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Epileptic features and survival in glioblastomas presenting with seizures

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ABSTRACT

Introduction: The prognostic value of seizures in patients with glioblastoma is currently under discussion. The objective of this research was to study the risk factors associated with seizures occurring at the diagnosis of glioblastoma and the role of seizures as a predictive factor for survival.
Material and methods: We prospectively analyzed the clinical data over the course of the disease, baseline MR imaging, and histological characteristics (p53 overexpression, the Ki67 proliferation index, and presence of the IDH1 R132H mutation), in glioblastomas treated in a single hospital from November 2012 to July 2014. The study follow-up cutoff point was October 2015.
Results: In total, 56 patients were recruited (57% men, mean age 57 years). Median baseline score on the Karnofsky performance scale was 80. Complete tumor debulking followed by radiochemotherapy was achieved in 58.9%. Mean survival was 13.6 months. Epileptic seizures were the presenting symptom in 26.6% of patients, and 44.6% experienced seizures at some point during the course of the disease. On multivariate analysis, the single factor predicting shorter survival was age older than 60 years (hazard ratio 3.565 (95%CI, 1.491–8.522), $p = 0.004$). Seizures were associated with longer survival only in patients younger than 60 years ($p = 0.035$). Younger age, the IDH1 R132H mutation, and p53 overexpression (>40%) were related to seizures at presentation. Baseline MRI findings, including tumor size, and the Ki67 proliferation index were not associated with the risk of epileptic seizures or with survival. Prophylactic antiepileptic drugs did not increase survival time.
Conclusions: Seizures as the presenting symptom of glioblastoma predicted longer survival in adults younger than 60 years. The IDH1 R132H mutation and p53 overexpression (>40%) were associated with seizures at presentation. Seizures showed no relationship with the tumor size or proliferation parameters.

1. Introduction

The main factors that predict a relatively favorable outcome in glioblastoma are complete tumor resection, followed by combined radiochemotherapy and patient age younger than 60 years (Preusser et al., 2011). Seizures have been associated with longer survival in some studies, but this finding remains controversial, as several confounding factors may have influenced the results, such as younger age in patients with epileptogenic glioblastomas, an earlier diagnosis, the histological origin of the tumor, or the use of antiepileptic drugs (AEDs) (Kerkhof and Vecht, 2013; Chaichana et al., 2011; Weller et al., 2011; Toledo et al., 2015; Berendsen et al., 2016).

Abbreviations: AED, antiepileptic drug; IDH, isocitrate dehydrogenase; MR, magnetic resonance.

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It has been reported that epileptogenic glioblastomas may show biochemical and histological characteristics different from those of glioblastomas without associated seizures. (Rosati et al., 2009; Kerkhof and Vecht, 2013). De novo or primary glioblastomas directly present as grade IV astrocytoma, whereas secondary glioblastomas derive from lower-grade gliomas. These tumor types differ in the molecular pathways leading to their development, and in the associated survival rates and clinical outcome. Survival is usually longer in secondary than primary glioblastoma, the condition more commonly occurs in younger adults, and it is more likely to be epileptogenic (Toledo et al., 2015; Berendsen et al., 2016; Mineo et al., 2007).

Isocitrate dehydrogenases (IDH) are proteins involved in cellular proliferation. IDH1 mutations are common in low-grade diffusely infiltrating gliomas and in 12% of glioblastomas (Balss et al., 2008). Molecular markers such as IDH and p53 mutations have been associated with an increased likelihood of secondary glioblastoma, but are not directly linked with the risk of seizures (Olar et al., 2012; Berendsen et al., 2016).

The incidence of seizures in glioblastoma ranges from 20% to 76% of patients, and 23% to 50% show seizures as the presenting symptom of the tumor (Kerkhof and Vecht, 2013). Occurrence of seizures late in the course of the disease has been related to disease progression in 19% of patients and to the end-of-life phase in 37% (Bruna et al., 2013). As secondary glioblastomas derive from tumors of a lower histological grade and epileptic seizures are often the only clinical manifestation, these factors could support the notion that glioblastomas associated with seizures are diagnosed at an earlier stage and for that reason are associated with longer survival (Lote et al., 1998; Kerkhof et al., 2013; Mineo et al., 2007).

Antiepileptic drug treatment has become a subject of discussion in glioblastoma, as an anti-oncogenic effect and increased survival have been linked to some AEDs, such as valproate and levetiracetam (Kerkhof et al., 2013). However, the potential survival increase has not been weighed against the likelihood of adverse events derived from AED use (Glantz et al., 2000; Vučićević et al., 2009). The literature contains controversial data in this line and there are no definitive conclusions regarding the recommendation of AED use in glioblastoma (Kerkhof et al., 2013)

The aim of this study was to assess the clinical, neuroimaging, and histopathological characteristics of the epileptic seizures occurring in patients with glioblastoma, and to determine the prognostic implications of epilepsy on survival in this disease.

