The Potential Effect of the IDH1 Mutation and MGMT Gene Promotor Methylation on the Control of Glioblastoma-Associated Epilepsy in Patients Receiving Anti-Epileptic Agents and Chemotherapies

Maier Kurdi (✉ Ahkurdi@kau.edu.sa)

King Abdulaziz University <https://orcid.org/0000-0002-8979-3849>

Nadeem Shafique Butt

King Abdulaziz University

Saleh Baeesa

King Abdulaziz University

Badrah Alghamdi

King Abdulaziz University

Yazid Maghrabi

King Faisal Specialist Hospital and Research Centre - Jeddah

Anas Bardeesi

King Faisal Specialist Hospital and Research Center

Rothaina Saeedi

King Abdulaziz University

Fahad Alghamdi

King Abdulaziz University

Najla Alghanmi

King Abdulaziz University

Mohammed O. Bari

King Abdulaziz University

Alaa Samkari

King Saud bin Abdulaziz University for Health Sciences

Ahmed I. Lary

King Saud bin Abdulaziz University for Health Sciences

Taghreed Alsinani

King Fahad General Hospital

Keywords: Glioblastoma, Epilepsy, MGMT promotor methylation, IDH1 mutation, Anti-epileptic drugs, Temozolomide

Posted Date: March 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-314962/v1>

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Abstract

Objective: (a) To assess the control of glioblastoma-associated seizure in patients receiving different anti-epileptic drugs and chemotherapies after total resection and its association with O-methylguanine-DNA methyltransferase (*MGMT*) promotor methylation and the isocitrate dehydrogenase 1 (*IDH1*) mutation; (b) to determine which anti-epileptic drug exerts the best effective control on glioblastoma-associated epilepsy; (c) to identify the relationship between seizure control and different anti-epileptic drugs and recurrence interval.

Methods: This was a retrospective cohort study of patients with postoperative glioblastoma-associated epilepsy in the period between 2014 and 2019. The correlations between the *IDH1* mutation and *MGMT* promotor methylation with anti-epileptic drugs, chemotherapy type, seizure control, and recurrence interval were analyzed using different statistical methods.

Results: This study included 53 adult patients with glioblastoma-associated epilepsy. The *IDH1* mutation was present in 20 patients, and *MGMT* promotor methylation was present in 13 patients. Out of 53 patients, 37 cases received chemoradiotherapy while 16 cases receive only radiotherapy. Levetiracetam was the most prescribed anti-epileptic drug ($n = 36$, 60%), and 36 and 16 patients had controlled and uncontrolled seizures, respectively. The *IDH1* mutation and unmethylated *MGMT* promotor were significantly present in cases with controlled epilepsy ($P < 0.05$). Among the anti-epileptic drugs, levetiracetam showed significantly better seizure control in cases with the *IDH1* mutation and unmethylated *MGMT* promotor ($P < 0.05$). Patients did not show significant differences in either seizure control or the tumor recurrence interval ($P > 0.05$).

Conclusion: (a) Glioblastoma-associated epilepsy can be better controlled in patients with the *IDH1* mutation and unmethylated *MGMT* promotor compared with patients with the methylated *MGMT* promotor, (b) Levetiracetam is considered the first-line anti-epileptic drug for controlling seizures but may not enhance the sensitivity of glioblastomas to chemotherapies, (c) Lack of seizure control in glioblastoma patients may not be related to tumor recurrence despite one-year treatment with anti-epileptic drugs, (d) Better understanding of the risk factors and mechanisms associated with glioma-associated epilepsy are needed to improve patient quality of life.

