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ORIGINAL ARTICLE

Short-term risk of relapse after a first unprovoked seizure in an adult population

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Short running title: Early relapse after unprovoked seizure

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Abstract

Objective: To evaluate the incidence of short-term recurrence (<1 month) after a first unprovoked seizure (FUS) and the associated risk factors.

Methods: This is a prospective monocentric one-year observational study on all consecutive adult patients admitted to the Emergency Department (ED) and diagnosed as FUS. Patients underwent neurological consultation at one and three months after the FUS. Demographic information, clinical examination and seizure features, seizure recurrence at 1 and 3 months, electroencephalogram (EEG), brain imaging, precipitating factors, seizure type, and prescribed antiepileptic drugs (AED) were prospectively collected.

Results: Among 140 patients diagnosed as FUS, 109 patients attended the neurological consultation at 1 month. FUS diagnosis was confirmed in 80/109 cases. Nine patients (11.2%) had seizure recurrence before the consultation at 1 month. Identified specific risk factors of short-term recurrence were focal seizure (p=0.015) and abnormal EEG in the first 48 hours (p=0.048). In the group of patients followed for three months (38 patients), the risk of seizure relapse was 15.7%.

Conclusion: Most patients with FUS diagnosed in the ED did not present seizure recurrence within the first month, especially if no specific risk factors were present (focal seizure, abnormal EEG within first 48 hours). The systematic use of prophylactic AED (benzodiazepines) is not recommended in the ED in the clinical setting of FUS. A specialized consultation within a one-month period is safe and adequate for FUS follow-up.

Keywords: antiepileptic drugs, epilepsy, first unprovoked seizure, seizure recurrence

Introduction

Epileptic seizures are one of the most frequent causes of admission with neurological symptoms to the Emergency Department (ED) [4,10,12,14]. Despite this finding, the seizure care pathway in the ED is not yet well defined and universally formalized [7,16]. A suspected first unprovoked seizure (FUS) requires time and real expertise in the epilepsy field. This reinforces the necessity for expert confirmation of the epilepsy diagnosis, with syndromic classification if possible; evaluation of risk of seizure recurrence; and optimization of the antiepileptic drug (AED) treatment strategy. The ED is not the appropriate place to perform this overview, given the acknowledged high risk of diagnostic and therapeutic errors in the acute setting [6,8]. In the light of this context, and the first seizure clinic experiences in Europe and the United States [10,14], European and French guidelines (SIGN, NICE, and French Society of Neurology) recommend specialist epilepsy consultation with minimal delay in order to overcome these challenges [13,15]. However, this time-delay is mostly not clearly defined, except by the French guidelines, which mention a maximal delay of 1 month after a FUS [15]. This choice was rather arbitrary, being a compromise between the practical delay in obtaining a specialized consultation and the mid/long-term risk of seizure relapse without AED [14,16]. So far, the rate and predictive factors of short-term recurrence have not been established. This leads to global heterogeneity of ED management of FUS, especially with regards to use of benzodiazepines (BZD) and other AED prescriptions. Inappropriate AED prescriptions carry the risk of complications and side effects, as well as the issue of subsequent AED withdrawal [5].

In this study, our main objective was to define the short-term (<1 month) risk for seizure recurrence after a FUS in adult patients. We also determined the specific risk factors for short seizure relapse. To compare our population to the literature, we also measured the mid-term risk of relapse (3 months) after FUS.

Methods

Study design and population sample

This one-year prospective observational study enrolled consecutive adult patients admitted for a suspected FUS at the ED of Nancy University Hospital between 1st January and 31st December 2016. All screened patients admitted and diagnosed as FUS in ED were prospectively included. Patients admitted for status epilepticus or for series of seizures were excluded. Included subjects

were systematically invited to attend a subsequent neurological consultation in the neurological department within 1 month following ED hospitalization. The neurologist assessed the final diagnosis of FUS during this consultation. Patients with a previously established diagnosis of epilepsy and those with unconfirmed FUS were excluded. Patients who did not attend the specialized clinic appointment at one month were also excluded (patients lost to follow up). A classical follow-up was proposed to FUS patients with a neurological consultation at 3 months after FUS. Patients who did not attend the 3-month neurological follow up were still included.

