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Etiology, seizure type, and prognosis of epileptic seizures in the emergency department

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ABSTRACT

Epileptic seizures are a common reason for emergency department (ED) admittance. We aimed to describe the etiological distribution of epileptic seizures and the relationships between etiology and semiology in patients admitted to the emergency room, and to identify early prognostic factors for recurrence and mortality.

Methods: A retrospective observational study was conducted in adult patients consecutively attended in the emergency room with epileptic seizures over a 2-year period. We recorded data on the etiological and syndromic classification of the seizure, and on recurrence and mortality at 1 year of follow-up.

Results: In total, 289 patients were included. Mean age was 55.9 (±21.9 years). There were 38.6% with a previous diagnosis of epilepsy and 49.8% with new-onset seizures. Among structural epilepsies, a vascular etiology was the most common overall (28.3%) but particularly in elderly (>65 years) patients (50.9%), followed by brain tumors (15.5%). In both etiologies, most patients presented with nonconvulsive seizures.

Seizure recurrence during follow-up was reported in 37.1% and was most common in patients with symptomatic remote seizures (50 patients, 41%). Brain tumors (odds ratio (OR): 5.1, confidence interval (CI): 1.7–11.8; $p < 0.01$), younger age (OR: 0.9, CI: 0.97–0.99; $p < 0.05$), and a previous diagnosis of epilepsy (OR: 3.5, CI: 1.9–6.3; $p < 0.01$) were independent predictors of recurrence. Overall mortality was 8.6%. Symptomatic epilepsy was an independent predictor of mortality (hazard ratio (HR): 6.3, CI 1.4–23.4; $p < 0.05$).

Conclusions: The most common etiologies of seizures in patients admitted to the ED are seizures of unknown cause and vascular disorder-related seizures. Seizures are more likely to recur in younger patients with a tumor whereas symptomatic epilepsy is associated with a higher risk of death at a 1-year follow-up.

1. Introduction

Epileptic seizures are a common neurologic disorder attended in the emergency department (ED) [1]. Approximately one-third of patients with epilepsy seek attention in the ED every year [2]. The incidence of epilepsy is higher in older patients, and the etiology is related with age [3]. Therefore, incidence and prevalence of epilepsy is expected to rise, particularly in the elderly, a population with an ever-increasing life span and a higher incidence of brain lesions that predispose to seizures, mainly secondary to cerebrovascular or degenerative diseases.

Seizure etiology is an established prognostic factor of both outcome and recurrence, and prompt emergent evaluation of this factor might decrease the impact of seizures in the daily life of patients with epilepsy [4]. Seizures have a negative impact on quality of life and mortality, as has been described in several observational studies showing higher mortality rates in patients with epilepsy than in the general population [4,5].

Our aim in this study was to describe the demographics, semiology, and etiology of unprovoked seizures attended in the ED and identify early clinical predictors of seizure recurrence and mortality.

2. Material and methods

2.1. Study population and data collection

The study included consecutive patients older than 15 years attended by a neurology team at an ED of a tertiary center due to epileptic seizures between January 2014 and December 2016, and completing at least 1 year of follow-up. The local ethics committee approved the study procedures. Patients were initially evaluated by emergency physicians;, and only those with an initial diagnosis of unprovoked seizures were referred to the emergency neurology team. We excluded patients with nonepileptic events, those admitted for any reason other than

Abbreviations: ED, emergency department; EEG, electroencephalogram; IGE, idiopathic generalized epilepsy.

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epileptic seizures, and patients with incomplete clinical records or follow-up.

For the purposes of the study, we recorded the patients' demographic and clinical data, including the previous diagnosis and etiology of epilepsy. Patients were divided into 4 groups according to their age (<40; 40 to 50, 50 to 65, and >65 years old) and the expected prevalence of brain lesions predisposing to epilepsy [3]. All the patients included in our analysis underwent a meticulous clinical assessment by neurologists, and most underwent an early (<12 h) electroencephalogram (EEG) study and neuroimaging examination (brain computed tomography (CT) or magnetic resonance imaging (MRI)). The diagnosis was retrospectively reviewed according to the data obtained, and in case of doubts, records were reviewed with epileptologists. Diagnosis was based on the current classification of the International League Against Epilepsy [6].

