Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Oct 13; 10(B):2465-2469.
https://doi.org/10.3889/oamjms.2022.10925
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Neurology*

Association of IDH1 Mutations with Epilepsies in Patients with Diffuse Adult Glioma according to the WHO 2021 Classification

Almir Dzurlic[1]*, Ibrahim Omerhodzic[1], Bekir Rovčanin[1], Faruk Alagić[2], Adi Ahmetspahic[1], Salko Zahirovic[1], Enra Mehmedika-Suljic[3]

[1]Clinic of Neurosurgery, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina; [2]Department of Neurosurgery, Cantonal Hospital Dr. Irfan Ljubijankić, Bihać, Bosnia and Herzegovina; [3]Clinic of Neurology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Edited by: Mirko Spiroski
Citation: Dzurlic A, Omerhodzic I, Rovčanin B, Alagić F, Ahmetspahic A, Zahirovic S, Mehmedika-Suljic E. Association of IDH1 Mutations with Epilepsies in Patients with Diffuse Adult Glioma according to the WHO 2021 Classification. Open-Access Maced J Med Sci. 2022 Oct 13; 10(B):2465-2469. https://doi.org/10.3889/oamjms.2022.10925
Keywords: Epilepsy; Diffuse Adult Glioma; WHO 2021 CNS classification; IDH mutation
***Correspondence:** Almir Dzurlic, Clinic of Neurosurgery, Clinical Center University of Sarajevo, Bolnička 25, Sarajevo, Bosnia and Herzegovina. E-mail: almir_dz86@hotmail.com
Received: 07-Sep-2022
Revised: 26-Sep-2022
Accepted: 03-Oct-2022

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

Keywords: Diffuse adult glioma; IDH1 mutations; Epilepsy

Abstract

BACKGROUND: Tumors of the central nervous system comprise a wide range of over 100 histological distinct subtypes with different descriptive epidemiology, clinical features, treatments, and outcomes. The presence of isocitrate dehydrogenase gene mutation 1 (IDH1) has become one of the most critical biomarkers for molecular classification and prognosis in adult diffuse gliomas. About 65–90% of patients with adult diffuse gliomas have seizures as their initial symptoms.

AIM: The objective of this study was to determine the association between IDH1 mutations in adult diffuse gliomas with an incidence of symptomatic epilepsy.

METHODS: The study was conducted as an observational, cross-sectional, and prospective clinically controlled study at the Clinic of Neurosurgery of the Clinical Center of the University of Sarajevo. The research included a total of 100 patients treated at the Clinic of Neurosurgery, with pathohistological confirmation of glioma Grades II–IV who were stratified by groups according to tumor grade. Data were collected on tumor localization and grade, the presence of IDH mutations, and the presence of epileptic seizures as the first symptom of the glioma.

RESULTS: Out of a total of 100 patients, 39 had IDH 1 mutations, while 61 patients were without them: Of these, diffuse astrocytoma Grade II 30 cases (30%), Grade III 5 (5%), and Grade IV 7 (7%), and the number of patients with glioblastoma was 58 (58%). In the group of patients with IDH 1 mutations, epileptic seizures were present in 87.2% compared to the group of patients without IDH 1 mutations (wild type) in which epileptic seizures were present in 16.4% of cases. Statistical analysis showed that the positive mutated IDH-type carries an almost 70% increase in the likelihood of epileptic seizures (χ^2 = 8.378; p = 0.0001). If we separate the group of diffuse astrocytomas in the IDH 1-positive subgroup, 34 patients (85.81%) had epileptic seizures, while in the IDH 1-negative subgroup, there were no patients with epileptic seizures, which carries a statistically significant difference in frequency in favor of IDH 1-positive tumors (p ≤ 0.001).

CONCLUSION: There is a clear connection between the presence of IDH1 mutations and the occurrence of epileptic seizures in the clinical picture of patients with diffuse adult glioma.

Introduction

Primary malignant brain tumors and other tumors of the central nervous system are generally rare. However, they represent a major challenge due to the high mortality rate, considering that only one-third of individuals survive at least 5 years after diagnosis [1]. In the US, primary brain tumors account for about 2% of all cancers, with a total annual incidence of 22 per 100,000 population, with nearly 80,000 new cases of which a third are malignant [1], [2]. The classification and understanding of these tumors has changed rapidly in recent years, in parallel with expanding molecular understanding and advances in detection and diagnosis, although much of the etiology still remains unknown [3].

