

Study of Histomolecular Classification of Glioma- Integrating Histology and Molecular Analysis in the Diagnosis of Brain Tumors

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Abstract

Introduction The updated 2016 classification of gliomas incorporates well-established molecular parameters into the classification of diffuse gliomas, taking into account isocitrate dehydrogenase 1 (IDH1) mutation, α -thalassemia/mental retardation syndrome X-linked (ATRX) loss, and 1p/19q co-deletion.

Aim and Objectives To study IDH1 and ATRX mutations in gliomas, 1p/19q co-deletion by fluorescent in situ hybridization (FISH) in oligodendroglioma, and to correlate IDH1, ATRX, and 1p/19q with tumor type and grade.

Material and Methods Total 73 cases of gliomas were diagnosed on histology and graded as astrocytoma (grades 2–4), oligodendroglioma (grades 2–3), and oligoastrocytoma (grades 2–3) by two pathologists independently. IDH mutation and ATRX expression were analyzed using immunohistochemistry in all cases whereas 1p/19q co-deletion was studied using FISH in cases with oligodendroglioma and oligoastrocytoma morphology.

Results Total 48 cases of astrocytoma, 9 cases of oligoastrocytoma, and 16 cases of oligodendroglioma were included. The maximum number of IDH1 mutation cases were seen in diffuse astrocytoma (7/10; 70%) as compared with anaplastic astrocytoma (5/15; 33.33%), glioblastoma multiforme (GBM) (3/23; 13.04%) grade II oligoastrocytoma (3/6; 50%), anaplastic oligoastrocytoma (2/3; 66.67%), and oligodendroglioma grade II (7/10; 70%). ATRX loss was seen in diffuse astrocytoma grade II (6/10; 60%), anaplastic astrocytoma (6/15; 40%), oligoastrocytoma grade II (2/6; 33.33%), and anaplastic oligoastrocytoma (1/3; 33.33%). 1p/19q co-deletion was seen in oligoastrocytoma (2/2; 100%), anaplastic oligoastrocytoma (1/2; 50%), oligodendroglioma (3/4; 75%), and anaplastic oligodendroglioma (1/3; 33.33%). Six of the seven cases with 1p/19q co-deletion also showed IDH1 mutation. One of seven 1p/19q co-deleted cases had loss of expression of ATRX.

Conclusion Incorporation of IDH1 mutation, ATRX loss, and 1p/19q co-deletion molecular studies help in a more accurate diagnosis and classification of gliomas.

Keywords

- ▶ ATRX loss
- ▶ IDH1 mutation
- ▶ 1p/19q co-deletion

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Introduction

Primary tumors of the central nervous system represent approximately 2% of all cancers diagnosed in the United States. They affect 4.95 to 8.97 of every 100,000 people in the United States every year and represent approximately 4% of all U.S. cancer deaths.¹ The incidence of brain tumors in India ranges from 5 to 10 patients per 100,000 population.²

Gliomas are the most common primary brain tumors that comprise a very heterogeneous group of neoplasms.¹ The 2007 World Health Organization (WHO) classification classified gliomas based on the morphologic appearance, though the clinical course, response to treatment, and molecular profiling indicate distinct entities. The prognosis of gliomas is based almost entirely on the grade rather than the stage, but there has been substantial variation in patient outcome within the tumor grade and within the tumor entity leading to investigation of molecular factors, which might help explain the variation in prognosis.

