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Impact of IDH1 Mutation on Long-Term Survival in Patients with Diffuse Glioma

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Objectives: Diffuse brain gliomas are common primary brain tumor associated with a poor prognosis. In this study, we aimed to determine the impact of IDH1 mutation status on long term survival. **Methods:** Patients who underwent surgery for diffuse brain glioma were selected. Based on IDH1 mutation status, patients were separated into IDH1 mutant and IDH1 wildtype groups. **Results:** A total of 124 patients with diffuse brain tumor were included (mean age 39±17, 48.4% male). The frequency of IDH1 mutant and IDH1 wildtype were 56.5% (n=70) and 43.5% (n=54), respectively. During follow-up, 76 patients (61.3%) died and the median follow-up was 8 months (IQR 4; 16). Patients with IDH1 mutant more likely younger (36±16 vs. 43±17, p<.05) and had low grade (grade II) tumor (64.3% vs. 20.4%, p<.001). After adjustment of possible predictors, such age, gender, tumor location and surgical type, IDH1 mutant was an independent predictor of all-cause mortality (HR=0.43, 95% CI 0.26-0.71, p<.001). Kaplan-Meier estimation showed IDH1 mutant is associated with longer survival compared with IDH1 wildtype in low grade tumor (log rank p<.001). **Conclusion:** Mutated IDH1 is an independent predictor of all-cause mortality in patients with diffuse brain glioma and resulted in longer survival compared with IDH1 wildtype.

Keywords: Glioma, Isocitrate Dehydrogenase, Prognosis, Survival

Introduction

Diffuse brain gliomas are most common type of primary brain tumors and they have variety of histologic subtypes. According to the histopathological and clinical manifestations established by the World Health Organization (WHO), gliomas are classified from grade I to grade IV[1]. Grade I gliomas are often considered to be benign, curable by complete surgical resection and have a good prognosis while grade II and III gliomas are malignant and capable of progression into invasive grade IV glioma having a poor prognosis[2,3].

The progression of primary brain tumor is dependent upon several genes such as tumor protein 53 (TP53), phosphatase and tensin homolog (PTEN), epidermal growth factor receptor (EGFR)[4-7]. The development of glioma tumor is sequential process and occurrence of above-mentioned gene mutations might be crucial for the transition from mild to aggressive form. For example, TP53 mutation occurs in the early stage of glioma tumors while PTEN mutation and an increase of EGFR is prominent in high grade tumors[8-10].

In high grade gliomas, mutations of the isocitrate dehydrogenase 1 (IDH1) gene are found in 70% of grade II and III astrocytomas and oligodendrogliomas and in secondary glioblastomas which arise from low grade gliomas[11]. Conversely, primary glioblastomas develop de novo without IDH1 gene mutation, and progress rapidly progression and have worse prognosis[12]. This has led to the hypothesis that IDH1 gene mutation has an important role in development of high-grade gliomas.

The IDH1 gene mutation can be detected by immunohistochemical (IHC) staining of the IDH1 mutant protein. The IHC staining method has several advantages. It is easily implemented in standard pathological laboratories, is cost effective and provides a way to evaluate morphologic expression of mutated protein[13,14]. The most frequent mutation which found in up to 95% of glioma cases is a substitution of amino acid arginine by histidine at the codon 132 (R132H)[15]. There are two monoclonal antibodies that can be used for anti-IDH1-R132H immunohistochemical analysis with good concordance with DNA sequencing method[14,16,17]. Capper et al. demonstrated that IHC staining using mouse monoclonal anti-mIDHR^{132H} antibody has 100% sensitivity and specificity to detect R132H mutation, while sensitivity and specificity to detect all type of IDH1 mutation including R132G, R132S and R132C were 94% and 100%, respectively[16].

In this study, we sought to determine the impact of IDH1 mutant protein on long term survival of patients with diffuse brain glioma.