According to the latest WHO classification from 2021, a new approach was given for the classification of glioma, glioneuronal and neuronal tumors, grouping them into six different groups. The presence of isocitrate dehydrogenase gene mutation (IDH1 or IDH2) has become one of the most critical biomarkers for molecular classification and prognosis in adult diffuse gliomas [4]. About 65–90% of patients with adult diffuse gliomas have seizures as their initial symptoms. In patients with temporal, insular, or frontal location of gliomas, the incidence of epilepsy is higher, especially oligodendrogliomas are closely related to pre-operative seizures [5]. The pathophysiological mechanism of epilepsy in patients with gliomas is very complex and many factors are included in it. However, our understanding is very poor. Many molecular biomarkers are thought to be associated with the onset of epileptic seizures. There are studies based on the investigation of biochemical changes in tumors and their microenvironment to establish the mechanisms and factors that influence the

development of cancer [5], [6]. One of the mechanisms that can explain epilepsy in patients with IDH 1 mutation is that IDH 1 enzyme reduces α-ketoglutarate to d-2-hydroxyglutarate (D2HG). D2HG bears a strong structural resemblance to glutamate. Glutamate is the prime excitatory neurotransmitter. IDH 1 mutant gliomas are producing D2HG which can potentially interact in the excitatory and inhibitory pathway, and in the end, they may produce seizure [7].

The aim of this study is immunohistochemical determination of the presence of IDH 1 mutations in a patient with supratentorial gliomas and determination of the association of IDH 1 mutations with symptomatic epilepsies.

Materials and Methods

The study was conducted as an observational, cross-sectional, and prospective clinically controlled study. The study was conducted at the Clinic of Neurosurgery of the Clinical Center of the University of Sarajevo, while additional immunohistochemical diagnostics was performed at the Department of Pathology, Clinical Center of the University of Sarajevo. The study included 100 patients aged 18−70, treated at Clinic of Neurosurgery during the period of September 2020 until July 2022. The study included those patients with pathohistological confirmation of glioma WHO Grades II–IV who were stratified by groups according to the tumor grade. Criteria for the inclusion of patients in the study were: Age 18−70 years, supratentorial gliomas WHO Grades II–IV (diffuse glioma Grades II–IV, GBM modified according to the WHO 2021), pre-operative neurodiagnostics (MRI of the brain), pathohistological diagnosis (with IDH status) of adult diffuse glioma WHO Grades II–IV, and GBM, modified according to the WHO 2021. At the beginning of the study, all subjects and/or families were thoroughly informed about the plan and procedure of the study, after which they gave written consent for voluntary participation in the study. The examination procedure of the examinee included the processing of previous medical documentation, medical history, neurological examination, pre-operative MRI of the brain with contrast, pathohistological verification of the tumor, and determination of the status of IDH 1 mutations, through glioma surgery or biopsy. The diagnosis of epilepsy is established on the basis of clinical manifestation of at least one epileptic attack with a verified tumor process in the brain, which is sufficient to establish the diagnosis of epilepsy. Standard statistical methods were used as a comparison using the Chi-square test, Fisher's exact test, and correlation analysis according to Spearman and regression multivariate analyses were performed to examine the impact. The results of all tests were considered significant at the confidence level of 95% or with values of $p < 0.05$. The analysis was performed using the statistical package IBM Statistics SPSS v23.0, R 4.2.1 and JASP 0.16.3.0.

Results

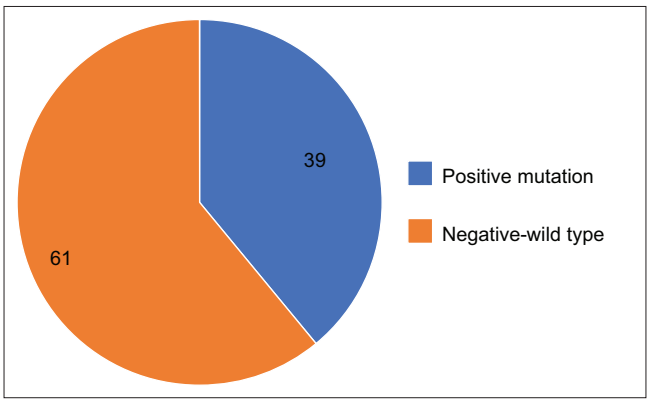
The average age of the patients was 51.8 ± 12.7 years (median – 52.5 years), with the youngest patient at the age of 22 and the oldest at the age of 70 years. Slightly higher representation of men in the sample with 57% compared to 43% of women.

