The end-of-life phase of high-grade glioma patients

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Chapter 2.2

Seizures in high-grade glioma patients: a serious challenge in the end-of-life phase

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Abstract

Background: to analyse the prevalence of seizures and use of anti-epileptic drugs (AEDs) in the end-of-life (EOL) phase of high-grade glioma (HGG) patients and to identify patient characteristics associated with the occurrence of seizures in the last week of life.

Methods: patients were recruited from a cohort of adult HGG patients diagnosed in 2005 and 2006 in three tertiary referral centres for brain tumour patients. Physicians involved in the EOL care for deceased HGG patients were asked to fill in a questionnaire regarding seizures and anti-epileptic treatment both in the last three months and in the last week of life. Data on seizures and use of AEDs before the EOL phase were obtained from medical correspondence and hospital medical charts.

Results: out of 155 deceased patients, data of 92 patients were eligible for analysis. Twenty-nine percent of these 92 patients had seizures during the last week of life; 33% of the patients with and 22% of the patients without a history of seizures. Besides a history of status epilepticus ($p=0.047$), we identified no other significant risk factors to develop seizures in the last week of life. Seventy percent of all patients used AEDs before the last week of life. In 35% of patients of whom AEDs were tapered, seizures occurred in the last week of life.

Conclusions: our results demonstrate that seizures are a common symptom in HGG patients during the last week of life and emphasize the importance of adequate AED treatment throughout the EOL phase.

Introduction

Epileptic seizures are very common in high-grade glioma (HGG) patients: in 30 - 50% of patients seizures are the presenting symptom and an additional 10-30% will develop seizures during the further course of their disease.[88] Little is known about the occurrence of seizures in the end-of-life (EOL) phase of HGG patients, when the goal of treatment is primarily maintaining quality of life as high as possible. High-grade glioma patients and their relatives fear seizures in the EOL phase[25] and the occurrence of seizures has proven to diminish patients' health-related quality of life.[89, 90] In a pilot study of our group we found that 45% of HGG patients experienced seizures after ending tumour treatment and 28% of patients even had seizures in the last week of life, suggesting seizures to be a serious problem in this disease stage.[47]

During the EOL phase, and particularly in the last week of life, the majority of HGG patients eventually lose consciousness and develop swallowing difficulties, interfering with the intake of oral anti-epileptic drugs (AEDs).[21, 46-48, 65] Since no strict guidelines exist for the anti-epileptic treatment in the EOL phase, currently the decision whether or not to continue AEDs in case of intake problems depends on the doctors' expert opinion. Improved knowledge regarding epilepsy in the EOL phase could contribute to the development of more specific treatment guidelines.

The aims of this study were (1) to systematically evaluate the prevalence of seizures and use of AEDs in the last week of life in a cohort of deceased HGG patients and (2) to identify patient characteristics predictive for development of seizures in the last week of life.

Methods

Subjects

The study population comprised a cohort of adult HGG patients diagnosed in 2005 and 2006 in three Dutch tertiary referral centres for brain tumour patients (VU University Medical Centre, Academic Medical Centre and Medical Centre Haaglanden). Physicians involved in the EOL care of deceased patients (i.e. general practitioners, nursing home physicians, hospice doctors or neurologists) were approached for participation, and asked to fill in a questionnaire regarding the EOL phase of the specific patient. The EOL phase is generally defined as the phase after ending anti-tumour treatment. As the EOL phase ranges widely in duration and the actual beginning is often difficult to determine even in retrospect, questions related to both the last three months and the last week of life. The study protocol was approved by the Ethics Committee of the three participating hospitals.

Study measures

Data regarding seizures *before* the EOL phase were obtained from the medical correspondence and hospital medical charts. We recorded (1) whether a seizure was the presenting symptom, (2) the most severe seizure type (focal, generalized or status epilepticus), (3) the epilepsy burden (one time event, multiple seizures using ≤ one type of AED, multiple seizures using multiple AEDs) and (4) the type of AEDs prescribed.

From the questionnaire filled in by physicians, data were obtained concerning the EOL phase: (1) place of death, (2) the occurrence of seizures in the last week of life and (3) the use and (dis)continuation of AEDs in the EOL phase.

Analysis

SPSS software 15.0 was used for statistical analysis. Descriptive statistics were used to summarise baseline data. Differences between groups were tested using the chi-square test/Fisher's Exact Test for categorical data and either the students T-test or Mann Withney U test for continuous data, depending on the distribution of the tested variable. All tests were two-tailed and $p<0.05$ was considered to be statistically significant.

Results

Subjects

Figure 1 shows the flow chart of patient identification and data collection. Data of seven patients who were reported to use an AED according to the questionnaires could not be confirmed by their hospital medical charts. As there was a gap between the last report in the hospital medical chart and the end of anti-tumour treatment, these cases were excluded from analysis to avoid bias. The median time between patients' death and completion of the questionnaires by the physicians was 27.0 months (range 1.2 - 50.5 months).

Patient and seizure characteristics are outlined in table one. Of the 92 patients, 61 died at home (66%), 13 in a nursing home (14%), 8 in a hospital (9%), 7 in a hospice (8%) and 3 elsewhere (3%). In 38 patients (41%), seizures were the presenting symptom. During anti-tumour treatment, 60 patients (65%) used at least one type of AED: 46 used valproic acid, 27 levetiracetam, 6 phenytoin, 3 lamotrigin, and 1 carbamazepine. No significant differences in sex, age and tumour grade were reported between the 92 patients analysed in this study and the cohort of 155 patients eligible for inclusion (data not shown).

