Clinical Neurology and Neurosurgery 139 (2015) 166–171

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

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

Prognostic implications of epilepsy in glioblastomas

Manuel Toledo[a,*], Silvana Sarria-Estrada[b], Manuel Quintana[a], Xavier Maldonado[c], Francisco Martinez-Ricarte[d], Jordi Rodon[e], Cristina Auger[b], Javier Salas-Puig[a], Estevo Santamarina[a], Elena Martinez-Saez[f]

[a] Epilepsy Unit, Neurology Department, Vall d'Hebron University Hospital, Hospital Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain
[b] MR Unit, Radiology Department, Institut Diagnostic per la Imatge, Vall d'Hebron University Hospital, Hospital Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain
[c] Oncologic Radiotherapy Department, Vall d'Hebron University Hospital, Hospital Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain
[d] Neurosurgery Department, Vall d'Hebron University Hospital, Hospital Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain
[e] Vall d'Hebron Institut of Oncology, Vall d'Hebron University Hospital, Hospital Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain
[f] Neuropathology Unit, Pathology Department, Vall díHebron University Hospital, Hospital Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain

ARTICLE INFO

Article history:
Received 15 December 2014
Received in revised form 4 September 2015
Accepted 5 October 2015
Available online 22 October 2015

Keywords:
Primary brain tumor
Epilepsy
Seizures
Antiepileptic drugs
Glioblastoma

ABSTRACT

Objectives: The role of seizures and antiepileptic treatments associated with glioblastoma is a current topic of discussion. The objective of this study is to characterize and establish implications of epilepsy associated with glioblastoma.
Patients and methods: We retrospectively analyzed the medical history, focused on epileptic features of 134 histologically diagnosed glioblastoma over a period of 4 years.
Results: The sample group had an average age of 56 years and 66% were male. Complete tumor resection was performed in 66% and 64.2% received further radio-oncologic treatment. The average survival rate was 12.4 months and 11.5% survived to 5 years. Epileptic seizures were the presentation symptom in 27% of cases and 51% suffered seizures during the disease, 26% become drug-resistant. Focal evolving to a bilateral convulsive seizures were the most frequent type. Epileptic seizures at presentation independently predicted longer survival ($p < 0.001$). Furthermore, a history of epilepsy or seizures during disease improved survival. Late onset seizures, recurrences or status epilepticus during the course of the disease indicated tumor progression or the final stages of life. Prophylactic antiepileptic drugs did not prevent seizures. Similarly, there was no difference in survival between patients who did not use antiepileptic drugs and those using valproate or levetiracetam. Patients under 60 years, full oncologic treatment and secondary glioblastomas were factors that improved survival ($p < 0.001$).
Conclusion: Previous history of epilepsy or the onset of seizures as a presentation symptom in glioblastomas predict longer survival. Half of patients have seizures during the course of the disease. Antiepileptic drugs alone do not increase survival in glioblastoma patients.

1. Introduction

The glioblastoma is the most common primary malignant brain tumor. Histologically, it is characterized as an astrocytic tumor with the presence of nuclear atypia, mitosis, endothelial proliferation and necrosis. Clinically, it is a tumor with short-term mortality with very few factors contributing to improving survival rates. Diagnosis in adults under the age of 50, extensive resection and radio-oncologic treatment are the best known prognostic factors that improve survival [1].

Glioblastomas can be classified as de novo or as secondary. De novo glioblastomas are those deriving directly from precursor cells that evolve to glioblastoma cells and those which are secondary derive from anaplastic transformations of less malignant glial tumors. Patients with secondary glioblastomas have an average life expectancy of nearly 19 months whilst those with de novo are around 12 months [1]. Molecular markers such as the IDH1 and p53 mutations have been associated with the increased likelihood of secondary glioblastomas with respect to primary glioblastoma [2]. It is a fact that secondary glioblastomas derive from tumors of a lower histological grade, which often show epileptic seizures as the

* Corresponding author.
E-mail address: mtoledo@vhebron.net (M. Toledo).

http://dx.doi.org/10.1016/j.clineuro.2015.10.002
0303-8467/

unique clinical manifestation [3,4]. That is a hypothesis to explain why epilepsy prior to the diagnosis of a glioblastoma or during the course of the disease has been related to a better prosnostic [1].

According to the literature, incidence of seizures related to glioblastoma varies between 20% and 76%, although most studies agree that epilepsy occurs in about half of all patients [5]. It is calculated that between 25% and 50% of patients suffer epileptic seizures as the first symptom of the tumor and a further 20–30% suffer seizures as the disease progresses. Late onset seizures in glioblastomas have been associated with tumor progression in 19% of cases or with end-of-life phase in 37% of subjects [5].

It must also be noted that antiepileptic treatment has become a subject of discussion in glioblastoma as the potential of the anti-oncogenic effect has been linked to valproate [6,7].

In this paper we seek to establish the clinical implications and characteristics of patients with glioblastoma associated with epilepsy.

2. Patients and methods

Data from patients with histological diagnosed glioblastomas between 2008 and 2012 was collected from our center. Patients were selected from the brain biopsy data bank of our institution. Clinical data was obtained from the electronic medical chart of our center when available, or having access to the medical electronic network of different hospitals in cases where they had dropped-out the follow-up in our hospital. The local Ethic Committee approved the conduction of the study and did not require further authorizations or inform consents.