Table 1: Percentage distribution according to isocitrate dehydrogenase status

IDH status	
Type	n (%)
Positive mutation	39 (39.0)
Negative wild type	61 (61.0)
Total	100 (100.0)

IDH: Isocitrate dehydrogenase.

If we look at the general representation of IDH 1 mutations, then negative wild type was more represented in 61% of cases compared to 39% of cases with positive mutated type, which is shown in Table 1 and Graph 1.



Graph 1: Distribution according to IDH status

In our study, in the group of patients with IDH-positive gliomas, epileptic seizures were present in 87.2%, but in the group of patients with IDH-negative wild-type gliomas epileptic seizures were present in 16.4% of cases.

Statistical analysis using Fisher's exact test shows a statistically significant difference ($\chi^2 = 8.378$; $p = 0.0001$), while correlation analysis using Spearman's rank correlation coefficient indicates a significant connection ($r = 0.696$; $p = 0.0001$) that means that positive mutated IDH-type carries an almost 70% increase in the odds of epileptic seizures (Table 2).

The analysis of the frequency of epileptic seizures according to the grade of diffuse astrocytomas shows that epileptic seizures as a symptom are present in 22 cases (63.63%) with diffuse astrocytoma Grade 2, while in the groups of diffuse astrocytomas Grades

3 and 4, they are present in 5 and 7 cases (100%), respectively.

Table 2: Distribution according to isocitrate dehydrogenase status

Seizure	IDH status		Total
	Positive mutation, n (%)	Negative wild type, n (%)	
Yes	34 (87.2)	10 (16.4)	44 (44.0)
No	5 (12.8)	51 (83.6)	56 (56.0)
Total	39 (100.0)	61 (100.0)	100 (100.0)

χ^2 = 8.378; *P* = 0.0001. r = 0,696; p = 0.0001. IDH: Isocitrate dehydrogenase.

The obtained p-value indicates that there is no statistically significant difference in the distribution of epileptic seizures according to the grade of diffuse astrocytomas (Table 3).

Table 3: Frequency of epileptic seizures according to grade of diffuse astrocytomas

Seizure	Diffuse astrocytomas			Chi-squared test
	Grade II	Grade III	Grade IV	
Yes	22 (63.63)	5 (100)	7 (100)	p = 0.1386
No	8 (36.37)	0	0	χ^2 = 3.9529

Within the group of diffuse astrocytomas, in the subgroup of IDH positive, 34 patients (85.81%) had epileptic seizures in the clinical picture, while in the subgroup of IDH negative, there were no patients with epileptic seizures (Table 4).

Table 4: Frequency of epileptic attacks in the subgroup of diffuse astrocytomas

Seizure	IDH status		Chi-squared test
	Positive	Negative	
Yes	34	0	p ≤ 0.001
No	5	3	χ^2 = 13.731

IDH: Isocitrate dehydrogenase.

Discussion

In our study, a significant association between epileptic seizures and IDH 1 mutations was demonstrated, which correlates with most of the earlier studies. In the group of patients with IDH1-mutated adult diffuse gliomas, epileptic seizures were present in 87.2%, while in the group with IDH1 wild type, epileptic seizures were present in 16.4% of patients, which represents an almost 70% increase in the likelihood of epileptic seizure attacks in IDH1-mutated tumors. By analyzing the frequency of epileptic seizures within the group of diffuse astrocytomas, and according to the presence of IDH mutations, a statistically significant difference in frequency is also obtained in favor of IDH-positive tumors.

After the discovery of IDH mutations, several studies reported a higher incidence of epileptic seizures in patients carrying these mutations [8]. In addition, even the different rate of epileptic seizures within histological subgroups of gliomas is primarily explained by the different prevalence of IDH mutation [9]. A meta-analysis published in 2017 that included low-grade gliomas (grade II) in a sample of 722 patients proved that IDH1 mutations are correlated with a higher incidence of pre-operative epileptic attacks in low-grade glioma [10]. In our study within the group of diffuse astrocytomas, in the subgroup of IDH positive, 34 patients (85.81%) had epileptic seizures in the clinical picture, while in the subgroup of IDH negative, there were no patients with epileptic seizures. This correlates with the previous published studies.

