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The risk of developing seizures before and after primary brain surgery of low- and high-grade gliomas

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ABSTRACT

Objective: To identify risk factors for developing seizures pre- and postoperatively in low- and high-grade gliomas.

Patients and Methods: 282 patients undergoing neurosurgical tumor resection between 2013–2015 were included in the present single-center retrospective cohort study. Seizure incidences according to various variables were described. Univariate and multivariate logistic regression analyses were performed to identify significant risk factors for both pre- and postoperative seizures.

Results: 37.6% of patients presented with seizures before surgery, 18.4% developed seizures in the postoperative course, and 55.0% had no record of seizures pre- or postoperatively.

Focal, cognitive, and other symptoms, tumors located in a non-eloquent area, and tumors ≥ 40 mm in diameter were found to be associated with a reduced risk of preoperative seizures, whereas hypertension or no comorbidity posed an increased risk. The presence of seizures pre- or perioperatively (≤ 24 h before and after surgery), and tumors located in the thalamus were associated with an increased risk of seizures in the postoperative course.

Conclusion: Predictors for pre- and postoperative seizures identified in this study should be taken into account and integrated into the present knowledge, when determining patients at increased risk of developing seizures. Future prospective studies investigating the efficacy of prophylactic antiepileptic therapy in subgroups of glioma patients are needed before applied into clinical practice.

1. Introduction

In Denmark, the age standardized incidence of a diagnosis of primary tumors in the brain, meninges and nerves are 23 for males and 25 for females per 100,000, of which approximately one third are gliomas [1]. A large proportion of these patients develop epileptic seizures in the course of the disease, either as the initial symptom leading to diagnostic investigation, during the time waiting for surgical intervention, or in the postoperative course [2]. Epileptic seizures have a considerable negative influence on the quality of life and are therefore desirable to minimize/eliminate.

Several studies have found surgical resection as well as oncologic treatment to have a seizure reducing effect among brain tumor patients presenting with seizures. Likewise, pharmacologic treatment with antiepileptic drugs (AEDs) has also been proven effective in reducing the incidence of seizures, although not as effective as surgical and oncologic treatment [3,4].

In a consensus report from the American Academy of Neurology [5], it is not recommended to use AEDs routinely as seizure prophylaxis in patients with newly diagnosed brain tumors but no history of seizures, and tapering and discontinuation of AED should be exerted after the first postoperative week. These recommendations are, however, based on studies including different kinds of brain tumors (gliomas, metastases, and meningeomas), as well as different, old generation AEDs, which lead to an inherent risk of overlooking subgroups, who might benefit from prophylactic AED-treatment, e.g. glioma patients. The European guidelines [6] also do not recommend prophylaxis outside the perioperative phase.

Recent studies investigating the efficacy of preoperatively prescribed AED prophylaxis in patients with brain tumors have found no evidence of significant efficacy towards seizure reduction [7,8]. However, again a potential confounder in these results is the heterogeneity

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of tumor types evaluated together. Studies including only malignant gliomas also did not find any significant effect, but suggest a modest risk reduction [9,10].

Several studies have investigated the rates of epileptic seizures in patients with low- and high-grade gliomas (LGG and HGG respectively) in relation to different variables. Higher rates of seizures are found in low-grade, slowly growing gliomas [2,11], tumors located in superficial cortical areas, fronto-temporal lobes or insula, multifocal lesions [2,3], and in association to acute pathophysiological phenomena such as hemorrhage and edema [12]. Younger patients also more often present with seizures than older [11,13].

In a review from 2010, it is proposed to consider short-term prophylaxis with newer generations of antiepileptic drugs up to one week after craniotomy [11], while other studies suggest further investigations in this area [2] by detecting subgroups of patients at increased risk of developing seizures [10]. Newer generations of AEDs, e.g. Levetiracetam, have less adverse effects, have a potentially synergistic effect on oncologic treatment, as well as an antiemetic and neuro-protective effect compared to the older AEDs [3,4,14].

The present study investigated how many patients with glial tumors developed seizures preoperatively as well as in the three months postoperative course. With the inclusion of potential risk factors for the development of epilepsy in brain tumors, the purpose of this study was to identify significant independent predictors to evaluate if any subgroup of patients is more prone to develop seizures postoperatively. If such a subgroup exists they may possibly benefit from prophylactic antiepileptic therapy in the postoperative course.

