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Potential influence of IDH1 mutation and MGMT gene promoter methylation on glioma-related preoperative seizures and postoperative seizure control

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ABSTRACT

Purpose: To examine the occurrence of glioma-related preoperative seizures (GPS) and post-operative seizure control (PSC) with respect to patients characteristics including five commonly tested tumor molecular markers (TMMs).

Methods: A single-center retrospective cohort study of patients with glioma evaluated at the Mayo Clinic, Florida between 2016 and 2018.

Results: 68 adult patients (mean age = 51-years, 45-males) were included. 46 patients had GPS. 57 patients underwent intra-operative electrocorticography during awake craniotomy-assisted glioma resection. All patients underwent glioma resection (53, gross-total resection) with histologies of pilocytic astrocytoma (n = 2), diffuse astrocytoma (n = 4), oligodendroglioma (n = 14), anaplastic astrocytoma (n = 16), anaplastic oligodendroglioma (n = 1), and glioblastoma (n = 31). 31 (67%) patients had PSC (median follow-up = 14.5 months; IQR = 7–16.5 months). IDH1 mutation ($IDH1^{mut}$) was present in 32, ARTX retention in 53, MGMT gene promotor methylation in 15, 1*p*/19*q* co-deletion in 15, and over-expression of *p*53 in 19 patients. Patients with $IDH1^{mut}$ were more likely to have GPS (***p*** **= 0.037**) and PSC (**p = 0.035**) compared to patients with IDH1 wild-type. Patients with MGMT gene promoter methylation were also likely to have PSC (***p*** **= 0.032**). GPS or PSC did not differ by age, sex, extent of surgery, glioma grade, location, and histopathological subtype, *p*53 expression, ARTX retention, or 1*p*/19*q* co-deletion status.

Conclusions: GPS and PSC may be associated with IDH1 mutation and MGMT gene promoter methylation status but not other glioma characteristics including tumor grade, location, or histopathology. Prospective studies with larger sample size are needed to clarify the exact mechanisms of GPS and PSC by the various TMMs to identify new treatment targets.

Abbreviations: ADs, after-discharges; AED, antiepilepticdrug; ARTX, α-thalassemia/mental-retardation-syndrome-X-linked gene; CG, circulargrid; DECS, directelectrical cortical stimulation; D2HG, D-2-hydroxyglutarate; EA, epileptiformactivity; EGFR, epidermalgrowth factor receptor; EOR, extentof resection; GBM, glioblastomamultiforme; GPS, gliomarelated pre-operative seizure; HD, highdensity grid; IDH1, isocitratedehydrogenase 1; ioECoG, intra-operativeEEG; MGMT, O6-methylguanine-DNAmethyltransferase; PSC, postoperativeseizure control; PTEN, phosphataseand tensin homolog; TERT, Telomerasereverse transcriptase gene; TMMs, tumormolecular markers; WHO, World Health Organization

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1. Introduction

Diffuse gliomas are the most common primary brain tumor in adults, affecting about 20,000 people in the US each year [1]. Epileptic seizures often develop in patients with gliomas (40%–70%) and approximately 30% are pharmaco-resistant even after glioma resection [2,3]. There is an abundance of literature supporting the association between tumor grade and histopathology and glioma-related epilepsy [3,4]. However, recent studies suggest that epileptogenesis is also influenced by tumor molecular genetic markers [4–7]. For example, studies show that isocitrate dehydrogenase 1 mutant (IDH1^{mut}) gliomas are more likely to cause seizures than IDH1 wild-type (IDH1^{wt}) [5,7]. Accumulating evidence also suggests that tumor growth stimulates seizures and that seizures encourage tumor growth, suggesting that the two conditions may share common pathogenic mechanisms and influence each other [4].

Insight into the mechanisms of glioma growth and epileptogenesis could provide the opportunity to develop interventions that target each of the dysregulated processes [4]. Despite tremendous progress in the field of Neuro-oncology; however, the exact pathogenesis of glioma-related seizures is poorly understood. For example, while IDH1 mutation has been shown to heighten the risk of glioma related pre-operative seizure (GPS), information on other genetic tumor molecular markers (TMMs) is limited. Further, little is known regarding how changes in TMMs can influence glioma-related postoperative seizure control (PSC). As such, the primary objective of the current study was to examine the association between the five routinely tested TMMs and GPS and PSC. Secondly, we sought to examine the occurrence of GPS and PSC with respect to other patient characteristics including age, sex, seizure semiology, scalp and intra-operative EEG (iECoG) findings, glioma grade, location, and histopathology.