Material and Methods

Study design

In this retrospective study, we evaluated tissue specimens from patients who underwent brain glioma removal surgery. Prior to beginning the study, the study design and ethics were approved by Institutional Review Board of Mongolian National University of Medical Sciences (№2017/3-201702, 17 February 2017). Data about age, gender, risk factors, previous co-morbidities, laboratory measurements and surgical reports were retrospectively collected from patients' medical record. All the tumors were graded according to the WHO criteria and classified into high and low grade tumor[1].

Study population

In this study, a total of 124 formalin fixed, paraffin embedded brain tumor tissue microarray (TMA) blocks which were collected and archived between 2006 and 2017 in the National Center for Pathology. The study population included tissue specimens collected from patients who had been diagnosed with diffuse glioma (WHO grade II-IV) confirmed by histological examination. Patients with WHO grade I glioma such as pilocytic astrocytoma and those whose tissue blocks were lost or too small were excluded.

Representative tumor areas were marked on hematoxylin and eosin (H&E) stained sections. Tumor areas needed to contain over 60% tumor cell infiltrations and no necrosis or hemorrhage. Corresponding areas were identified on the paraffin blocks and tissue microarray blocks constructed and new 4 μm thick sections were prepared.

Immunohistochemical staining

In this study, we used IHC staining method to reveal IDH1 R132H mutation using mouse monoclonal anti-mIDHR^{132H} antibody (1:10 dilution, DIANOVA, Hamburg, Germany). For IHC staining, 4 μm thick tissue sections were deparaffinized in xylene and hydrated by immersing in a series of graded ethanol baths. Antigen retrieval was performed in a microwave by placing the sections in epitope retrieval solution (0.01 M citrate buffer, pH 6.0) for 20 minutes; endogenous peroxidase was inhibited by immersing the sections in 0.3% hydrogen peroxide for 10 minutes. Sections were then incubated with IDH1 antibodies. Next, an Ultra View universal DAB kit was used following the manufacturer's recommendations (VENTANA, Tucson, Arizona, USA) in conjunction with an automated staining procedure. Finally, the samples were counterstained with haematoxylin, dehydrated, mounted, evaluated and photographed (20× and 40× objective) under a light microscope equipped with an Olympus CX21 camera. The immunoreactivity to mIDH1R132H antibody was evaluated for positive cytoplasmic or nuclear brown staining (Figure 1)[18,19]. Based on IDH1 mutation status, patients were separated into IDH1 mutant (IDH1^{mut}) and IDH1 wildtype (IDH1^{wt}) groups.

Study endpoint

In this study, we choose all-cause mortality after hospital discharge for primary endpoint. Data on the occurrence of