There are multiple studies done on molecular markers that are seen in gliomas. Based on these studies, there has been definite evidence that these mutations help in refining the subgroups of gliomas regarding prognosis and response to therapy. The most common markers in relation to these tumors are mutations in isocitrate dehydrogenase 1 (IDH1), mutations in critical chromatin modifier α -thalassemia/mental retardation syndrome X-linked (ATRX), 1p/19q co-deletion, and methyl guanine methyl transferase (MGMT) promoter methylation.¹

IDH1 mutation leads to activation of alternate pathway leading to conversion of α -ketoglutarate to 2-hydroxyglutarate that acts as a oncometabolite.^{3,4} It also leads to decreased levels of nicotinamide adenine dinucleotide phosphate (NADPH), an important cofactor required to produce normal levels of glutathione to combat reactive oxygen species (ROS).^{5,6} IDH1 mutations are identified in most low-grade gliomas, suggesting that IDH1 mutations are an early event in gliomagenesis and its identification in both oligodendroglioma and astrocytoma suggests that they have a common cell of origin.⁷

ATRX belongs to the SWI2/SNF2 family of chromatin remodeling proteins. ATRX gene is required for normal telomere homeostasis by regulating incorporation of H3.3 histone. Mutations in ATRX are associated with alternative lengthening of telomeres.^{4,8} Co-deletion of 1p/19q is a well-established prognostic marker in oligodendrogliomas.^{9,10} There has been inactivating mutations in two tumor suppressor genes: CIC (homolog of *Drosophila capicua*) and FUBP1 (far-upstream-binding protein 1). CIC is located on chromosome on 19q and FUBP1 on chromosome 1p.¹¹ The 2016 WHO Classification of Central Nervous System has classified gliomas by incorporating these three important molecular markers IDH1 mutation, ATRX loss, and 1p/19q co-deletion.

To summarize, including the molecular information into the integrated diagnosis of brain tumors will help in redefining the glial tumors. Knowledge of these molecular markers will help in more accurately predicting the prognosis, outcome, and also help improve the treatment of these tumors.¹²

Material and Methods

The study was done for a period of 5 years—4 years retrospective (January 2012 to September 2015) and 1 year prospective (October 2015 to December 2016) in our center. Seventy cases of gliomas diagnosed on histology as astrocytoma (grades 2–4), oligodendroglioma (grades 2–3), and oligoastrocytoma (grades 2–3) were selected. On formalin-fixed, paraffin-embedded (FFPE) tissues, hematoxylin and eosin staining was done. Diagnosis and grade were then assessed by two pathologists (the pathologists reporting the cases had > 10 years' experience in neuro-oncology) independently followed by staining for IDH1 and ATRX on Ventana Benchmark using monoclonal antibody cloneH09 (Dianova) and anti-ATRX (Sigma-Aldrich), respectively.

1p/19q co-deletion detection by fluorescent in situ hybridization (FISH) was done on FFPE section by Vysis LSI 1p36/LSI 1q25 and LSI 19p13/LSI 19q13 dual-colored FISH probe set. IDH1 mutations by immunohistochemistry (IHC) was interpreted as positive when a combined cytoplasmic and perinuclear staining was seen¹³ (► Fig. 1). ATRX mutation was interpreted as positive when there was loss of nuclear immunostaining. Endothelial cells, benign neurons, and infiltrating inflammatory cell,¹⁴ which demonstrate strong nuclear immunostaining, were taken as internal control⁹ (► Fig. 2). 1p/19q co-deletion by FISH was interpreted as positive when the ratio was < 0.8 (► Fig. 3).

The 73 cases studied were analyzed for demographic data. The total number (%) of tumors along with tumor grades was noted. The proportion (%) with IDH1 mutation, ATRX loss, and 1p/19q co-deletion was compared with tumor type and grade (astrocytoma, oligodendroglioma, and oligoastrocytoma) (► Table 1). IDH1 mutation, ATRX loss, and 1p/19q co-deletion in the cases studied were correlated and assessed. Comparison of proportion of cases with (certain)