2. Methods

2.1. Patients

This is a single-center retrospective cohort study of 68 patients with glioma that underwent resective surgery at the Mayo Clinic, Florida between October 2016 to August 2018. Patients with non-glial brain tumors including dysembryoplastic neuroepithelial tumors, gangliogliomas, papillary glioneuronal tumor, and hemangiopericytoma were excluded from the study. A majority (84%) also had intraoperative electrocorticography (iECoG) during the awake craniotomy assisted surgical resection. Clinical data including demographics, GPS, tumor location, tumor grade (per to the revised WHO 2016 classification) [8], as well as the status for α -thalassemia/mental-retardation-syndrome-X-linked gene (ATRX) retention, *p*53 overexpression, IDH1 mutation, 1p/19q co-deletion, and O6-methylguanine-DNA methyltransferase (MGMT) gene promotor methylation were assessed. All clinical episodes occurring before surgery that were considered seizures by treating providers were classified as GPS. PSC outcome was determined by the patient and family reports to the provider during post-operative follow-up visits.

2.2. Intra-operative electrocorticography

At our center we have been using iECoG assisted surgical resection in patients with glioma in eloquent areas during awake craniotomy assisted tumor resections [5]. An 8 × 8 high density grid (HD), depth electrodes, strips (Ad-Tech, Racine, WI, U.S.A.), 22 contact circular grid (CG) [PMT Corp., Chanhassen, MN], or a combination thereof were placed around the tumor to be resected. The HD contacts are composed of 3 mm diameter with 4 mm center-to-center distance. The strips and depth electrodes are composed of 4.0 mm diameter Platinum/Iridium discs (2.3 mm exposed) with 10 mm center-to-center distance. CG contacts are arranged in the shape of a ring with a cut-out hole measuring 3 cm at the inner diameter and 4 cm at the outer diameter associated cables was also used. Placement of the grids, strips and depth electrodes was guided by neuro-navigation (StealthStation™ S7 surgical navigation, Medtronic, USA) as determined by the location of the craniotomy. Recording was performed as a baseline (prior to resection), during direct electrical cortical stimulation (DECS) for cortical and subcortical mapping (using Ojemann stimulator) (2–6 mA, 1 s trains of 1 msec biphasic pulses at 60 Hz), and post-resection (in few cases). iECoG and hand-held DESC led by the surgeon (AQH or KLC), was performed according to a pre-established institutional protocol.

Recording was displayed with 70 Hz low-pass filter and with 10 s a page. The iECoG was recorded with a 128-channel EEG acquisition system (Xltek, Natus Inc, Pleasanton, CA) set at a 512-Hz sampling rate. Montages were individually created if additional electrodes were utilized. Recordings were analyzed for the presence of epileptiform discharges (spikes, and sharp waves), electrographic seizures, and after-discharges (ADs). Channels with excess line noise (60 Hz) or artifacts or containing no visible EEG signal were discarded before analysis. All artifact-free epochs recorded were reviewed, regardless of their durations. Visual detection and analysis of epileptogenic activity was performed by one electrocencephalographer (AMF or WOT) during the operation and a second interpreter assessed uninterrupted artifact-free ECoG following acquisition by investigators retrospectively (AMF or WOT).

2.3. Pathology

Fresh-frozen samples were obtained at the time of initial surgical resection from patients. Resected specimens were snap-frozen and stored in liquid nitrogen until DNA extraction or paraffin-embedding. Touch preps were made from the specimen and a representative portion was submitted for frozen section as sample A1. The remainder was subsequently submitted for frozen section as sample A2. Microscopic examination was performed by a pathologist only to identify areas of tumor for enrichment by macrodissection and tumor grade according to the WHO criteria [8]. Immunohistochemical stains were performed on paraffin-embedded tissue on block A2 using antibodies for five routinely tested molecular markers: ARTX retention, IDH1^{mut} (IDH1-R132 H), expression of *p*53, and MGMT gene promotor methylation. When applicable, Next Generation Sequencing was performed to test for the presence of a mutation within targeted regions of the IDH1 genes, including exon 4 (codons 113–138) of IDH1. In some cases polymerase chain reaction (PCR) was also used to test tumor DNA for the presence of MGMT gene promoter methylation. Chromosomal microarray analysis was performed using molecular inversion probes on a whole genome array (Affymetrix OncoScan platform) to determine the presence of 1p and 19q co-deletion. Mutation nomenclature was based on GenBank accession number NM_005896 and NM_002168, respectively (build GRCh37 (hg19)).

