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Wild Seizing Gliomas! Time-Dependent Characteristics and Prognosis of Glioblastoma-Related Epilepsy

Characteristics and Prognosis of Tumor-Related Epilepsy During Tumor Evolution in Patients With IDH Wild-Type Glioblastoma

Pallud J, Roux A, Moiraghi A, Aboubakr O, Elia A, Guinard E, Oppenheim C, Tauziede-Espariat A, Parraga E, Gavaret M, Chrètien F, Huberfeld G, Zanello M. *Neurology*. 2024;102(1): e207902. doi:10.1212/WNL.0000000000207902

Background and Objectives: Tumor-related epilepsy is a well-known symptom of glioblastoma. However, the particular characteristics of epileptic seizures related to glioblastoma, isocitrate dehydrogenase (IDH)-wild-type is almost unexplored longitudinally during the whole course of the disease. We assessed tumor-related epilepsy and seizure control during tumor evolution and the prognostic significance of tumor-related epilepsy. Methods: We performed an observational, retrospective single-center study at one tertiary referral neuro-oncology surgical center (2000-2020). We included adult patients treated for a newly diagnosed supratentorial glioblastoma, IDH-wild-type with available preoperative and postoperative MRI and with available epileptic seizure status at diagnosis. To determine factors associated with tumor-related epilepsy or seizure control, univariate analyses were performed using the χ^2 or Fisher exact tests for categorical variables and the unpaired *t* test or Mann-Whitney rank-sum test for continuous variables. Predictors associated with tumor-related epilepsy and seizure control in unadjusted analysis were entered into backward stepwise logistic regression models. Results: One thousand six patients were enrolled. The cumulative incidence of tumor-related epilepsy increased during tumor evolution (33.1% at diagnosis, 44.7% after oncologic treatment, 52.4% at progression, and 51.8% at the end-of-life phase) and is related to tumor features (cortex involvement, no necrosis, and small volume). Uncontrolled epileptic seizures increased during tumor evolution (20.1% at diagnosis, 32.0% after oncologic treatment, 46.7% at progression, and 41.1% at the end-of-life phase). Epileptic seizure control after oncologic treatment was related to seizure features (uncontrolled before oncologic treatment and focal-to-bilateral tonic-clonic seizures) and to the extent of resection. Epileptic seizure control at tumor progression was related to seizure features (presence at diagnosis and uncontrolled after oncologic treatment) and to the time to progression. Tumor-related epilepsy at diagnosis was a predictor of a longer overall survival (adjusted hazard ratio, 0.78; 95% CI 0.67-0.90; $p < 0.001$) independent of age, Karnofsky Performance Status score, tumor location and volume, extent of resection, standard combined chemoradiotherapy, levetiracetam use, and MGMT promoter methylation. Discussion: The progression of tumor-related epilepsy with the evolution of glioblastoma, IDH-wild-type, and the effects of surgery on seizure control argue for proper antiseizure medication and maximal safe resection. Tumor-related epilepsy is an independent predictor of a longer survival.

Commentary

Glioma is the most common form of central nervous system (CNS) tumor that arises from glial cells. Glioblastoma multiforme (GBM), the most aggressive form of glioma, affects ~75 000 people worldwide annually.[1] The invasion of the neocortex by GBM is accompanied by seizures, with at least 25% to 30% of patients experiencing seizures as the presenting clinical sign, and 40% to 70% develop seizures at some point during the disease's course.[2] Although glioma-related seizures often correlate with longer survival,[3] seizures significantly contribute to patient morbidity and negatively impact quality of life. Accumulating evidence also indicates that seizures encourage tumor proliferation and invasion while glioma growth stimulates seizures, suggesting that the two conditions may share common pathogenic mechanisms.[4,5]

Glioma classification was mainly based on histological and immunohistochemical characteristics and their resemblance to the presumed cell of origin. The rapidly increasing knowledge of tumor molecular biomarkers (TMMs) over the last 2 decades has allowed more robust diagnostic TMMs to be introduced into clinical practice. This is more evident in the 5th edition of the World Health Organization (WHO) Classification of Tumours of the CNS, updated in 2021.[6] Gliomas are first broadly divided into isocitrate dehydrogenase 1 mutated

(IDH^{mut}) and IDH1 wild-type (IDH^{wt}) gliomas.[6] Besides their role in prognosis, TMMs have improved our understanding of the pathophysiology of glioma-related epilepsy. For example, IDH^{mut} gliomas have been shown to have a higher rate of seizures, with an incidence approaching 80%.[7]

Although the epileptogenic effects of IDH^{mut} gliomas have been highlighted,[7] seizures are also a practical concern in IDH^{wt} gliomas including, GBM.[2] Little is known regarding the time-dependent risk factors, prognosis, and mechanism for epileptogenesis in GBM.[8,9] Prior studies evaluating GBM-related epilepsy are restricted by the inclusion of patients diagnosed with GBM according to the pre-2021 revised WHO classification, likely resulting in a misclassification bias.[8] Using a retrospective monocentric study of 1006 adults with IDH^{wt} GBM, Pallud et al have attempted to address these.[9] They longitudinally (at histomolecular diagnosis, early postoperative period, before and after oncologic treatment, at tumor progression, and the end-of-life phase) studied the prevalence and control rates of GBM-related epilepsy, predictors of GBM-related epilepsy and seizure control, and prognostic significance of GBM-related epilepsy on survival.

