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FREQUENCY OF ISOCITRATE DEHYDROGENASE (IDH) MUTATIONS IN PATIENTS WITH GLIOMAS PRESENTING TO NEUROSURGERY DEPARTMENT HMC HOSPITAL PESHAWAR

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Abstract:

Introduction: Gliomas are common and aggressive brain tumors, with their prognosis largely influenced by genetic alterations, including mutations in the isocitrate dehydrogenase (IDH) gene. IDH mutations, particularly prevalent in lower-grade gliomas, are associated with better survival rates and have become key biomarkers for diagnosis and treatment strategies. This study aimed to determine the frequency of IDH mutations in glioma patients at Hayatabad Medical Complex (HMC) in Peshawar.

Materials and methods: A descriptive, cross-sectional study was conducted on 127 glioma patients in the Neurosurgery Department at HMC. Non-probability consecutive sampling was used. Patients aged 12-60 years, diagnosed with gliomas, and undergoing surgery were included. Exclusion criteria were prior brain surgery, preoperative radiotherapy or chemotherapy, and refusal of DNA sequencing consent. Tumor tissue was analyzed for IDH mutations using polymerase chain reaction (PCR). Data were analyzed using SPSS, with a chi-square test used to determine statistical significance ($p \leq 0.05$).

Results: Of the 127 patients, the mean age was 41.7 years. Glioma types included Astrocytoma (46.5%), Oligodendroglioma (29%), and Ependymoma (24.5%). IDH mutations were present in 57% of cases. IDH mutations were significantly more common in Glioma Grades 2 and 4. The age distribution and IDH mutation status showed statistically significant differences across the glioma grades ($p < 0.05$).

Conclusion: IDH mutations were found in over half of the glioma cases, predominantly in lower and higher tumor grades.

Keywords: Glioma, IDH mutations, Astrocytoma, Oligodendroglioma, Brain tumor, Glioma grading.

INTRODUCTION:

Gliomas are among the most common and aggressive types of brain tumors, with varying prognoses based on their genetic and molecular characteristics. One of the key genetic alterations in gliomas is mutations in the isocitrate dehydrogenase (IDH) gene, which have become an important biomarker for both diagnosis and prognosis. IDH mutations are particularly prevalent in lower-grade gliomas and secondary glioblastomas, significantly affecting tumor biology and patient outcomes. The presence of IDH mutations has been associated with better survival rates compared to IDH wild-type gliomas, making it a crucial factor in personalizing treatment strategies. **[1]**

The role of IDH mutations in gliomas was first recognized in 2008, and since then, extensive research has focused on understanding its implications in tumorigenesis. IDH mutations occur primarily in two isoforms, IDH1 and IDH2, with the IDH1 mutation being more common in gliomas. These mutations lead to the production of an oncometabolite, 2-hydroxyglutarate (2-HG), which disrupts normal cellular metabolism and promotes tumorigenesis. Recent studies highlight the significance of detecting IDH mutations not only for prognostication but also for guiding therapeutic decisions, such as the potential use of targeted therapies against IDH-mutant gliomas. **[2]**

The frequency of IDH mutations varies across different populations and tumor grades. Studies from Western countries report that IDH mutations are present in about 70-80% of lower-grade gliomas, whereas their frequency in higher-grade gliomas, particularly primary glioblastomas, is much lower. **[3]** In contrast, data from Asian populations are limited, and the prevalence of IDH mutations in gliomas among Pakistani patients remains underreported. Understanding the local epidemiology of these mutations is essential to optimize diagnostic and treatment protocols in resource-limited settings. **[4,5]**

This study aims to determine the frequency of IDH mutations in glioma patients presenting to the Neurosurgery Department of HMC Hospital in Peshawar. By establishing the prevalence of these mutations in a local population, this research can contribute to the growing body of evidence on the clinical significance of IDH mutations and help improve outcomes for glioma patients in the region.

MATERIAL AND METHODS:

The study was conducted in the Department of Neurosurgery at Hayatabad Medical Complex, Peshawar, using a descriptive, cross-sectional design. A total of 127 patients were selected based on a 95% confidence level, and an 8% margin of error, calculated using the WHO sample size calculator. The sampling technique employed was non-probability consecutive sampling, ensuring that all eligible patients within the defined time frame were included in the study.

