Seizure 51 (2017) 157–162

Contents lists available at ScienceDirect

Seizure

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

Full length article

Epileptic seizures heralding a relapse in high grade gliomas

Carlo Di Bonaventura[a,*,1], Mariarita Albini[a,1], Alessandro D'Elia[b], Jinane Fattouch[a], Martina Fanella[a], Alessandra Morano[a], Giulia Lucignani[a], Mario Manfredi[a], Claudio Colonnese[a,b], Maurizio Salvati[a], Nicola Vanacore[c], Alfredo Berardelli[a,b], Anna Teresa Giallonardo[a]

[a] Department of Neurology and Psychiatry, "Sapienza" University, Rome, Italy
[b] IRCCS Neuromed, "Sapienza" University of Rome, Pozzilli, IS, Italy
[c] National Centre of Epidemiology, Surveillance and Health Promotion, National Institute of Health, Rome, Italy

ARTICLE INFO

Article history:
Received 9 November 2016
Received in revised form 4 April 2017
Accepted 18 August 2017
Available online xxx

Keywords:
High grade glioma
Relapse
Seizures
Epilepsy

ABSTRACT

Purpose: Seizures are a common clinical symptom in high-grade gliomas (HGG). The aim of the study was to investigate the relationship between seizures and HGG relapse (HGG-R).
Methods: We retrospectively evaluated 145 patients who were surgically treated for HGG-R. By analyzing clinical characteristics in these patients (all operated and treated by the same protocol), we identified 37 patients with seizures during follow-up. This cohort was divided into four subgroups according to a) presence or absence of seizures at the time of diagnosis and b) temporal relationship between seizure occurrence and HGG-R during follow-up: subgroup A (25 pts) had seizures at follow-up but not at onset, subgroup B (12 pts) had seizures both at follow-up and onset, subgroup C (30 pts) had seizures before MRI-documented HGG-R, and subgroup D (7 pts) had seizures after MRI-documented HGG-R.
Results: Although the datum was not statistically significant, survival was longer in patients with seizures during follow-up than in those without seizures (59.3% vs 51.4% alive at 2 years). In 30 patients (subgroup C) seizures heralded HGG-R. In a correlation analysis for this last subgroup, the time interval between seizure and the HGG-R was significantly associated with the number of chemotherapy cycles ($r = 0.470$; $p = 0.009$) and follow-up duration ($r = 0.566$; $p = 0.001$). A linear regression model demonstrated a reciprocal association between the above factors and that it may be possible to estimate the timing of HGG-R by combining these data.
Conclusions: Seizures may herald HGG-R before MRI detection of relapse, thus suggesting that seizures should always be considered a red flag during follow-up.

1. Introduction

The clinical manifestations of high-grade gliomas (HGG) vary according to the extension of the tumor, its location and its possible clinical complications, which include intracranial hypertension and hemorrhage. Seizures are the first clinical sign in 30–50% of patients, whereas they occur later in the course of the disease in 10–30% of patients [1–3]. Seizures in low-grade, slow-growing tumors, unlike those in HGG which are believed to be caused by neuronal necrosis and hemosiderin deposits, are facilitated by cellular and tissue changes [1]. Indeed seizures are widely known to be more frequent in low grade gliomas, in which they may represent the first clinical manifestation; in such cases, gross-total resection of the lesion may yield a better outcome that allows full seizures control [4], probably as a result of the removal of epileptogenic zone or of the disruption of the related network. By contrast, seizures in HGG are less common and have been shown to be an independent prognostic factor for longer survival when they occur at onset [5]. In HGG, the factors underlying cellular proliferation are likely to be the same as those involved in the pathophysiology of seizures. Consequently, it is conceivable that epileptic phenomena are a direct expression of tissue damage, thereby representing a possible clinical cue of tumor progression [6]. Knowing whether seizures play a predictive role in disease relapse is a clinically relevant issue. In this paper, we investigated the relationship between seizures and the features of HGG. To do so, we retrospectively evaluated 145 patients affected by HGG who had a relapse after surgical treatment (HGG-R).

* Corresponding author.
E-mail address: c_dibonaventura@yahoo.it (C. Di Bonaventura).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.seizure.2017.08.009
1059-1311/

2. Patients and methods

Out of a total population of 496 patients who were referred to the Department of Neurology and Psychiatry (Policlinico Umberto I, Rome) in the period between 1st January 2005 and 1st August 2013, we selected 145 cases who experienced a post-surgical HGG-R.

All of these 145 patients were consecutively enrolled in the study according to the main inclusion criteria: 1) HGG-R after neurosurgery (NSG); 2) availability of complete clinical documentation, EEG and laboratory data; 3) complete neuroimaging data including serial MRI scans (performed by using the same scanner and reviewed by the same neuroradiologist); 4) stable schedule of antiepileptic drugs (AEDs) regimen; 5) adequate compliance by the patients (adherence to therapies and follow-up).