Study protocol

For each patient, clinical and demographic data were collected on ED and neurological consultation charts: 1. gender, age, medical history; 2. seizure provoking factors: alcohol, drug abuse, fever, sleep deprivation; 3. type of seizure (generalized or focal onset); 4. objective neurological examination; 5. complementary diagnostic tests: standard serum biology, EEG (paroxysmal events, focal slowing, delay of EEG), brain imaging (computed tomography (CT) scan or magnetic resonance imaging (MRI)); 6. AED (benzodiazepine BZD and other AED) prescribed in the ED; 7. seizure relapse at one month and three months. Seizure relapse was defined as a seizure occurring more than 24h after the first event. The local ethics committee approved the study.

Statistical analysis

We performed a descriptive analysis of the data. The chi-squared test for independence was used for direct comparisons between groups, based on categorical variables. When it was not possible to use the chi-squared test (less than five patients), Fisher's exact test was applied. Statistical analysis was performed using the SPSS (IBM SPSS Statistics for Mac, version 20.0, USA). $P<0.05$ was considered statistically significant.

Results

During the 1-year inclusion period, 140 patients were referred by the ED to our specialist first seizure clinic for FUS (Figure 1). Thirty-one patients (22.1%) were lost to follow-up and were excluded from the present study; 109 patients attended the neurological consultation at 1 month. FUS was wrongly diagnosed in 29/109 patients (26.6%) by ED. In those patients with an

erroneous diagnosis, only 2/29 had focal EEG slowing and none had paroxysmal events on EEG. Finally, according to our inclusion criteria, we selected 80/140 patients (57.1%). Most cases were male (49/80, 61.2%), and the mean age was 54.4 +/-11.2 years. EEG was performed for 78 patients (97.5%) and neuroimaging (CT or MRI) in 100% of patients. Fifty-eight patients (74.3%) had their first EEG within the first 48 hours after FUS. The percentage of patients prescribed an antiepileptic drug in the ED was 12.5%, including 6 cases of benzodiazepines.

Within 1 month of admission to the ED, a seizure relapse occurred in 9 patients (11.2%; Table 1). In those patients with relapse: 6/9 patients had a focal seizure (66.7%) and 4/9 EEG was abnormal with a focal slowing (44.5%). When EEG was performed less than 48h after FUS, EEG was abnormal, with a focal slowing in 57.1%. No paroxysmal event was observed in EEG for these nine patients. Three patients (33.3%) had abnormal imaging: stroke sequelae, cerebral tumor sequelae, and cerebral abscess sequelae.

Between the two groups (short-term seizure recurrence versus no short-term seizure recurrence), the following factors were significantly associated with a higher risk of seizure relapse within 1 month after FUS: initial focal seizure (p=0.015), focal slowing on early EEG (p=0.048) and prophylactic prescription of BZD from the ER. Concerning patients prescribed BZD (Table 2), relapse was observed in 50% of patients compared to 4.4% in patients without BZD (p=0.017). BZD were mostly prescribed in patients with focal seizures (p = 0.004) and imaging anomalies (p= 0.008).

In the group of patients followed for three months (38 patients), the risk of seizure relapse was 15.7% (6/38). We found two main risk factors: abnormal EEG within the first 48 hours with focal slowing and focal (rather than generalized) seizure (p= 0.01 and 0.026, respectively; Table 3). The presence of focal slowing on EEG (at 48h and after) showed a trend towards significance with regards to early seizure recurrence (p= 0.075). Two out of six patients had recurrence at one month. Out of 9 patients with relapse at one month, five of them were followed at 3 months whereas four patients were lost to follow up.

Discussion

Our study is the first to address the question of short-term seizure relapse risk after a FUS in an adult population. These results cannot be applied to the pediatric population, since the risk of recurrence and its risk factor are different from the adult population presented in this study. In

this prospective study, we estimated the risk of relapse within the first month to be 11.2%. No comparison with previous studies in the literature can be made because most of these evaluated FUS and mid/long-term risk of relapse (3, 6, 12, 24, and 60 months) [1,2,9,11]. However, our result concerning mid-term relapse risk (at three months) (15.7%) is equivalent to results from the FIRST study (18%), suggesting that our studied population was similar [1]. In our study, 31 patients (22.1%) did not attend the proposed neurological consultation after ED management. A similar proportion of patients lost to follow up is classically observed in most ED studies concerning FUS [1,2,9,11]. In our population, we also checked that these patients were not admitted for seizure relapse at ED during the subsequent year. Exclusion of patients lost to follow-up from our analysis may have led to somewhat overestimate the relapse risk in our study.

