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Original Research Article

Expression of isocitrate dehydrogenase-1 in glioblastoma, Bangladesh perspective

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ABSTRACT

Background: Glioblastoma is the most frequent malignant brain tumor in adults. Various studies have identified IDH (isocitrate dehydrogenase) mutation as a hallmark genetic alteration in glial tumors. The World Health Organization (WHO) has classified glioblastoma based on IDH mutation status, including IDH-mutant glioblastoma, IDH-wildtype glioblastoma along with its variants and glioblastoma, NOS (not otherwise specified) (where IDH mutation status cannot be evaluated).
Methods: It was a cross-sectional observational study, conducted on 35 histologically diagnosed cases of glioblastoma, within the period of March, 2018 to December 2019.
Results: Among the 35 glioblastoma cases, 6 (17.14%) were found to be IDH-mutant (positive for IDH1 immunostain), while the remaining 29 cases were negative for IDH1 immunostain (therefore designated as IDH-wildtype glioblastoma). In the IDH-mutant group, 3 out of 6 patients were in the younger age group (≤40 years). On the other hand, IDH-wildtype glioblastoma was more common in elderly and most frequent was in the age group of 51-60 years (11 out of 29 cases).
Conclusions: In this study, IDH1 expression was observed in 17.14% of all glioblastoma cases (designated as IDH-mutant glioblastoma). Whereas, most (~82.86%) of the glioblastoma cases did not express IDH1 (designated as IDH-wildtype).

Keywords: Brain tumors, Glioblastoma, IDH1

INTRODUCTION

Glioblastoma is the most frequent malignant brain tumor in adults, that has a poor prognosis and survival of only 15-31 months, despite all current treatment modalities.[1] IDH mutation is a hallmark genetic alteration in glial tumors and a subtype of glioblastoma (secondary glioblastoma). This group defining genetic alteration occurs as an early event of glioma genesis.[2] Therefore, the WHO suggests classifying glioblastoma based on IDH (Isocitrate dehydrogenase) mutation status. Glioblastoma is now classified into IDH-mutant glioblastoma, IDH-wildtype glioblastoma along with its variants and glioblastoma, NOS (not otherwise specified) (where IDH mutation status cannot be evaluated).[1]

The IDH-mutant glioblastoma has better prognosis and survival over IDH-wildtype glioblastoma.[3] However, IDH-wildtype glioblastoma is more common than IDH-mutant glioblastoma.[1]

The objective of the study was to find out the expression of IDH1 (isocitrate dehydrogenase-1) in glioblastoma patients of Bangladesh.

METHODS

It was a cross sectional observational study, conducted on 35 histologically diagnosed cases of glioblastoma. Study was carried out in the department of pathology, Sir Salimullah Medical College, Dhaka, within the period of March, 2018 to December 2019.

Sampling method of this study was purposive and convenient sampling. Histopathologically diagnosed cases of glioblastoma were included in this study. Too small samples to be processed for immunohistochemical staining and samples without proper ID, clinical and other relevant information including histopathology and radiologic reports were excluded.

After routine histological diagnosis, sections were made for immunostaining of IDH1. Immunostaining was done in National Institute of Neuroscience and Hospital, Dhaka, at the department of neuropathology according to manufacturers' guideline. As positive control previously reported IDH1 positive astrocytic tumor was used. Cases with >10% stained cells were rated as IDH mutation positive, and cases with <10% stained cells were rated as negative.

Ethical clearance and permission was taken from the institutional ethical committee of Sir Salimullah Medical College, Dhaka.

All the collected data was analyzed by using the Statistical Package for Social Sciences Version 20.0 for windows (SPSS INC Chicago, Illinois, USA). Statistical significance was set at $p<0.05$.

RESULTS

IDH1 immunohistochemical study was conducted on all 35 study samples. The results obtained were as follows.

In this study, it was observed that, overall glioblastoma was more common in the 5th decade of life. 34.4% of glioblastoma cases occurred in the age group of 51-60 years, while it was least common in the age group ≤40 years as well as 61-70 years (Figure 1).