2.4. Imaging analysis

The tumor location was considered the lobe or region of the brain within which the bulk of the glioma resided. The pre and postoperative tumor volumes were measured using a T1-weighted MRI with gadolinium when the tumor was enhancing, while the T2 FLAIR-weighted MRI was used for non-enhancing tumors. The OsiriX software (Pixmeo SARL, Bernex, Switzerland) was used to calculate the tumor volumes as previously reported [9,10]. The extent of resection (EOR) was calculated using the formula (preoperative – postoperative tumor volume)/preoperative tumor volume [10]. EOR over 70–80% has been reported to be equivalent to gross total resection [10] with EOR > 70% considered as a threshold for post-operative seizure freedom in patients with low-grade gliomas [11].

2.5. Statistical analysis

Data were expressed as mean, median, range, and standard deviation for continuous variables, and counts (percentages) for categorical variables. The occurrence of GPS and PSC by age ($\geq$45 years vs < 45 years), sex, tumor grade, presence of absence of scalp EEG or iECoG recording, tumor side, extent of resection, IDH1 mutation, ARTX retention, MGMT gene promotor methylation, *p*53 expression, and 1p/19 co-deletion status was compared using Fisher's exact test. A multivariate analysis was performed with all factors that were analysed in the univariate analysis. All analyses were performed using SAS software (version 9.3). All statistical tests were 2 sided, and $p < 0.05$ was considered statistically significant.

2.6. Standard protocol approvals, registrations, and patient consents

This study was approved by the Mayo Clinic Institutional Review Board.

3. Results

3.1. Patient and pre-operative seizure characteristics

68 consecutive patients (mean age = 51 years, 45 males) were included. Gliomas were located in the frontal (n = 29), temporal (n = 22), parietal (n = 14), and occipital lobe (n = 3). Forty-six patients had GPS: 24 (52%) with only focal aware or unaware seizures while 22 also had focal to bilateral tonic-clonic seizures (median seizure duration = 4.5 months). All except nine patients were receiving pre-operative antiepileptic drugs (AEDs). Levetiracetam was the most commonly prescribed AED (48 patients, 82%). 32 patients had pre-operative scalp EEG with epileptiform activity (EA) seen in only two. Summary of clinical characteristics is in the Table 1. GPS did not differ by age, sex, seizure semiology and duration of epilepsy, or glioma grade, histopathology, or location. However, patients with GPS were more likely to have had pre-operative EEG recording than those without GPS (27/46 of vs 5/ 22, ***p* = 0.009**) [see Table 2].

3.2. Electrocorticography

57 patients underwent awake craniotomy: 12 patients with HD alone, 12 with strips alone, 7 with CG alone, 12 with HD and CG combination, 5 with HD and strip combination, 5 with HD, CG and depth combination, and 4 with HD and depth combination. The mean duration of recording was 24.5 min. During iECoG EA was present in 36 patients (63%): spike and sharp waves in 23 patients, intraoperative seizures in 7 (12%) patients (4 spontaneously and 3 during DECS), and ADs in 30 patients. Intraoperative seizures were aborted by cold irrigation and/or using electrical stimulation as previously described [12]. The tumors of the four patients with spontaneous intraoperative seizures were located within the frontal (1), temporal (2), and parietal (1) lobes. All except one had GPS: 3 cases with GBM and 1 with polycystic astrocytoma. One of the four cases patients had a postoperative early seizure, however no late seizures were observed in these patients. The tumors of the three patients with DECS induced seizures were located within the frontal (2) and parietal (1) lobes. All except one had GPS: 2 cases with oligodendroglioma and one with GBM. Of note, iECoG was primarily employed for cortical mapping and detection of intraoperative seizures and did not influence the extent of resection.

3.2.1. Extent of resection

A majority of those presenting with GPS underwent tumor resection within a month of seizure onset. The median post-operative EOR was 85.2% (range, 10.1%–100%). Gross total resection (70–80%) was observed in 53 (77.9%) patients. Subtotal or partial total resection (< 70%) was seen in 15 (22%) patients. In a univariate analysis, EOR using a 70% cut-off did not correlate with PSC **[*p* = 0.53, see Table 2].** All of the patients with GPS remained on AEDs at the most recent follow-up (median 10.5months, IQR 7–16 months).

Table 1
Clinical characteristics of the study cohort.

