Seizure xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seizure

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

Nonconvulsive status epilepticus in patients with brain tumors

Lara V. Marcuse [a,*], Guido Lancman [a], Alexis Demopoulos [b], Madeline Fields [a]

[a] Department of Neurology, Mount Sinai School of Medicine, 1468 Madison Avenue, New York, NY 10029, USA
[b] North Shore University Hospital, North Shore University Hospital, 200 Community Drive, Manahasset, NY 11030, USA

ARTICLE INFO

Article history:
Received 24 February 2014
Accepted 4 April 2014

Keywords:
Critical care
EEG
Epilepsy monitoring
Status epilepticus
Brain tumors

ABSTRACT

Purpose: The prevalence of nonconvulsive status epilepticus (NCSE) in brain tumor patients is unknown. Since NCSE has been associated with significant mortality and morbidity, early identification is essential. This study describes the clinical and EEG characteristics, treatment, and outcome in brain tumor patients with NCSE.

Method: All patients admitted to Mount Sinai Hospital from 2009 to 2012 with an ICD-9 brain tumor code were cross-referenced with the epilepsy department's database. EEGs from matching patients were reviewed for NCSE. Relevant information from the medical records of the patients with NCSE was extracted.

Results: 1101 brain tumor patients were identified, of which 259 (24%) had an EEG and 24 (2%) had NCSE. The vast majority of seizures captured were subclinical with 13 patients (54%) having only subclinical seizures. Treatment resolved the NCSE in 22 patients (92%) with accompanying clinical improvement in 18 (75%) of those patients. Tumor recurrence or progression on MRI was associated with decreased 2-month survival (75% mortality, $p = 0.035$) compared to stable tumors (20% mortality). Patients with metastatic disease had median survival from tumor diagnosis of 1.2 months.

Conclusion: NCSE in brain tumor patients may be under diagnosed due to the frequent lack of outward manifestations and highly treatable with improvement in the majority of patients. NCSE patients with progressing brain lesions, tumor recurrence, or metastatic disease are at serious risk of mortality within 2 months. Continuous EEG monitoring in brain tumor patients with recent clinical seizures and/or a depressed level of consciousness may be critical in providing appropriate care.

1. Introduction

Seizures are commonly associated with brain tumors, with 40–80% of brain tumor patients experiencing a seizure during the course of the disease.[1] However, the prevalence of nonconvulsive status epilepticus (NCSE) in these patients is unknown. NCSE was found in 8% of 236 comatose patients[2] and in 6% of cancer patients with altered mental status but no CNS involvement,[3] and is generally thought to be under diagnosed.[4] NCSE can be confused with altered mental status from other causes, such as tumor progression, edema, or hemorrhage. While NCSE has been associated with significant mortality[5] and neurological morbidity,[6] it is not yet clear if early identification and treatment improve outcome. Furthermore, NCSE can be the presenting sign of new brain tumors or metastatic lesions.[7,8] Although imaging abnormalities have been described in these patients,[9,10] there is a scarcity of data on manifestations, electrographic characteristics, treatment, and outcomes of NCSE in brain tumor patients.

This retrospective case series describes the characteristics of brain tumor patients with NCSE and examines which variables may influence NCSE duration and overall survival.

2. Methods

2.1. Data collection

This study was approved by the Icahn School of Medicine at Mount Sinai's Institutional Review Board. Medical records from Mount Sinai Hospital were queried from July 1, 2009 to July 1, 2012 for brain tumor *International Classification of Diseases, Ninth Revision* (ICD-9) codes 191, 198.3, 200.5, 225, and 239.6. These codes represent primary malignant brain tumors, secondary malignant brain tumors, primary CNS lymphoma, benign brain

* Corresponding author at: 1468 Madison Avenue, New York, NY 10029, USA. Tel.: +1 212 241 2627; fax: +1 646 537 9690.
E-mail addresses: lara.marcuse@mssm.edu, laramarcuse@gmail.com, Lara.Marcuse@mountsinai.org (L.V. Marcuse).

http://dx.doi.org/10.1016/j.seizure.2014.04.003
1059-1311/

and other CNS tumors, and other unspecified intracranial neoplasms, respectively. These lists were matched with the epilepsy department's database containing all EEGs conducted at the hospital during this time period. EEG recordings of all matching patients were evaluated to determine if they had NCSE. All patients with NCSE had continuous EEG monitoring. Medical records of the identified patients were reviewed to collect information on demographics, tumor type and treatment, NCSE clinical and EEG characteristics, NCSE treatment, radiography, and overall survival.

2.2. Definitions

As of yet, there are no widely accepted criteria for the definition of NCSE. We defined NCSE as ongoing seizure activity, lasting >30 min, without generalized convulsions. Patients were described as being alert or having a depressed (lethargic, obtunded, or comatose) level of consciousness.

