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Clinicopathological factors predictive of postoperative seizures in patients with gliomas

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ABSTRACT

Purpose: Epilepsy is one of the most common manifestations in gliomas and has a severe effect on the life expectancy and quality of life of patients. The aim of our study was to assess the potential connections between clinicopathological factors and postoperative seizure.

Method: We retrospectively investigated a group of 147 Chinese high-grade glioma (HGG) patients with preoperative seizure to examine the correlation between postoperative seizure and clinicopathological factors and prognosis. Univariate analyses and multivariate logistic regression analyses were performed to identify factors associated with postoperative seizures. Survival function curves were calculated using the Kaplan–Meier method.

Results: 53 patients (36%) were completely seizure-free (Engel class I), and 94 (64%) experienced a postoperative seizure (Engel classes II, III, and IV). A Chi-squared analysis showed that anaplastic oligodendroglioma/anaplastic oligoastrocytoma (AO/AOA) ($P = 0.05$), epidermal growth factor receptor (EGFR) expression ($P = 0.0004$), O^6-methylguanine DNA methyltransferase (MGMT) expression ($P = 0.011$), and phosphatase and tensin homolog (PTEN) expression ($P = 0.045$) were all significantly different. A logistic regression analysis showed that MGMT expression ($P = 0.05$), EGFR expression ($P = 0.001$), and AO/AOA ($P = 0.038$) are independent factors of postoperative seizure. Patients with lower MGMT and EGFR expression and AO/AOA showed more frequent instances of postoperative seizure. Postoperative seizure showed no statistical significance on overall survival (OS) and progression-free survival (PFS).

Conclusion: Our study identified clinicopathological factors related to postoperative seizure in HGGs and found two predictive biomarkers of postoperative seizure: MGMT and EGFR. These findings provided insight treatment strategies aimed at prolonging survival and improving quality of life.

1. Introduction

The World Health Organization (WHO) classifies gliomas into four grades, and grades III and IV are defined as high-grade gliomas (HGGs) [1]. Medical advances have improved the effectiveness of surgery, radiation, and chemotherapeutic drugs. However, HGGs are extremely invasive, and the prognosis of patients with HGGs remains poor with median survival times of 22 months for AA (anaplastic astrocytoma) and 12 months for GBM (glioblastoma)

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[2]. Thus, it is important to enhance the therapeutic efficacy and reduce the neurological symptoms induced by HGGs, such as seizures, which significantly affect quality of life [3]. It is essential to identify patients at risk of developing a HGG-associated postoperative seizure such that better targeted therapies can be designed for controlling postoperative seizures and improving patient prognosis [4].

Seizures are common in HGGs in the brain and are frequently an initial symptom of this deadly disease [5–7]. Seizures are common in diffuse gliomas, occurring in 50–90% of low-grade astrocytoma patients and in 20–50% of glioblastoma patients [8]. The pathogenesis of seizures induced by HGGs remains uncertain and most likely differs from that of LGGs. Seizures have been reported in 6% of patients with malignant glioma during the postoperative period [9,10]. Thus, patients with brain tumours need to take antiepileptic drugs (AEDs) after neurosurgery. When uncontrolled, tumour-related epilepsy and antiepileptic drug toxicities substantially contribute to neurological morbidity and have a significant effect on the patients' quality of life (QOL) [11–14]. Although epilepsy is more frequently observed in patients with LGGs, it is more difficult to control in patients with HGGs [15]. There is a vast difference between the pathogenesis of tumour-related seizure and that of other types of seizure [16]. Although patients with HGGs experience symptomatic postoperative seizures, many patients do not experience postoperative seizures despite exhibiting similar histology and performance status. Thus, postoperative seizures cannot be entirely explained by tumour-related or peritumoural factors. Instead, such seizures may result from a complex interaction between tumour-related and genetic factors [16].

