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IMMUNOHISTOCHEMICAL ANALYSIS OF IDH1, p53 AND ATRX IN DIFFUSE GLIOMAS AND THEIR CORRELATION WITH CLINICAL AND HISTOLOGICAL PARAMETERS.

Pathology

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ABSTRACT

Background: Diffuse gliomas account for more than half of all central nervous system (CNS) tumours. The 2016 WHO update of CNS neoplasms incorporates histomorphological as well as molecular features of diffuse gliomas for their categorization. The present study aimed to evaluate the immunohistochemical expression of IDH1, p53 and ATRX mutations in diffuse gliomas and to correlate their expression with clinical and histological parameters. **Methods:** All adult patients diagnosed as Diffuse glioma (WHO grade II-IV) over the period of January 2015 to January 2020 were included in the study. Immunohistochemical analysis of IDH1R132H, p53 and ATRX was performed. Various demographic, histological and molecular variables were correlated with clinical outcome and assessed for significant impact, if any. **Results:** Forty-eight cases of Diffuse glioma included in the current study had mean age of 42.2 years with majority of the tumours being Glioblastoma, WHO grade IV (n=30). Overall, IDH1R132H, p53 expression and ATRX loss was observed in 83.3%, 70.8% and 25% cases, respectively. Age at diagnosis (p-value=0.001), WHO histological grades (p-value=0.038), ATRX loss (p-value=0.025) and IDH1 expression with ATRX loss (p-value=0.036) had significantly better clinical outcome in adult diffuse glioma cases. **Conclusion:** IDH and ATRX mutations are commonly seen in diffuse gliomas and are important prognostic markers. It is feasible to detect these mutations by IHC and incorporation of these results in routine histopathology report will help in better prognostication of the patients.

KEYWORDS

Adult diffuse glioma, ATRX, IDH1, p53.

INTRODUCTION

Primary Central nervous system (CNS) cancers are an important cause of mortality and morbidity worldwide, with a reported annual incidence of over three million cases. According to Global Burden of Disease, Injuries and Risk Factor Study 2016, India ranks amongst the top three countries with highest annual incidence of CNS cancers (1). Diffuse gliomas are the most common histological subtype of primary CNS cancers, and have been traditionally classified based upon their histogenesis and morphology into different subtypes and histological grades (WHO Grade II-IV) with higher grades showing increasing pattern of aggressiveness (2).

The current WHO 2016 classification scheme of CNS tumours incorporates molecular profile of the tumour into the morphological classification scheme, not only aiming to attain more objectivity in the classification that was achieved prior to implementation of this scheme, but also to provide better management and more accurate prognostication of tumours which is achieved by grouping together of biologically homogenous group of tumours (3). The WHO 2016 classification schemes recommends determination of Isocitrate Dehydrogenase (IDH) mutation status by Immunohistochemistry (IHC) or by molecular analysis in all cases of diffuse gliomas. IDH is a cytosolic enzyme which acts as a catalyst for oxidative decarboxylation of isocitrate into alpha ketoglutarate and nicotinamide adenine dinucleotide phosphate. Most common mutation in gliomas involves aminoacid 132 of IDH 1 (R132H) which can be detected by molecular studies or by IHC using specific antibody. Mutations of IDH2, which functions in mitochondria, are less common and are noted in R172 amino acid. The mutant IDH converts isocitrate to 2 hydroxyglutarate instead of alpha ketoglutarate and is considered to be the oncometabolite responsible for tumour formation. If IHC result for mutant R132H IDH1 protein is negative, sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations should be done before classifying the case as IDH wildtype (4). IDH 1 and 2 gene mutations occur in approximately eighty percent of Grade II and III oligodendrogliomas and astrocytomas, and in around ten percent of all glioblastomas, corresponding closely to secondary glioblastomas (4). IDH mutant Grade II and Grade III gliomas are known to have better prognosis as compared to IDH wildtype gliomas. Similarly overall survival for secondary glioblastomas which are commonly IDH mutant is significantly better than primary glioblastomas which are more commonly of IDH wildtype (4-6). C-IMPACT (Consortium to Inform molecular and practical approaches to CNS tumor taxonomy) has recommended that IDH wild type grade II or grade III astrocytomas may behave in an aggressive fashion as glioblastomas if they harbor EGFR amplification, or have combined chromosome 7 gain, chromosome 10 loss or TERT promoter mutation and have recommended the use of term Diffuse Astrocytic glioma, IDH wild type with molecular features of glioblastoma, WHO grade IV for such cases (7).