Unprovoked seizures were classified according to their etiology into structural, unknown, or idiopathic generalized epilepsy (IGE), according to the clinical history, and the EEG and neuroimaging findings. Among the structural epilepsies, we differentiated between vascular (including poststroke epilepsy and vascular malformations), tumor-related, traumatic brain injury, and neurodegenerative disorders. Uncommon etiologies in our sample (n ≤ 5) were grouped into a miscellaneous category (*Others*). Acute symptomatic seizures were defined as those occurring within the first week after an insult or concurrent metabolic disorder [7]. Patients diagnosed with acute symptomatic seizures were analyzed separately.

Follow-up lasted for 1 year or until the patient's death. Data on recurrence and mortality during this period were recorded.

2.2. Statistical analysis

Statistical analysis of the data was carried out using IBM SPSS Statistics 22.0. Comparisons were performed with the Pearson chi-square test or Fisher exact test for categorical variables and the chi-square test for trend for ordinal variables. A multiple logistic regression analysis was conducted to establish variables independently associated with higher recurrence during the first year. Kaplan–Meier curves were performed using the log-rank as a contrast statistic to determine which variables were associated with higher mortality during follow-up, and multiple Cox regression analysis was used to obtain independent predictors of mortality. A p-value of less than 0.05 was considered statistically significant in all the comparisons.

3. Results

In total, we analyzed 289 patients, with a mean age of 55.9 ± 21.9 years (range: 16–97). Twenty patients (6.9%) had acute symptomatic seizures. Among the 269 patients with unprovoked seizures, 38.6% had been previously diagnosed with epilepsy and 134 (49.8%) presented with new-onset seizures. The remaining 31 patients had a previous history of seizures but did not meet the definition of epilepsy.

In 38.3% of the patients, seizure etiology remained unknown at discharge, but in two-thirds of them, diagnosis of epilepsy was made after identifying previous seizures in the clinical assessment or identifying epileptiform discharges in EEG (Table 1).

A structural lesion was identified as the probable cause in 52.8%: vascular-related lesions were the most common in this group, followed by tumors and degenerative disorders. Idiopathic generalized epilepsy was diagnosed in 8.9% (Table 1). Among patients without a previous history of epilepsy, a structural etiology was identified in 59.7%; vascular lesions remained as the main structural cause of new-onset seizures, but incidence of epilepsy related to degenerative disorders was higher than related to brain tumors (Table 2).

Table 1
Demographic and clinical characteristics of the patients.

Sex: male	154 (54%)
Age (years), mean (SD)	55.9 (21.9)
Age groups	
<40	84 (29.1%)
40–50	39 (13.5%)
50–65	46 (15.9%)
>65	120 (41.5%)
Prior epilepsy	104 (38.6%)
New-onset seizures	134 (49.8%)
Acute symptomatic seizures	20 (6.9%)
Etiology	
Structural etiologies	142 (52.8%)
Vascular	76 (53.5%)
Tumor	22 (15.5%)
Degenerative	13 (9.2%)
Traumatic brain injury	9 (6.3%)
Others*	22 (15.5%)
IGE	24 (8.9%)
Unknown etiology	103 (38.3%)
Isolated unprovoked seizures	37 (36%)
Epilepsy of unknown etiology	66 (64.1%)

Abbreviations: IGE, idiopathic generalized epilepsy; SD, standard deviation. **Others* includes infectious diseases, perinatal anoxia, mesial temporal sclerosis, multiple sclerosis, systemic lupus erythematosus, and neurofibromatosis. All values are n (%) unless otherwise specified.

3.1. Analysis by age group

We analyzed the cause of the seizure according to age. Nonstructural epilepsy was more frequent in patients younger than 50 years. Structural lesions accounted for 72.3% of seizures in patients older than 65 years, with the main cause being vascular-related lesions (70.4% of structural epilepsies) in this group. In patients aged 50 to 65 years, we found a higher percentage of tumors than in other groups (30.4% of structural epilepsies) ($p < 0.05$) (Fig. 1).