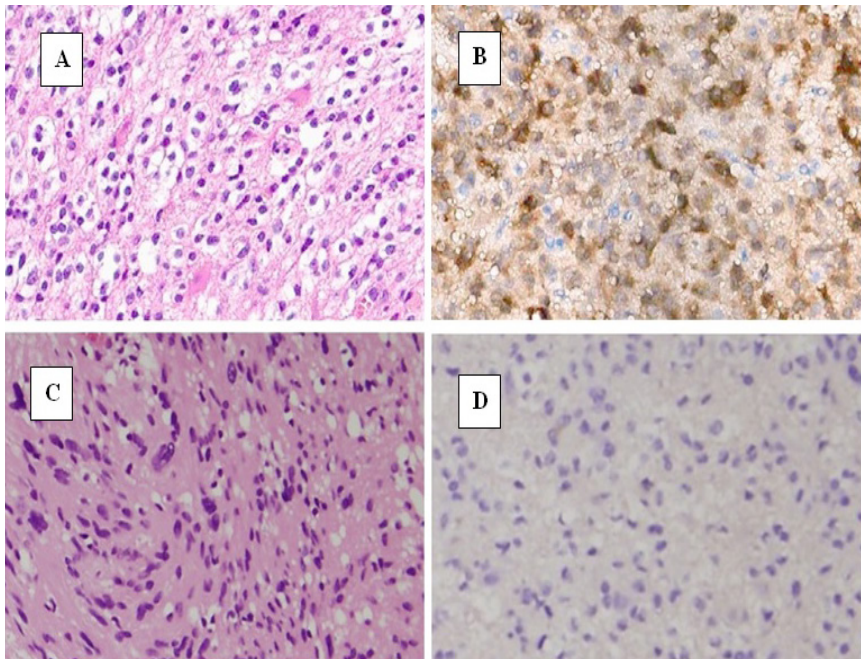

Figure 1. IDH1 immunohistochemical marker staining of diffuse brain glioma. (A) Definite fried egg appearance of oligodendroglioma (arrow) in H&E staining x100. (B) The tumor cells stained positive for IDH1 immunostaining in the cytoplasm (white arrow), and also in the nucleus (black arrow). The unstained cells in the brain parenchyma represent non neoplastic cells. (C) H&E staining of anaplastic astrocytoma with spindle shape, hyperchromatic nucleus (arrow) x100. (D) No staining of IDH1 marker in tumor cell cytoplasm or nucleus.

endpoint was collected from the database of General Authority for State Registration.

Statistical analysis

Continuous variables that were normally distributed (as evaluated by Kolmogorov–Smirnov tests) were presented as the mean ± standard deviation (SD) and categorical data were presented as frequencies and percentages. Differences in baseline characteristics between patients with and without IDH1 mutation were compared using the independent sample t-test and chi-squared test.

Separate univariate and multivariate Cox proportional hazard regression analysis was used to determine the relationship between possible predictors and mortality. Variables were selected for univariate Cox proportional hazard regression one-by-one. Those variables identified as significant in the univariate analysis were used in multivariate analysis to evaluate their independent association between IDH1 mutation and all-cause mortality. Variables including age, gender, tumor location, surgery type and IDH1 mutation were simultaneously compared using multivariate Cox proportional hazard regression. Additionally, Kaplan-Meier estimation was used to evaluate association between IDH1 mutation and long-term survival.

All statistical tests were two-sided, and $p<.05$ was considered statistically significant. The statistical analyses were performed using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The mean age of diagnosis was 39±17 years old and the prevalence of diffuse brain glioma was equal in both genders (male 48.4% and female 51.6%). Prevalence of WHO grade II, grade III and grade IV tumors were 45.2% (n=56), 26.6% (n=33) and 28.2% (n=35), respectively.

Based on IDH1 mutation status, 70 patients (56.5%) were $IDH1^{mut}$ and 54 (43.5%) were $IDH1^{wt}$.Patients with $IDH1^{mut}$ were more likely to be younger compared with patients with $IDH1^{wt}$ (36±16 vs. 43±17, $p<.05$). Occurrence of IDH1 mutation was

not different between male and female genders (47.1% vs. 52.9%, p=.752).

The WHO tumor grade was less aggressive in IDH1^{mut} group (grade II tumor 64.3%, grade III tumor 35.7% and grade IV tumor 0%) compared with IDH1^{wt} group (grade II tumor 20.4%, grade III tumor 14.8% and grade IV tumor 64.8%) and this difference was statistically significant (p<.001). Using the WHO tumor grade, all the tumors were classified into low grade (WHO grade II) and high grade (WHO grade III and grade IV). Patients with IDH1^{mut} were more likely had low grade tumor than patients with IDH1^{wt} (64.3% vs. 20.4%, p<.001).

There was no statistically significant difference in tumor location between patients with and without IDH1 mutation (p=.247). There was a trend towards a higher percentage of complete tumor removal surgery in the IDH1^{mut} group than in IDH1^{wt} group (54.3% vs. 37%, p=.056). The baseline characteristics of study population were summarized in Table 1.

IDH1 mutation and long-term survival

The median survival time was 8 months (interquartile range [IQR] 4; 16) for study population and all-cause mortality occurred in 76 patients (61.3%). The frequency of IDH1^{mut} and IDH1^{wt} was 56.5% (n=70) and 43.5% (n=54), respectively. Univariate Cox proportional hazard regression analysis was showed that IDH1^{mut} (HR=0.42, 95% CI 0.26-0.68, p<.001) and complete tumor removal (HR=0.53, 95% CI 0.33-0.85, p<.01) were significant predictor of all-cause mortality. Multivariate analysis which considered age, gender, tumor location, surgical type and IDH1 mutation status revealed that IDH1^{mut} (HR=0.43, 95% CI 0.26-0.71, p<.001) and complete tumor removal (HR=0.60, 95% CI 0.37-0.98, p<.05) were independent predictors of all-cause mortality (Table 2).