Multiple key findings were reported.[8] First, the cumulative incidence of GBM-related epilepsy increased during GBM evolution (33.3% at histomolecular diagnosis, 44.7% after oncologic treatment, 52.4% at progression, and 51.8% at the end-of-life phase) and is related to tumor features (cortex involvement, no necrosis, small tumor volume <30 mL), competitive presenting symptoms, and a longer time to diagnosis. Similarly, uncontrolled seizures progressed during tumor evolution (20.1% at histomolecular diagnosis, 32.0% after oncologic treatment, 46.7% at progression, and 41.1% at the end-of-life phase). Interestingly, seizure control after radiochemotherapy is related to seizure features (uncontrolled before oncologic treatment and focal-to-bilateral tonic–clonic seizures) and to the time of tumor progression. Predictably, the extent of resection is the main predictor of seizure control, with supramarginal removal associated with better seizure control. The authors found that tumor-related epilepsy at diagnosis was an independent predictor of longer overall survival.

The findings of the article reviewed in this commentary have several implications. First, identifying the risk factors of seizures during tumor evolution may help manage anti-seizure medication (ASM) therapy (introduction, withdrawal, and continuation) to improve the quality of life for these patients. Since uncontrolled seizures progress during tumor evolution despite oncologic treatments and are associated with tumor progression, ASMs could be pursued after oncologic treatment, even in seizure-controlled patients. This decision must be carefully balanced with the various serious adverse effects associated with ASMs.

Secondly, the finding that epilepsy is more frequent in cases with a small tumor, without necrosis, and with no signs of raised intracranial pressure suggests that the interaction between glioma cells and functional neocortex may trigger GBM-related epilepsy. Indeed, recent studies have elegantly demonstrated neurogliomal synapses, in which neuronal hyperexcitation stimulates bona fide glutamatergic synapses on glioma cells and orchestrates glioma cell growth and invasion.[10] These observations provide an impetus for future studies to identify drugs specifically targeting these synapses for potential dual anti-tumorigenic and anti-seizure effects, similar to IDH^{mut} gliomas, for which several IDH inhibitors are being investigated for the same purpose.[11]

Four main stages are associated with clinical GBM progression: pre-resection, post-resection (with/without radiochemotherapy), recurrence or progression (with/without radiochemotherapy), and end-of-life. The third key finding of the current study is that only the presence of tumor-related epilepsy at diagnosis confers a survival benefit. This indicates the highly malignant, dynamic character of GBM and the apparent differences in implications for patient survival when seizures occur earlier or later in the disease's treatment. This difference also suggests that the mechanisms underlying seizure occurrence at these respective time points differ in GBM progression.

Finally, the current study reinforces the importance of a maximal safe resection for both epileptologic and oncologic purposes in patients with IDH^{wt} GBM, similar to patients with IDH^{mut} gliomas. Despite its poor oncologic prognosis, supramarginal resection is a worthwhile consideration (with a higher probability of seizure freedom), as uncontrolled epilepsy negatively impacts the quality of life in this already vulnerable population.

Despite its strengths, including being the largest ever study on exclusively IDH^{wt} GBM cohort and long-term follow-up, the study is plagued with limitations inherent to its retrospective monocentric study design. Also, the authors fail to explain the unexpected finding that the time to diagnosis was longer in patients with GBM-related epilepsy than in those presenting with other symptoms. Similarly, among patients with GBM-related epilepsy, the time to diagnosis was shorter in patients with a single seizure than in those with recurrent seizures. This is in contrast to prior observations that seizures could trigger earlier presentation for care, thus accelerating diagnosis and initiating earlier treatment of smaller GBMs.[3] This also contradicts their discussion that the earlier detection of GBM because of the "sentinel" seizures, as suggested by their smaller tumor volume, might have accounted for the longer survival. Significantly, the current study did not address the question of how the process of epileptogenesis evolves throughout GBM progression.

In summary, this publication nicely demonstrates the progression of GBM-related epilepsy and uncontrolled seizures during IDH^{wt} GBM evolution. However, these findings should be interpreted with caution given the limitations and must be confirmed within prospective large databases. Also, studies are needed to elucidate the exact mechanism of epileptogenesis during GBM evolution. Significantly, we need further insight into the bidirectional neuron-glioma interactions and a better understanding of how seizures beget glioma proliferation and invasion and vice versa.[5] Doing so has the potential to generate exciting candidate drugs with simultaneous anti-tumorigenic and anti-seizure properties for further clinical trials in GBM,

in which a majority eventually require ASM therapy until they succumb to this deadly cancer.

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Declaration of Conflicting Interests

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