Inactivating mutations of alpha thalassemia/mental retardation syndrome X linked (ATRX) gene in gliomas, manifested as loss of staining of ATRX protein by IHC are associated with telomere dysfunction and other mutations including *IDH1* and TP53, but are mutually exclusive from 1p/19q-codeletion, hence are used as a part of diagnostic algorithm for differentiating astroglial from oligodendroglial lineage if facility for cytogenetic analysis is not available. ATRX loss in IDH mutant gliomas is associated with a better prognosis (8). P53, a tumour suppressor gene is one of the most commonly mutated gene in gliomas with higher reported prevalence of mutations in higher grade of gliomas and different prevalence of mutations in various molecular subtypes of glioblastomas (9). Apart from these, other molecular markers like Phosphatase and Tensin Homolog (PTEN), Cyclin Dependent kinase inhibitor 2A(CDKN2A) and Epidermal growth factor receptor (EGFR) have also been identified with significant roles in the initiation and progression of gliomas (10). The biological behavior of gliomas, like most other malignant neoplasms, is dependent upon complex interplay between various molecular alterations which may also be detected using IHC.

The aim of this study was to evaluate the immunohistochemical expression of IDH1, p53 and ATRX mutations in diffuse gliomas and to correlate the expression of these markers with various clinical and histological parameters. Though many studies on prognostic factors and expression of various molecular markers in gliomas have been conducted in Western world, there is a paucity of studies which have correlated the expression of a combination of markers with patients survival in Indian literature (10,11).

MATERIAL AND METHODS

***Setting And Ethics Statement*:**

This was a cross-sectional study conducted in the Department of Pathology at tertiary care hospital in Central India. The study was approved by the Ethics Committee of the institute for conducting research on human subjects and an informed consent was obtained from all the study participants and/or their first degree relatives.

Case selection:
All those adult patients diagnosed histopathologically with Diffuse Gliomas (Grade II-IV) who underwent surgery between January 2015 and January 2020 constituted our study group. Those consenting participants for whom complete medical history, survival data (at least 6 month follow-up post surgery) and enough formalin fixed paraffin embedded tissues (FFPE) was available in the archived blocks for subsequent IHC analysis were included. Patient's demographic data and clinical details were noted from the clinical records. Archived hematoxylin and eosin (H&E) stained slides were re-evaluated by two trained pathologists for confirmation of diagnosis and tumour grade. A consensus diagnosis was obtained in case of any discrepancy. IHC was performed on representative tissue block using 3-5 micron thick sections on three slides previously coated with poly L-lysine.

IHC procedures:
IHC was performed for IDH, p53 and ATRX according to manufacturer's protocol using VENTANA Benchmark ULTRA (automated immunohistochemical slide staining system, Roche Diagnostics, Tucson, Arizona, USA), using primary antibodies against IDH1 (IDH1 R132H, Mouse monoclonal antibody, H09 Lyophilised powder; 1:30 dilution, Dianova, Hamburg, Germany); P53 (p53-BP-53-12, Mouse monoclonal Antibody, PM101 6ml RTU; PathnSitu, Pleasanton, CA); and ATRX (ATRX D5, Mouse monoclonal antibody, PM229 6ml RTU; Pathnsitu, Pleasanton, CA).

Interpretation of IHC:
IHC expression was evaluated by two separate observers and consensus score was agreed upon. IHC expression was determined based upon preset cut-off values. A strong cytoplasmic immunoreactivity for IDH1 in more than 10% tumor cells was considered positive. Nuclear staining was noted for assessing immunoreactivity for p53 and ATRX. For p53, strong nuclear staining in more than 10 percent nuclei was considered positive. For ATRX, loss of nuclear staining in more than 90% of cells was taken as ATRX loss. Cases showing lack of expression in tumor cells along with negative internal control were excluded from further analysis.