	N = 68 (%)
Sex (male)	45 (68%)
Age (mean years ± SD) [Range, years]	50+/-11 [19-76]
Pre-operative seizures	46 (68%)
Semiology	
Focal (aware or non-aware)	24 (52%)
Focal to bilateral tonic-clonic or GTCs	22 (48%)
Duration (median)	4.5 months
Tumor location	
Hemisphere	
Right	26 (38%)
Left	42 (62%)
Lobe	
Frontal	29 (42%)
Temporal	22 (31%)
Parietal	14 (20%)
Occipital	3 (4%)
Pre-operative scalp EEG	32 (47%)
Normal	13 (39%)
Abnormal	20 (60%)
Epileptiform	2 (6%)
Non-epileptiform	18 (54%)
Awake intra-operative electrocorticography	57 (84%)
Without epileptiform discharge	21 (36%)
With epileptiform discharges	23 (40%)
Intraoperative seizures	7 (12%)
Spontaneous	4 (7%)
DECS induced	3 (5%)
After discharges	6 (10%)
Extent of resection	68 (100%)
≥ 70%	45 (67%)
< 70%	23 (33%)
WHO grade*	
Polycystic astrocytoma	2
Diffuse astrocytoma, $IDH1^{mut}$	3
Diffuse astrocytoma, $IDH1^{wt}$	1
Oligodendroglioma, $IDH1^{mut}$ and 1p/19q-codeleted	14
Anaplastic astrocytoma, IDH1 ^{mut}	9
Anaplastic astrocytoma, IDH1 ^{wt}	7
Anaplastic oligodendroglioma, $IDH1^{mut}$ and 1p/19q-codeleted	1
Glioblastoma, $IDH1^{mut}$	4
Glioblastoma, $IDH1^{wt}$	27
Tumor molecular marker status	
$IDH1^{mut}$	32 of 68 tested
Over-expression of *p*53	19 of 57 tested
1*p*/19*q* co-deletion	15 of 22 tested
MGMT gene promotor methylation, present	15 of 36 tested
ARTX retained	53 of 62 tested
Post-operative adjuvant therapy	
None	8 (12%)
Chemotherapy alone	8 (12%)
Radiotherapy alone	4 (6%)
Concomitent chemoradiotherapy	48 (70%)
Post-operative seizure control	31 (67%)
Postoperative seizure freedom duration (months) median, IQR	14.5 (7-16.25)
Follow-up (months) median, IQR	10.5 (7-16)

* per to the revised World Health Organization 2016 classification [8].
ATRX, α -thalassemia/mental-retardation-syndrome-X-linked gene; DECS, direct electrical cortical stimulation; GTCs, generalized tonic-clonic seizures; $IDH1^{mut}$, isocitrate dehydrogenase 1 mutant; $IDH1^{wt}$, isocitrate dehydrogenase 1 wild type; IQR, interquartile range; MGMT, O6-methylguanine-DNA methyltransferase; WHO, World Health Organization.

3.2.2. Tumor characteristics

Glioma grade according to the 2017 World Health Organization (WHO) classification and other tumor characteristics is provided in Table 1. IDH1 mutation was present in 32, ARTX retention in 53,

Table 2
Predictors of pre-operative seizure and post-operative seizure control.

Variable	Total (N)	GPS Yes No		p-value	PSC Yes No		p-value
Sex							
Male	45	28	17	0.273	16	12	0.361
Female	23	18	5		13	5	
Age							
< 45 years old	21	16	5	0.405	11	5	1.000
≥ 45 years old	47	30	17		21	9	
Tumor side							
Right	26	19	7	0.595	12	7	0.331
Left	42	27	15		21	6	
Lobe							
Frontal	29	21	8	0.736	15	6	0.245
Temporal	22	15	7		11	4	
Parietal	14	9	5		3	6	
Occipital	3	1	2		1	1	
Pre-operative scalp EEG							
Yes	32	27	5	**0.009**	15	12	1.000
No	36	19	17		10	9	
Intra-operative ECoG							
Yes	57	41	16	0.155	28	13	1.000
No	11	5	6		3	2	
Extent of resection*							
> 70%	45	29	16	0.585	21	9	0.528
< 70%	23	17	6		10	7	
Tumor grade							
High grade	48	30	18	0.255	20	10	0.740
Low grade	20	16	4		12	4	
Tumor histopathology							
Astrocytoma	6	5	1	0.168	5	1	0.250
Oligodendroglioma	14	11	3		8	3	
Anaplastic astrocytoma	16	12	4		10	2	
Anaplastic oligodendroglioma	1	1	0		1	0	
Glioblastoma	31	17	14		10	7	
IDH1^{mut}	32	26	6	**0.037**	20	6	**0.035**
IDH1^{wt}	36	20	16		9	11	
MGMT gene promotor methylation +	15	8	7	0.176	6	2	**0.032**
MGMT gene promotor methylation-	21	16	5		4	12	
ARTX retained	53	32	21	0.140	22	10	1.000
ART not retained	9	8	1		5	3	
1p/19q co-deletion present	15	11	4	0.255	10	1	0.528
1p/19 co-deletion absent	7	7	0		5	2	
p53 over expressed	19	13	6	1.000	8	5	0.714
p53 not over-expressed	38	25	13		18	7	

