FULL-LENGTH ARTICLE NPub.org/qr3cpt

Association of Clinical, Tumor, and Treatment Characteristics With Seizure Control in Patients With *IDH1/2*-Mutant Lower-Grade Glioma

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Cite as: *Neurology*® 2024;102:e209352. doi:10.1212/WNL.0000000000209352

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Study Question

How do clinical characteristics, histologic and molecular features, and antineoplastic treatments influence seizure control in patients with *IDH*-mutant lower-grade gliomas?

What Is Known and What This Paper Adds

Patients with *IDH1/2*-mutant lower-grade glioma have a high frequency of seizures. In these patients, seizures may be present from the time of diagnosis to the latest stages of the disease, and their frequency often parallels tumor control. Factors affecting brain tumor-related epilepsy include tumor location, histologic type, grade of malignancy, extent of resection, and tumor response to adjuvant treatments (i.e., radiotherapy [RT] and chemotherapy). In addition, the altered product of the *IDH* mutation—D-2-hydroxyglutarate—has been associated with an increased risk of seizures, probably because of its similarity to glutamate on the excitatory neuronal synapses. For this reason, new IDH inhibitors (such as vorasidenib) are expected to have a potential role in seizure control. Few studies have comprehensively drawn the natural history of seizures in patients with molecularly defined *IDH*-mutant lower grade gliomas along the entire disease trajectory, and the impact of clinical factors and conventional antineoplastic treatments on seizure control from diagnosis to recurrence within histologic and molecular subgroups is not fully understood. This study's results show that grade 3 gliomas were associated with better seizure control throughout the entire disease trajectory, and seizure freedom after surgery and adjuvant treatments correlated with a longer progression-free survival (PFS) regardless of tumor grade.

Methods

For this retrospective study, we included patients with *IDH1/2*-mutant lower-grade glioma who underwent surgery at the Neurosurgery Divisions of the University of Turin and Milan and were treated at the Division of Neuro-Oncology of Turin. Inclusion criteria were a diagnosis according to the 2021 World Health Organization Classification and clinical presentation with seizures; exclusion criteria were the presence of *CDKN2A/B* homozygous deletion, intense/ring contrast enhancement on MRI at presentation, and small tissue biopsy. Seizure frequency was calculated as the number of seizure days based on a patient diary that was reviewed at each clinical visit. Information about the frequency of seizures was collected for each patient at 2 months after surgery, at 6 months after either observation with MRI or adjuvant treatments, at disease recurrence, and at 6 months after treatment of recurrence.

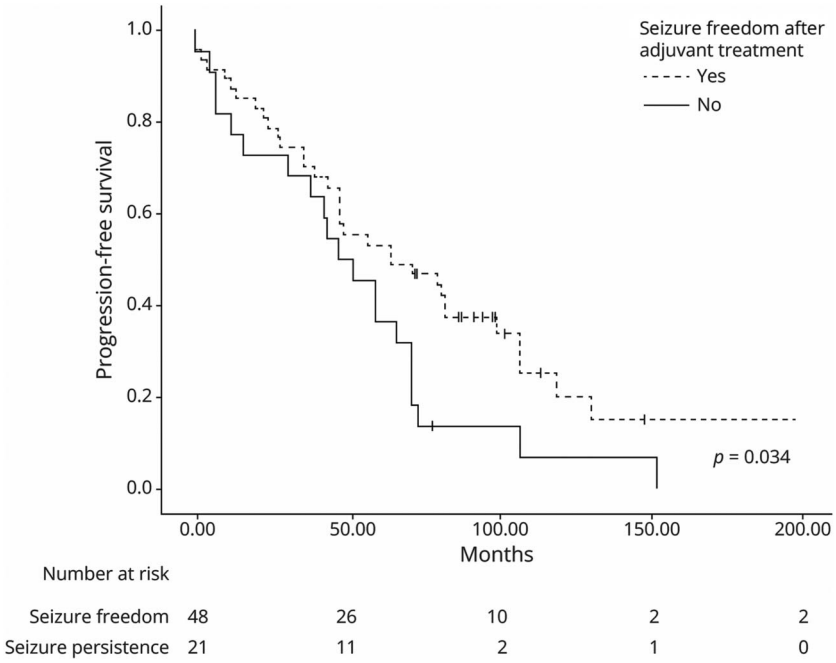
The primary end point was to evaluate whether seizure freedom was affected at the aforementioned time points by any of the following factors: age, tumor location, integrated histologic and molecular diagnosis, tumor grade, extent of resection (EOR), and adjuvant treatments (i.e., RT and/or CT). Total resection was defined as the absence of any signal abnormality around the surgical cavity on T2/FLAIR images on an MRI obtained at 2 months after surgery.