The inclusion criteria for the study encompassed patients diagnosed with gliomas as per operational definitions, aged between 12 and 60 years, of both genders, and willing to undergo surgical procedures for glioma treatment. Patients with a history of prior brain surgery, those who had received preoperative radiotherapy or chemotherapy, and those unwilling to consent to DNA sequencing of their tumor tissue were excluded from the study.

Before data collection, ethical approval was obtained from the Hospital Ethical Committee and the College of Physicians and Surgeons Pakistan (CPSP). Informed consent was obtained from all eligible patients, explaining the study's nature and methodology. The glioma diagnosis was confirmed via MRI, which was interpreted by experienced radiologists. Patients who consented to undergo surgery, including craniotomy and biopsy, were included in the study. All surgical procedures were performed by expert neurosurgeons, ensuring adherence to safety protocols. Post-surgery, tumor specimens were preserved in formalin and sent to the hospital laboratory for histopathological examination and polymerase chain reaction (PCR) analysis to detect IDH mutations. Demographic and clinical data, such as patient name, age, gender, and tumor characteristics, were meticulously recorded by the researcher.

For data analysis, SPSS version 20 was employed. Descriptive statistics were used, with the mean and standard deviation (± S.D.) calculated for continuous variables like age, weight, height, blood pressure, and tumor size. Categorical variables such as gender, glioma subtype, and the presence of IDH mutations were analyzed using frequencies and percentages. To assess the impact of IDH mutations across various patient and tumor characteristics, data were stratified by age, gender, weight, height, blood pressure, tumor size, and glioma subtype. Chi-square testing was performed post-stratification to evaluate the significance of differences, with a P-value of ≤ 0.05 considered statistically significant. All findings were presented in detailed tables for clarity and interpretation.

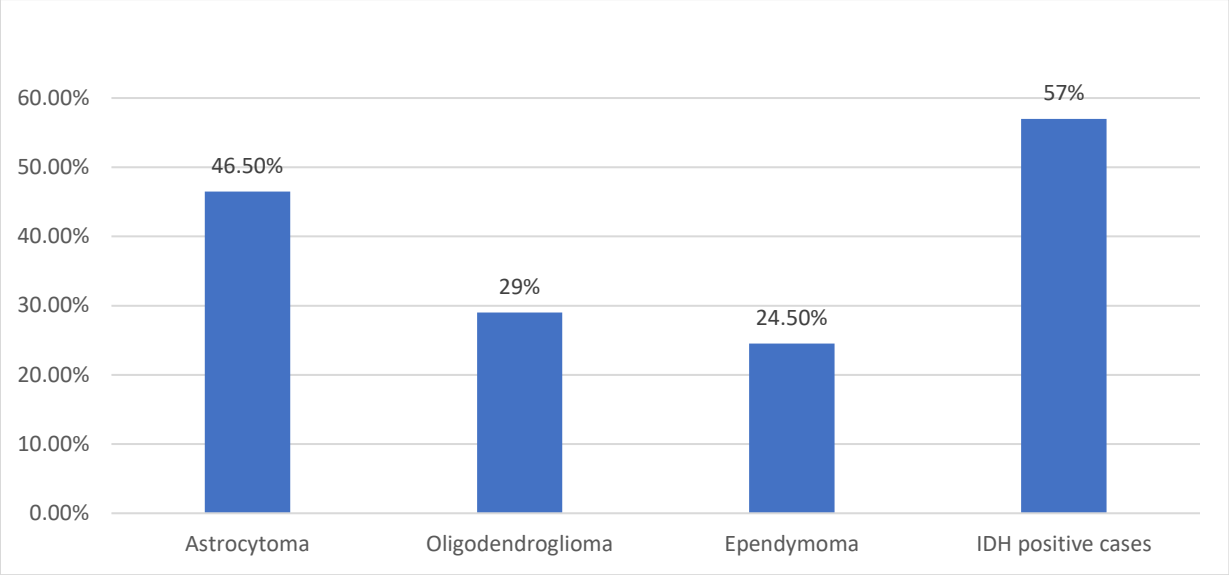
RESULTS:

Among 127 patients included in the study, the mean age of participants was 41.7 years. The main glioma type was Astrocytoma (46.5%), followed by Oligodendroglioma (29%) and Ependymoma (24.5%). IDH positive cases were 57%. Frequencies are shown in **table 1** and percentages in **Figure 1.**

Table 1: Mean age and Frequencies table.

Variable	Value (n=127)
Age (Mean)	41.7
Glioma type	
Astrocytoma	59
Oligodendroglioma	37
Ependymoma	31
IDH positive cases	73

Figure 1: Percentages of Glioma types and IDH positive cases.