GPS; glioma-related pre-operative seizures; iECoG; intra-operative electrocorticography; IDH1^{mut}, isocitrate dehydrogenase 1 mutant; IDH1^{wt}, isocitrate dehydrogenase 1 wild type; PSC; post-operative seizure control.

MGMT gene promotor methylation in 15, 1*p*/19*q* co-deletion in 15, and *p*53 overexpression in 19 patients. The MGMT methylation status was only reported in 36 patients (entire GBM cohort [n = 31] and 5 cases with anaplastic astrocytoma), the status of IDH2 mutation was unknown for the majority. Similarly, the status of Ki-67 expression, Telomerase reverse transcriptase gene (TERT) mutation, TP53 expression, phosphatase and tensin homolog (PTEN) expression, epidermal growth factor receptor (EGFR) expression, and other TMMs were not reported for the majority. The occurrence of GPS by TMMs is also summarized in Table 2. Overall, 20 of 36 patients (55%) with the IDH1^{wt}genotype experienced GPS, compared with 26 of 32 patients (81%) with IDH1^{mut} genotype ($\boldsymbol{p} = \mathbf{0.037}$) [see Fig. 1A]. The occurrence of GPS did not differ by glioma WHO grade, and histopathological subtype, expression of *p*53, ARTX retention, or 1p/19q co-deletion status (see Table 2). Further, the occurrence of GPS did not differ by MGMT gene promotor methylation status (see Table 2 and Fig. 1B). In multivariate analysis, after adjusting for factors previously suggested being associated with GPS including tumor location, grade, location, histopathology, tumor markers tested (p53 expression, ARTX retention, MGMT gene promotor methylation, and 1p/19q co-deletion status), and extent of resection, GPS remained significantly associated with IDH1 mutation status ($\boldsymbol{p} = \mathbf{0.048}$)

3.2.3. Post-operative seizure control

Postoperatively, 31 (67%) become seizure free (median follow-up = 14.5 months; IQR = 7–16.5 months) with median seizure freedom duration of 10.5 months (IQR = 7–16 months). PSC occurred in 9 of 20 patients (45%) with IDH1^{wt} and in 20 of 26 patients (77%) with IDH1^{mut} glioma ($\boldsymbol{p} = \mathbf{0.035}$) [see Fig. 1C]. In multivariate analysis, after controlling for factors previously suggested being associated with GPS including tumor location, grade, histopathology, and extent of resection, PSC remained significantly associated with IDH1 mutation status ($\boldsymbol{p} = \mathbf{0.041}$). PSC also occurred in 4 of 16 patients without MGMT gene promotor methylation (25%) and in 6 of 8 patients (75%) with MGMT gene promotor methylation ($\boldsymbol{p} = \mathbf{0.032}$) [see Fig. 1D]. In multivariate analysis, after controlling for factors previously suggested being associated with PSC including tumor location, grade, location, histopathology, iECoG recording, findings and duration, and extent of resection, PSC remained significantly associated with the presence of MGMT gene promotor methylation $\boldsymbol{p} = \mathbf{0.045}$). PSC did not differ by age, sex, seizure semiology and duration, scalp EEG findings, the presence or absence of iECoG recording, duration or findings of iECoG, glioma location, grade, histopathology, or extent of resection. Further, PSC did not differ by the expression of *p*53, ARTX retention, or 1p/19q co-deletion status (see Table 2). Of note, three patients without history of GPS later developed post-opertaive seizures.