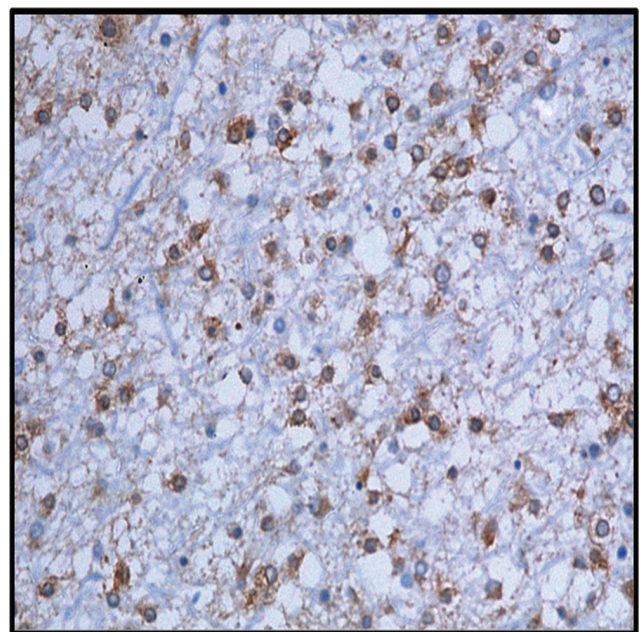


Fig. 1 IDH1 mutation by IHC—diffuse combined cytoplasmic and perinuclear staining.

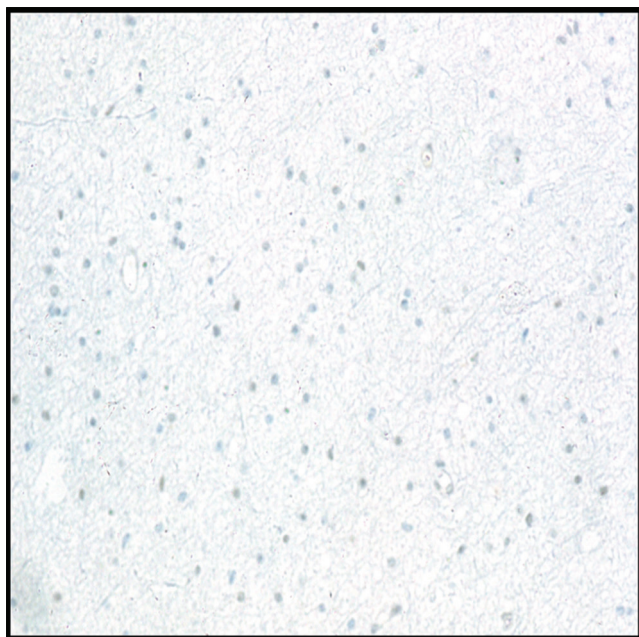


Fig. 2 ATRX loss by IHC—loss of nuclear immunostaining in tumor cells.

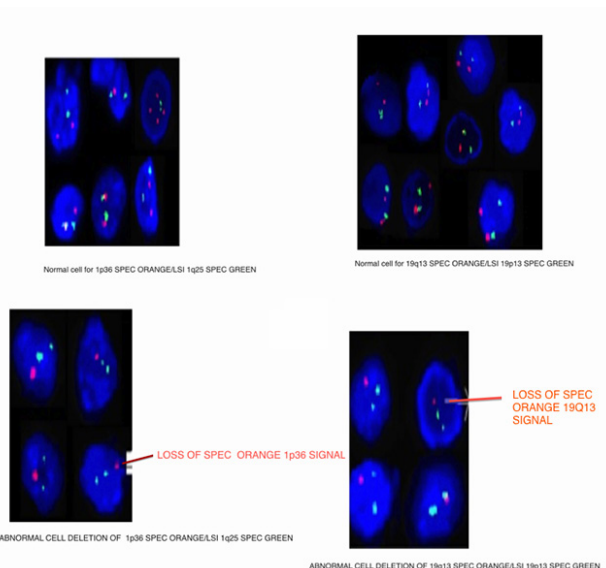


Fig. 3 1p/19q co-deletion by FISH.