2. Material and methods

This is a prospective study including consecutive patients with glioblastoma diagnosed at our institution between November 2012 and July 2014. To be enrolled, patients had to be older than 18 years, have histologically confirmed glioblastoma, and have undergone determination of IDH1 status, the Ki67 index, and p53 expression by immunohistochemistry. The study was approved by the local ethics committee for clinical research.

1 Preoperative MR imaging was carried out with a 1.5-T or 3-T system (Siemens, Erlangen, Germany). In brief, the MR protocol included the following sequences: unenhanced and enhanced T1-weighted, T2-weighted, fluid-attenuated inversion recovery, diffusion-weighted, susceptibility-weighted, and dynamic susceptibility contrast-enhanced T2*-weighted perfusion sequences. MR perfusion images were acquired using the same section orientations as those obtained in conventional MR imaging and covered the entire tumor volume. Images were processed using OLEA software (OLEA SPHERE® 3.0, Olea Medical®).

2 The MR morphological images were analyzed by two neuroradiologists blinded to the clinical information (S.S., C.A.). In all MR examinations performed with the required sequences, images were assessed according to the controlled *VASARI* terminology for describing the MR features of human gliomas, which, in brief, describes the tumor size, location, invasion, extension, peritumoral edema, necrosis, bleeding, and contrast enhancement (National Cancer Institute, https://wiki.cancerimagingarchive.net/display/Public/VASARI+Research+Project, updated May 25, 2012). In addition, we sought to determine whether involvement of the hippocampus was related to the risk of seizures. For this purpose, hippocampal involvement was defined as *normal*, *tumor invasion*, *tumor compression*, *edema*, or *sclerosis*. Features on the baseline MR study anticipated to lead to a poor surgical outcome were eloquent cortex involvement, deep brain invasion, a bihemispheric tumor, or a multicentric tumor.

Surgery consisted of either biopsy or resection, and was classified as partial or complete based on the postoperative CT or MR findings. The surgical specimens were placed in 10% buffered formalin for 24–48 h. For the histological analysis, paraffin-embedded tissue blocks were cut in sections and stained with hematoxylin-eosin. The diagnosis of glioblastoma was based on the WHO classification of 2007 (Louis et al., 2007). A representative block was selected and immunohistochemistry for Ki67, p53, and IDH1 R132H was performed on complete slides. Immunohistochemical staining was done on 4-μm sections, using the Benchmark XT platform with the ultra-View Universal DAB Detection kit (Ventana Medical Systems) with a prediluted antibody against the mutated IDH1 R132H protein (Master Diagnostica), and antibodies against p53 (Dako, DO-7) and Ki67 (Dako, MIB1). The proliferation index and p53 expression were evaluated as the percentage of stained nuclei in the lesion, whereas the IDH1 R132H mutation was evaluated as the presence or absence of staining. A neuropathologist blinded to the clinical information examined the biopsies. The diagnosis of secondary glioblastoma was based on previous histological evidence of a lower-grade tumor.

The standard treatment following surgical resection was Stuppís protocol, which includes radiotherapy combined with temozolomide chemotherapy (Stupp et al., 2005). Oncologic treatment was considered complete in patients who had received at least one full cycle of fractionated external radiotherapy at doses of 45–60 Gy and chemotherapy with temozolomide for at least one full cycle of one month. Tumor progression was diagnosed by MR monitoring performed every 3 months or as needed for clinical requirements.

Epileptic seizures were classified according to the 2010 criteria of the International League Against Epilepsy (Berg et al., 2010). Patients were considered to have epilepsy if they had a prior medical history of tumor-related seizures or if they experienced one or more seizures at the diagnosis or during treatment of the tumor. Epileptic seizures occurring during the course of the disease and due to other causes such as subdural hematoma, sepsis or toxic-metabolic etiologies were excluded as glioblastoma-related seizures. Epilepsy refractory to medical treatment was established when seizures persisted despite the use of at least two antiepileptic drugs at the maximum tolerated doses.

The survival analysis was performed from the date of the diagnosis to the date of death or the study end (15 October 2015). Patients were considered as having undertaken antiepileptic treatment when they had received the drug at the recommended therapeutic doses for at least 3 months. AED combinations taken in end-of-life situations or status epilepticus were not included in the analyses.

Descriptive and frequencies statistical analyses were carried out and comparisons were made using the SPSS 17.0 software. Statistical significance for intergroup differences was assessed by Pearson's chi-square test for categorical variables and Student's *t*-test for continuous variables. Survival rates were analyzed using the Kaplan-Meier product limit survival method with a log-rank test to determine statistical significance between groups.