Introduction

Glioblastoma-associated epilepsy is an uncommon manifestation of infiltrative gliomas, and approximately 30% of cases are drug-resistant even after glioma resection (1) (2) (3). The cause of this is still unclear; however, it is likely that genetic factors of the peritumoral brain tissue are responsible for these seizures (1) (4) (5) (6). There is evidence that tumor growth may stimulate the epileptic focus, suggesting that the two conditions may share common pathogenic mechanisms and influence each other (5). Another possible explanation is the association of gliomas with the isocitrate dehydrogenase 1 (*IDH1*) mutation. Previous studies showed that *IDH1*-mutant gliomas are more likely to cause seizures

than *IDH1*-wildtype (wt) gliomas (6) (7) (8), as the mutant enzyme reduces α -ketoglutarate to D-2-hydroxyglutarate. Hence, D-2-hydroxyglutarate overproduction and its structural similarity to glutamate have been suggested to play a role in the neuronal excitation leading to seizures (6). While the association of the *IDH1* mutation with preoperative seizures has been previously reported, the influence of the *IDH1* mutation in the postoperative glioma microenvironment is yet to be clarified. Multimodal strategies fail to control seizures (9), and a better understanding of the risk factors and mechanisms of glioma-associated epilepsy are needed to improve patient quality of life.

Gliomas with O6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation are more treatment-sensitive to temozolomide (TMZ) chemotherapy (10). However, the association of glioma-associated epilepsy with *MGMT* promoter methylation has not been extensively studied. Patients with *MGMT* methylated gliomas show more seizure control than those with non-methylated *MGMT* (11) (8). In this study, we assessed seizure control among glioblastoma patients, after total resection, receiving different anti-epileptic drugs and chemotherapies and investigated its associations with *MGMT* promoter methylation and the *IDH1* mutation. Levetiracetam is the most potent *MGMT* inhibitor among several anti-epileptic medications with diverse *MGMT* regulatory actions and is considered the first-line drug to control seizures in glioma patients (12). Multiple studies concluded that levetiracetam and valproic acid are the main anti-epileptic drugs that exhibit antitumor effects and decrease the mortality rate among glioblastoma patients with epilepsy (13) (14) (15). In this study, we also have investigated which anti-epileptic drug exerts the best effective control of glioblastoma-associated epilepsy in Saudi Arabia and have also identified the relationship of seizure control with different anti-epileptic drugs and the recurrence interval. The only limitations we faced in this current study were the limited number of glioblastoma-associated seizure and the unknown biological cause of seizure progression or patient death when they showed late recurrence.

Materials And Methods

Patient stratification

This study included 53 patients with glioblastoma-associated epilepsy from two medical hospitals in Saudi Arabia in the period between 2014 and 2019.

This study was ethically approved by the National Biomedical Ethics Committee at King Abdulaziz University (HA-02-J-008).

All patients underwent total surgical resection of the tumor followed by a standard protocol of adjuvant therapies. The histological diagnosis was made according to the classification of the World Health Organization (WHO). Clinical data were retrieved from hospital records, including patients' age at diagnosis, gender, postoperative adjuvant therapies, anti-epileptic medications, history of seizure control, and *MGMT* methylation profile. The patients were stratified into different groups based on the types of chemotherapies and anti-epileptic drugs. Standard radiotherapy with a total dose of 60 Gy and TMZ (150–200 mg/m² for 6–12 cycles) were administered to all patients at the time of management.

Unfortunately, all patients who had recurrence have died. Patients who showed no recurrence for more than year eventually passed away because of other comorbidities.

Tumor samples

Archival routine formalin-fixed and paraffin-embedded tumor tissues were collected from 53 patients diagnosed with glioblastoma-associated epilepsy. Hematoxylin-and-eosin-stained sections were re-examined by a certified neuropathologist (MK) to assure the histopathological diagnosis followed the WHO's classification. Unstained positive-charged slides from 46 tissue blocks were prepared for *IDH1* immunostaining.

Immunohistochemistry for IDH1

To qualitatively identify wt and mutant IDH1 in tissue sections on an automated slide stainer, the mouse monoclonal antibody anti-IDH1 R132H (clone H09) and OptiView detection kit from Ventana on a BenchMark XT automated staining system were used. The assay procedure consisted of deparaffinization with EZ Prep at 75°C, heat pre-treatment with Cell Conditioner for 68 min, and incubation with 1:20–1:50 diluted antibody for 32 min at 37°C. The slides were counterstained with Hematoxylin II for 16 min, and bluing reagent was used for 16 min. Afterwards, the slides were removed from the slide stainer and then immersed into successive alcohol buffers at different concentrations for 3 min. Sections in which > 10% of tumor cells were positively stained were defined as IDH1-mutant (Fig. 1).