Statistical Analysis:
Survival analysis was performed using the Kaplan-Meier estimator and log-rank test to assess the significant association of demographic variables, WHO histological grade of the tumor and results of IHC analysis (P53, IDH1 and ATRX) with overall survival (OS). A p-value <0.05 was taken as significant. All statistical analysis was performed using SPSS Statistics software V22.0.

RESULTS
A total of 73 cases of glioma were diagnosed on histopathology between 2015 and January 2020. Of these, 48 cases satisfying the inclusion criteria were included in the study (Figure 1). The mean age of patients was 42.2 ±15.6 years. Out of 48 cases, 36 (75%) were males and 12 (25%) were females with a male to female ratio of 2.5:1 .The majority of the cases of diffuse glioma in this study were located in the frontal lobe of the brain (19/48 cases). Of the total 48 cases included in the study, 13 cases were diagnosed as WHO Grade II gliomas (27.1%), 05 cases were diagnosed as Anaplastic gliomas, WHO grade III (10.4%) and 30 cases were diagnosed as Glioblastoma, WHO Grade IV (62.5%). Amongst WHO Grade II gliomas, twelve cases were diagnosed as astrocytomas and one case as oligodendroglioma. Amongst WHO grade III gliomas, 4 cases were diagnosed as Anaplastic oligodendrogliomas and one case as Anaplastic astrocytoma.

Immunohistochemical profile Table 1 depicts IHC expression of IDH1, p53 and ATRX in different histological grades of gliomas. IDH1 expression was detected in 84.6% Grade II gliomas (11/13 cases), 100% Anaplastic gliomas (5/5 cases) and 80% of GBM (24/30 cases). P53 expression was detected in 69.2% of WHO Grade II gliomas (9/13 cases), 60.0% of Anaplastic gliomas, WHO grade III (3/5 cases) and 73.3% of GBM (22/30 cases). Loss of ATRX expression was observed in 38.5% of Grade II glioma (5/13 cases), 40% of Grade III gliomas (2/5 cases) and in 16.7% GBM cases (5/30 cases).

The histomorphological and immunohistochemical features are depicted in Figure 2 A-O. The mean age of gliomas showing immunoexpression for IDH-1, p53 mutation or ATRX loss was less as compared to those gliomas showing negative immunoexpression for IDH-1 and p53 or showing ATRX retention (41.2 and 47.1 years for gliomas positive and negative for IDH-1 immunoexpression, 39.7 years and 43.3 years for those with or without p53 immunoexpression, 37.1 and 44.1 for those with ATRX loss and retention respectively) .

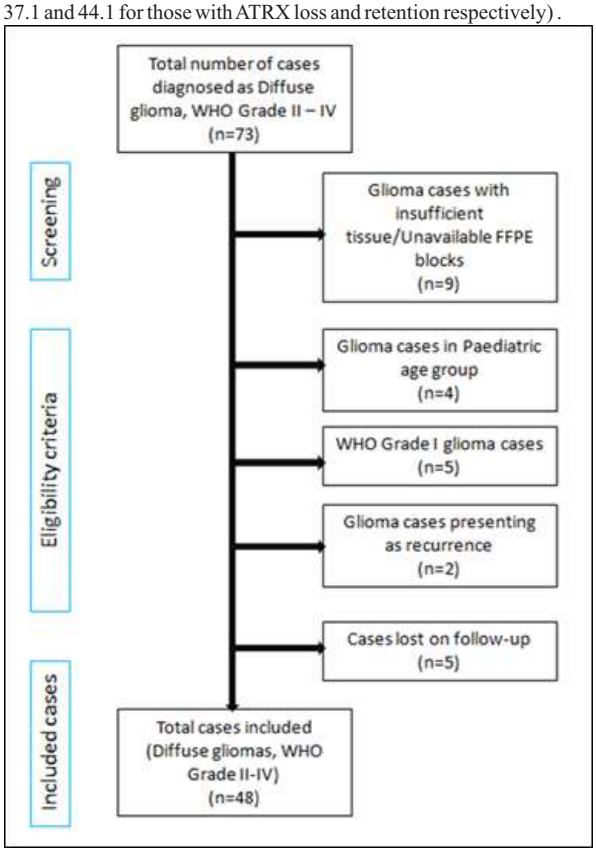

Figure 1: Case Selection Criteria.

