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Original Article

Pathology Section

# Isocitrate Dehydrogenase and Alpha Thalassemia/Mental Retardation, X-linked Mutation Status in Human Gliomas at a Tertiary Care Hospital in Southern India: A Cross-sectional Study

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## ABSTRACT

**Introduction:** The molecular subtyping of human gliomas in the current World Health Organisation (WHO) 2021 classification highlights the diagnostic and prognostic significance of neoplastic entities. This subsequently contributes to a better understanding of immunohistochemistry markers in various glioma patients.

**Aim:** The study aimed to determine the Isocitrate Dehydrogenase (IDH1) gene mutation and Alpha Thalessemia/Mental retardation X-linked (ATRX) mutation in gliomas through immunohistochemistry and clinically categorise them into various subgroups.

**Materials and Methods:** The present cross-sectional study was conducted in the Department of Pathology and Neurosurgery on 50 glioma samples collected from patients who underwent surgery at ESIC Medical College and Super Speciality Hospital in Hyderabad, Telangana, India from June 2018 to June 2023. Histopathological evaluation and Immunohistochemistry (IHC) study for IDH1 and Alpha Thalessemia/Mental retardation X-linked were performed on all patients. Clinical variables such as age, gender, duration of symptoms, and clinical presentation were collected from medical records and tabulated.

**Results:** Total 50 cases of glioma were studied. The expression of IDH1 wild type was observed in 30 (60%) cases, which was more common than IDH1 mutation observed in 20 (40%) cases. The mean age in the study was 41.9 years, with a majority of male patients 33 (66%). IDH1 mutation was commonly observed in diffuse fibrillary astrocytomas (34%) followed by 12% of cases in anaplastic Astrocytomas. Glioblastoma was the most common histopathological diagnosis in 40% of cases, but the observed IDH mutation was least frequent in glioblastomas. Out of the 20 glioblastoma cases, only one tested positive for IDH mutation. In contrast, ATRX loss was predominantly seen in glioblastomas, with three out of the five positive cases. IDH1 mutation was more common in adults than in children, and a female preponderance (60%) was noted. ATRX mutation was observed in only 10% of cases.

**Conclusion:** The IDH1 and ATRX are reliable prognostic markers, and their analysis through immunohistochemistry provides a practical and dependable method for categorising gliomas compared to molecular analysis, thus assisting clinicians in achieving promising treatment outcomes.


**Keywords:** Immunohistochemistry, Mutant, Prognostic, Wild type

## INTRODUCTION

The World Health Organisation (WHO) established a morphology-based classification of Central Nervous System (CNS) tumours in 1979, which was subsequently revised in 1993, 2000, 2007, and 2016 [1]. The 2016 [2] and the latest 2021 [3] WHO classifications have incorporated molecular parameters as crucial factors for diagnosis, as well as for their prognostic significance. Gliomas, which primarily belong to the astrocytic or oligodendroglial variety, are the most common CNS tumours in both children and adults, with a global annual prevalence rate of 3.5 million [4].

Gliomas pose significant diagnostic challenges due to their variable histology and differentiation features. Therefore, advancements in Immunohistochemistry (IHC) and biomarkers play a crucial role in their diagnosis [5]. IHC is a widely available, efficient, and affordable method that was first described by Coons et al., in 1941 [5]. The presence of Isocitrate Dehydrogenase (IDH) mutations is commonly observed in gliomas. The latest WHO classification reclassifies diffuse astrocytomas (WHO Grade 2) and anaplastic astrocytomas (WHO Grade 3) into IDH mutant, IDH wild type, and Nitric Oxide Synthases (NOS) variants. Glioblastoma (WHO Grade 4) is reclassified into glioblastoma IDH mutant and glioblastoma NOS [6].