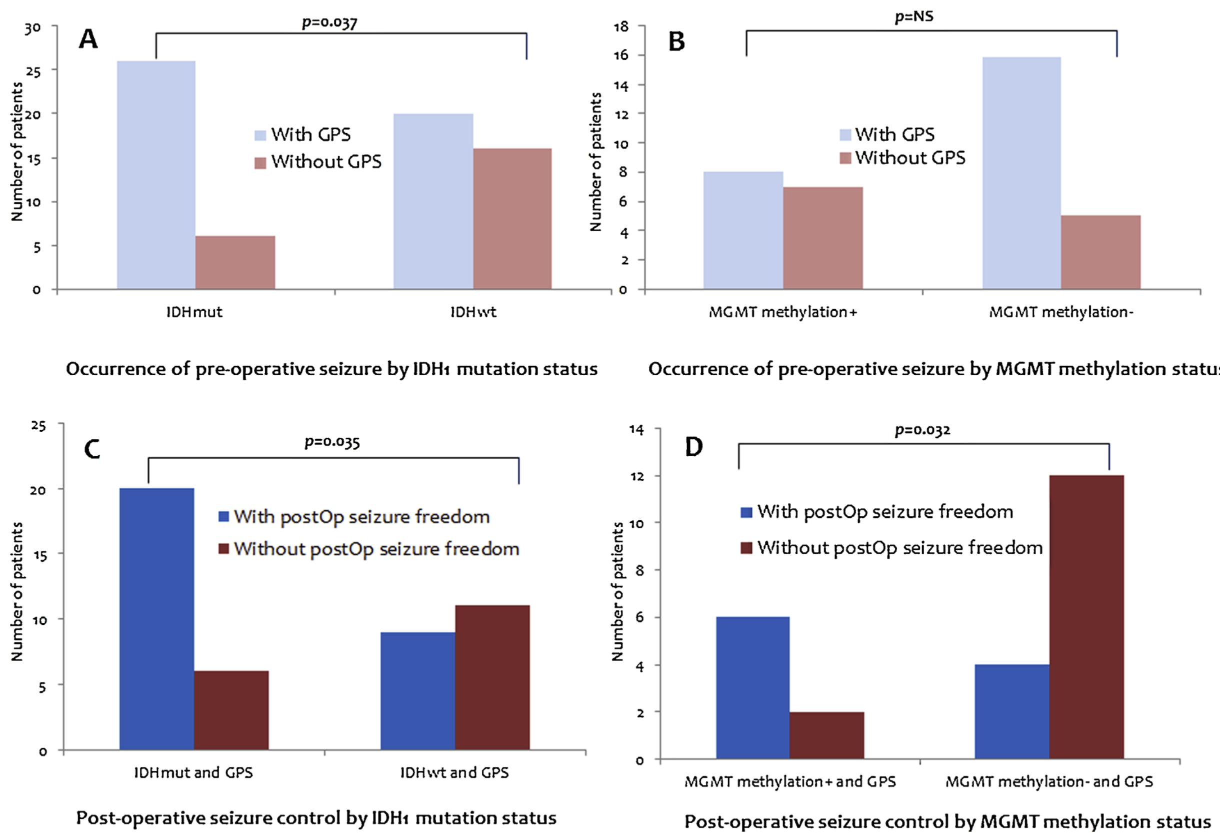

Fig. 1. Pre-operative seizures and post-operative seizure freedom by IDH1 mutation and MGMT gene promotor methylation status.

4. Discussion

This study examined the occurrence of GPS and PSC with respect to patient and glioma characteristics. We have observed that patients with IDH1^{mut} are more likely to have GPS and PSC than IDH1^{wt} gliomas. We also find that patients with MGMT gene promotor methylation are likely to have PSC. However, the occurrence of GPS or PSC does not differ by age, sex, presence of iECoG recording, glioma location, grade, and histopathological subtype, expression of *p*53 over-expression, ARTX retention, or 1*p*/19*q* co-deletion status. Two illustrative cases from our cohort with identical clinical characteristics except for the IDH1 mutation status, one presenting with GPS and the other without GPS, are provided in Fig. 2.

