal cord, 3 cases of Pilocytic Astrocytoma occupied

the Optic nerve and one in hypothalamus. In the cerebral hemisphere, the common region involved is the frontal hemisphere, followed by parietal and by frontoparietal hemispheres. According to a study by Larjavaara et al. [33], most of the Gliomas were located in the cerebral lobes 86%. Gliomas in the frontal lobe accounted for 40%, temporal lobe for 29%, parietal lobe for 14%, and occipital lobe for 3.0% of the cases. In addition, 6.4% were located primarily in the deep structures of the cerebrum, 2.2% in the ventricles, 1.5% in the cerebellum, and 4.1% in the brainstem. This was more or less in concordance with our study.

4.5 Signs and Symptoms

In the present study the patients had multiple symptoms among which head ache was the common symptom (73.3 %), followed by vomiting (70%) and the by convulsions (60 %). The other symptoms included motor weakness, giddiness, neurological defects, visual disturbances, altered consciousness, lower back ache, speech defects and gait disturbances. The study conducted by Tamkeen masoodi et al. [34], showed Headache (69.6%) was the most common symptom followed by seizures (35.9%) correlating with the results of the present study.

4.6 Radiological Histopathological Correlation

Out of 30 cases we had Radiological and Histopathological correlation in 26 cases (86.7%). This proves CT/MRI is one of the most important investigation in diagnosing Glioma. According to Chisty et al. [35], for low grade and high grade Gliomas sensitivity of MRI was 100% while for intermediate grade Gliomas sensitivity was 95%. Two false positive cases diagnosed as intermediate grade Glioma, in which one turned out to metastases and other was lymphoma on histopathology. One false negative case preoperatively diagnosed as lymphoma proved to be an anaplastic astrocytoma (Intermediate grade Glioma) on histopathology. All patients with Glioblastoma multiforme (GBM), pilocytic astrocytoma were correctly diagnosed by magnetic resonance imaging. This study showed more accuracy of Radiological investigation compared to our study.

5. CONCLUSION

Many recent investigators now mainly focus on the search for molecular markers in cancers. The

present WHO Classification of CNS tumors are based on molecular genetics. Several genetic mutations occur in brain tumors depending on the type and Grade but there are not much studies about these mutations and no proper hypothesis is formulated.

In this study we chose to study the Histomorphology and p16 Immunohistochemical expression in the Gliomas. Loss of p16 protein either by deletion or promoter methylation of p16 gene is one important mutation among the several with respect to Gliomas or its IHC expression is done in this study. The results of this study gives the conclusion that in High grade Astrocytomas (Grade III & IV) there is a predominant negative expression of p16 signifying the loss of p16 where as in Low Grade Astrocytomas (Grade I & II) there is a predominant positive expression of p16 which signifies no loss of p16 protein has occurred. Therefore, in Astrocytomas, higher the grade of the tumor, loss of p16 was found and vice versa. Myxopapillary Ependymomas showed p16 negativity and goes by the previous studies which proved there is no correlation between the Grades and p16 expression in Ependymomas. Therefore detecting loss of p16 protein by IHC can be used as a screening test for accessing p16 loss widely and is an easily available technique compared to other ancillary techniques.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was conducted after getting proper approval from ethical committee (Ref. no. 002/SBMC/IHEC/2017/871).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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