IDH mutations are found in three distinct isoforms: IDH1, IDH2, and IDH3. These mutations are clustered at codon 132 of the IDH1 gene and codon 172 of the IDH2 gene, leading to the production of mutated IDH protein and elevated levels of D2 Hydroxyglutarate, an oncometabolite, which contributes to gliomatogenesis [6]. The presence of IDH1 mutation is associated with a better prognosis in gliomas of all grades [4]. IDH1 mutation is observed in the majority of low-grade gliomas (70-80%) and a subset of patients with glioblastoma (12%) [7]. ATRX mutation, depicted as loss of ATRX expression on IHC staining, is more commonly found in Grade II and Grade III gliomas and rarely in glioblastomas. The molecular classification of diffuse gliomas is based on ATRX status, along with IDH1/IDH2 mutation and 1p/19q co-deletion. Since 1p/19q co-deletion and ATRX mutation are mutually exclusive, testing for IDH1 and ATRX status is necessary for all glioma cases [5].

Although Deoxyribonucleic Acid (DNA) sequencing for IDH and ATRX mutations is considered the gold standard, IHC serves as a practical alternative method with high sensitivity and specificity [6]. The present research aims to molecularly subtype gliomas using immunohistochemistry for IDH1 and ATRX mutations, which is useful for prognostic stratification in clinical practice.

## MATERIALS AND METHODS

The present cross-sectional study was conducted at a single centre, specifically the Department of Neurosurgery at ESIC Medical College and Super Speciality Hospital in Hyderabad, Telangana, India. The study included 50 patients who underwent surgery between June 2018 and June 2023. Institutional Ethical Clearance was obtained in accordance with the protocol, with the IEC number being ESIC MC/SNR/IEC-F512/03-2023.

**Inclusion criteria:** The inclusion criteria consisted of all cases of gliomas (Grade 1 to 4) according to the WHO 2021 classification, confirmed through histopathological analysis, along with relevant clinical data obtained from hospital records. All age groups were included in the study.

**Exclusion criteria:** Inadequate tumour tissue in the paraffin blocks and incomplete clinical data were the exclusion criteria.

### Study Procedure

**Immunohistochemical analysis:** Paraffin blocks from 50 glioma cases were retrieved from the pathology department's archives. Three representative sections were cut from each paraffin block using a microtome at a thickness of 5 microns. One section was stained with Haematoxylin and Eosin (H&E) for histopathological analysis and confirmation of diagnosis according to the latest WHO 2016 classification. Another section was used for immunohistochemical analysis of IDH1-R132H protein using the Dianova kit from Hamburg, Germany, with the H09 (mouse monoclonal) ready-to-use clone of IDH1 antibody. The third section was used to analyse ATRX using the Bio SB kit with the BSB-108 clone of ATRX antibody. All tests were performed using the fully automated Ventana Benchmark GX machine.

The expression of IDH mutation was determined by the presence of positively stained tumour cells (cytoplasmic and perinuclear). Positivity was defined as specimens showing >=10% stained cells. Endothelial cells served as negative controls. Similarly, ATRX expression was analysed based on positive staining in >=10% of tumour cells [4]. Since ATRX loss indicates the presence of a mutation, the term "ATRX retained" was used to describe positive staining of ATRX on IHC in the present study. Non tumour cells such as endothelial cells and cortical neurons served as positive internal controls. Clinical variables such as age, gender, duration of symptoms, and clinical presentation were collected from medical records.

## STATISTICAL ANALYSIS

Charts and tables were prepared using Microsoft Excel. The mean (±Standard Deviation, SD) was calculated for normally distributed continuous variables. Percentages were used to represent categorical data.

## RESULTS

A total of 50 glioma cases were analysed for IDH1 and ATRX, along with clinicopathologic variables. In the present study, 33 (66%) were male patients, and 17 (34%) were female patients. A male preponderance was noted with a male-to-female ratio of 1.94. The mean age of the patients was 41.9 years, ranging from 45 days to 70 years. Five patients were in the paediatric age group (less than 18 years) [Table/Fig-1].

| Age group (years) | No. of patients |
|---|---|
| 0-18 | 5 |
| 19-30 | 6 |
| 31-40 | 11 |
| 41-50 | 13 |
| 51-60 | 8 |
| 61-70 | 7 |

**[Table/Fig-1]:** Age-wise distribution of patients.

The duration of symptoms before admission ranged from less than one month in 10 patients (20%), 1-6 months in 22 patients (44%), and more than 6 months in 18 patients (36%). The most common clinical presentation was headache (84% of patients), followed by seizures (56% of patients) and motor deficit (24% of patients).