Table 1 Proportion of IDH1, ATRX mutation, and 1p/19q co-deletion within tumor type and grade

Sr. No.	Tumor type with grade	IDH1 mutation	p Value	ATRX mutation	p Value	1p/19q co-deletion	p Value
1	Astrocytoma 2	7/10; 70%	0.005	6/10; 60%	< 0.001		
2	AA	5/15; 33.33%		6/15; 40%			
3	GBM	3/23; 13.04%		0/23; 0%			
4	OA	3/6; 50%	0.635	2/6; 33.33%	0.999	2/2; 100%	0.248
5	AOA	2/3; 66.67%		1/3; 33.33%		1/2; 50%	
6	Oligodendroglioma II	7/10; 70%	0.424	1/10; 10%	0.696	3/4; 75%	0.27%
	AO	3/6; 50%		1/6; 16.67%		1/3; 33.33%	

Abbreviations: AA, anaplastic astrocytoma; Ab, antibody; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma; ATRX, α -thalassemia/mental retardation syndrome X-linked; GBM, glioblastoma multiforme; IDH1, isocitrate dehydrogenase 1; OA, oligoastrocytoma.

mutation between tumor grades was done using chi-square and Z-test, regarding $p < 0.05$ as significant.

Results

In this study, total 73 cases were selected and studied. Molecular studies were done for IDH1 mutation, ATRX loss, and 1p/19q co-deletion. Analysis was done using chi-square test and p value recorded.

Demographic Data

The cases included had a wide age group distribution with the minimum being 5 years and maximum being 69 years. Mean age of patients in this study was 41.81 years (standard deviation [SD] = 14.95). An overall male predominance was seen ($n = 51/77$). Of 73 cases, the maximum number of cases were reported as glioblastoma multiforme (GBM, $n = 23$),

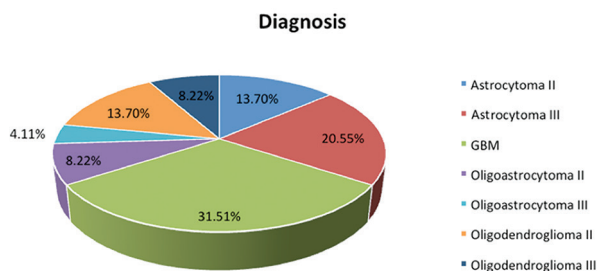


Fig. 4 Pie chart showing distribution of cases according to diagnosis ($n = 73$). GBM, glioblastoma multiforme.

whereas the least number of cases were found to be oligoastrocytoma grade 3 ($n = 3$). Of the 23 cases of GBM, 4 were secondary GBM ($n = 4/23$) (► Fig. 4).

IDH1 Mutation Analysis

Of the 48 cases of astrocytoma analyzed, 15 cases showed IDH1 mutation. The maximum number of IDH1 mutation cases were seen in diffuse astrocytoma (7/10; 70%) as compared with anaplastic astrocytoma (5/15; 33.33%), GBMs (3/23; 13.04%), and the three GBM cases that were positive for IDH1 mutation were secondary GBM ($p = 0.005$). Proportion of IDH1 mutation in other tumor grades were grade 2 oligoastrocytoma (3/6; 50%), anaplastic oligoastrocytoma (2/3; 66.67%), oligodendrogloma grade 2 (7/10; 70%), and oligodendrogloma grade 3 (3/6; 50%).

ATRX Mutation Analysis

Of 48 cases, 12 cases showed ATRX loss. The highest number of ATRX loss were seen in astrocytoma grade 2 ($n = 6/10$) whereas none of the GBM showed ATRX loss of expression ($p < 0.001$). ATRX loss in the other tumor grades were diffuse astrocytoma grade 2 (6/10; 60%), anaplastic astrocytoma (6/15; 40%), oligoastrocytoma grade 2 (2/6; 33.33%), and anaplastic oligoastrocytoma (1/3; 33.33%).

1p/19q Co-deletion Analysis

1p/19q co-deletion was seen in oligoastrocytoma (2/2; 100%), anaplastic oligoastrocytoma (1/2; 50%), oligodendrogloma (3/4; 75%), and anaplastic oligodendrogloma (1/3; 33.33%).