All data were obtained from the medical records of each patient and included as variables in the statistical models. The baseline characteristics of patients were summarized using median and interquartile range (IQR) and percentages and frequencies (n, %). PFS was measured as the time from surgical resection to tumor recurrence (months). The distribution of characteristics across patient subgroups was evaluated using the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. A binary logistic regression model was used to estimate the multivariable-adjusted odds ratios (ORs) with 95% CIs to evaluate possible factors affecting seizure control at different time points. Kaplan-Meier curves were drawn for PFS, and a Cox proportional hazard model was used to estimate the crude hazard ratios with 95% CIs to evaluate possible predictors of recurrence.

Results and Study Limitations

We included 150 patients. The median age was 38 years (IQR 20–48). Patients with oligodendroglioma *IDH*-mutant, 1p19q-codeleted grades 2 and 3 were 77 (51.3%) and 31 (20.7%), respectively, and those with astrocytoma *IDH*-mutant grades 2 and 3 were 30 (20.0%) and 12 (8.0%), respectively. All patients presented with seizures, and the median seizure frequency at baseline (i.e., before surgery) was >2 seizures/month in 76 (50.7%). Total resection was accomplished in 68 patients (45%). Seizure freedom was obtained by 88 patients (58.7%) at 2 months after surgery, and it was associated with both age and tumor grade in a multivariable model (age ≥40 years vs <40 years: OR 2.5, 95% CI 1.1–5.6, $p = 0.027$; grade 3 vs grade 2: OR 3.5, 95% CI 1.4–8.9, $p = 0.008$). Seventy-five patients (50%) received adjuvant treatments while the remaining 75

Figure Progression-Free Survival in Patients With or Without Seizure Freedom for 6 Months of Adjuvant Treatments



were observed with MRI. Seizure freedom was maintained for 6 months in 42 of 75 patients (56%) who were observed after surgery, and it was associated with the EOR in a multivariable model (total resection vs non-total OR 3.4, 95% CI 1.0–11.0, $p = 0.045$). Similarly, among patients who underwent adjuvant treatments, seizure freedom was maintained for 6 months in 46 of 75 patients (61.3%) who had already achieved seizure freedom after surgery; also, a reduction of seizure frequency was obtained in 28 of 29 patients (96.5%) who still had seizures when adjuvant treatments were started, 5 of 28 (17.9%) achieving seizure freedom. In a multivariable analysis, factors significantly associated with seizure freedom at 6 months after adjuvant treatments were tumor grade and involvement of temporal lobe (grade 3 vs grade 2: OR 9.0, 95% CI 1.5–54.9, $p = 0.017$; temporal lobe vs other: OR 0.2, 95% CI 0.04–0.7, $p = 0.016$). One hundred twenty-four patients (83%) showed tumor recurrence, and all received treatment(s) accordingly. Patients with seizure freedom after surgery and adjuvant treatments displayed longer PFS (65 months, 24.5–105, vs 48, 32–63.5, $p = 0.034$; Figure). After 6 months following second-line treatments, 60 of 66 patients (91%) had seizure reduction, with 11 (17%) becoming seizure-free. In multivariable analyses, grade 3 histology correlated with seizure freedom for 6 months after treatment of recurrence (OR 4.9, 95% CI 1.5–16.5, $p = 0.009$); also, adjuvant RT reduced seizures at recurrence in a univariate analysis (OR 0.14, 95% CI 0.03–0.7, $p = 0.020$).

Our study has some limitations. We analyzed seizure frequency, but we were not able to analyze seizure severity on affecting quality of life. In addition, patients with oligodendroglioma outnumbered those with astrocytomas (ratio 3:1), which might have affected the interpretation of the results. Finally, as single-center analysis, the reliability of the study results may be limited by the fact that different RT, chemotherapy, or strategies for ASM management exist across institutions.

Study Funding and Competing Interests

This study received no targeted funding. The authors report no competing interests. Go to Neurology.org/N for full disclosures.