In terms of histopathology, the most common diagnosis was glioblastoma (WHO Grade 4) in 40% of cases (20 cases), followed by diffuse fibrillary astrocytoma (WHO Grade 2) in 34% of cases (17 cases), anaplastic astrocytoma (WHO Grade 3) in 12% of cases (6 cases), pilocytic astrocytoma (WHO Grade 1) in 6% of cases (3 cases), oligoastrocytoma (WHO Grade 2) in 6% of cases (3 cases), and gemistocytic astrocytoma in 2% of cases (1 case) [Table/Fig-2].

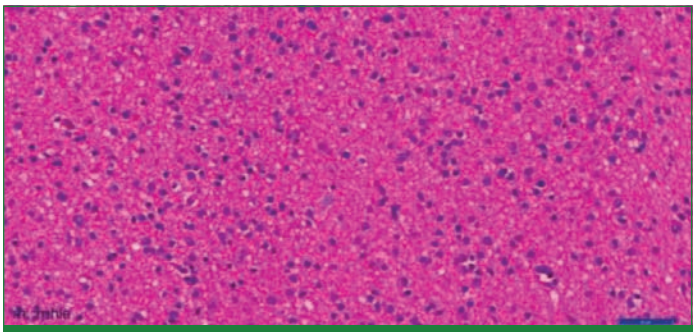
| Clinicopathological variables | n (%) |
|---|---|
| **Gender** | |
| Male | 33 (66.00) |
| Female | 17 (34.00) |
| **Age (years)** | |
| Median (average) | 23 (46) |
| **Tumour site** | |
| Right-side hemisphere | 22 (44.00) |
| Left-side hemisphere | 28 (56.00) |
| **Duration of symptoms** | |
| Less than 1 month | 10 (20.00) |
| 1-6 months | 22 (44.00) |
| More than six months | 18 (36.00) |
| **Clinical presentation** | |
| Headache | 42 (84;00) |
| Seizures | 28 (56) |
| Motor deficit | 12 (24) |
| **WHO grades** | |
| Grade-I | 3 (6.00) |
| Grade-II | 21 (42.00) |
| Grade-III | 6 (12.00) |
| Grade-IV | 20 (40.00) |
| **Histologic type** | |
| Pilocytic astrocytoma | 3 (6.00) |
| Diffuse astrocytoma | 17 (34.00) |
| Gemistocytic astrocytoma | 1 (2.00) |
| Oligoastrocytoma | 3 (6.00) |
| Anaplastic astrocytoma | 6 (12.00) |
| Glioblastoma | 20 (40.00) |
| **IDH expression** | |
| Positive (IDH mutant) | 20 (40.00) |
| Negative (IDH wild type) | 30 (60.00) |
| **ATRX expression** | |
| Positive (retained) | 45 (90.00) |
| Loss (presence of mutation) | 5 (10.00) |

**[Table/Fig-2]:** Clinicopathological characteristics of the studied cohort.

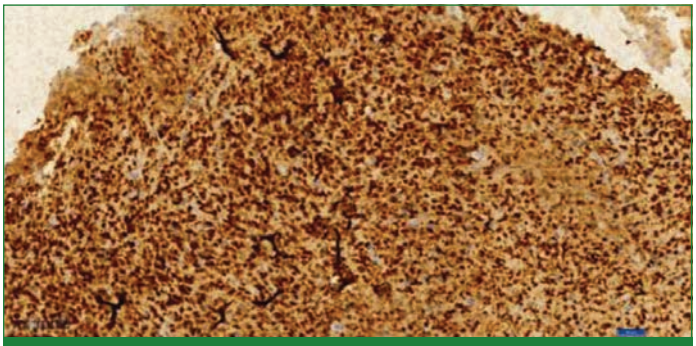
The IDH1 mutation was found in 20 (40%) patients, while 30 (60%) patients were diagnosed as IDH1 wild type. The expression of IDH1 was significantly higher in adults compared to children. Similarly, IDH1 mutation expression was higher in females (60%) compared to males. The ATRX mutation (ATRX loss) was found in 5 (10%) patients. When comparing the relation of the IDH1 marker with histopathological grade, IDH1 expression was observed in 20 cases, with diffuse fibrillary astrocytoma being the most common in 12 (60%) cases, followed by anaplastic astrocytoma in 5 cases (25%), oligoastrocytoma (2 cases, 10%), and glioblastoma 1 (5%). Similarly, ATRX loss was observed mostly in glioblastoma followed

by diffuse fibrillary astrocytoma. Of the five cases that showed ATRX loss, three were glioblastomas, one was diffuse astrocytoma, and one was anaplastic astrocytoma. ATRX was significantly retained in all cases of pilocytic astrocytoma, oligoastrocytoma, and ependymomas.