Patients older than 65 years mainly had focal seizures whereas convulsive generalized seizures were more prevalent in the younger age groups, (<40 years, 76%; 40–50 years, 63.2%; 50–65 years, 62.8%) ($p < 0.05$).

3.2. Seizure type

Among the total, 45.1% of patients with structural lesions and 64.1% with seizures of unknown origin debuted with either generalized onset

Table 2
Demographic and clinical characteristics of the patients with new-onset seizures.

Sex: male	64 (47.8%)
Age (years), mean (SD)	62 (21.8)
Age groups	
<40	23 (17.2%)
40–50	20 (14.9%)
50–65	17 (12.7%)
>65	74 (55.2%)
Etiology	
Structural etiologies	80 (59.7%)
Vascular	52 (38.8%)
Tumor	9 (6.7%)
Degenerative	12 (9%)
Traumatic brain injury	2 (1.5%)
Others*	5 (3.7%)
IGE	3 (2.2%)
Isolated unprovoked seizures	37 (27.6%)
Epilepsy of unknown etiology	14 (10.4%)

Abbreviations: IGE, idiopathic generalized epilepsy. **Others* includes infectious diseases, perinatal anoxia, mesial temporal sclerosis, multiple sclerosis, systemic lupus erythematosus, and neurofibromatosis. All values are n (%) unless otherwise specified.