Table 1. Baseline characteristics.

Variables	All patient (n=124)	Patients with IDH1^{mut} (n=70)	Patients with IDH1^{wt} (n=54)	p-value
Age	39±17	36±16	43±17	.025[a]
Gender				.752[b]
male	60 (48.4%)	33 (47.1%)	27 (50%)	
female	64 (51.6%)	37 (52.9%)	27 (50%)	
WHO tumor grade				.001[b]
Grade II	56 (45.2%)	45 (64.3%)	11 (20.4%)	
Grade III	33 (26.6%)	25 (35.7%)	8 (14.8%)	
Grade IV	35 (28.2%)	0 (0%)	35 (64.8%)	
Tumor grade				.001[b]
Low grade	56 (45.2%)	45 (64.3%)	11 (20.4%)	
High grade	68 (54.8%)	25 (35.7%)	43 (79.6%)	
Tumor location				.247[b]
temporal	17 (13.7%)	6 (8.6%)	11 (20.4%)	
multiple	37 (29.8%)	23 (32.9%)	14 (25.9%)	
frontal	34 (27.4%)	20 (28.6%)	14 (25.9%)	
talamus	13 (10.5%)	6 (8.6%)	7 (13%)	
cerebellum	7 (5.6%)	6 (8.6%)	1 (1.9%)	
parietal	16 (12.9%)	9 (12.9%)	7 (13%)	
Surgery type				.056[b]
complete removal	58 (46.8%)	38 (54.3%)	20 (37%)	
partial removal	66 (53.2%)	32 (45.7%)	34 (63%)	

[a]independent sample t-test, [b]Chi-Square test.WHO, World Health Organization; IDH1^{mut}, isocitrate dehydrogenase-1 mutated; IDH1^{wt}, isocitrate dehydrogenase-1 wild type.

Table 2. Univariate and multivariate *Cox* proportional hazard regression for all-cause mortality.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.99	0.98-1.01	.737			
Gender	0.76	0.48-1.20	.238			
Tumor location	1.08	0.93-1.25	.319			
Complete tumor removal	0.53	0.33-0.85	.009	0.60	0.37-0.98	.04
$IDH1^{mut}$	0.42	0.26-0.68	.001	0.43	0.26-0.71	.001

HR-hazard ratio; $IDH1^{mut}$-isocitrate dehydrogenase-1 mutated.