Two epileptologists (MF, LM) independently reviewed EEGs and unanimously agreed on inclusion in the study. Seizures were termed subclinical if there was no definite outward manifestation of seizure with the understanding that for some individuals the seizures were depressing the level of consciousness. For the purposes of this review the authors delineate NCSE into four different seizure patterns:

1. Focal nonconvulsive seizures (NCS): A focal onset followed by clear electrographic evolution. A pattern was said to evolve if there were at least 2 unequivocal, sequential changes in frequency, morphology or location as defined by the ACNS guidelines.[11]
2. Ictal interictal continuum (IIC): This category was used for ictal patterns without evolution as defined by the ACNS.[11] It is a convention that lateralized periodic discharges (LPD) faster than 3 Hz represent an ictal pattern.[12] In addition, LPD which were slower in frequency with a clinical correlate or which responded to treatment with AEDs were considered a pattern of NCSE.[12] Rhythmic or spikey theta and alpha activity without evolution which may wax and wane was placed in this category. Most LPD were NOT considered a form of NCSE.
3. Epilepsia partialis continua (EPC): Defined as unremitting motor seizures involving part or all of one side of the body lasting for hours to days. There is disagreement in the literature regarding the inclusion of this type of seizure under the category of NCSE. Ebersole and Pedley[12] include EPC in the category of NCSE whereas Maganti et al.[4] exclude motor seizures from NCSE. Since EPC was seen relatively frequently in this population, the authors opted to use Ebersole and Pedley's definition. EPC was often without EEG correlate.
4. Generalized nonconvulsive status epilepticus: Generalized periodic discharges (GPD) 3 Hz or greater on EEG or seizures with a generalized onset and evolution.

The categorization of background EEG characteristics in this paper is described in Table 1.

2.3. Outcomes and statistics

All variables were tested against two outcomes: NCSE duration (greater than or less than 24 h) and 2-month survival. Student's t-tests were used for continuous variable and chi-squares and Fisher's exact test were used for categorical variables. Where appropriate, linear-by-linear association was used for graded categorical values. *P*-values <0.05 were considered significant for this study.

3. Results

A total of 1101 patients were identified by the queried brain tumor ICD-9 codes. Of these, 259 (24%) had an EEG and 24 (2%) had NCSE.

The reason for the continuous EEG was a clinical seizure for 20 (83%) patients and altered mental status for 4 (17%) patients.

3.1. Demographics

There were 12 males and 12 females with a mean age of 62 years (SD 15, range 25–84). Tumor types consisted of 6 primary benign (4 meningioma, 1 acoustic neuroma, 1 central neurocytoma), 10 primary malignant (5 glioblastoma multiforme, 1 high grade glioma, 2 WHO III anaplastic astrocytoma, 1 WHO grade II astrocytoma, 1 oligodendroglioma), and 8 secondary malignant (4 lung cancer, 1 breast cancer, 1 multiple myeloma, 1 oral pharynx, 1 unknown primary).

Five patients (21%) had NCSE lasting less than 24 h while 19 patients (79%) had NCSE for greater than 24 h. Eleven (48%) patients died within 2 months of their episode of NCSE (data missing for one patient). Age, gender, and tumor type were not associated with 24-h NCSE duration or 2-month survival.

Median survival time from first onset of NCSE was 3 months for primary benign, 1.9 months for primary malignant, and 1.2 months for secondary malignant. Median survival time from tumor diagnosis was 84 months for primary benign, 18 months for primary malignant, and 1.2 months for secondary malignant.

3.2. NCSE clinical characteristics

Mental status exam showed 2 patients in coma, 10 patients with obtunded or lethargic mental status, and 12 alert patients. Alert patients were more likely to have NCSE duration of greater than 24 h ($p = 0.002$), however there was no effect on 2-month survival.

Motor signs (either jerking/twitching or automatisms) were observed in 10/24 (42%) patients and were nearly significantly correlated with NCSE duration of greater than 24 h ($p = 0.053$) but

Table 1
Categorization of EEG characteristics.

Characteristic	Categorization	Definition
Reactivity	Reactive	Noxious stimulation caused an increase in brain wave frequency
	Non-reactive	Noxious stimulation did not cause a change in background activity
Organization	Good	An anterior to posterior gradient with a posterior dominant rhythm (PDR) between 8–12 Hz and a faster lower amplitude frequency anteriorly
	Fair	The EEG lacked an anterior to posterior gradient and/or there was a slower PDR (6–8 Hz).
	Poor	A PDR <6 Hz or no PDR without an anterior to posterior gradient
Slowing	Generalized-mild	Predominant high theta frequency (7–8 Hz)
	Generalized-moderate	Predominant low theta frequency (4–7 Hz)
	Generalized-severe	Predominant delta frequency (0–4 Hz)
	Focal slowing	One area of the brain had slower frequencies either intermittently or continuously

Please cite this article in press as: Marcuse LV, et al. Nonconvulsive status epilepticus in patients with brain tumors. *Seizure: Eur J Epilepsy* (2014), http://dx.doi.org/10.1016/j.seizure.2014.04.003