Statistical analysis

Data was described as frequencies and percentages. The recurrence interval was calculated from the time of adjuvant therapy initiation after surgical resection until the first day of tumor recurrence. The Pearson's Chi-Square test was used to explore the associations between the *IDH1* mutation, *MGMT* promotor methylation status, seizure control, anti-epileptic drug, and chemotherapy with various study factors. Kaplan-Meier curves and log-rank tests were used to compare the distribution of recurrence times. All statistical analyses in this study were performed using IBM SPSS1 ver. 24 statistical software programs (SPSS Inc., Chicago, IL).

Results

1. Descriptive analysis

In total, 53 postoperative patients with glioblastoma-associated seizures were included in this study (36 men and 17 women). The mean age was 51 years. The predominant locations were the frontal ($n = 21$, 39.6%) and temporal lobes ($n = 17$, 32.1%). We observed the *IDH1* mutation in 20 patients (37.7%), *MGMT* methylation in 13 patients, and the unmethylated *MGMT* promotor in 40 patients. Furthermore, 37 patients received a standard treatment protocol of chemoradiotherapy, whereas 16 patients received only radiotherapy. Of those who received chemotherapy, 29 (78.4%) patients received TMZ alone, and 8 (21.6%) patients received TMZ together with other chemotherapies. Epilepsy was controlled in 36 patients

(69.2%), and 16 patients (30.8%) had uncontrolled epilepsy. Table 1 and Fig. 2 summarize the descriptive distribution of the data and the study plan.

2. Statistical analysis

2.1 *The IDH1 mutation and MGMT methylation with seizure control*

Although the *IDH1* mutation was significantly present in glioblastoma patients with controlled seizure ($P = 0.002$; Fig. 3a–b), there was no significant difference in seizure control between cases with mutant or wt *IDH1* ($P = 0.085$; Table 2). However, the unmethylated *MGMT* promotor was significantly more abundant in patients with controlled seizure than in *MGMT* methylated patients; a significant relationship in seizure control was found between different groups of *MGMT* methylation ($P = 0.037$). Although seizure in patients with the *IDH1* mutation and unmethylated *MGMT* promotor was significantly controlled ($P = 0.002$; Fig. 3c–d), there was no significant difference in seizure control among unmethylated *MGMT* cases with mutant and wt *IDH1*.

2.2 *The relationship between the IDH1 mutation and MGMT methylation with different types of anti-epileptic drugs and seizure control*

Regardless of the status of the *IDH1* mutation and *MGMT* profile, there were no significant differences in seizure control among cases treated with different anti-epileptic drugs ($P = 0.737$; **Table 3**). However, levetiracetam showed significantly better seizure control in cases with the *IDH1* mutation and unmethylated *MGMT* promotor than in cases with methylated *MGMT* ($P = 0.002$; Fig. 4). There were no significant differences in seizure control among cases with wt *IDH1*, regardless of the *MGMT* profile.

2.3 *The relationship between anti-epileptic drugs and chemotherapies with seizure control and the tumor recurrence interval*

There was no significant relationship between chemotherapies and anti-epileptic drugs with seizure control ($P = 0.486$; **Table 4**). Our analysis also showed no significant difference in seizure control among cases treated with TMZ ($P = 1.6$), levetiracetam ($P = 0.25$), TMZ plus levetiracetam ($P = 0.8$), or TMZ plus phenytoin ($P = 0.75$). Moreover, there was no significant difference in the tumor recurrence interval in glioblastoma patients receiving chemotherapeutic agents with controlled or uncontrolled epilepsy ($P = 0.88$; **Table 5**; Figs. 5–6).

Discussion

Secondary epilepsy is a common manifestation of infiltrative gliomas and occurs in high-grade gliomas less commonly than in low-grade gliomas; however, the reason for this is still unclear (1). Patients with temporal and frontal gliomas are more likely to experience seizures, and low-grade gliomas with oligodendroglial pathology are strongly associated with preoperative seizures (16). Approximately 30% of gliomas are drug-resistant even after resection (2) (3); however, the underlying mechanisms of this are still poorly understood. It is likely that epilepsy occurrence rates are not merely explained by peritumoral changes and that the internal relationship of genetic factors of the peritumoral brain tissue could be responsible for these seizures (4). Multiple studies suggested that epileptogenesis is actually influenced by tumor molecular genetic markers (5) (6) (1). Another study also found that tumor growth may stimulate the epileptic focus, suggesting that the two conditions may share common pathogenic mechanisms that influence each other (5).