In this cohort 46/68 (68%) patients had GPS, consistent with rates reported previously (40–70%) [13–16]. Of these, 15 patients (32%) continued to have postoperative seizures, which is consistent with findings obtained in previous studies that reported post-operative seizures at a rate of 30–40% [15,17]. 25 of 31 patients with the IDH1^{mut} genotype had GPS while only 20 of 37 patients with IDH1^{wt} genotype presented with GPS. Our finding is similar to the recent studies that reported heighten risk of GPS in IDH1^{mut} than IDH1^{wt} gliomas [5–7]. The overproduction of D-2-hydroxyglutarate (D2HG) and its structural similarity to glutamate have been suggested to play a role in the mechanism of neuronal excitation leading to seizures [5,6]. Exposure to exogenous D2HG has been shown to increase the duration of synchronized network burst firing, a finding that was subsequently blocked by a selective NMDA antagonist [6]. We also found that patients with IDH1^{mut} genotype were likely to have favorable PSC than those with IDH1^{wt} genotype. This is in contrast to previous reports that found either no difference [7] or poorer PSC ([17] in patients with IDH1^{mut} gliomas, albeit with much larger sample size of 311 and 100 patients respectively. While the association of IDH1 mutation and GPS has been extensively reported, the influence of IDH1 mutation in the post-operative glioma microenvironment is yet to be clarified. Moreover, previous studies have suggested that the mechanisms of GPS may be different from postoperative seizures, which may partly explain the unexpected finding in our cohort [13]. Further studies are needed to elucidate impact of IDH1 mutation status in the epileptogenesis of the post-operative tumor microenvironment.

Several studies have shown that gliomas with MGMT gene promoter methylation are more treatment-sensitive to temozolomide chemotherapy as they are less able to repair the alkylating effect [18]. However, data on the relationship between GPS and PSC and MGMT gene promotor methylation status is limited. Recently, Yang et al [16], reported that patients with lower expression of MGMT protein (anaplastic oligodendroglioma/anaplastic oligoastrocytoma) had more frequent postoperative seizures. They speculated that the lack of MGMT gene promotor methylation would indicate that these tumors are more malignant and that malignant tumors are less associated with postoperative seizure. In contrast, here in we found higher rate of PSC in those with MGMT gene promotor methylation. The observed favorable PSC in those with MGMT gene promotor methylation could stem from the better response to adjuvant chemoradiation therapy in this patient population. However, our results should be interpreted cautiously given that we did not examine other TMMs that have been pervious suggested to be correlated with PSC, which might have confounded our findings. Well-designed prospective studies with larger sample size are needed to confirm the link between MGMT gene promotor methylation status and PSC.

As in previous reports in our cohort, GPS and PSC did not differ by age or sex [16,19]. Consistent with others we also found no difference in GPS and PSC by glioma location, grade, or histopathology [20,21]. Previous studies have also suggested that not all patients with similar glioma localization and histology have seizures [21,22]. This strongly supports the emerging view that TMMs may play a major role in tumor development and GPS and the variability in epilepsy may follow