Duan *et al*. proved that IDH1 mutations are significantly associated with pre-operative seizures in patients with IDH1 mutation [5]. Recently, Feiissa *et al*. confirmed that IDH1 mutation and MGMT methylation are associated with the occurrence of perioperative seizures [11]. However, another study found that the presence of IDH1 mutations was not associated with the incidence of epilepsy, although the results of that study may have been influenced by the inclusion of higher-grade tumors [12]. Yang *et al*. reported that patients with low MGMT protein expression were more likely to experience seizures after surgery [13]. In contrast, Feiissa *et al*. found that MGMT gene promoter methylation is associated with increased post-operative seizure control [11].

The results of a large meta-analysis that included a total of 12 studies showed that the isocitrate dehydrogenase 1 mutation is significantly associated with the incidence of perioperative epilepsy. Subgroup analysis showed that IDH1 was significantly associated with the incidence of pre-operative epilepsy, but not with intraoperative and post-operative epilepsy. There was no correlation between O6-methylguanine-DNA methyltransferase methylation and 1p/19k deletion and the incidence of perioperative epilepsy [12].

A more recent study that examined the impact of IDH1 and IDH2 mutations in different types of tumors with special reference to gliomas showed that in a sample of 923 patients, the total prevalence of IDH1 mutations was 34%. In diffuse astrocytomas, the percentage of IDH1 mutations was 76.7%, while in glioblastoma, this percentage was 5.6% [14]. Furthermore, a more recent study that included astrocytic and oligodendroglial tumors proved the presence of IDH1 mutations in 60% of diffuse astrocytomas, 33% of anaplastic astrocytomas, 67% of anaplastic oligodendrogliomas, and 5% of glioblastomas [15]. An earlier meta-analysis analyzing IDH1 and IDH2 mutations from 55 different studies with 9487 glial tumors showed that both mutations were independently and statistically significantly associated with better overall survival and progression of free survival and disease-free survival in glioma patients [16]. These results provide additional evidence of an important role for these genes and suggest that IDH mutations are strong prognostic markers for survival in glioma and epileptic seizures.

Today, there are approved two drugs used in the treatment for IDH mutant acute myeloid leukemia (AML): Ivosidenib (IDH1 inhibitor) and enasidenib

(IDH2 inhibitor). Ivosidenib is an oral drug used for AML with suspected IDH1 mutation [17]. In a case report, authors reported post-operative drug resident epilepsy in a patient with oligodendroglioma. They treated the patients with ivosidenib, his seizure frequency decreased substantially after starting ivosidenib [18]. The inhibition of D2HG production by drug inhibition of IDH1 shows us the importance of IDH1 mutation in the pathophysiology of epilepsy in adult diffuse gliomas. Additional in one study with 170 patients glioma authors showed that IDH1 inhibitors may help manage seizures in patients with IDH1 mutant glioma and epilepsy [13].

Limitations of this study were a small sample size, the determination of IDH was performed only immunohistological, we did not perform PCR, short study period, the evidence of epileptic seizure was not completely documented by our team (sometime family or emergency room).

Conclusion

In this study, we have shown that there is a clear connection between the presence of IDH1 mutations and the occurrence of epileptic seizures in the clinical picture of patients with diffuse adult gliomas. In the future, there is a need for more clinical and molecular studies to evaluate the role of IDH1 in epilepsy for patients with diffuse adult gliomas and potential therapeutics.