Another possible explanation is the association of gliomas with the *IDH1* mutation. Studies showed that mutant *IDH1* gliomas are more likely to cause seizures than wt *IDH1* (6) (7) (8). *IDH1* is a metabolic enzyme located in the cytosol catalyzing the oxidative decarboxylation of isocitrate to α -ketoglutarate. The mutant enzyme reduces α -ketoglutarate to D-2-hydroxyglutarate. Hence, overproduction of D-2-hydroxyglutarate and its structural similarity to glutamate may be involved in the mechanism of neuronal excitation leading to seizures (7) (Fig. 1). Exposure to exogenous D-2-hydroxyglutarate increased the duration of synchronized network burst firing, and this was subsequently blocked by a selective N-methyl-D-aspartate receptor (NMDA) antagonist (1).

While the association of the *IDH1* mutation with preoperative seizures was extensively reported, the influence of the *IDH1* mutation in the postoperative glioma microenvironment is yet to be clarified. Chen et al. found that seizures are more likely to be present in low-grade gliomas with the *IDH1* mutation and 1p19q codeletion than in high-grade gliomas with the *IDH1* mutation. However, epilepsy during the end-of-life phase in glioblastoma patients became uncontrolled (17). Yang et al. studied the relationship of 172 gliomas with epilepsy (18) and found that 27% of glioblastomas were associated with epilepsy but that 64% of these epilepsy patients had low-grade gliomas. Furthermore, *IDH1*-mutant gliomas were associated with preoperative seizure mainly in cases of grade II gliomas (73%) but not glioblastomas. Our current study also found that the *IDH1* mutation is significantly associated with controlled epilepsy in glioblastoma patients.

Currently, multimodal strategies fail to control seizures in up to a third of patients (9). Thus, a better understanding of the risk factors and mechanisms associated with glioma-associated epilepsy are needed to improve patient quality of life. To the best of our knowledge, although gliomas with *MGMT* gene promoter methylation are known to be more treatment-sensitive to TMZ chemotherapy [10], the association of glioma-associated epilepsy and *MGMT* promoter methylation has never been extensively studied. The relationship between preoperative and postoperative seizure control, in regard to *MGMT* gene promoter methylation status, is also limited. Patients with low expression of *MGMT* protein or *MGMT* methylated gliomas had more frequent postoperative seizure control than those with non-methylated *MGMT* or high *MGMT* protein activity (11) (8). The observed favorable postoperative seizure

control in those with *MGMT* gene promotor methylation could stem from the better response to adjuvant chemoradiation therapy in this patient population (8). Nevertheless, these findings did not clarify whether *MGMT* methylation was the main reason for postoperative seizure control or whether anti-epileptic drugs act as potent *MGMT* methylation inhibitors. The results of our current study have demonstrated that the unmethylated *MGMT* promotor had more significant seizure control.

Bobustuc et al. reported that levetiracetam was the most potent *MGMT* inhibitor among several anti-epileptic medications with diverse *MGMT* regulatory actions and is thus considered the first-line drug to control seizure in glioma patients receiving TMZ (12). This is because levetiracetam enhances *P53*-mediated *MGMT* inhibition, which sensitizes glioblastoma cells to TMZ (17) (12). This mechanism has never been investigated thoroughly, and thus further studies are necessary.

Scattered studies found that levetiracetam and valproic acid are the main anti-epileptic drugs that exhibit antitumor effects and have shown an actual decrease in the mortality rate among glioblastoma patients with epilepsy (13) (14) (15). Valproic acid exhibits antitumor effects via inhibition of mSin3A/histone deacetylase 1 and modulation of the mitogen-activated protein kinase pathway. Additionally, owing to the radio-sensitizing properties of valproic acid, radiotherapy with valproic acid is more effective than radiotherapy with other drugs (19). Another study on 418 patients with glioblastoma-associated seizures in Korea found that levetiracetam treatment in cases with the methylated *MGMT* promoter positively influenced the overall survival rate. In our study, we also found that levetiracetam is the first-line drug for glioblastoma-associated epilepsy. However, we reject the idea that levetiracetam sensitizes glioblastoma cells to chemotherapy, as there was no significant relationship with tumor recurrence interval when both anti-epileptic drugs and chemotherapies were used in glioblastoma patients.