For 109 patients examined at the neurological consultation after ED workup, FUS was not confirmed for 29 patients (26.6%). In previous studies, the high number of erroneous diagnoses resulting from the ED evaluation has already been described [8,13]. The incorrect diagnosis reached in the ED emphasizes the importance of subsequent assessment in a specialist clinic to confirm the appropriate diagnosis and to avoid misdiagnosis and misuse of prescribed medications [2,15,18]. ED should be devoted only to the differential diagnosis workup (seizure or not), to the distinction between provoked and unprovoked seizure, to the assessment of clinical severity and the need for immediate management +/- hospitalization [7].

The most recent studies on first seizure ED pathway recommend evaluation at a first seizure clinic [2,6,18]. While European guidelines [13,18] suggest that FUS patients have to be seen "as soon as possible" by a specialist in order to prescribe to first AED, no maximal delay is however specified. The French Society of Neurology [15] suggested a maximal limit of 1 month. However, this time period was arbitrary and was set as a compromise between the usual delay in obtaining a specialist appointment and the mid/long-term risk of seizure relapse without AED [14,16]. Despite these guidelines [13,15], most ED still treat FUS patients with prophylactic AED and specifically with a short course of benzodiazepines, to avoid possible seizure recurrence before the first neurological consultation. In order to improve this practice, the following question must be addressed: is the recommended delay of 1 month acceptable if there is no increased risk of seizure recurrence? According to our study, the seizure relapse risk is only 11.2% after a FUS. This result indicates that 88.8% of patients do not present additional seizures

during the month following the FUS. Considering the low risk of short-term relapse and the high risk of diagnostic error in the ED (26.6%), we consider that AED, including benzodiazepines, should not be prescribed for FUS in the ED. This result could have a potentially large impact on the treatment approach of patients in emergency departments [13]. AED prescription for FUS, including benzodiazepines, should only be given following specialist evaluation, as suggested by European guidelines.

In this study, we tried to extract the different specific risk factors of short-term seizure relapse to distinguish patients at high risk of early seizure recurrence. Excluding patients admitted for status epilepticus or series of seizures, the main risk factors were focal seizure and abnormal focal slowing on the EEG in the first 48 hours. These tendencies were reinforced by the analysis of patients prescribed BZD at the end of ED workup with a higher risk of relapse (50% with BZD versus 4.4% without BZD). These high-risk patients (prescribed BZD) presented to the ED with specific features including focal seizure type and imaging anomalies ($p = 0.004$ and $p=0.008$ respectively). These features are similar to those previously described for long-term seizure relapse risk and confirms their relevance.

EEG performed in the first 48h appears to be relevant in helping to define this short-term relapse risk. Most previous studies evaluating EEG results highlighted increased sensitivity of EEG in the first hours after FUS [3,17]. These results emphasize the importance of implementing ready access to EEG for all suspected unprovoked seizures in the ED [3,17].

Specific attention should be paid to patients with focal seizures, focal slowing in early EEG, and abnormal imaging, since this group presents a higher risk of seizure relapse. Considering the small number of patients involved by these criteria, a specific consultation should be performed if possible within the week following the ED management. For all other patients, a delay of 1 month for the specialized consultation seems to be reasonable and does not lead to a higher risk of relapse. This delay should not prompt ED medical staff to prescribe prophylactic BZD for a FUS.

Conclusion

In conclusion, the risk of short-term seizure relapse (<1 month) after FUS is estimated here at 11.2%. Most of the patients who present to the ED do not have recurrent seizures within this short period (88.8%). Therefore, prophylactic AED prescription at ED is not indicated, especially

in the absence of criteria of higher risk of relapse (EEG showing focal slowing in the first 48 hours, focal seizure). After FUS, a specialized consultation with a neurologist is indicated to confirm the diagnosis and to evaluate the risk/benefit balance of AED. The time delay of 1 month between FUS and outpatient specialist consultation is safe. Our results confirm the indication for a specialized protocol following ED presentation, including neuroimaging, EEG, and specialist neurological evaluation within one month.