Correlation analysis between IDH1 mutation and 1p/19q co-deletion showed a positive correlation, with six of seven cases with 1p/19q co-deletion showing IDH1 mutation ($p = 0.05$). Of 17 cases with ATRX mutation, 15 also showed IDH1 mutation showing a significant correlation between the ATRX loss and IDH1 mutation ($p < 0.001$) whereas 1 of 7 1p/19q co-deleted cases had loss of expression of ATRX.

Discussion

The authors analyzed the distribution of IDH1 mutation, ATRX mutation, and 1p/19q co-deletion in these cases and its diagnostic utility. The cases included had a wide age group distribution with the minimum being 5 years and maximum being 69 years. Mean age of patients in this study was 41.81 years (SD = 14.95). These findings were similar to studies done by Dehais et al,¹⁵ Lassman et al,¹⁶ and Jiang et al.¹⁷ IDH1 mutation analysis in 48 cases of astrocytoma showed 15 cases to be positive for IDH1 mutation. The highest number of mutation was seen in astrocytoma grade 2 ($n = 7/10$; 70.0%) and the least in GBM ($n = 3/23$; 13.04%). The three GBM cases that were positive for IDH1 mutation were secondary GBM (3/4). The authors found a significant correlation between the tumor grade and IDH1 mutation ($p = 0.005$). These findings were at par with various studies. Watanabe et al¹⁸ found that IDH mutations were common in low-grade diffuse astrocytomas (88%) and secondary glioblastomas (82%), whereas these mutations were rarely seen in primary glioblastoma (5%).

Of the nine cases of oligoastrocytoma, five showed IDH1 mutation, of which three were grade 3 oligoastrocytoma (3/3; 50%) and two were anaplastic oligoastrocytoma (2/3; 75%). We found a higher mutation rate in anaplastic oligoastrocytoma though various other studies report an

otherwise higher rate in grade 2 oligoastrocytoma. This difference may be attributed to the small sample size in this category. Ten of the total 16 cases of oligodendrogloma showed IDH1 mutation (10/16), of which 7 were oligodendrogloma grade 2 (7/10; 70%) and three were anaplastic oligodendrogloma (3/6; 50%). This study showed a higher rate of IDH1 mutation in low-grade oligodendrogloma compared with anaplastic oligodendrogloma. These findings were similar to those reported in the literature. In their study, Watanabe et al¹⁸ found that IDH mutations were common in low-grade diffuse astrocytomas. It was also observed in oligodendrogloma (79%) and anaplastic oligodendrogloma (75%). Similarly in a study done by Cai et al,¹⁹ IDH1 mutations among the oligodendrogloma grades included oligodendrogloma grade 2 (9/12; 75%) and anaplastic oligodendrogloma (5/9; 55.56%).

ATRX mutation is a lineage marker, and the new WHO classification uses it to classify diffuse gliomas because it is intact in IDH1 mutant and 1p/19q co-deleted oligodendrogloma cases and is exclusively seen in IDH1 mutant astrocytoma.²⁰ Of 48 cases, 12 cases showed ATRX loss. The highest frequency of ATRX loss was seen in astrocytoma grade 2 (6/10; 60%) whereas none of the GBM cases showed ATRX loss of expression. Thus ATRX loss correlated with astrocytoma tumor grade. These findings were similar to most of the studies reported in the literature. Cai et al¹⁹ in their study also observed similar findings to this study, with the frequency of ATRX loss being higher in astrocytoma, anaplastic astrocytoma, and secondary GBM (A, 49/64, 76.56%; AA, 21/27, 77.78%; sGBM, 45/59, 76.27%) and low in primary GBM (14/114, 12.28%).