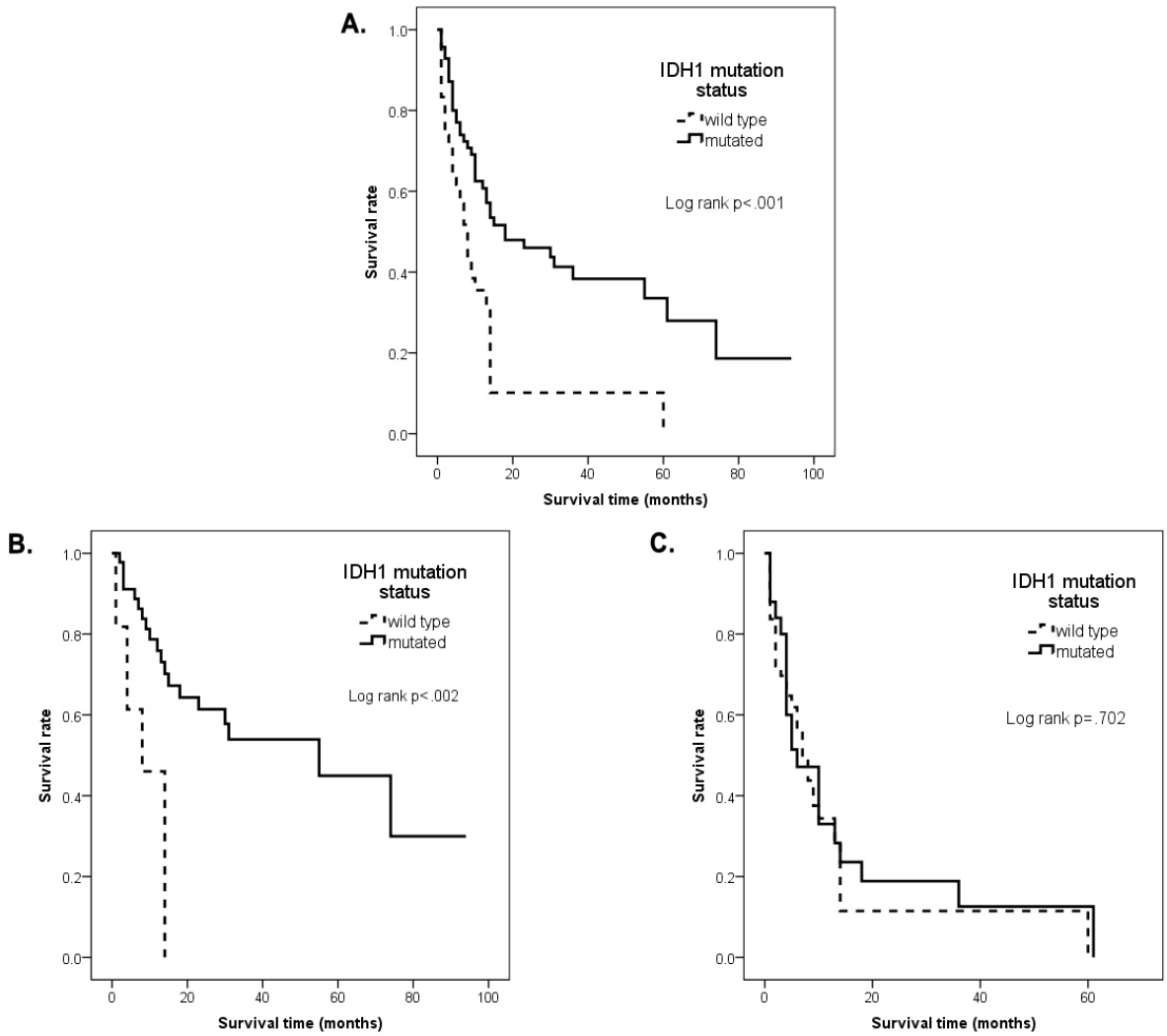

Figure 2. Kaplan-Meier estimation for survival rate. (A) all patients, (B) patients with low grade tumors, (C) patients with high grade tumors. $IDH1^{mut}$, isocitrate dehydrogenase-1 mutated; $IDH1^{wt}$, isocitrate dehydrogenase-1 wild type.

Furthermore, Kaplan-Meier estimation was revealed that patients with $IDH1^{mut}$ (median survival 18 months, 95% CI 2-34 months) were had longer survival compared with patients with $IDH1^{wt}$ (median survival 8 months, 95% CI 6-10 months, log rank p<.001). However, the association was only observed for low grade tumors ($IDH1^{mut}$ median survival 55 months 95% CI 13-96 months vs. $IDH1^{wt}$ median survival 8 months 95% CI 2-14 months, log rank p=.002). For patients with high grade

tumors, $IDH1^{mut}$ didn't show survival benefit compared with $IDH1^{wt}$ ($IDH1^{mut}$ median survival 6 months 95% CI 2-10 months vs. $IDH1^{wt}$ median survival 8 months 95% CI 5-10 months, log rank p=.702) (Figure 2).