Conclusion

Our study has come to three main conclusions. First, glioblastoma-associated epilepsy can be better controlled in patients with the *IDH1* mutation or unmethylated *MGMT* promotor than in patients with the methylated *MGMT* promotor. Second, levetiracetam can be considered the first-line anti-epileptic drug for controlling seizures yet may not enhance the sensitivity of glioblastomas to chemotherapies. Third, the lack of seizure control in glioblastoma patients is not related to tumor recurrence despite one-year treatment with anti-epileptic drugs. We recommend using *IDH1* and the *MGMT* gene promotor as parameters in seizure control. We also recommend using levetiracetam as first-line treatment, regardless of the type of chemotherapeutic agent.

Declarations

Note

Unknown cases are not included in this table. Pearson's Chi-squared test¹

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Unknown cases are not included in this table. Pearson's Chi-squared test¹

Funding:

No funding received for the current study.

Consenting

The study did not include any patient information required consent for publications.

Authors' contributions:

MK, idea, IRB submission, writing, study design and data, and histological analysis; NS, Statistical analysis; SB, data provider, writing, and analysis; BG, study design, writing, and editing; YM, data entry, tissue collection, and writing; AB, data entry, and tissue collection; RS, data entry, tissue collection, and writing; FA, Histological and data analysis, NA, Data collection, MB: IHC analysis and histological correlation; AS, data provider, writing, and histological revision; AL, data provider, and IRB submission; TA, Clinical information provider.

Acknowledgment:

none.

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Tables

Table 1. Characteristics of patients and therapies. Isocitrate dehydrogenase 1 mutation (IDH1); O-methylguanine-DNA methyltransferase (MGMT).

Overall (N=53)	
Age	
Mean (SD)	51.4 (17.6)
Gender	
Female	17 (32.1%)
Male	36 (67.9%)
Tumor Location	
Frontal	21 (39.6%)
Occipital	2 (3.8%)
Parietal	13 (24.5%)
Temporal	17 (32.1%)
Anti-Epileptic Drug	
Carbamazepine	1 (1.9%)
Levetiracetam	23 (43.4%)
Levetiracetam + Carbamazepine	2 (3.8%)
Levetiracetam + Lacosamide	1 (1.9%)
Levetiracetam + Lamotrigine	3 (5.7%)
Levetiracetam + Phenytoin	5 (9.4%)
Levetiracetam + Valproic acid	2 (3.8%)
Phenytoin	12 (22.6%)
Others	2 (3.8%)
Phenytoin + Lacosamide	2 (3.8%)
Epilepsy Control Status	
Unknown	1
Controlled	36 (69.2%)
Uncontrolled	16 (30.8%)
IDH1 Mutation	
IDH mutant	20 (37.7%)
IDH wildtype	26 (49.1%)

	Overall (N=53)
Undetermined	7 (13.2%)
MGMT Profile	
MGMT hypermethylation	13 (24.5%)
No MGMT methylation	40 (75.5%)
Adjuvant Therapy	
Radiation and Chemotherapy	37 (69.8%)
Radiotherapy	16 (30.2%)
Chemotherapy	
Temozolomide	29 (78.4%)
Temozolomide plus others	8 (21.6%)
Recurrence Status	
No recurrence	21 (39.6%)
Recurrence	32 (60.4%)

Table 2. Seizure control in cases with *IDH1* mutation and *MGMT* promotor methylation. There were no significant differences between seizure control and *IDH1* status among cases with glioblastoma-associated epilepsy. However, a significant relationship in seizure control was found between different groups of *MGMT* methylation.

