Seizure 40 (2016) 76–80

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Status epilepticus secondary to glioma

Kristin M. Knudsen-Baas [a,b,*], Kjersti N. Power [a,b], Bernt A. Engelsen [a,b], Stig Erik Hegrestad [c], Nils Erik Gilhus [a,b], Anette M. Storstein [a,b]

[a] Department of Neurology, Haukeland University Hospital, Bergen, Norway
[b] Department of Clinical Medicine, University of Bergen, Bergen, Norway
[c] Department of Neurology, Central Hospital Sogn and Fjordane, Førde, Norway

ARTICLE INFO

Article history:
Received 13 April 2016
Received in revised form 30 May 2016
Accepted 15 June 2016

Keywords:
Glioma
Seizures
Semiology
Sequelae
Treatment
Tumor progression

ABSTRACT

Purpose: Epilepsy is common in glioma patients, but clinical data on the course of status epilepticus (SE) in this group are sparse. The aim of this study was to investigate the relationship of SE to tumor grading, seizure semiology, trigger factors, treatment response, recurrence and outcome of SE in patients with glioma.
Methods: Adult patients with SE and glioma WHO grade II–IV were identified from a prospective clinical study at two neurological departments. We identified 31 SE in 20 patients during a period of 7 years.
Results: SE was more frequent in patients with high-grade glioma. Half of the seizures were secondary generalized. Patients with a clinical and radiological stable glioma had SE as often as patients with untreated tumor or tumor in progression. The majority of patients had a well-controlled epilepsy prior to SE. SE responded well to first and second line treatment. Patients with SE and tumor progression were not more refractory to treatment than patients without progression.
Conclusion: SE secondary to glioma responded well to treatment and should be treated aggressively regardless of the oncological prognosis. Seizures during tumor progression were not more treatment refractory than SE in patients with stable glioma disease.

1. Introduction

Brain tumor related epilepsy is an important aspect of the burden of disease for patients with glioma and often pose a therapeutic challenge. The risk of epileptic seizures is 70–90% for patients with low grade glioma (LGG) and 30–60% for patients with high grade glioma (HGG) [1–5]. In this study, we explored status epilepticus (SE) in a prospective patient database with glioma and epilepsy. SE is a life-threatening medical emergency in which seizure activity continues for a prolonged period of time, or where seizures recur before full clinical recovery from the preceding seizure [6,7]. The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) have proposed a new definition of SE: Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. It is a condition which can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures [8]. SE is often operationally defined as $\geq$5 min of continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness [9]. If inadequately treated and lasting beyond 30 min, which is the older definition of SE, this condition can result in permanent pathophysiological changes [6,10]. Thus, SE requires immediate treatment, often in an intensive care unit (ICU). Brain tumor is the cause of SE in 3–12% of adult cases [11–14]. Previous studies on SE in glioma patients [15–18] have been retrospective, of small sample size and including tumors of various histologies.

The aim of our study was to investigate SE in a prospective material of adult patients with verified glioma. We investigated the relationship of SE to tumor grading, seizure semiology, trigger factors and treatment response, in addition to recurrence and outcome. Our research is important to gain a better understanding of this challenging epileptic condition in a patient group with complicating underlying tumor.

Abbreviations: AEDs, antiepileptic drugs; GBM, glioblastoma; HGG, high grade glioma; LGG, low grade glioma; RSE, refractory status epilepticus; SE, status epilepticus.

* Corresponding author at: Department of Neurology, Haukeland University Hospital, 5021 Bergen, Norway. Tel.: +47 97564429; fax: +47 55975164.
E-mail address: kristinmkb@hotmail.com (K.M. Knudsen-Baas).

http://dx.doi.org/10.1016/j.seizure.2016.06.013
1059-1311/

2. Material and methods

Patients with SE and glioma were identified from a prospective clinical study of adult patients with verified glioma WHO grade II–IV and one or more epileptic seizures during the course of disease. The study has been ongoing since 2008 with inclusion of all eligible patients at the only two neurological departments in two counties of western Norway (Haukeland University Hospital in Bergen, Hordaland County and Central Hospital, Sogn and Fjordane County) since 2009. These two counties have a population of 620,527 (Statistics Norway 01.01.15). The glioma patients are followed clinically and radiologically from their first seizure until death. Neurological, oncological and paraclinical data are collected every 6 months and at other admittances to the hospitals. By 10.12.2014, 20 patients had been registered with SE, once or on several occasions. These 20 glioma patients had in total 31 SE. We adhered to the old definition of SE as seizures lasting beyond 30 min, as this is regarded as the threshold for neurological damage. We evaluated the medical records, prehospital information, blood analyses, cerebral CT and MRI, EEG and follow-up data of all patients. For descriptive purposes, all 31 status episodes were included. In patients with multiple SE episodes, only the first episode was included in the statistical analyses, to avoid the bias of repeated measurements in one subject. The study was approved by Regional Committees for Medical Research Ethics (REK 2008/11243) and all patients gave a written consent.