References

1. Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, *et al*. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. Neuro Oncol. 2017;19 Suppl 5:v1-88. https://doi.org/10.1093/neuonc/nox158
   PMid:29117289
2. Lapointe S, Perry A, Butowski NA. Primary brain tumours in adults. Lancet. 2018;392(10145):432-46. https://doi.org/10.1016/S0140-6736(18)30990-5
   PMid:30060998
3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33. https://doi.org/10.3322/caac.21654
   PMid:33433946.
4. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, *et al*. The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro Oncol. 2021;23(8):1231-51. https://doi.org/10.1093/neuonc/noab106
   PMid:34185076
5. Duan WC, Wang L, Li K, Wang WW, Zhan YB, Zhang FJ, *et al*. IDH mutations but not TERTp mutations are associated with seizures in lower-grade gliomas. Medicine (Baltimore). 2018;97(50):e13675. https://doi.org/10.1097/MD.0000000000013675
   PMid:30558073
6. Pitkänen A, Ekolle Ndode-Ekane X, Lapinlampi N, Puhakka N. Epilepsy biomarkers – Toward etiology and pathology specificity. Neurobiol Dis. 2019;123:42-58. https://doi.org/10.1016/j.nbd.2018.05.007
   PMid:29782966
7. Chen H, Judkins J, Thomas C, Wu M, Khoury L, Benjamin CG, *et al*. Mutant IDH1 and seizures in patients with glioma. Neurology. 2017;88(19):1805-13. https://doi.org/10.1212/WNL.0000000000003911
   PMid:28404805
8. Zou Y, Bai HX, Wang Z, Jiang Y, Yang L. Association of IDH1/2 mutation with preoperative seizure in low-grade gliomas: How strong is the evidence? Epilepsy Res. 2015;112:154-5. https://doi.org/10.1016/j.eplepsyres.2015.02.012
   PMid:25769499
9. Skardelly M, Brendle E, Noell S, Behling F, Wuttke TV, Schittenhelm J, *et al*. Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: A retrospective observational single center study. Ann Neurol. 2015;78(6):917-28. https://doi.org/10.1002/ana.24522
   PMid:26385488
10. Li Y, Shan X, Wu Z, Wang Y, Ling M, Fan X. IDH1 mutation is associated with a higher preoperative seizure incidence in low-grade glioma: A systematic review and meta-analysis. Seizure. 2018;55:76-82. https://doi.org/10.1016/j.seizure.2018.01.011
    PMid:29414139
11. Feyissa AM, Worrell GA, Tatum WO, Chaichana KL, Jentoft ME, Guerrero Cazares H, *et al*. Potential influence of IDH1 mutation and MGMT gene promoter methylation on glioma-related preoperative seizures and postoperative seizure control. Seizure. 2019;69:283-9. https://doi.org/10.1016/j.seizure.2019.05.018
    PMid:31141785
12. Song L, Quan X, Chen C, Chen L, Zhou J. Correlation between tumor molecular markers and perioperative epilepsy in patients with glioma: A systematic review and meta-analysis. Front Neurol. 2021;12:692751. https://doi.org/10.3389/fneur.2021.692751
    PMid:34539550
13. Yang Y, Mao Q, Wang X, Liu Y, Mao Y, Zhou Q, *et al*. An analysis of 170 glioma patients and systematic review to investigate the association between IDH-1 mutations and preoperative glioma-related epilepsy. J Clin Neurosci. 2016;31:56-62. https://doi.org/10.1016/j.jocn.2015.11.030
    PMid:27406953
14. Murugan AK, Alzahrani AS. Isocitrate dehydrogenase IDH1 and IDH2 mutations in human cancer: Prognostic implications for gliomas. Br J Biomed Sci. 2022;79:10208. https://doi.org/10.3389/bjbs.2021.10208
    PMid:35996504
15. Sporikova Z, Slavkovsky R, Tuckova L, Kalita O, Megova Houdova M, Ehrmann J, *et al*. IDH1/2 mutations in patients with diffuse gliomas: A Single Centre Retrospective Massively Parallel Sequencing Analysis. Appl Immunohistochem Mol Morphol. 2022;30(3):178-83. https://doi.org/10.1097/PAI.0000000000000997
    PMid:35262523
16. Xia L, Wu B, Fu Z, Feng F, Qiao E, Li Q, *et al*. Prognostic role of IDH mutations in gliomas: A meta-analysis of 55 observational

studies. Oncotarget. 2015;6(19):17354-65. https://doi.org/10.18632/oncotarget.4008
PMid:26220714

17. Mellinghoff IK, Ellingson BM, Touat M, Maher E, De La Fuente MI, Holdhoff M, *et al*. Ivosidenib in isocitrate dehydrogenase 1-mutated advanced glioma. J Clin Oncol. 2020;38(29):3398-406. https://doi.org/10.1200/JCO.19.03327
PMid:32530764

18. Vo AH, Ambady P, Spencer D. The IDH1 inhibitor ivosidenib improved seizures in a patient with drug-resistant epilepsy from IDH1 mutant oligodendroglioma. Epilepsy Behav Rep. 2022;18:100526. https://doi.org/10.1016/j.ebr.2022.100526
PMid:35198955