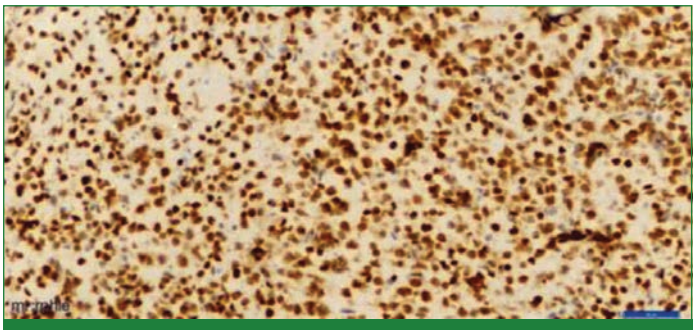
[Table/Fig-3] shows histopathological images of diffuse Astrocytoma with diffusely infiltrating tumour cells with oval to elongated astrocytic nuclei with IDH positivity [Table/Fig-4] and ATRX retained [Table/Fig-5]. Anaplastic astrocytoma shows hypercellularity with higher nuclear grade and atypia [Table/Fig-6] but IDH is positive [Table/Fig-7] and ATRX is also retained [Table/Fig-8].



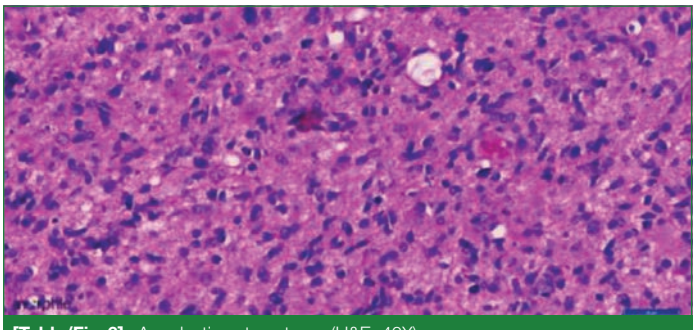
**[Table/Fig-3]:** Diffuse astrocytoma (H&E, 40X).