Table 1: Expressions of IDH1, p53 and ATRX in different grades of Diffuse glioma

Diffuse gliomas	Total number of cases	IDH1 expression	P53 expression	ATRX loss
WHO Grade II	13	11 (84.6%)	9 (69.2%)	5 (38.5%)
WHO Grade III	05	5 (100%)	3 (60%)	2 (40%)
WHO Grade IV	30	24 (80%)	22 (73.3%)	5 (16.7%)
Overall	48	83% cases	70.8% cases	25% cases

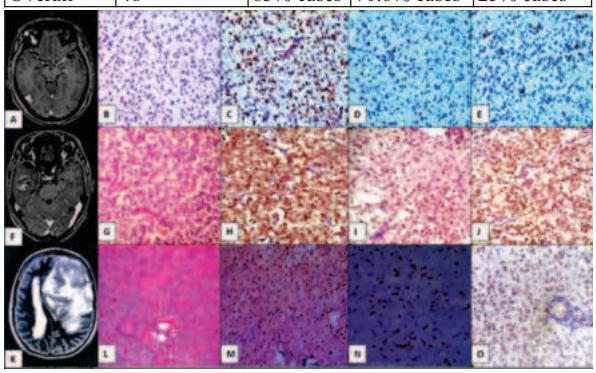

Figure 2: A to E) Diffuse Astrocytoma, WHO grade II: Radiological presentation, Histomorphology (H&E stain, X400), IDH1 IHC (X400), P53 IHC (X400) and ATRX IHC (X400); F to J) Anaplastic Oligodendroglioma, WHO grade III: Radiological presentation, Histomorphology (H&E stain, X400), IDH1 IHC (X400), P53 IHC (X400) and ATRX IHC (X400); and K to O) Glioblastoma, WHO grade IV: Radiological presentation, Histomorphology (H&E stain, X100), IDH1 IHC (X100), P53 IHC (X400) and ATRX IHC (X400).

Survival status A total of seventeen deaths were recorded, in 14/36 males and 3/12 females, however, the difference in OS between males

and females was not found to be statistically significant (p-value =0.387). On performing survival analysis, significance was established between WHO histological grades and OS (p value =0.038)(Table 4) Also, on comparing survival pattern of cases included in Low grade glioma (Grade II) with those of High grade glioma (Grade III and IV), it was seen that former had significantly better survival than latter group (p value = 0.014). However, comparison of survival pattern between WHO grade III and WHO Grade IV glioma cases did not yield any significance (p-value = 0.354). OS pattern according to expression of individual molecular marker was also assessed. In isolation, IDH1 expression and p53 expression did not show any significant impact on OS of patients. However, ATRX loss was associated with better OS (p-value= 0.025) (Table 2). No statistically significant difference in OS was obtained while using the various combinations of all these three markers (p-value =0.367) (Table 4). Statistically significant OS (p-value = 0.036) was obtained amongst patients with IDH1 expression and ATRX loss group (mean OS=51.04 months) as opposed to IDH1 expression with ATRX retained group (mean OS=25.58 months) (Table 3 and Figure 3)

Table 2: Molecular Markers: Mean Overall Survival And Statistical Analysis

Molecular Marker	Status	Mean Overall Survival (months)	P-value
IDH1	Expression	37.38	0.592
	No expression	20.15	
P53	Expression	33.07	0.638
	No expression	33.66	
ATRX	Retained	25.19	0.025
	Loss	51.38	

Table 3: Clinical, Histological And Immunohistochemical Predictors Of Survival In Diffuse Gliomas