Of the nine cases of oligoastrocytoma in this study, ATRX loss was seen in three cases. These three cases will be reclassified according to the new WHO classification that states that diffuse gliomas with this mixed or ambiguous histologic features should be classified as astrocytoma if the molecular testing shows IDH1 and ATRX loss or absent 1p/19q co-deletion whereas tumors with combined IDH1 mutation and 1p/19q co-deletion should be classified as oligodendrogloma irrespective of mixed or ambiguous histology.²⁰ In this study, the authors observed no significant correlation between ATRX mutation and oligoastrocytoma tumor grade as found in some studies. Similarly, Kannan et al⁴ in their study found that ATRX-mutated tumors constituted 70% of IDH-mutant, 1p/19q-intact low-grade gliomas. ATRX mutation was strongly associated with astrocytic and oligoastrocytic gliomas as compared with pure oligodendroglial tumors. They observed no significant correlation between ATRX mutation and tumor grade.

Of the total 16 cases of oligodendrogloma, 2 cases showed ATRX loss, 1 in each tumor grade. Because ATRX loss is lineage specific for astrocytoma, the two phenotypic oligodendrogloma cases that showed ATRX loss in this study will be reclassified as astrocytoma according to the new molecular classification.²¹ These findings were at par with various studies. Kannan et al⁴ in their study found that ATRX-mutated tumors constituted 70% of IDH-mutant, 1p/19q-intact low-grade gliomas. ATRX mutation was strongly associated with astrocytic and oligoastrocytic gliomas as compared with pure oligodendroglial tumors ($p = 0.0009$).

Of the total seven cases of oligodendroglioma that were analyzed for 1p/19q co-deletion, four were positive (4/7; 57.14%), and of these, three were oligodendroglioma grade 2 (3/4; 75%) and one in oligodendroglioma grade 3 (1/3; 33.33%). According to the criteria laid down in the new 2016 WHO classification to diagnose oligodendroglioma, the three phenotypic oligodendrogliomas that were negative for 1p/19q co-deletion and positive for IDH1 will be reclassified as astrocytoma because 1p/19q co-deletion is a necessary molecular marker for oligodendroglioma.²¹ Out of the total 14 cases of oligoastrocytoma analyzed for 1p/19q co-deletion, 3 showed 1p/19q co-deletion (3/4; 75%). The two cases of astrocytoma that were analyzed for 1p/19q co-deletion were negative (0/2; 0%). As seen in this study, various other studies also report a higher rate of 1p/19q co-deletion among oligodendroglioma and lowest in astrocytoma, establishing the lineage specificity of 1p/19q co-deletion. Jenkins et al²² in their study found the distribution of 1p/19q co-deletion to be highest in oligodendrogliomas (57%), oligoastrocytoma (32%), and lowest among astrocytoma (0%). The prevalence of 1p/19q co-deletion was significantly different between the three histologic groups ($p < 0.001$, χ^2 test).²²

1p/19q co-deletion has both diagnostic and prognostic significance. Tumors with this deletion carry good prognosis and are extremely chemosensitive. In a study done by Kaloshi et al^{23,24} to assess the predictive impact of 1p/19q loss to treatment with temozolomide, they observed that the objective response rate was higher in the 1p/19q co-deleted group (26/36; 72%) than in the 1p/19q intact group (23/50; 46%) ($p = 0.02$). Also, 1p/19q co-deleted cases had a better progression-free survival ($p = 0.00004$) and overall survival ($p = 0.04$).

Correlation analysis showed a positive co-relation between IDH1 mutation and 1p/19q co-deletion, with six of seven cases (85.71%) with 1p/19q co-deletion showing IDH1 mutation. The p value for difference between these entities was 0.05. The phenotypic oligodendroglioma with intact 1p/19q co-deletion and negative IDH1 mutation are not true oligodendrogliomas, and they are not considered a distinct tumor entity but should be carefully evaluated for genetic changes associated with IDH wild-type glioblastomas.²¹

Sanson et al²⁵ in their study also observed a positive correlation between 1p/19q co-deletion and IDH1 mutation, with 38 of 42 1p/19q co-deleted oligodendrogliomas showing IDH1 mutation whereas only 27 of 61 non-co-deleted oligodendroglioma showing IDH1 mutation ($p = 10^{-6}$).