**[Table/Fig-4]:** Diffuse astrocytoma IDH positive (IHC, 40X).

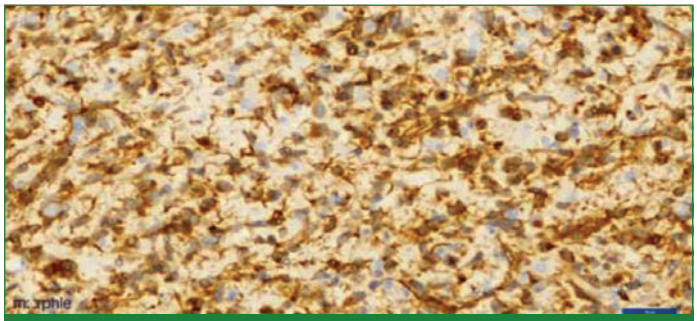


**[Table/Fig-5]:** Diffuse astrocytoma ATRX (IHC, 40X).

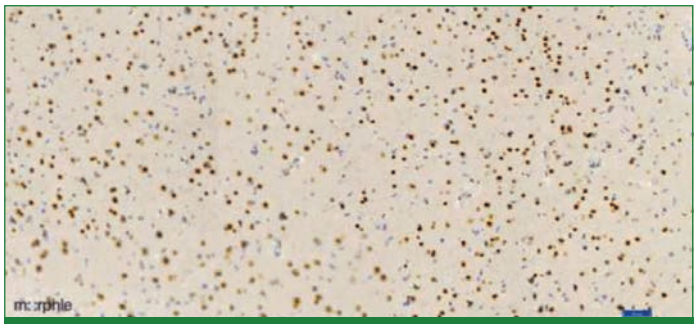


**[Table/Fig-6]:** Anaplastic astrocytoma (H&E, 40X).

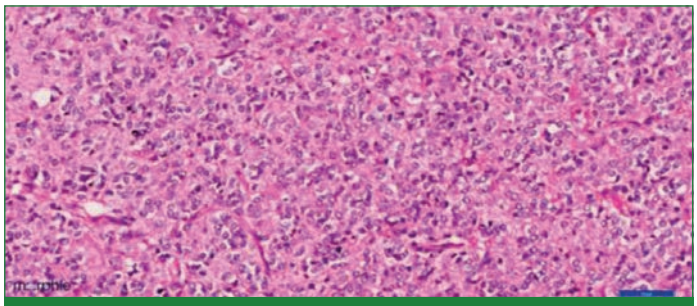
Histopathological images were provided for diffuse astrocytoma, anaplastic astrocytoma, oligoastrocytoma. In oligoastrocytoma there is cellular tumour with diffuse admixture of oligodendrocytes and fibrillary astrocytes [Table/Fig-9] also, both IDH [Table/Fig-10] and ATRX [Table/Fig-11] are positive. In contrast in glioblastomas, there is infiltrating hypercellular neoplasm with hyperchromatic elongated nuclei and microvascular proliferation [Table/Fig-12,13], where ATRX is retained [Table/Fig-14,15] but IDH stained negative [Table/Fig-16].



**[Table/Fig-7]:** Anaplastic astrocytoma IDH positive (IHC, 40X).

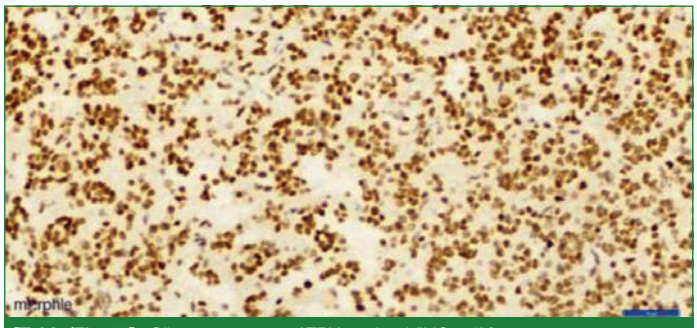


**[Table/Fig-8]:** Anaplastic astrocytoma ATRX retained (IHC, 40X).



**[Table/Fig-9]:** Oligoastrocytoma (H&E, 40X).

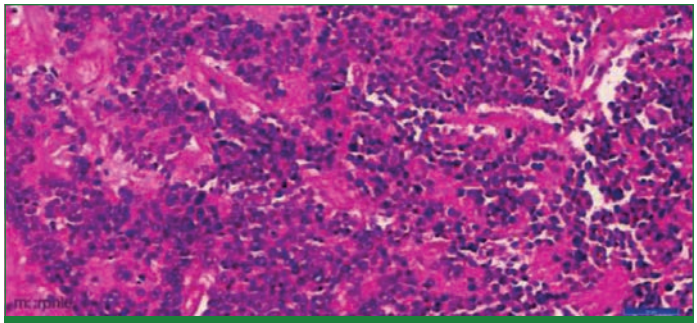
**[Table/Fig-10]:** Oligoastrocytoma IDH positive (IHC, 40X).



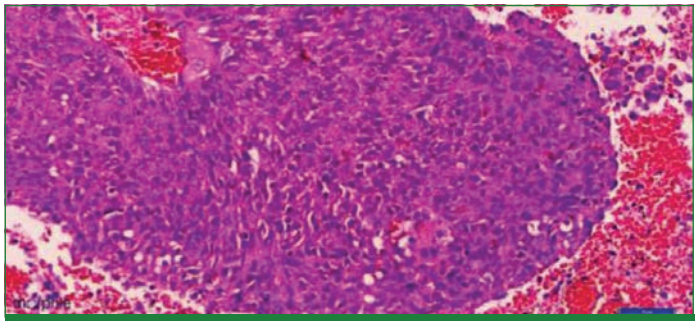
**[Table/Fig-11]:** Oligoastrocytoma ATRX retained (IHC, 40X).