		Mortality status						p-value
		Alive		Dead		Total		
		Count	(%)	Count	(%)	Count	(%)	
Age (mean age in years)		37.7	13.6	53.2	15.2	42.2	15.7	0 .001*
Gender	Male	22	61.2	14	38.8	36	75.0	0.387
	Female	9	75.0	3	25.0	12	25.0	
WHO Histological grade	II	12	38.7	1	5.8	13	27.1	0.0.38*
	III	4	12.9	1	5.8	5	10.4	
	IV	15	48.4	15	88.4	30	62.5	
Histology Grade	Low grade glioma	12	38.7	1	5.8	13	27.1	0.021*
	High grade glioma	19	61.3	16	94.2	35	72.9	
IDH1	No expression	5	16.1	3	17.6	8	16.7	0.592
	Expression	26	83.9	14	82.4	40	83.3	
P53	No expression	8	25.8	6	35.3	14	29.2	0.638
	Expression	23	74.2	11	64.7	34	70.8	
ATRX	Loss	12	38.7	1	5.8	13	27.1	0.025*
	Retained	19	61.3	16	94.2	35	72.9	
IDH1 and ATRX expression	IDH1 expression with ATRX loss	11	42.3	1	7.2	12	30	0.036*
	IDH1 expression with ATRX retained	15	57.7	13	92.8	28	70	
Molecular groups	IDH1 expression, p53 no expression and ATRX retained	3	9.7	5	29.4	8	16.6	0.367
	IDH1 no expression, p53 expression and ATRX retained	3	9.7	2	11.8	5	10.4	
	IDH1 expression, p53 expression and ATRX loss	7	22.5	1	5.8	8	16.6	
	IDH1 expression, p53 expression and ATRX retained	12	38.8	8	47.2	20	41.7	
	IDH1 expression, p53 no expression and ATRX loss	4	12.9	0	0.0	4	8.4	
	IDH1 no expression, p53 no expression and ATRX retained	1	3.2	1	5.8	2	4.2	
	IDH1 no expression, p53 no expression and ATRX loss	1	3.2	0	0.0	1	2.1	

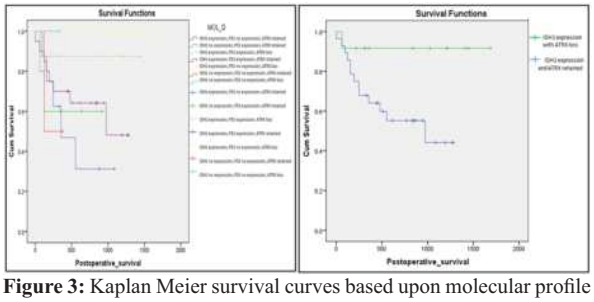

Figure 3: Kaplan Meier survival curves based upon molecular profile of diffuse gliomas: Left: Molecular groups using combination of three markers; Right: Between molecular groups with IDH1 expression with or without ATRX loss. Cum survival: Cumulative survival.

DISCUSSION

The revised 2016 WHO classification for CNS neoplasms stratifies these neoplasms based upon their histological features and molecular expressions of IDH1 and 1p/19q co-deletion status. Gliomas harboring IDH mutation or ATRX loss are likely to have improved survival outcomes (12,13). In the current study, we evaluated the immunohistochemical expression of IDH-1,p53 and ATRX in diffuse gliomas and correlated the expression of these markers and other clinical and histological parameters with survival outcome. Like other published studies in literature (14-16), age at diagnosis and histological grade of the tumor emerged as good prognostic factors for overall survival (p value=0.001 and 0.038 respectively). Significant prolongation of overall survival was seen in patients having ATRX expression loss (p-value =0.025) as well as in cases with concurrent IDH1 expression with ATRX loss (p-value =0.036). Though the mean overall survival was more in patients exhibiting immunoexpression for IDH-1, the difference was not statistically significant.

IDH1 immunoexpression was seen in 84.6%, 100% and 80% of WHO grade II, grade III and grade IV gliomas respectively. The increased expression in Grade II and Grade III gliomas is in concordance with other studies described in literature (17). Previous studies have shown IDH1 mutation to be an independent prognostic marker in Anaplastic gliomas and Glioblastomas (13). Higher IDH positivity (80%) in Grade IV gliomas in the current study may suggest that these cases might have been that of secondary glioblastomas, where IDH mutation is common. A possible supporting evidence for this explanation is that the majority of GBM lesions in the current study were located in the frontal lobe, which has been established as predilection site for secondary GBMs (9). GBMs with increased IDH1 expression had better survival as compared to those with no IDH1 expression but the

difference was not found to be statistically significant. Though previous studies have shown that IHC can reliably detect IDH1 mutations (18), since molecular testing was not performed, this discrepant finding could not be confirmed.