As shown in **table 2** The majority of patients with Glioma Grades 2, 3, and 4 were in the 20-40 age group, with a notable increase in Grade 4 gliomas in patients under 20. Patients aged 40-60 were distributed more evenly across Grade 2 and Grade 4 gliomas, with fewer cases in Grade 3.

IDH Mutation Status:

Glioma Grade 1: All 9 cases were IDH-negative.

Glioma Grade 2: 22 cases were IDH-negative, while 31 were IDH-positive.

Glioma Grade 3: 11 cases were IDH-negative, and 8 were IDH-positive.

Glioma Grade 4: 12 cases were IDH-negative, and 34 were IDH-positive.

There is a higher proportion of IDH-positive cases in Grade 2 and Grade 4 gliomas, suggesting that IDH mutations may be more common in these grades.

The differences in both age distribution and IDH status across the glioma grades were analyzed. The p-value for both comparisons (age and IDH status) was found to be <0.05, indicating statistically significant differences across the grades.

This suggests that age and IDH mutation status are important factors that vary with glioma grade in this cohort.

Table 2: WHO Grades of Glioma and their age wise distribution.

Total Number of cases (n=127)		Glioma Grade 1 (n=11)	Glioma Grade 2 (35)	Glioma Grade 3 (n=19)	Glioma Grade 4(n=62)	P value
Age (years)	<20 20-40 40-60	2 4 5	3 18 14	2 10 7	14 28 20	0.038
IDH	Negative Positive	9 0	22 31	11 8	12 34	0.043

DISCUSSION:

About 80% of all brain tumors are gliomas, which are further divided into four tumor grades: grade 1 is the least aggressive type of glioma, while grade 4 is the most aggressive. Numerous mutations, including those affecting IDH1, p53, ATRX, Cyclin-dependent Kinase Inhibitor 2B (CDKN2B), and a few others, have been linked to the formation of gliomas. Through an increase in 2-hydroxyglutarate, the IDH1 mutation gives cells expressing it a growth advantage. Because the p53 mutation encourages unchecked cell growth, tumors occur as a result. The patient's age, the tumor's grade, and its location all influence the sort of therapy that will be administered **[6].**

Surgery is typically used to treat grade 1 and grade 2 tumors, whereas chemotherapy, radiation therapy, and surgery are used to treat grade 3 and 4 tumors **[6,7].**

In this study, the participants had an average age of 41.7 years. In their investigations, Lewandowska MA et al. and Deng L et al. found that the mean age was 36 years and 42.06 years, respectively **[8,9].**

Forty cases (or 50%) of the 80 cases of anaplastic astrocytoma that Hartmann C et al. investigated had IDH1 immunopositivity **[11].** In the current investigation, IDH1 positive was seen in 75% of grade 3 astrocytomas. 94% of grade 3 oligodendrogliomas tested positive for IDH1 immunoreactivity, according to a research by Capper D et al. **[12].** The current study showed that IDH immunopositivity was present in 57% of gliomas.

Lewandowska MA et al.'s study examined the observation that patients with lower IDH expression had higher survival times **[8].** As an illustration, they looked at two cases of grade 2 astrocytoma: one had low expression of IDH (1+ or 2+) and the other had high expression (3+ or 4+). It was reported that the patient with the low expression of grade 2 astrocytoma had a longer survival than the patient with the high expression **[8].** IDH mutation was once thought to be the only indicator of prognosis for Glioblastoma Multiforme (GBM) **[13].** For these, prognostic, therapeutic, and diagnostic goals, IDH mutations in gliomas are targeted **[14].**

According to Mellai M et al., patients with grade 3 and grade 4 gliomas with IDH mutations were reported to have a superior prognostic significance and a higher survival rate than patients with gliomas without IDH mutations **[10].**

Since the current study's sample size was small, more research with a larger number of cases is needed to get greater corroboration. There was not a uniform distribution of patients across all glioma tumor grades, and it was not feasible to follow up on the cases. As a result, factors including the tumor's recurrence, the patients' prognosis, and survival studies were neglected. Since this was a single institutional study, selection bias cannot be completely eliminated out.

Conclusion:

This study highlights the prevalence of IDH mutations in glioma patients at Hayatabad Medical Complex, with 57% of cases being IDH-positive, particularly in Grade 2 and Grade 4 gliomas. The presence of IDH mutations was statistically significant across different tumor grades and is associated with better survival outcomes, consistent with previous research.

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