Discussion

In our study, we determined that $IDH1^{mut}$ is independent prognostic marker of all-cause mortality (HR=0.43, 95% CI 0.26-0.71, p<.001). Also, Kaplan-Meier curve estimation showed that patients with $IDH1^{mut}$ were had longer survival compared with $IDH1^{wt}$. However, association was only evident for low grade tumors (grade II) (p<.001). For patients with high grade tumors (grade III and IV), there was no long-term survival difference between IDH1 mutant and wild-type IDH1 (p=.702). These results are consistent with findings of Akagi et al. and Tabouret et al[20, 21].

Labussiere et al. determined that IDH1 gene mutation is relatively early event in pathogenesis of glioma and Lv et al. noted that patients with IDH1 gene mutation are younger than patients with wild-type IDH1 gene[22,23]. Those results are similar to the findings of our study where we too found that patients with $IDH1^{mut}$ were younger than patients with $IDH1^{wt}$ (p<.05). We also found that patients in $IDH1^{mut}$ group were more likely to have a low-grade gliomas (grade II) compared with IDH^{wt} group. These findings replicate those of the above-mentioned studies.

The IDH1 gene mutation status is important prognostic marker in patients with diffuse gliomas. Yan et al. revealed that both IDH1 and IDH2 mutations were associated with better survival for patients with diffuse brain gliomas[11]. Moreover, Tabouret et al. demonstrated that IDH^{mut} subgroup has significantly higher survival than IDH^{wt} subgroup for anaplastic astrocytoma and glioblastoma[21]. These results indicate that gliomas with IDH^{mut} are heterogeneous subgroup in diffuse brain gliomas. However, the mechanism by which IDH1 gene mutation affects survival time is still unclear. One of the possible mechanisms is that gliomas which arise from a IDH1 gene mutation require more time to convert into more aggressive glioblastomas and this might explain of why patients with IDH1 gene mutation have better survival. The majority of primary glioblastomas occur without IDH1 mutation in older patients, whereas secondary glioblastomas which arise from low grade gliomas often occur with IDH1 mutation in younger patients[12].

The IDH1 protein is a cytosolic soluble enzyme which is encoded by IDH1 gene on chromosome 2 and catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate[24]. The IDH1 protein is involved in various type of intracellular processes, such as cellular metabolism, epigenetic regulation and DNA damage[25]. Different types of IDH1 gene mutations at codon R132 have been identified such as c.395G>A (p.R132H) mutation accounts for about 93%, c.394C>T (p.R132C) for 4%, c.394C>A (p.R132S) for 1.5% in the different types of gliomas[26,27]. The point mutation affects the highly-conserved arginine residue at codon 132 (R132) in IDH1 gene are detected in 70% of low-grade gliomas such as oligodendrioglioma, oligoastrocytomas as well as secondary glioblastomas[11]. But primary glioblastomas and other systemic cancers very rarely contain IDH1 gene mutation.

Mutations at the codon 132 of IDH1 gene causes loss of its regular function and promotes tumorigenesis including diffuse brain gliomas[28,29]. Mutated IDH1 enzyme will produce 2-hydroxyglutarate which is considered oncometabolite and it may affect DNA methylation[30]. The recent genome-wide analysis demonstrated that IDH1 gene mutation is observed in greater than 80% of low-grade gliomas or secondary glioblastomas[11,25,31]. Therefore, IDH1 gene mutation might be key regulator in development of diffuse brain gliomas such as those evaluated in this study.

Our study has some limitations. We had relatively small sample size compared with other similar studies[11,23]. We used IHC staining method to reveal IDH1 gene mutation and this method has less sensitivity and specificity than a sequencing method. Also, several different types of IDH1 gene mutations at the codon 132 including R132H, R132S and R132C could be exist[18]. We only identified IDH1 mutation R132H in this study. Therefore, future confirmative studies which have larger numbers of patients and utilize sequencing methods are needed to validate these results.

The main conclusions of this study are as follows: 1) IDH1 mutation is independent predictor of long-term prognosis in patients with diffuse brain gliomas, 2) IDH1 mutation is associated with better survival compared with wild-type IDH1.

Conflict of interest

The authors state no conflict of interest.

Acknowledgements

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