3. Theory/calculation

3.1. Definitions

SE was defined as either 30 min of continuous seizure activity or two or more sequential seizures without recovery of full consciousness between the seizures [19]. Although the definition was recently modified, we adhered to this version which is often used in evaluating prognosis and has been used throughout the study period [8,20]. Seizures were classified as focal SE without consciousness impairment, focal SE with consciousness impairment or secondary generalized SE. Refractory status epilepticus (RSE) was defined as SE unresponsive to two AEDs and/or requiring anesthetic agents for seizure control [21,22]. If the patient was treated with two different benzodiazepines as first line treatment, this was considered as the same AED.

The patients were grouped according to histological diagnosis at onset of disease, or, in case of malignant transformation, according to the most recent histological diagnosis. The LGG group includes astrocytoma and oligodendroglioma of WHO grade II. HGG includes anaplastic astrocytoma (WHO grade III) and glioblastoma (GBM) (WHO grade IV) [23]. SE was categorized as onset symptom if the seizure unfolded within 30 days prior to glioma diagnosis. Progression was defined as radiographic changes and clinical signs consistent with tumor progression within 30 days of the SE. Mortality was defined as death within 30 days after the SE. Sequela was defined as a neurological deficit acquired during the SE and documented in the medical record as persistent at time of discharge, or at the next control appointment at the hospital. Mild sequelae were defined as transient neurological deficits lasting less than 1 month. Moderate sequelae were defined as neurological deficits that were still present more than 1 month after SE. Major sequelae were defined as permanent neurological deficits which severely impaired functional ability.

3.2. Statistical methods

Statistical analyses were carried out in IBM SPSS Statistics for Windows, versions 22.0 and 23.0 (Armonk, NY: IBM Corp). Background variables were compared using cross-tables with Fisher's exact test of independence. Two-sided P values ≤ 0.05 were interpreted as statistically significant dependence of variables.

4. Results

4.1. Patient and tumor characteristics

We identified 31 SE in 20 patients (Table 1). Five patients had LGG and 15 had HGG. Two of the HGG were transformed from previous LGG. The glioma was localized in the left hemisphere in 60%. Four tumors had a frontal location, ten were localized in the parietal lobe or frontoparietal region, four were temporal lobe tumors, one was occipital and one multilobal.

4.2. SE characteristics

The SE was secondary generalized in 15/31 (48%), focal with consciousness impairment in eight (26%) and focal without consciousness impairment in eight (26%) (Fig. 1). Repeated SE was seen in seven of the 20 patients. Six of them had HGG, including two patients with four SE each. The single LGG patient had oligodendroglioma with SE as onset symptom and a second SE several years later, at a time with no AED use.

The duration of SE varied from 30 min to 4 days (Table 2). The focal seizures more often persisted longer than 5 h than the secondary generalized seizures ($P = 0.01$). In patients where SE led to initial glioma diagnosis (seven SE) or diagnosis of progression (eight SE), we regarded the tumor as the main SE trigger factor. In the other 16 SE, the tumor was stable and other possible trigger factors were identified, as ongoing radiotherapy with or without concomitant chemotherapy (four), intercurrent disease (one) or changes in AED regimen (two). Most SE occurred in a setting of well-controlled epilepsy with no or few seizures the last month (Table 2). Four SE occurred in patients with no prophylactic AED treatment, in addition to the seven SE which heralded glioma diagnosis. Of the 20 SE in patients taking prophylactic AEDs, only six were during polytherapy. Two patients had serum AED levels below and one patient above the reference areas at SE.

First line treatment was sufficient to terminate the seizures in 15/31 SE (48%) and second line treatment was needed in 7/31 (23%) (Table 2). Eight cases were RSE; additional levetiracetam and/or valproate were needed in six SE and general anesthesia with

Table 1
Characteristics of patients ($n = 20$).

Gender	Frequency
Male	16
Female	4
Tumor histology	
Oligodendroglioma	3
Astrocytoma	2
Anaplastic astrocytoma	3
Glioblastoma	12
Number of SE	
1 SE	13
2 SE	5
3 SE	0
4 SE	2
Age at glioma diagnosis	Years
Median	55
Minimum	24
Maximum	95