Seizures in the last week of life

Of all evaluated 92 HGG patients, 29% had seizures in the last week of life. No significant differences were identified in baseline characteristics and place of death between patients with and without seizures in the last week of life (table 1). Seizures in the last week of life did not occur more often in patients who experienced seizures before the EOL phase (table 1). Patients with a previous status epilepticus, however, showed a significantly higher seizure incidence in the last week of life (p = 0.047). Seven of the 32 patients without seizures before the EOL phase (22%) had seizures in the last week of life (table 1). In four patients, seizures in the last week were the first seizure ever, and the other three patients had their first seizure ever in the last three months of life after ending all anti-tumour treatment.

Table 1: Patient characteristics and seizure frequency in the last week of life

	Baseline characteristics all patients [a] N (%)	Patients with seizures in the last week of life [b] N (%)
Sex		
▪ Male	68 / 92 (74%)	18 / 68 (27%)
▪ Female	24 / 92 (26%)	9 / 24 (38%)
Age at diagnosis		
▪ < 60 years	51 / 92 (55%)	16 / 51 (31%)
▪ > 60 years	41 / 92 (45%)	11 / 41 (27%)
Tumour grade (WHO)		
▪ Grade 3	12 / 92 (13%)	3 /12 (25%)
▪ Grade 4	80 / 92 (87%)	24 / 80 (30%)
Seizures anytime during disease		
• Yes	60 / 92 (65%)	20 / 60 (33%)
• No	32 / 92 (35%)	7 / 32 (22%)
Seizure burden (before EOL phase)		
• No seizures	32 / 92 (35%)	7 / 32 (22%)
• 1 seizure, ≤ 1 AED	10 / 92 (11%)	3 /10 (30%)
• > 1 seizure, ≤ 1AED	29 / 92 (31%)	10 / 29 (35%)
• > 1 seizure, ≥ 2 AED	21 / 92 (23%)	7 / 21 (33%)
Type of seizures		
• Focal	11 / 92(12%)	1 / 11 (9%)
• Generalized	43 / 92 (47%)	15 / 43 (35%)
• Status epilepticus	6 / 92 (7%)	4 / 6 (67%)*

[a] data obtained from medical chart; [b] data obtained from physician's questionnaire; * p=0.047 (Fischer's' exact)

Anti-epileptic treatment in the EOL phase

According to the questionnaire filled in by the physicians, 64 HGG patients (70%) used AEDs before the last week of life. In 29 cases, AEDs were tapered close before death due to difficulties with oral intake. In 10 of the 29 patients of whom AEDs were tapered (35%),

seizures occurred during the last week of life. In 35 patients whose AEDs were continued until death, 15 patients (43%) still experienced seizures in the last week. None of the patients without seizures before the EOL phase received prophylactic AEDs.

Discussion

To our knowledge, this is one of the first studies on the prevalence of seizures and its anticonvulsant treatment in the EOL phase of HGG patients from a well-defined cohort. The retrospective design, which is a generally acknowledged practice in EOL research, might have caused recall bias of our results and thus requires cautious interpretation of the data. Unfortunately, prospective data collection in this patient population in this disease stage is subjective to substantial bias, as the identification of patients approaching the EOL is often complicated.[91] As a precaution, we excluded patients of whom the information in the medical chart was incomplete.

Our results corroborate with a previous retrospective study which showed a prevalence of 36.9% of seizures in the last month before death and confirms that seizures are a common symptom during the EOL phase.[21, 46-48, 92] Apart from a history of status epilepticus, we were unable to establish predictive factors for the occurrence of seizures in the last week before dying.

Our findings are mainly focused on the last week before dying, as most intake problems develop at this time, requiring an alteration in the administration (routes) of AEDs. [8] About one third of the patients with a history of epilepsy developed seizures in the last week, irrespective whether AEDs were tapered close to death or not, which suggests a relative inefficacy of AEDs in preventing seizures towards the EOL. Almost a quarter of patients without a history of epilepsy had seizures during the last week of life. The pathogenesis of the relatively high seizure frequency in the EOL phase remains unknown. Both tumour progression and the development of metabolic disturbances during the last stage of the disease might cause an elevated seizure risk in the last week of life. Changes in administration routes coinciding with insufficient drug absorption could lead to subtherapeutic AED levels, which might explain the occurrence of seizures in patients whose AEDs were not tapered.

This retrospective cohort study demonstrates the high frequency of seizures in the EOL phase and shows the complexity of effective AED treatment throughout the disease course in HGG patients with a history of seizures. To improve seizure control in the EOL phase, the development of treatment guidelines for both recurrent and *de novo* seizures is warranted. Furthermore, the occurrence of seizures in the EOL phase in patients without a history of epilepsy raises the question whether prophylactic AEDs should be prescribed in all HGG patients. Future studies should focus on the identification of risk factors for the development of *de novo* seizures in the EOL in glioma patients and on alternative AED

administration in the EOL phase, such as buccal or intranasal routes, contributing to an improvement of quality of life in HGG patients.