Disclosures

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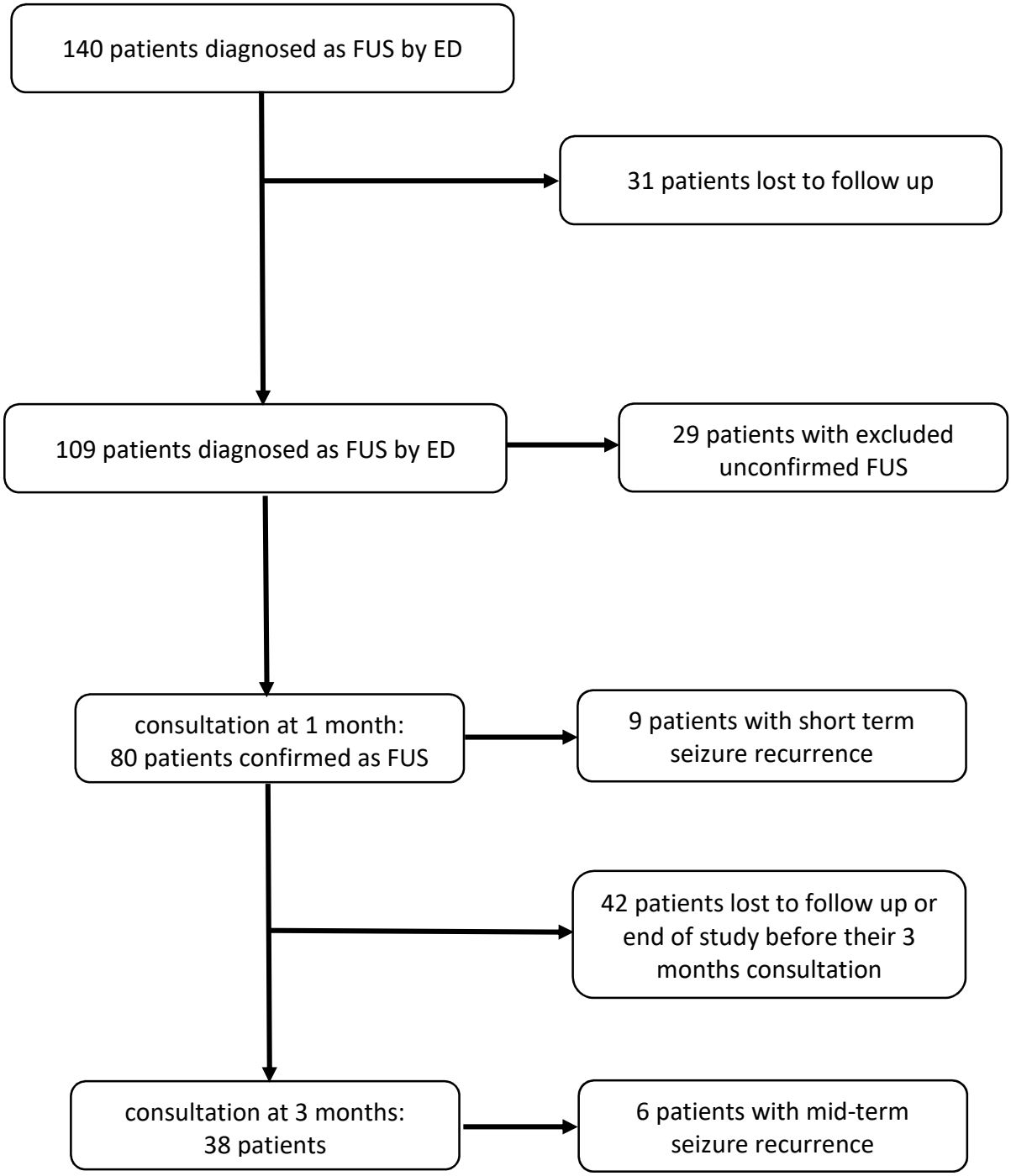