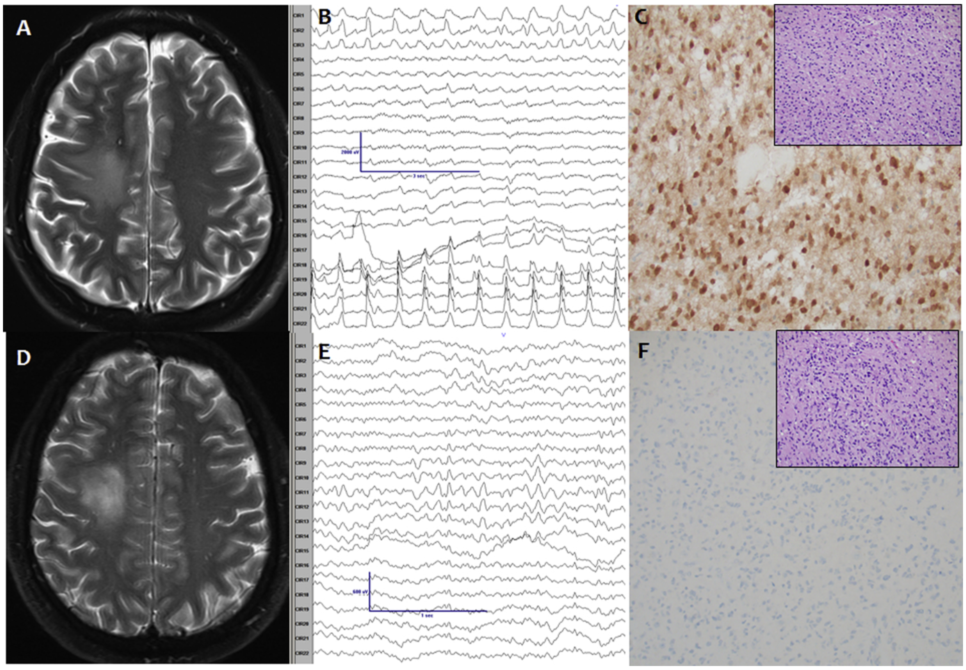

Fig. 2. Two illustrative cases from our cohort with similar clinical characteristics except for the IDH1 mutation status, one presenting with GPS and the other without GPS. *Top panel*: A 35 year-old man presented with GPS. Brain MRI showed T2 hyperinstense non-enhancing right frontal lesion [A]. Intraoperative ECoG recording using a 22-contcat circular grid captured an electrographic seizure discharge in contacts overlying the middle inferior portions of the right frontal tumor [B]. Photomicrographs showing diffuse astrocytoma (HE, ×20) [black box] with tumor cells exhibiting diffuse and strong IDH1-R132H positivity (immunohistochemistry, ×20) [C]. Bottom panel: A 38 year-old man without history of GPS. Brain MRI showing T2 hyperinstense non-enhancing right frontal lesion [D]. Intraoperative ECoG using a 22-contact circular grid did not identify epileptogenic discharges (E). Photomicrographs showing diffuse astrocytoma (HE, ×20) [black box] with tumor cells negative for IDH1- R132H staining (immunohistochemistry, ×20) [F].

directly from the TMM heterogeneity of gliomas [4]. Curiously, in our cohort PSC did not differ by the presence of iECoG monitoring, duration, or findings of iECoG, or extent of resection. iECoG is being increasingly utilized to increase PSC by facilitating localization of epileptogenic foci adjacent to or independent from the tumor [5,23,24]. Although iECoG has been shown to significantly improve PSC [23], others have shown that iECoG may not provide improved PSC compared to surgical resection alone [24]. In our cohort iECoG was primarily employed for cortical mapping and detection of intraoperative seizures and did not influence the extent of resection, which may partly explain the lack of improved PSC with its use. Nevertheless, iECoG will continue to be employed during glioma resection for its use of cortical mapping and to identify intra-operative seizures (12% in the current cohort). Although several studies have found an association between PSC and extent of surgery [21,25–27], some have reported no association [16]. The process of tumor delineation and gross-total resection has also been questioned since seizures could arise from the peri-tumoral tissue rather than the tumor proper. Further, for a large glioma there are likely regions of the tumor that may not promote epileptogenicity [13]. One hypothetical assumption could be that subtotal-resection could improve seizure control as gross-total resection through decreased release of pro-epileptogenic factors in and around the tumor.

The most important limitations of this study are its relative small sample size (low power) and the lack of information on important TMMs that has been linked with GPS and PSC. As such, the lack of association between glioma histopathology or the other factors (including tumor grade and other TMMs) and GPS in the current study could be due to our sample size and the over representation of GBM cases in our cohort (˜50%). Although only 46 patients were labelled as having GPS, 59 patients were receiving pre-operative AEDs. This might have resulted in erraneoulsy categorizing some of the 13 patients that were receiving prophyalatic AEDs as if they had no GPS and may have skewed our findings. This may also partly explain the occurance of post-operative seizures in the three patients without GPS. Current available data on the link between TMMs and GPS and PSC are heterogeneous due to the different histologies, the pathophysiology of seizures, the natural history of the tumor, and concomitant treatments [28]. Prospective larger multicenter studies, including low- and high-grade gliomas with and without symptomatic seizures are needed. Importantly, in our cohorts TMMs such as EGER, TERT, PTEN, TP53, and Ki-67 expression, which have been suggested to be correlated with GPS and PSC [15,20,28], were not examined and might have confounded our findings. Lastly, given our small sample size, we have not examined survival outcomes by TMMs and the influence of adjuvant therapies (chemotherapy and radiotherapy) on PSC. Therefore, we suggest caution in interpreting our findings particularly with regards to the importance of extent of surgery and iECoG recording, since these could have potential impact on morbidity and survival beyond PSC [29]. In order to clarify the link between GPS and PSC, and TMMs, future studies should focus on identifying susceptibility candidate TMMs for GPS and PSC.

5. Conclusions

GPS and PSF may be more associated with IDH1 mutation and MGMT methylation status than glioma grade, location, or histopathology. Our findings may provide useful information for the management of glioma-related pre and post-operative seizures. However, studies are needed to clarify the exact mechanisms of GPS and PSC by TMMs status to identify new treatment targets and provide better evidence to guide clinical decision making.

Disclosure of conflict of interest

Drs. Feyissa, Worrell, Tatum, Chaichana, Jentoft, Guerrero Cazares, Ertekin-Taner, Rosenfeld, ReFaey, and Quinones-Hinojosa report no disclosures relevant to the manuscript.

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