2. Materials and methods

2.1. Patient selection

491 unique personal identification numbers were extracted from Electronic Medical Records (EMR) according to the ICD-10 diagnoses C71x and D33x for patients aged 18 or above who underwent surgery at the Department of Neurosurgery, Odense University Hospital, Denmark, in the period 01 January 2013 to 31 December 2015. Inclusion criteria were first time diagnosis of supratentorial LGG or HGG, according to the grading of the World Health Organization (WHO). Exclusion criteria were tumor recurrence, metastasis or another primary tumor type than glioma, previous history of intracranial tumors or epilepsy not related to the tumor.

2.2. Study variables

The study period for each included patient was from initial magnetic resonance imaging (MRI) till three months after surgery. The time span was divided into a pre-, peri-, and postoperative period. The occurrence of seizures and information regarding the use and administration of AEDs were obtained for all three periods. The vast majority of prescribed AED was Levetiracetam according to national guidelines. Seizures included all episodes interpreted as epileptic in the EMR. In case of atypical clinical presentation an EEG was usually done. In addition to this, demographic (age, gender), pre-, peri-, and postoperative variables were collected.

Preoperative variables included focal neurological symptoms (e.g. paresis, motor or sensory disturbances, anopsia, aphasia), cognitive symptoms (behavioral/personality change or cognitive deficits, which could not be ascribed primary dementia, psychiatric disorder or abuse), presence of headache, or “other” symptoms (e.g. dizziness). Furthermore comorbidity (ischemic heart condition, hypertension, diabetes mellitus, or “other” comorbidities like previous stroke/transient cerebral ischemia or present drug/alcohol abuse), previous radiation of the head or neck (e.g. as part of cancer treatment), and tumor characteristics based primarily on T1 with contrast and T2 MRI including number of tumors/focality, size (longest diameter), anatomical location, side, and functional area (non-eloquent, near eloquent, or eloquent, with the latter being e.g. primary motor, sensory, or language areas, visual cortex and its connections, insula, thalamus, internal capsule, deep grey substance, and corpus callosum). Multiple tumors placed in both hemispheres as well as a single tumor crossing the midline was marked as “midline/bilateral” regarding the side of tumor location.

Perioperative variables were limited to 24 h before and after surgery and included physical status according to the American Society of Anesthesiologists’ classification (ASA) and treatment with high dose glucocorticoids.

Postoperative variables included complications, defined as circumstances leading to surgical intervention or as death in the immediate postoperative course, degree of residual tumor on a < 72 h postsurgical MRI according to the Response Assessment in Neuro-Oncology Criteria (RANO criteria), tumor histology and pathology according to the WHO grading I-IV, postoperative chemotherapy and radiation treatment. The degree of residual tumor was marked as” unknown” if the < 72 h postoperative MRI was not performed. This was typically the case when only biopsies were performed. If patients had seizures in the postoperative period, the time of the first seizure was recorded (≤ 1 week, ≤ 1 month, ≤ 3 months postoperatively). In addition, the type of oncological treatment was recorded [15]. Postoperative oncological treatment regimens that were not fully completed, were changed, or otherwise differed from the protocol, were listed as "other".

Data for all variables were collected and managed in the Research Electronic Data Capture tool (a secure web application for building and managing online surveys and databases, REDCap) hosted by the University of Southern Denmark.

2.3. Approvals

Permission to obtain patient sensitive data was granted from the Danish Patient Safety Authority (3-3013-1842/1) and the Danish Data Protection Agency (16/33082) prior to data collection.

2.4. Statistical analyses

A descriptive analysis was used to characterize the study population regarding demographics, variable outcomes and seizure incidences.

With pre- and postoperative seizures as dependent variables, univariate logistic regression analyses were performed to examine a possible crude association for each relevant variable. Variables with a significance level of $P < 0.20$ were included in the subsequent multivariate logistic regression analyses with a significance level of $P < 0.05$, and where backward stepwise selection was used to exclude non-significant variables consecutively.

Age and tumor size were dichotomized (< 50 and ≥ 50 years, < 40 and ≥ 40 mm, respectively) before included in any of the analyses. Similarly, pathology was dichotomized (low grade (WHO I + II) and high grade (WHO III + IV)) before included in the logistic regression analyses. As multiple outcomes were possible for the variables location, comorbidities, and complications, each of the outcomes was analyzed separately as a dichotomous variable, providing each of them with a P-value.

All univariate and multivariate analyses were performed using STATA 15.0 (College Station, Texas 77,845 USA).

3. Results

3.1. Study population characteristics and seizure incidences

Of the 491 patients, 282 met the inclusion criteria (119 females). Ninety-three were excluded due to surgery for recurrent tumor, 109 had metastasis or another tumor type than glioma, errors in diagnostic codings, or a history of other intracranial tumors, while seven had a