Figure 1. Flow chart

	Recurrence at 1 month (n=9)	*No recurrence at 1 month (n=71)*	*P value*
Age >60 years	4(44.4%)	28(39.4%)	1.00
Sex	M:3(33.3%) F:6(66.7%)	M:46(64.8%) F:25(35.2%)	0.07
Generalized Seizure	2(22.2%)	7(9.9%)	0.27
Focal Seizure	6(66.7%)	19(26.8%)	0.015
Seizure of unknown type	1(11.1%)	45(63.4%)	0.03
Precipitating factors	1(11.1%)	21(29.6%)	0.432
BDZ	3(33.3%)	3(4.2%)	0.017
EEG N	5(55.5 %)	46(64.8%)	0.59
EEG AbN	4(44.5%)	23(32.4%)	0.271
EEG P	0	5(7%)	1.00
EEG FS	4(44.5%)	14(19.7%)	0.109
EEG<48H n=	7	51	
EEG<48 AbN	4(57.1%)	19(37.2%)	0.232
EEG <48 N	3(42.9%)	32(62.8%)	0.724
EEG <48 P	0	5(9.8%)	1.00
EEG <48 FS	4(57.1%)	11(21.6%)	0.048
Imaging anomalies	3(33.3%)	11(15.5%)	0.18

Table 1: Specific risk factors of short term seizure relapse.

n: number;EEG N: EEG Normal; EEG<48H AbN: Abnormal EEG performed in less than 48 hours after the first epileptic seizure; EEG < 48 N: Normal EEG performed less than 48 hours after the first epileptic seizure; EEG P: Paroxysm discharges on EEG; EEG < 48 P: Paroxysm discharges observed on EEG performed less than 48 hours after the first epileptic seizure; EEG FL: Focal slowness on EEG, EEG < 48 FS: Focal Slowing on EEG performed less than 48 hours after the first epileptic seizure; BDZ: Benzodiazepine. Generalized: clinical generalized seizure type; Focal: clinical focal seizure type.

	Patients treated with BDZ N=6(7.5%)	*Not treated with BDZ n=74(92.5%)*	*P value*
Recurrence at 1 month	3(50%)	6(8%)	0.017
Focal seizure	5(83%)	20(27%)	0.004
Imaging anomalies	4(66%)	10(13.5%)	0.008

Table 2: patients treated with BDZ Vs patient non treated with BDZ.
n: number, BDZ: Benzodiazepine, Focal: clinical focal seizure type.

	Recurrence at 3 months (n=6)	*No recurrence at 3 months (n=32)*	*P value*
Age >60 years	1(17%)	13(41%)	0.384
SEX	M:4(67%) F:2(33%)	M:19(59%) F:13(41%)	0.737
Generalized Seizure	1(17%)	5(16%)	1.00
Focal Seizure	5(83%)	11(34%)	0.026
BDZ	0	2(6%)	1.00
Precipitating factors	1(17%)	10(31%)	0.650
EEG N	1(17%)	16(50%)	0.197
EEG Abnormal	5(83 %)	14(44%)	0.075
EEG<48H Abnormal	5(83%)	9(28%)	0.010
EEG <48 N	0	15(47%)	0.063
EEG P	0	3(9%)	1.00
EEG <48 P	0	3(9%)	1.00
EEG FL	5(83%)	14(44%)	0.075
EEG <48 FL	5(83%)	9(28%)	0.010
Imaging anomalies	1(17%)	6(19%)	1.00

Table 3: Specific risk factors of seizure relapse at 3 months

EEG N: EEG Normal; EEG<48H Abnormal: Abnormal EEG performed in less than 48 hours after the first epileptic seizure; EEG < 48 N: Normal EEG performed less than 48 hours after the first epileptic seizure; EEG P: Paroxysm discharges on EEG; EEG < 48 P: Paroxysm discharges observed on EEG performed less than 48 hours after the first epileptic seizure; EEG FL: Focal slowness on EEG, EEG < 48 FL: Focal slowness on EEG performed less than 48 hours after the first epileptic seizure; BDZ: Benzodiazepine. Generalized: clinical generalized seizure type; Focal: clinical focal seizure type.