ATRX mutation and 1p/19q co-deletion were found to be mutually exclusive with only one of seven 1p/19q co-deleted cases showing simultaneous ATRX loss, and this one odd case may represent the true dual-genotype oligoastrocytoma. Mur et al²⁰ observed in their study that most of the tumors lacking ATRX expression were IDH mutated (41/48; 85.5%) with intact 1p/19q (25/25; 100%) tumors ($p < 0.0001$). Their findings also established the mutual exclusivity of these two molecular markers as seen in this study. Similarly, in a study done by Jiao et al,⁹ they observed similar finding to this study with only one cases showing 1p/19q co-deletion and ATRX loss ($p < 0.001$).

This study observed a significant correlation between ATRX mutation and IDH1 mutation. Of the 17 cases with ATRX mutation, 15 cases also showed IDH1 mutation. The p value for difference between these entities was < 0.001 in this study and is significant. This study had similar findings to most studies. Jiao et al⁹ also observed in their study a significant correlation between IDH1 mutation and ATRX mutation, with 87 of 88 adult gliomas with ATRX loss showing IDH1 mutation (98.86%). In another similar study by Mur et al.²⁰ the authors observed that most of the tumors lacking ATRX expression were IDH mutated (41/48; 85.5%) establishing a positive correlation between the two molecular markers. Different studies have established the utility of these molecular markers with tumors carrying IDH1 mutation and 1p/19q co-deletion carrying the best prognosis, those with IDH1 mutation and ATRX loss carrying intermediate prognosis whereas IDH1 wild-type tumors carry the worst prognosis.

One such study is by Mur et al²⁰ in which the gliomas were grouped as follows and overall survival within each group was studied:

Group 1 (I-CD)—IDH 1 mutation, 1p/19q co-deletion, and ATRX positive cases

Group 2 (I-A)—IDH1 mutation, absence of ATRX protein, and intact 1p/19q

Group 3 (I)—IDH1 mutation but intact 1p/19q and expression of ATRX

Group 4 (NA)—Wild-type IDH, intact 1p/19q, and ATRX-positive expression

Overall survival within the groups included group 1—179.5 months, group 2—118.0 months, group 3—82.7 months, and group 4—10.6 months. Kaplan-Meier curves showed significant difference in overall survival between the molecular groups ($p < 0.0001$).

Conclusion

The authors analyzed 73 cases of diffuse gliomas for IDH1 mutation, ATRX mutation, and 1p/19q co-deletion. The highest number of IDH1 mutation was seen in astrocytoma grade 2 ($n = 7/10$) and the least in GBM ($n = 3/20$) ($p = 0.005$). 1p/19q co-deletion and IDH1 mutation showed positive correlation with six of seven cases (85.71%) with 1p/19q co-deletion showing IDH1 mutation. 1p/19q co-deletion and ATRX loss were almost mutually exclusive with one of seven 1p/19q co-deleted cases showing simultaneous ATRX loss, and this one odd case represents the true dual-genotype oligoastrocytoma ($p = 0.906$). ATRX loss was seen in astrocytomas and oligoastrocytoma but never seen in oligodendrogliomas with 1p/19q co-deletion and thus is lineage specific. All the cases of primary GBMs were IDH1 wild (0/19; 100%) whereas all three cases of secondary GBM were IDH mutant.

Thus including the molecular information into the integrated diagnosis of brain tumors will help in redefining the glial tumors. It also helps in more accurately predicting the prognosis and outcome.

Limitations of This Study

1p/19q co-deletion was not done in all the cases studied but was restricted mostly to the oligodendroglioma phenotype. A small proportion (4%) of IDH mutant tumors will have IDH2 and IDH3 mutations. IHC with antibody anti-human IDH1R132H identifies only IDH1 mutation; hence, polymerase chain reaction (PCR) is recommended in all IDH1-negative tumors by IHC to identify the small proportion of cases with IDH2 and IDH3 mutations. In this study, however, only IHC was done and PCR was not done. Prognostic correlation of these molecular markers was not done due to lack of follow-up.

Conflict of Interest

None.

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