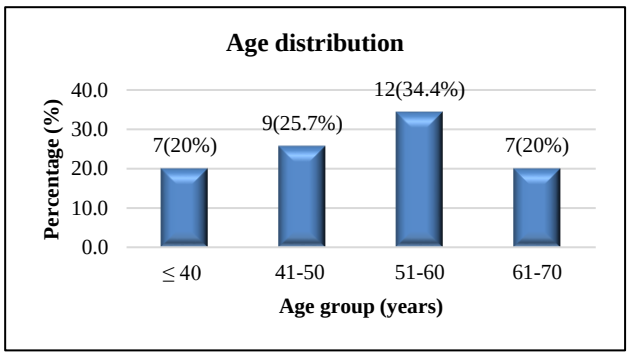

Figure 1: Age distribution of study patients (n=35).

IDH mutation was more frequent in the younger age group. Out of 6 patients, 3 (50%) were ≤40 years of age. IDH-wildtype glioblastoma was less frequent in the younger age group, with only 13.8% of cases occurring in ≤40 years of age. On the other hand, IDH-wildtype glioblastoma was more frequent in elderly patients and the age group 51-60 years showed the highest frequency of occurrence (accounting for 37.9% cases). However, this finding was not statistically significant (Table 1).

Table 1: Association of age distribution of the study patients with IDH1 expression (n=35).

Age groups (years)	IDH1 expression		P value
	Positive (Mutant) (n=6) N (%)	Negative (wildtype) (n=29) N (%)	
≤40	3 (50.0)	4 (13.8)	0.242ns
41-50	1 (16.7)	8 (27.6)	
51-60	1 (16.7)	11 (37.9)	
61-70	1 (16.7)	5 (20.7)	
Total	6 (100.0)	29 (100.0)	
Mean±SD	46.50±12.11	52.76±11.92	

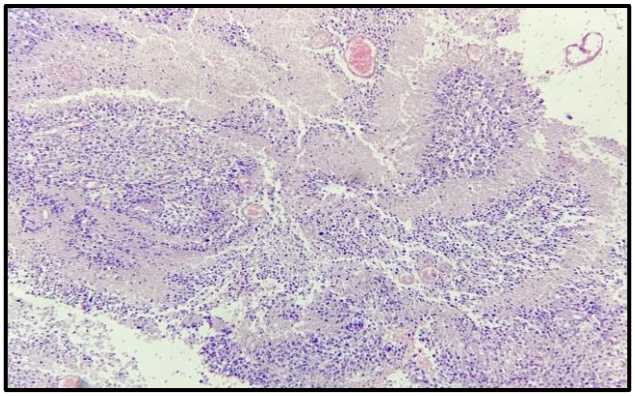

Figure 2: H and E stained slide of glioblastoma.
It shows high cellularity, pleomorphism and geographic necrosis (100X).

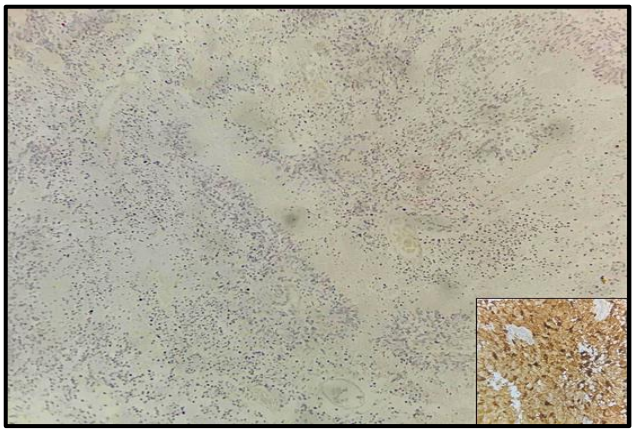

Figure 3: IDH1immunostain.
IDH1 stain is negative in this slide (100X) (Inset- positively stained control slide).

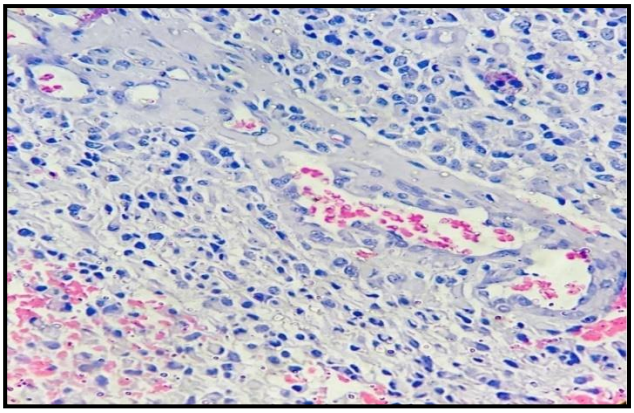

Figure 4: H and E stained slide of glioblastoma.
It shows high cellularity, pleomorphism and microvascular proliferation (200X).