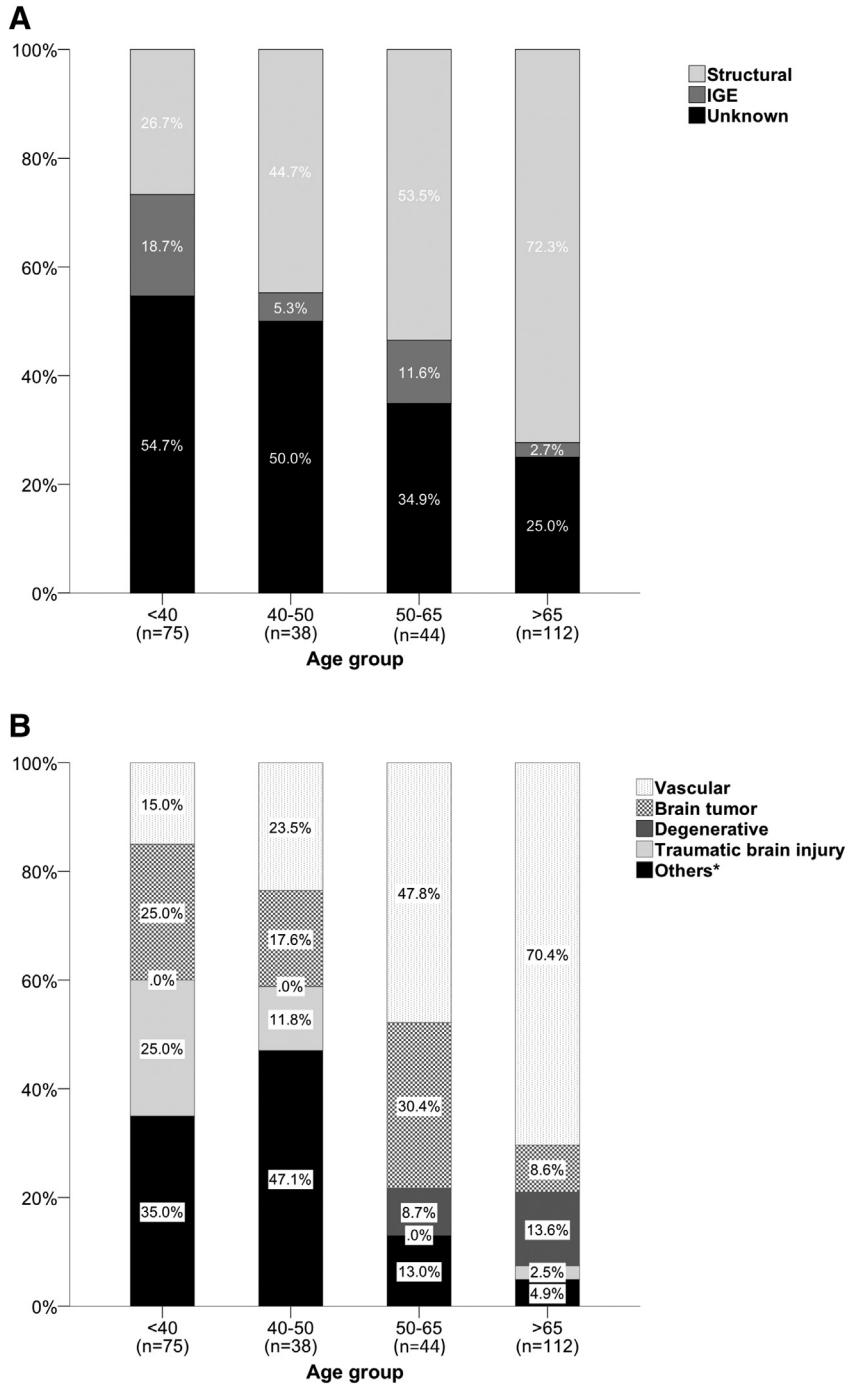

Fig. 1. Distribution of seizure cause according to age group. A) Distribution of patients into epilepsy syndrome groups by age (n = 269). B) Distribution of the causes of structural lesion-related seizures (n = 142). IGE, idiopathic generalized epilepsy. **Others* includes infectious diseases, perinatal anoxia, mesial temporal sclerosis, multiple sclerosis, systemic lupus erythematosus, and neurofibromatosis.

seizures or focal to bilateral tonic–clonic seizures (Table 2). In the group with structural epilepsy, patients with vascular-related lesions and tumors mainly had focal seizures whereas patients with neurodegenerative disorders and seizures related to traumatic brain injury had a higher prevalence of generalized seizures (61.5% and 55.6%, respectively) ($p < 0.05$) (Table 3).

3.3. Recurrence

Up to 86 (37.1%) patients with unprovoked seizures experienced a recurrence within the first year of follow-up. Patients with remote symptomatic seizures were more likely to recur (41%) than those

Table 3
Seizure type according to etiology.

Etiology	Generalized onset seizures or focal to bilateral tonic–clonic	Focal seizures
Vascular	30 (39.5%)	46 (60.5%)
Brain tumor	10 (45.5%)	12 (54.5%)
Degenerative	8 (61.5%)	5 (38.5%)
Traumatic brain injury	5 (55.6%)	4 (44.4%)
IGE	24 (100%)	
Unknown	66 (64.1%)	37 (29.6%)

Abbreviations: IGE, idiopathic generalized epilepsy.

with seizures having an unknown cause (32.2%) or IGE (35%), although differences between the groups were not statistically significant ($p = 0.42$) (Fig. 2).

Within the group of symptomatic epilepsies, patients with seizures caused by tumors (72.2%) and traumatic brain injury (62.5%) recurred more often than those with vascular disorder-related seizures (27%) ($p < 0.05$). The seizure recurrence rate was higher in patients younger than 40 years ($p < 0.05$), and recurrence was in the form of status epilepticus in only 2.48% of patients.

On multivariate analysis, tumor etiology (OR: 5.1, CI: 1.7–11.8; $p < 0.01$), younger age (OR: 0.9, CI: 0.97–0.99; $p < 0.05$), and a previous diagnosis of epilepsy (OR: 3.5, CI: 1.9–6.3; $p < 0.01$) were identified as independent risk factors for recurrence.

3.4. Mortality

The overall mortality rate was 8.6% ($n = 17$). No unexpected sudden deaths occurred, but 7 patients (31.8%) died because of seizure-related complications (4 patients with respiratory infections due to aspiration, 1 patient admitted to the ICU due to nosocomial infection, and 2 patients with status epilepticus whose seizures did not respond to initial pharmacological treatment, with further therapies withheld because of background comorbidities). The other 10 patients (45.5%) died because of their underlying diseases.