The 145 patients had all undergone a NSG. Following the NSG, according to the Stupp protocol [7–10], all the patients had been treated with radiotherapy (RT) (60 Gy in fractions of 1.8–2 Gy/day, 5 days a week, in 30 sessions over 6 weeks) and chemotherapy (CT) with temozolomide (TMZ) (75 mg/m2) for 6 weeks. Thereafter, after a one-month interval, all the patients underwent cycles of CT (TMZ 200 mg/m2 5/28 days) [11]. The TMZ dosage in each patient was defined according to the clinical and radiological findings. Fotoemustine and/or bevacizumab were added to the therapy of patients in whom a clinical relapse was detected. Patients were treated with AEDs during the RT/CT period. AEDs were initiated in all the patients just before the NSG and were maintained at a stable regimen for each patient during follow-up. The AEDs used were valproate, levetiracetam, carbamazepine and phenytoin. The laboratory follow-up included monthly monitoring of blood count and liver/kidney functions, and periodical measurements of AED serum levels to test the patients' therapeutic plasmatic levels.

The radiological follow-up in all the patients included a brain MRI 24–48 h after surgery, 30 days after surgery, 30–40 days after the end of RT and, lastly, every 3 months. In case of any major clinical events, including occurrence of a seizure, an MRI had been performed.

The MRI scan was performed according to the following protocol: T1-weighted images [volumetric 3D, fast-spin echo (T1 FSE) or gradient (T1 MPRAGE)]; T2-weighted images [T2 FSE; FLAIR]; diffusion-weighted imaging (DWI) and ADC; post-contrast sequences [fast-spin echo (T1 FSE) or gradient (T1 MPRAGE)]; susceptibility-weighted imaging (SWI); MR perfusion (PWI); MR spectroscopy [(MRS) single or multi-voxel spectroscopy]. All MRI scans were carefully reviewed by an expert neuroradiologist with special attention to possible HGG-R and/or of edema.

Patients were excluded from the study if they did not adhere to the planned (clinical and neuroimaging) follow-up, if they did not comply with the therapies or if their documentation was incomplete.

We analyzed the following data for every patient enrolled: sex, age, symptoms at onset, location of the lesion, NSG date, extent of tumor removal (defined as total or partial), presence of edema, histological findings, time of RT, number of CT cycles with TMZ, time of first seizure, type of seizure, timing of HGG-R documented by neuroimaging, time interval between NSG and HGG-R, time interval between seizure and HGG-R, time interval between NSG and seizure, and outcome.

In the cohort of 145 patients with a HGG-R, we identified 100 patients who did not have a seizure at the onset of HGG (group 1) and 45 patients who did have a seizure at the onset of HGG (group 2). Thirty-seven of the 145 patients developed seizures during follow-up; we further analysed this subset by dividing the 37 patients into 4 subgroups according to a) presence or absence of seizures at the time of diagnosis and b) temporal relationship between seizure occurrence and HGG relapse (HGG-R) during follow-up: subgroup A (25 pts) had seizures at follow-up but not at onset, subgroup B (12 pts) had seizures both at follow-up and onset, subgroup C (30 pts) had seizures before MRI-documented HGG-R, and subgroup D (7 pts) had seizures after MRI-documented HGG-R. The distribution of the 145 patients is reported in Fig. 1.

Seven patients who experienced seizures within two months of the NSG were excluded (this criterion was adopted to minimize the risk of acute symptomatic seizures in the early post-surgical and radiotherapy period).

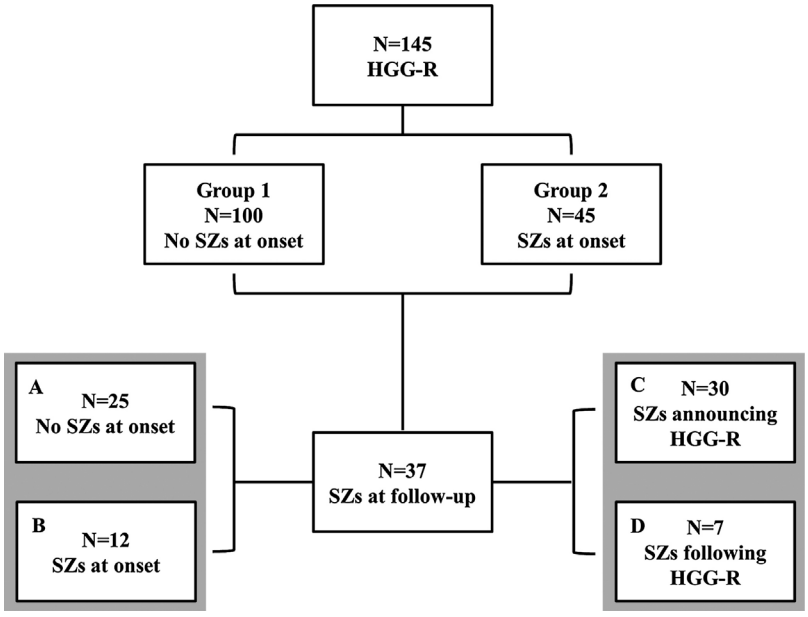

Fig. 1. Schematic representation showing the different clinical situations observed in the enrolled patients. The cohort of 37 patients with seizures (SZs) during follow-up, specifically analyzed in the present study, was further distributed: Box on the left, including subgroups A and B, refers to the patients distributed according to the presence or absence of seizures at the time of diagnosis; Box on the right, including subgroups C and D, refers to the same patients distributed according to the temporal relationship between seizure occurrence and HGG relapse (HGG-R) during follow-up.