## DISCUSSION

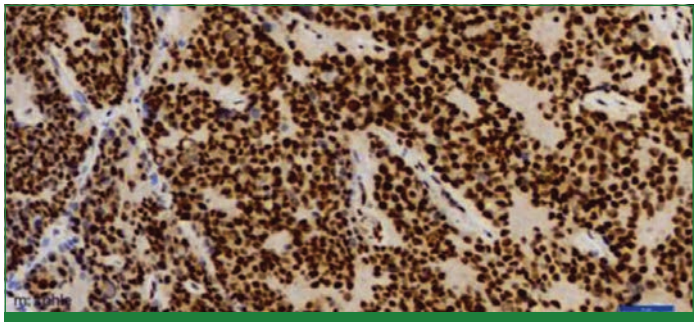
The discussion section provides a comprehensive analysis of the study's findings, comparing them to previous studies and discussing the significance of IDH1 and ATRX mutations in glioma.



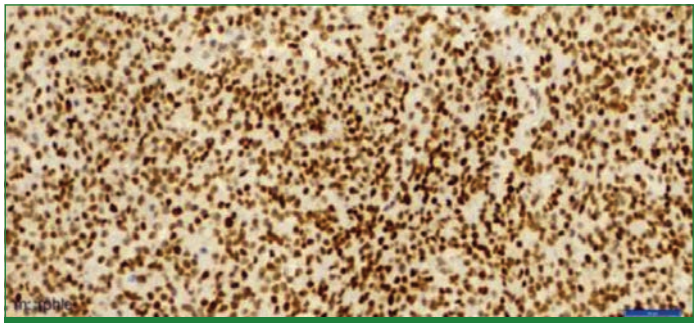
**[Table/Fig-12]:** Glioblastoma multiforme (H&E, 40X).



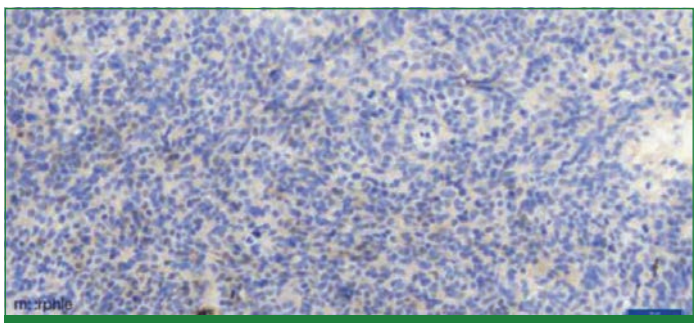
**[Table/Fig-13]:** Glioblastoma multiforme (H&E, 40X).



**[Table/Fig-14]:** Glioblastoma multiforme ATRX retained (IHC, 40X).



**[Table/Fig-15]:** Glioblastoma multiforme ATRX retained (IHC, 40X).



**[Table/Fig-16]:** Glioblastoma multiforme IDH negative (IHC, 40X).

One important point discussed is the molecular classification of glioma according to the latest WHO amendments. This gives better diagnostic and prognostic outcomes clinically and paves the pathway for molecular target therapy as the primary treatment option for gliomas [8-10].

Apart from the molecular subtyping, the assessment of mitotic counts has been changed in the latest WHO edition from number of mitoses per High Power Field (hpf) to a defined area in $mm^2$ (requiring adjustments to individual microscopes). Even though Ki 67 (MIB 1) proliferative index significantly increases with tumour grade, no cut-off value to reliably identify patients with increased risk of recurrence has been established. Differences in techniques and determination make it problematic to establish reliable cut-off values [11].

The discussion also delves into the role of IDH mutations in gliomagenesis. Mutations in the IDH1 gene lead to a decrease in alpha ketoglutarate production and an increase in D-2 hydroxyglutarate is increased. This D2-Hydroxyglutarate (D2HG) is the main cause of gliomagenesis [10]. D2 HG is also known to stimulate Vascular Endothelial Growth Factor (VEGF), which in turn promotes angiogenesis and tumour growth [12-13].