ATRX mutation, manifested as loss of nuclear expression on IHC, is considered as a feature of astrocytic tumours and has been more frequently observed in Grade II and Grade III gliomas than in glioblastomas. In the current study, ATRX loss was observed in 38.5% of Grade II gliomas, 40% of Grade III gliomas and 16.7% of Grade IV gliomas. Most studies have reported higher frequency of ATRX mutations in Grade II and Grade III gliomas and lower frequency in Grade IV gliomas (19). Relatively small sample size of our study can be a possible explanation for this finding. ATRX mutation is considered exclusive of 1p19q codeletion and loss of ATRX expression on IHC is used as a part of diagnostic algorithm to exclude a diagnosis of oligodendroglioma. In the current study, we found loss of ATRX expression in one case which was morphologically diagnosed as Anaplastic Oligodendroglioma. Though around 10% of anaplastic oligodendrogliomas may show ATRX mutation (8),since cytogenetic studies for 1p19q codeletion were not performed, the morphological diagnosis could not be confirmed. Like other studies, ATRX emerged as a good predictor of survival for diffuse gliomas both as an independent marker and also in association with IDH1 in the current study. Previous studies including those by Mukherjee et al. suggested that mutant IDH may work synergistically with ATRX loss and confer a survival advantage in this subset of glioma patients (20).

p53 expression was seen in almost similar frequency across all grades of diffuse gliomas in the current study and no statistically significant difference was observed in survival between the groups with or without P53 immunoexpression. (p-value=0.638). Though the results of a published meta-analysis reported higher immunopositivity for p53 in higher grade tumours and also correlated it with decreased overall survival, no such association was found in the current study(21). p53 with concurrent IDH1 expression was seen in 58.3% of all diffuse glioma cases included in our study. The presence of p53 expression and IDH1 expression as early tumorigenesis events as well as co-expression in same tumour has also been shown by other studies as well (22). However, the exact role of p53 as prognostic marker still needs to be elucidated (21). Though IHC for p53 has often been used as a surrogate marker for detecting p53 mutations, the results need to be interpreted with caution as most monoclonal antibodies directed against p53 protein detect both mutant as well as wild type p53 protein. Though wild type p53 protein has much shorter half-life and the resultant nuclear staining is not intense, increased accumulation of wild type protein under conditions of cellular stress can lead to errors in interpretation. False negative results on IHC can also be seen in cases of nonsense mutations of p53 gene (23).

We correlated the expression pattern of these three markers in various combinations for survival outcome, however except for IDH+/ATRX loss group which had a statistically significant survival benefit, no other molecular group showed a significant impact on survival. IDH+/ATRX loss molecular subgroup was shown to have a better survival in glioblastomas in a study conducted by Chaurasiya et al as well (9). Significant difference in survival outcomes in different histomolecular groups of anaplastic gliomas was also reported by Rajmohan et al, however in the current study no significant difference in survival was noted within the seven molecular groups classified on the basis of expression pattern of all the three markers (14).

The limitations of the current study include small sample size, inadvertent selection bias in the cross-sectional study design and lack of molecular and cytogenetic analysis which might have influenced our results. Our study also has several strengths. The present study is an attempt to classify and prognosticate diffuse gliomas on the basis of IHC expression of IDH, p53 and ATRX at a newly established tertiary care centre in Central India. Though molecular analysis is often not possible in resource constrained settings, classifying CNS tumors according to recent WHO classification scheme is still feasible using IHC studies. This study has also generated evidence in Indian literature regarding prognostic significance of IDH+/ATRX loss group as a distinct molecular group of diffuse gliomas with better survival.

To conclude, IDH and ATRX mutations are commonly seen in diffuse gliomas and along with histological grade are important prognostic markers. Since these mutations can be detected by IHC analysis, it is possible to classify gliomas into various histomolecular groups during routine reporting. This shall facilitate better prognostication of these patients. Future prospective studies with larger sample size and incorporation of molecular and cytogenetic analysis are required to validate the findings from this study, to delineate pattern of molecular alterations, and to deduce their significance and scope in targeted therapy development.

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