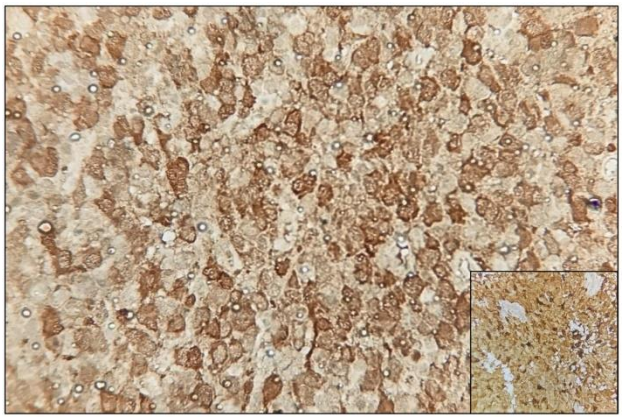

Figure 5: IDH1immunostain.
IDH1 stain is positive in this slide (400X) (Inset- positively stained control slide).

DISCUSSION

This cross-sectional observational study was conducted on 35 histologically diagnosed glioblastoma cases at the department of pathology, Sir Salimullah Medical College, Dhaka. IDH gene mutation status of the selected glioblastoma cases was detected using immunohistochemical methods, irrespective of the patient's age. Only IDH1 antibody (OT12H9; clone 1152, dilution 1:100; ABCAM) was used to determine the mutation status. In this study, immunostaining for IDH2 or sequencing was not performed. Immunohistochemistry for detection of IDH1 has been reported as a cheap, easy-to-perform, and clinically feasible technique for detecting mutation status, which is very well comparable to gene sequencing.[4] In different studies on glial tumors, the findings of sequencing and immunohistochemical results are found to be about 88-99% similar.[4-11] Moreover, IDH2 mutation is much rarer than that of IDH1 mutation and accounts for only less than 5% of all IDH mutations.[12] Therefore, only IDH1 antibody was used to detect the mutation.

A total of 35 samples were collected, which were histomorphologically diagnosed as glioblastoma. Among the cases, the highest age of diagnosis was 70 years, whereas the lowest age was 11 years. From this data, it was noticeable that glioblastoma was most frequent among the 50-60 years age group; a total of 12 out of 35 patients belonged to this age group (Figure 1).

In the present study, 82.86% (29) of glioblastoma cases were found to be IDH-wildtype, i.e., negative for IDH mutation status. This finding was slightly lower but closely comparable to the level referred by WHO in 2016 (90%). On the other hand, 17.14% (6) of cases were IDH-mutant, which was slightly higher than the level referred by WHO in 2016 (10%).[1] Among the IDH-wildtype glioblastoma cases, the maximum age of the patient was 70 years and the minimum was 11 years. The mean age was 52.76 (52.76±11.92; mean±SD) years, which is quite higher than the mean age of IDH-mutant glioblastoma cases in this study. The age of the IDH-mutant glioblastoma group ranges from 35 to 65 years, with a mean age of 46.5 (46.50±12.11; mean±SD) years (Table 1). The trend of the age of occurrence of disease is similar to the findings of studies conducted by Nobushawa et al and Yan et al, who found that the mean age of patients with IDH-mutant glioblastoma was 48 years, significantly younger than that of patients lacking IDH1 mutations (61 years).[3,12]

However, the study has some limitations. For financial constraints, as well as the smaller size of the tissues, genetic sequencing was not done for detection of IDH mutation status of glioblastoma cases.

CONCLUSION

IDH1 expression was observed in 17.14% of all glioblastoma cases (designated as IDH-mutant glioblastoma) in a comparatively younger age group. In contrast, IDH1 was not expressed in most (~82.86%) glioblastoma cases, which were therefore designated as IDH-wildtype and occurred mostly in an older age group.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Sir Salimullah Medical College, Dhaka, Bangladesh

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