Despite the frequency of postoperative seizures, factors influencing seizures associated with HGGs have not been addressed in a detailed manner. Thus, the purpose of the present study was to identify the prognostic importance of postoperative seizures as well as predictors of seizure control after surgical resection. It is presently popular to investigate correlations between tumour-related biomarkers and surgical outcomes. Although previous studies [17–19] have identified some susceptibility candidate biomarkers associated with seizure control after surgery for LGGs, little is known regarding how the expression of these biomarkers may influence postoperative seizure in patients with HGGs. Here, we report our findings concerning postoperative seizure obtained from a large retrospective single-centre series of 147 patients with WHO grade III and IV gliomas with epileptic seizures prior to surgical treatment. In this analysis, we examined the prevalence and predictors of postoperative seizures and the prognostic significance of postoperative seizure on progression-free survival and overall survival.

2. Methods

2.1. Patients

We retrospectively identified all patients with preoperative seizure who were 17 years of age or older; who demonstrated biopsy-proven anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic oligoastrocytoma (AOA), and glioblastoma multiforme (GBM) from the Chinese Glioma Genome Atlas (CGGA); and who underwent surgical resection at the Glioma Treatment Center of Beijing Tiantan Hospital from January 2006 to July 2013. Histological diagnosis was reaffirmed by two independent neuropathologists and graded according to the WHO classification. Cases with discrepancies were re-reviewed by another pathologist until a consensus was reached. Based on these criteria, we included a total of 147 patients. The clinical characteristics of the patients, which were systematically collected at the time of histopathological diagnosis from medical records, were the following: patient's age at diagnosis, sex, type of seizure (simple partial, complex partial and generalized seizures), tumour location, extent of resection, pathological examinations, and adjuvant therapy. The overall survival (OS) time, defined as the period from surgery to death, was collected when the patients visited the clinics and during phone interviews with the patients and/or their relatives. Progression-free survival (PFS) was defined as the time from surgery to image progression (appearance of a new lesion or 25% increase in tumour size).

The enrolment criteria included the following: age of at least 17 years, histologically confirmed anaplastic glioma or glioblastoma, occurrence of preoperative seizure and patient's consent. Patients who only underwent biopsy and those who were lost to follow-up or who had died of non-primary diseases were excluded. This study was approved by the Ethics Committee of Beijing Tiantan Hospital, and written informed consent was obtained from all of the patients.

2.2. Assessment and measurements of seizure outcome

The primary outcome variable was seizure status, which was evaluated after surgery using the Engel Classification of Seizures: class I = free of disabling seizures (completely seizure free; non-disabling, simple partial seizures only; some disabling seizures but free of disabling seizures for at least 2 years; generalized convulsion with AED withdrawal only); class II = rare disabling seizures (initially free of disabling seizures but rare seizures at the time of study; rare disabling seizures since surgery; more than rare disabling seizures but rare seizures for at least 2 years; nocturnal seizures only); class III = worthwhile improvement (worthwhile seizure reduction; prolonged seizure-free intervals amounting to more than half of the follow-up period but not less than 2 years); and class IV = no worthwhile improvement (no significant seizure reduction; no appreciable change; worse seizures). We divided the patients with preoperative seizure into two groups based on the epileptic outcome after surgery: 53 patients (36%) were completely seizure-free (Engel class I), whereas 94 patients (64%) experienced postoperative seizures (Engel classes II, III, and IV). The use of AEDs was based on the clinician's preference. All of the selected 147 patients experienced a preoperative seizure and took sodium valproate for seizure prophylaxis prior to surgery. After surgery, these patients typically continued AED treatment for 3–6 months and were gradually weaned off the medication. If the patients had any evidence of seizures, the AED treatment was continued.

2.3. Samples

Tumour tissue samples were obtained by surgical resection. Resected specimens were snap-frozen and stored in liquid nitrogen until DNA extraction or paraffin-embedding.

2.4. DNA extraction

The genomic DNA from frozen tumour tissues was isolated using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. The DNA concentration and quality were measured using a NanoDrop ND-1000 spectrophotometer (Nano-Drop Technologies, Houston, TX, USA).

2.5. Molecular evaluations

All of the data from the CGGA (Chinese Glioma Genome Atlas) for which biomaterial was available were obtained. Immunohistochemistry staining was performed for seven routinely tested