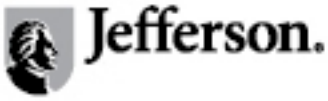

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Factors associated with tonic-clonic seizures in patients with drug-resistant mesial temporal epilepsy.

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Abstract:

Purpose: Among different seizure types, tonic-clonic seizures are more significant because they are more often associated with morbidity. No prior study has been done to investigate risk factors associated with tonic-clonic seizures in patients with mesial temporal epilepsy.

Methods: In this retrospective study, all drug-resistant mesial temporal epilepsy patients in the database of patients who underwent epilepsy surgery at Jefferson comprehensive epilepsy center were recruited. These patients were prospectively registered in a database from 1986 till 2014. Patients' age, gender, epilepsy risk factors, age at seizure onset, and preoperative seizure type(s) were registered routinely. Potential risk factors associated with experiencing preoperative tonic-clonic seizures were investigated.

Results: Two hundred seventy-five patients (132 males and 143 females) were studied. Aura type was associated with experiencing perioperative tonic-clonic seizures. Patients with epigastric auras less frequently reported having tonic-clonic seizures compared with those who had other types of auras (odds ratio: 0.37 and 95% confidence interval: 0.19-0.70; $p = 0.001$) and those who did not have any auras (odds ratio: 0.35 and 95% confidence interval: 0.16-0.77; $p = 0.008$).

Conclusion: Epigastric auras may indicate that a specific anatomic location is involved in epileptogenesis from which generalization is harder because of that location's poor connections with other brain regions.

Key words: Associated factors; Temporal lobe epilepsy; Tonic-clonic seizure.

1. Introduction

Focal epilepsies account for about two-thirds of all adult epilepsy patients, and temporal lobe epilepsy (TLE) is the most common type of focal epilepsy [1, 2]. Mesial temporal sclerosis (MTS) is the most common pathological substrate of TLE [3]. Complex partial seizures are the most common seizure type observed in patients with TLE; however, other seizure types including simple partial seizures (i.e., auras) and tonic-clonic seizures are also commonly observed in these patients [4]. Among these seizure types, tonic-clonic seizures are more significant because they are more often associated with morbidity (e.g., severe injuries [5]) and even mortality (e.g., sudden unexpected death in epilepsy [6]). No prior study has been done to investigate potential risk factors associated with experiencing tonic-clonic seizures in patients with MTS-TLE. This has important clinical implications in the management process of patients.

In this study, we investigated potential risk factors associated with experiencing tonic-clonic seizures in a larger group of patients with drug-resistant MTS-TLE.

2. Material and methods

In this retrospective study, all drug-resistant MTS-TLE patients in the database of patients who underwent epilepsy surgery at Jefferson comprehensive epilepsy center were recruited. These patients were prospectively registered in a database from 1986 till 2014. Historical data was obtained by board certified neurologists. The diagnosis of TLE was made by the epileptologists working at this institution and was based on clinical grounds (semiology) and electroencephalographic (EEG) findings. There was no age limit to enter this study. All patients underwent a comprehensive presurgical evaluation including a brain MRI (epilepsy protocol; techniques changed with equipment modernization), prolonged video-EEG monitoring, neuropsychological evaluation, etc. Magnetic resonance imaging studies were analyzed by neuroradiologists, neurologists, and neurosurgeons with expertise in epilepsy. We diagnosed patients with MTS if they had clear signs of mesial temporal atrophy and/or sclerosis in their brain MRI. Patients with dual pathology and patients with incomplete data with regard to preoperative seizure information (i.e., type and frequency) were excluded from this study.

Patients' age, gender, epilepsy risk factors (e.g., history of febrile seizures in childhood, family history of epilepsy, etc.), age at seizure onset (i.e., the first afebrile habitual seizure), and preoperative seizure type(s) and history were registered routinely.

Demographic and relevant clinical variables were summarized descriptively to characterize the study population. Potential risk factors associated with experiencing preoperative tonic-clonic seizures were investigated. Statistical analyses were performed using Pearson's Chi-square test, Fisher's exact test, Mann-Whitney *U* test, and Kolmogorov-Smirnov tests. Odds ratios and 95% confidence intervals were calculated. A p value less than 0.05 was

considered significant. This study was conducted with the approval of the Thomas Jefferson University Institutional Review Board.