Most deaths (81.8%) occurred in patients older than 65 years ($p < 0.05$). Mortality was higher in patients with symptomatic epilepsy (90.9% of deaths were in these patients, $p < 0.05$), mainly in those with tumors or vascular lesions. Only two deaths occurred in patients with epilepsy of unknown cause, and neither of these deaths was related to epilepsy [Fig. 2].

On multivariate analysis, symptomatic seizures (HR: 6.3, CI: 1.4–23.4; $p < 0.05$) and age >65 years (HR: 4.4 CI: 1.5–13.3; $p < 0.01$) were independent predictors of mortality.

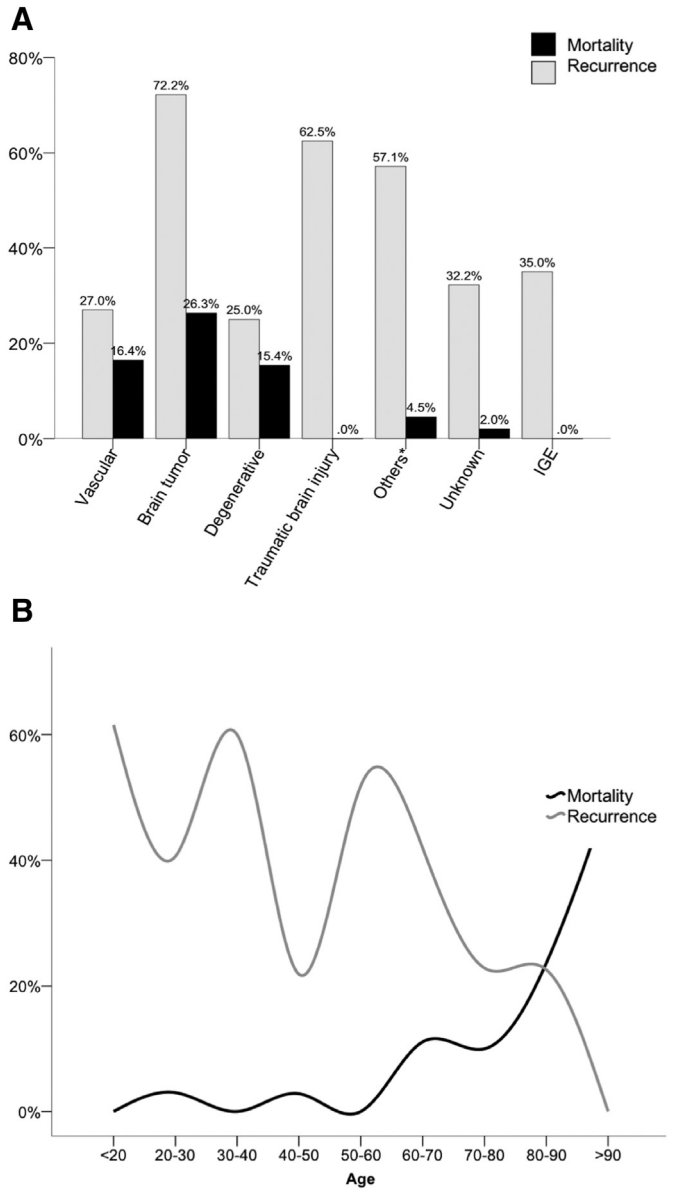

Fig. 2. Recurrence and mortality rates by etiology (A) and age (B). IGE, idiopathic generalized epilepsy. *Others includes infectious diseases, perinatal anoxia, mesial temporal sclerosis, multiple sclerosis, systemic lupus erythematosus, and neurofibromatosis.

3.5. Acute symptomatic seizures

Twenty patients were eventually diagnosed with acute symptomatic seizures. Most were secondary to metabolic disorders (7, 35%), followed by acute ischemic or hemorrhagic stroke (6, 30%), and drug use or deprivation (illicit drug or medication) (6, 30%). Four patients recurred during follow-up (28.6%), and 2 (13%) died, both in the setting of an acute stroke. There were no statistical differences in recurrence or mortality rates between acute symptomatic and unprovoked seizures.