The inclusion criteria comprised of: patients above the age of 14 with confirmed histological glioblastoma, a full medical record from the start of the disease, preoperative assessment and complete postoperative follow up until the current date or until the death.

Images of preoperative MR scans were used to determine the location and size of the tumor according to the lobe (frontal, temporal, temporo-parietal, parietal and occipital) and subcortical regions including "poor surgical locations" (corpus callosum, thalamus, basal ganglia, internal capsule and brain stem), which are related to a poor surgical accessibility and survival.

Surgery was classified according to whether it had been biopsy or resection. The resections were considered partial or extensive (complete) as assessed by postoperative MR or CT scanning.

Secondary glioblastoma patients were diagnosed when there was previous histologic evidence of a less malignant tumor, or when evidence from prior neuroimaging showed a tumor of a lower malignancy grade. The diagnostic of lower grade gliomas was based on the finding in previous MR studies obtained at least one year before the histological diagnostic of glioblastoma, which showed features of low-grade gliomas as assessed by expertise neuroradiologists (SS, CA) using the Vasari assessment.

Tumor progression was diagnosed by monitoring MR images of patients with glioblastoma every 3 months, or as needed for clinical requirements.

Radio-oncologic treatment was considered complete in patients who had received fractionated external radiotherapy with at least one full cycle with doses between 45 and 60 Gy and chemotherapy with temozolomide for at least one full cycle of one month. Most patients received Stupp's protocol which includes radiotherapy combined with temozolomide [8].

Epileptic seizures were classified according to those set out by the International League Against Epilepsy, as focal with or without impairment of consciousness, or evolving to a bilateral convulsive seizure [9]. Patients were considered as having epilepsy in cases with history of epilepsy or if they suffered at least one seizure during the diagnosis and treatment of the tumor. Epileptic seizures that occurred during the course of the disease but were in fact secondary to other etiologies such as subdural hematoma, sepsis or toxic-metabolic causes were excluded as glioblastoma related seizures. Refractory epilepsy to medical treatment was considered when at least two antiepileptic drugs were used, consecutively or in combination, to the maximum tolerated doses and still seizures persisted.

Patients were considered as having undertaken antiepileptic treatment when they had taken the drug at therapeutic doses for a period of at least 3 months. Antiepileptic drugs taken in end-of-life situation or status epilepticus were not considered in the analyses.

Descriptive and frequency statistical analysis were obtained and comparisons were made by use of software SPSS Statistics 17.0. We included the following variables into the analysis: Age, gender, history of epilepsy, seizure frequency and type, status epilepticus, antiepileptic treatment, drug-resistance to antiepileptic medication, clinical presentation, mortality, tumor type, tumor location, tumor progression, baseline tumor size, radioncologic treatment and surgical treatment. Continuous variables were checked for normality using Kolmorov-Smirnov test and Q-Q plot. Statistical significance for intergroup differences was assessed by Pearson's chi-square for categorical variables and the Student's t test for continuous variables. Survival rates were analyzed with the Kaplan–Meier survival curves using log-rank test to determine statistical significance between groups, and simple Cox models to assess differences in continuous variables. An optimal cut-off point for age with best sensitivity and specificity to predict survival was obtained using a receiver characteristic operator curve (ROC). Multivariate analysis was performed using an adjusted Cox regression model in order to identify factors independently associated with better rates of survival during follow-up. A p-value <0.05 was considered statistically significant.

3. Results

We analyzed 134 patients out of the 137 patients with recorded histologic glioblastoma. During the follow-up, information of 27 out of 134 patients was obtained from external electronic chart. Three cases were excluded for a lack of clinical information or confusing data in one case. The average patient follow-up was 19.2 months (±14.5) with a range between 0.2 and 175 months.

The demographic characteristics, the location of the tumor and the oncological treatment are summarized in Table 1. The overall survival rate during the first year was 50.6% and was reduced to 22.6% in the second year and to 11.5% in the fifth year of follow-up.

The most typical tumor location in over half of patients was the frontotemporal region. The full tumoral resection followed by radiochemotherapy was completed on 86 patients (64.2%).

Table 1
Demographic characteristics and oncological treatment (N = 134).

Age	56 years-old (±14.7) [14–78]
Gender	♂ 66% (n = 88)/♀34% (n = 46)
De novo/secondary GB	84% (n = 113)/16% (n = 21)
Tumor location	Frontal 32.8% (n = 44)
	Temporal 25.8% (n = 36)
	Parietal 11.2% (n = 15)
	Temporo-parietal 14.9% (n = 20)
	Occipital 4.5% (n = 6)
	Poor surgical location 9.7% (n = 13)
Radiotherapy	76.9% (n = 103)
Chemotherapy	73.1% (n = 98)
Complete resection	66.4% (n = 89)
Median survival	12.4 months (Standard error 9.4–15.5)

'Poor surgical location' includes Corpus Callosum, basal ganglia, internal capsule, brain stem and cerebellum. GB, glioblastoma.