			Seizure Control Status	
Molecular Profile	Controlled	Uncontrolled	Total (n=53)	P-value
IDH1-mutant	17.0 (85.0%)	3.0 (15.0%)	36.0 (69.2%)	0.085 ¹
IDH1-wildtype	16.0 (64.0%)	9.0 (36.0%)	16.0 (30.8%)	
Methylated MGMT	6.0 (16.7%)	7.0 (43.8%)	13.0 (25.0%)	0.037 ¹
Unmethylated MGMT	30.0 (83.3%)	9.0 (56.2%)	39.0 (75.0%)	

Note: Unknown cases are not included in this table. Pearson's Chi-squared test¹

Table 3. The relationship of anti-epileptic drugs and seizure control, regardless of the status of the *IDH1* mutation and *MGMT* promotor methylation. There were no significant differences in seizure control

among cases treated with levetiracetam, phenytoin, or levetiracetam with phenytoin.

	Controlled (n=36)	Uncontrolled (n=16)	Total (n=52)	P-value
Anti-Epileptic Drugs				0.737 ¹
Levetiracetam	17.0 (47.2%)	5.0 (31.2%)	22.0 (42.3%)	
Phenytoin	8.0 (22.2%)	4.0 (25.0%)	12.0 (23.1%)	
Levetiracetam + Phenytoin	3.0 (8.3%)	2.0 (12.5%)	5.0 (9.6%)	
Others	8.0 (22.2%)	5.0 (31.2%)	13.0 (25.0%)	

Pearson's Chi-squared test¹

Table 4. The relationship between anti-epileptic drugs and chemotherapies with seizure control. Patients with glioblastoma-associated epilepsy, regardless of the type of anti-epileptic drugs and chemotherapies, showed no significant differences in seizure control.

Type of Chemotherapy	Seizure Control Status			P-value
	Controlled	Uncontrolled	Total	
Anti-Epileptic Drugs + Temozolomide	21.0 (80.8%)	7.0 (70.0%)	28.0 (77.8%)	0.486 ¹
Anti-Epileptic Drugs + Temozolomide plus Other	5.0 (19.2%)	3.0 (30.0%)	8.0 (22.2%)	

Note: Unknown cases are not included in this table. Pearson's Chi-squared test¹

Table 5. The relationship between seizure control in glioblastoma patients and tumor recurrence interval. Patients with glioblastoma-associated epilepsy, regardless of the status of seizure control, showed no significant differences in the recurrence interval.

Seizure Control Status	Tumor Recurrence Interval			P-value
	Before 1 Year (N=30)	After 1 Year (n=23)	Total (n=53)	
Controlled	21.0 (70.0%)	15.0 (68.2%)	36.0 (69.2%)	0.888 ¹
Uncontrolled	9.0 (30.0%)	7.0 (31.8%)	16.0 (30.8%)	

Figures

Figure 1

The expression of the IDH1 in glioblastoma-associated epilepsy. The positively expressed IDH1 mutant (left) and the negative wild-type IDH1 (right). Scale bar: 100 µm.

Figure 2

The algorithm of the study objectives. Cases with glioblastoma-associated epilepsy were stratified into subdivided groups based on the IDH1, O-methylguanine-DNA methyltransferase (MGMT) methylation, and seizure control.

Figure 3

The IDH1 and O-methylguanine-DNA methyltransferase (MGMT) methylation with seizure control. The IDH1 mutation is significantly present in glioblastoma patients with controlled seizure (a,b). Seizure in patients with the IDH1 mutation and unmethylated MGMT promotor was significantly controlled (c,d).

Figure 4

Levetiracetam shows significantly more seizure control in cases with the IDH1 and unmethylated O-methylguanine-DNA methyltransferase (MGMT) promotor than in cases with methylated MGMT.

Figure 5

The relationship between seizure control and chemotherapies with the tumor recurrence interval, illustrated by Kaplan-Meier analyses. There is no significant difference in the tumor recurrence interval between glioblastoma patients with controlled epilepsy receiving chemotherapeutic agents.

Figure 6

The relationship between seizure control and chemotherapies with the tumor recurrence interval, illustrated by Kaplan-Meier analyses. There is no significant difference in the tumor recurrence interval between glioblastoma patients with uncontrolled epilepsy receiving chemotherapeutic agents.