3. Results

During the study period, 794 patients had temporal lobe surgery for drug-resistant temporal lobe epilepsy. Magnetic resonance imaging results were as follows: mesial temporal sclerosis in 306, dual pathology in 19, other findings in 278, normal results in 168, and missing results in 23 patients. Two hundred seventy-five patients (132 males and 143 females) had reasonably complete data with regard to preoperative seizure information (i.e., type and frequency) and were studied. One hundred seventy-seven patients (64.4%) had experienced at least one afebrile tonic-clonic seizure in their lifetime, and 98 patients (35.6%) never had such an experience. Aura type was strongly associated and the only associated factor with history of tonic-clonic seizures in these patients. Aura types were as follows among patients with no history of tonic-clonic seizures: epigastric in 30, affective in 6, cognitive in 2, auditory in 1, multiple auras in 14, other auras in 26, and no aura in 17 patients. Aura types were as follows among patients with history of tonic-clonic seizures: epigastric in 25, affective in 10, cognitive in 10, auditory in 10, multiple auras in 36, other auras in 43, and no aura in 40 patients. Some data were missing. Patients with epigastric auras less frequently (odds ratio: 0.37 and 95% confidence interval: 0.19-0.70; $p = 0.001$) reported having tonic-clonic seizures (25 out of 55 patients; 45.5%) compared with those who had other types of auras (109 out of 158 patients; 68.9%). Similarly, patients with epigastric auras less frequently (odds ratio: 0.35 and 95% confidence interval: 0.16-0.77; $p = 0.008$) reported having tonic-clonic seizures compared with those who did not have any auras with their seizures (40 out of 57 patients; 70.1%). No other significant difference was identified in two by two comparisons of auras. Other risk factors potentially associated with experiencing tonic-clonic seizures are shown in Table 1.

4. Discussion

Temporal lobe epilepsy due to mesial temporal sclerosis (MTS-TLE) is a common epilepsy syndrome. This epilepsy syndrome often presents itself with a combination of different seizure types, including auras, complex partial seizures and tonic-clonic seizures. Among these seizure types, tonic-clonic seizures pose more risks (e.g., injury or death) to the patients [1-6]. No prior study has been done to investigate potential risk factors associated with experiencing tonic-clonic seizures in patients with MTS-TLE. In our study, we observed that aura type was associated with tonic-clonic seizures in these patients. Patients with epigastric (abdominal) auras less frequently reported having tonic-clonic seizures compared with those who had other types of auras and those who did not have any auras with their seizures. Epigastric auras constitute the most common type of autonomic auras. These auras include sensations of nausea, pain, and/or indescribable discomfort in the abdominal or periumbilical area. This discomfort can remain static, rise to the chest and throat, or descend into the lower abdominal region. In one study, the seizures of 491 consecutive patients with focal epilepsies were prospectively classified [7]. Abdominal auras were more frequent with TLE (117 of 223 patients, 52%) than in extratemporal epilepsy (13 of 113 patients, 12%, $p < 0.0001$), and they were more frequent in mesial TLE (70 of 110 patients, 64%) than in neocortical TLE (16 of 41 patients, 39%, $p = 0.007$). The authors concluded that an abdominal aura is associated with TLE with a probability of 73.6%. The evolution of an abdominal aura into an automotor seizure however increases the probability of TLE to 98.3% [7]. In a previous study, we observed that the presence of an abdominal aura was a good prognostic indicator for a seizure free outcome after temporal lobectomy in patients with TLE-MTS [8]. In that study, two hundred thirty-seven patients were investigated. We showed that

the probability of patients with abdominal auras becoming free of seizures after surgery was 65.1%, while in others the probability was 43.3% ($p = 0.01$) [8].

5. Conclusions

Patients with MTS-TLE and epigastric (abdominal) auras less frequently reported having tonic-clonic seizures compared with those who had other types of auras and those who did not have any auras with their seizures. It is probable that epigastric (abdominal) auras indicate a more localized and restricted circuit for epileptogenesis that less often generates generalized tonic-clonic seizures. In other words, epigastric auras may indicate that a specific anatomic location is involved in epileptogenesis from which generalization is harder because of that location's poor connections with other brain regions. The observation that an epigastric aura is a good prognostic indicator for success after temporal lobectomy in patients with TLE-MTS [8] is indirect evidence for the speculations mentioned above. Besides, evidence obtained with fMRI in a previous study suggests significant, more widespread derangements in brain function and connectivity in TLE patients with tonic-clonic seizures (compared with those without these seizure type) [9].

Conflict of interest

Ali A. Asadi-Pooya, M.D., reports no disclosures.

Cyrus Rostami, reports no disclosures.

Amin Rabiei, M.D., reports no disclosures.

Michael R. Sperling, M.D., Consulting: UCB Pharma; Research: contracts with Thomas Jefferson University, Eisai, UCB Pharma, Sunovion, SK Life Sciences, Marinus, Lundbeck, Medtronics, Visualase, Accorda, Upsher-Smith, and Brain Sentinel.

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