4. Discussion

This study assesses the etiologies and types of epileptic seizures attended in the ED of a tertiary center, as well as the impact of seizure characteristics on the prognosis. In line with previous population-based studies [3], seizures secondary to structural lesions predominated, and there was a higher percentage of remote symptomatic seizures in older patients.

Acute symptomatic seizures account for around 40% of afebrile seizures in developed countries [8]. In our sample, only patients without an initial identifiable acute systemic disorder were referred to the neurology emergency team. After a complete diagnostic work-up, approximately 7% of our sample were diagnosed with acute symptomatic seizures. Only 13.8% were discharged with a diagnosis of an isolated seizure of unknown etiology. We believe that prompt evaluation by neurologists leads to a higher percentage of both specific syndromic and etiological diagnosis.

Both the etiology and patient age predicted the risk of recurrence and mortality. As would be expected, mortality is higher in older patients [8,9] and mainly related to underlying lesions [10,11], which is consistent with the results of our analysis.

Vascular-related seizures were the most common, likely because of the overall high prevalence of cerebrovascular disease [3,12]. In our study, these patients had predominantly focal seizures, which contrasts with the findings in previous studies in which secondarily generalized seizures were the most prevalent [13,14]. These differences may be explained by the inclusion of other vascular lesions in addition to poststroke seizures in our study, whereas other studies only included poststroke seizures.

In some population studies, 5% to 10% of structural seizures have been related to brain tumors [3,15]. In our sample, the percentage was higher, around 15%, which is likely explained by the median age of the study population, higher than that reported in other series [3,16]. In line with the literature [17], we observed a likelihood for recurrence in tumor-related epilepsy, which is reported to be commonly drug-resistant.

Seizures related to neurodegenerative diseases were more often generalized in our sample. In contrast, population-based studies have reported a higher incidence of focal seizures with impaired awareness in these patients [18,19]. It is likely that some nonconvulsive seizures may not have been recognized in our population, and affected patients

may not have come to the ED. Giorgi et al. [20] have noted that focal seizures with impaired consciousness can be difficult to detect by untrained caregivers. Most patients with neurodegenerative disorders presented with incident new-onset seizures and over follow-up, neurodegenerative disorders had the lowest recurrence rate. These findings are in line with previous reports showing that these patients' seizures respond favorably to antiepileptic drugs [18].

Patients with no structural lesions showed a greater tendency to present seizures with a generalized onset. On the other hand, patients with seizures of unknown cause and IGE both had a better prognosis regarding recurrence and mortality than those with remote symptomatic seizures. Patients with seizures related to a prior brain lesion are known to have an increased risk of seizure recurrence [21]. Therefore, these patients would be expected to start antiepileptic therapy at discharge, and this could explain why we found no significant differences in the risk of recurrence according to the syndromic diagnosis.

Mortality is lower in patients who have no structural lesions [5,8,11], and a meta-analysis by Nevalainen et al. [22] showed that in contrast to cryptogenic epilepsy, IGE is not associated with mortality, which highlights the importance of a correct early diagnosis of these disorders.

This study has the limitations of a retrospective design and selection of ED patients attended by neurology department physicians in a tertiary center. Patients with certain conditions causing the seizure, such as systemic disorders, traumatic brain injury, or another acute cause, are generally not referred to a neurologist. For that reason, some patients with new-onset seizures may not have undergone an etiological study, with the episode labeled as “unknown cause”, and the percentage of structural seizures may actually have been higher. Therefore, the results cannot be extrapolated to other populations.

5. Conclusion

In summary, by etiology, nonstructural causes account for nearly 50% of all seizures attended in the ED, and vascular causes are the second in frequency. In terms of the prognosis, seizures of unknown origin and IGEs had lower recurrence and mortality rates, younger patients and those with tumors had a greater risk of recurrence, and finally, older patients with structural epilepsy showed higher mortality.

Conflict of interest

The authors have no conflicts of interest to declare.

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