The IDHI mutations decrease immunity and anti-tumour response in patients with gliomas. The IDH mutation is followed by epigenetic remodelling leading to occurrence of lineage specific alterations like 1p/19q deletion and ATRX mutation. Furthermore tertiary alterations like activation of tyrosine kinase receptors and mutations in intracellular signalling pathways may cause the tumour to progress to higher grade [14-16]. Apart from mutations in IDH, ATRX mutation is another potent biomarker. ATRX loss causes changes in the genome and the resultant Deoxyribonuleic Acid (DNA) damage affects the outcomes of glioma patients [17].

The study's findings regarding the histopathological diagnosis of glioma align with previous studies. Glioblastoma was the most common diagnosis, followed by anaplastic astrocytoma and diffuse astrocytoma. The expression of IDH1 was positive in 40% of cases in the present study similar to that reported by Liu HQ et al., [18]. Priambada D et al., observed a positive expression of IDH1 in 76.1% of cases [4], Singh A et al., reported a 38.7% positivity, Dahuja G et al., 54% and Ayad E et al., 46.67%, Louis NJ et al., 57.1% in their studies [1,5-7].

The IDH mutation was most commonly associated with grade 2 astrocytoma and least common in glioblastoma. This is similar to that reported by Ayad E et al., and Mellai M et al., [6,19]. Mellai M et al., reported that in adult patients, IDH 1 mutations are significantly and inversely associated with the histologic grade [19].

The correlation between IDH1 expression and age was explored, with the study finding no significant correlation in adults. This is in line with some previous studies, while others have reported different findings. The study also noted that IDH1 expression was higher in adults (53%) [16]. Wang PF et al., reported that patients carrying IDH 1 mutation were younger than the patients without the mutation [20]. However, the difference was not statistically significant. Whereas in the study by Shaban ZM et al., IDH 1 expression was predominantly seen in young and middle ages (20-40 years) and was statistically significant [21].

The ATRX loss was observed in only 10% of patients, and no significant correlation was found with age or sex, which is consistent with findings from Singh A et al., and Ikemura M et al., [1,22]. Ikemura M et al., reported that glioblastoma cases with ATRX loss were younger than those with ATRX retained tumours [22]. Singh A et al., also reported a similar finding [1]. In contrast to the study by Dahuja G et al., ATRX loss was mostly observed in glioblastomas. Dahuja G et al., found ATRX loss in 73.6% of diffuse astrocytomas and 64.2% of anaplastic astrocytomas [5].

Singh A et al., showed an increase in the prevalence of ATRX loss from low grade to high grade (grades I to IV). In grade IV gliomas, the prevalence of ATRX loss further increased to 66.6%. Additionally, IDH mutation was more common in astrocytic tumours with ATRX retained (90%) compared to those expressing ATRX loss, which aligns with the findings of Singh A et al., who also reported that IDH1 mutation was more common in astrocytic tumours with ATRX retained (60%) compared to those expressing ATRX loss (50%). It is

widely accepted that IDH mutation plays a role in the prognosis of gliomas, with mutated IDH1 gliomas showing longer overall survival. Studies have also demonstrated that loss of ATRX in grade II and III IDH-mutated tumours leads to a better prognosis [1].

### Limitation(s)

Cytogenetic studies were not conducted due to limited financial resources. Several prognostic factors, such as tumour size before surgery, metastatic disease, details of radiotherapy or chemotherapy, and data on co-morbid conditions, were not included in the present study. Another limitation is that the cohort was obtained from a single centre, and the sample size was limited. However, it should be noted that IDH1 and ATRX mutation testing is routinely performed for all glioma cases in our institute.

## CONCLUSION(S)

The molecular characterisation of gliomas using immunohistochemical markers such as IDH and ATRX reduces the need for expensive investigations. In our study, IDH expression was most commonly observed in diffuse astrocytomas, indicating its involvement in early gliomagenesis. Furthermore, when combined with ATRX analysis, these markers serve as reliable prognostic indicators for gliomas and open the door for clinicians to explore newer treatment strategies using IDH inhibitors. It is recommended to validate the current results by applying molecular analysis to a larger sample size.

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