Original article

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Epileptology of the first tonic-clonic seizure in adults and prediction of seizure recurrence*

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ABSTRACT – *Aims*. The risk of seizure recurrence after a first unprovoked seizure is influenced by certain risk factors. To understand their effect in people with early diagnosed new epilepsy, we assessed the risk of recurrence of focal to bilateral tonic-clonic or generalized tonic-clonic seizures and the associated factors in a clinically well-characterized cohort of adults with a first unprovoked tonic-clonic seizure.

Methods. We prospectively studied 150 consecutive adults with a first unprovoked tonic-clonic seizure and full clinical, EEG, and brain imaging assessment within the first four weeks. New epilepsy was diagnosed and classified according to the International League Against Epilepsy criteria. Time to second focal to bilateral tonic-clonic or generalized tonic-clonic seizure was analysed using the Kaplan-Meier method.

Results. Early diagnosis of new epilepsy, including type or syndrome and aetiology, was possible in 109 patients (72.7%). The diagnostic yield of sleep-deprived EEG was high in both genetic and non-genetic localized focal epilepsies. A second focal to bilateral tonic-clonic or generalized tonic-clonic seizure occurred in 100 patients (66.7%) during a three-year mean observation period. The risk was higher in non-genetic focal epilepsies and lower in genetic epilepsies. Concurrent absences or myoclonic seizures and a first occurrence after awakening were predictors of a second generalized tonic-clonic seizure in patients with genetic generalized epilepsy, while diagnosis of temporal or frontal lobe epilepsy, focal EEG discharges, and focal changes on brain imaging were related to an increased risk of focal to bilateral tonic-clonic seizure recurrence, showing additive effects. Identifiable modulators or triggers for the first tonic-clonic seizure, early treatment, and older age showed inverse association.

Conclusion. The risk of a second generalized or focal to bilateral tonic-clonic seizure and the factors involved vary across epilepsy aetiologies and syndromes. Early diagnosis and classification of new epilepsy is possible in most patients and may enable important adjustments to their management and treatment.

Key words: incident epilepsy, epilepsy classification, sleep deprivation, sleep EEG, risk factors

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The evaluation of the risk of seizure recurrence after a first unprovoked seizure is important for patients' management including the decision to treat immediately or defer treatment pending a second seizure. A recent meta-analysis (Krumholz *et al*., 2015) indicated that:
– most recurrences occur within the first two years and the risk is greatest in the first year;
– immediate antiepileptic drug (AED) therapy can reduce the risk, but may not improve quality of life, while it is unlikely to lead to long-term seizure remission;
– there are four risk factors, namely a prior brain insult, an EEG with epileptic discharges (ED), a significant brain-imaging abnormality, and a nocturnal seizure.
The primary clinical advantage of these four variables is that they may be *readily identifiable* by history or obtained by *early* EEG and brain scan to help physicians stratify the chance for seizure recurrence and guide decisions about treatment as soon as possible. Their predictive role first emerged almost 30 years ago (Annegers *et al*., 1986; Hopkins *et al*., 1988) but despite subsequent clinical research, there has been no further major advance in our understanding of seizure recurrence, including possible interactions between the known factors (First Seizure Trial Group, 1993; Marson *et al*., 2005; Krumholz *et al*., 2015). For instance, direct associations between risk factors and specific epilepsy types or syndromes have not been thoroughly addressed yet, perhaps because of the conceptual constraint of the old operative definition of epilepsy that required a second unprovoked seizure more than 24 hours after the first (Guidelines for epidemiologic studies on epilepsy, 1993).
Diagnosis of the epilepsy type and syndrome guides the search for the underlying aetiology, allowing rationalisation of management and treatment and long-term prognostication, and can be achieved early in patients with new epilepsy (King *et al*., 1998). The new definition of epilepsy by the International League Against Epilepsy (ILAE) (Fisher *et al*., 2014) appears to effortlessly include most patients with a first unprovoked seizure *and* a single risk factor, such as a prior stroke, and certainly those with a recognized epilepsy type that is also identifiable from the pattern of another customary epidemiological risk factor, the ED on the EEG. A recent retrospective multicentre study clinically validated the long-term applicability of the new definition showing a recurrence rate of 83.6% at 10 years, but clinical and laboratory evidence at the time of the first seizure, to help identify people at high risk of seizure recurrence, is still missing (Beretta *et al*., 2017). A clinical epileptology approach to the riddle of the first seizure could reveal that risk factors may variably apply to different epilepsy types and syndromes, and help optimize the management of patients with clinically well-defined new epilepsy.
We studied a cohort of adults with a definite or clinically highly probable first unprovoked tonic-clonic (TC) seizure to assess the extent to which early diagnosis and classification of new epilepsy can predict the occurrence of a second TC (focal to bilateral tonic-clonic (BTC), generalized tonic-clonic (GTC), or TC seizure of unknown onset (Fisher *et al*., 2017).

Methods

Study population

We studied all consecutive adults (≥17 years of age), referred by the emergency department of St Thomas' Hospital to our first seizure outpatient clinic (FSC) between 1/7/2009 and 31/12/2015 with a first definite or highly probable TC seizure, henceforth called "index seizure". Index seizures included witnessed TC seizures with independently verified postictal behavioural suppression, as well as not witnessed seizures, deemed to be TC seizures with a high degree of certainty on account of appropriate circumstantial evidence, including postictal stertorous breathing and a slow recovery with carefully verified confusion, described by relatives who attended promptly, or preictal symptoms recalled by the patient, such as an aura or a volley of myoclonic jerks.
We excluded patients with:
– non-epileptic seizures;
– acute symptomatic seizures (Beghi *et al*., 2010);
– previously diagnosed seizures or epilepsy;
– a single first TC seizure, but who were lost to follow-up soon after diagnosis precluding meaningful assessment of risk of seizure recurrence;
– non-attendance for clinical appointments or diagnostic tests.
We also excluded patients with *newly diagnosed epilepsy*, *i.e*. those in whom we identified pre-existing, but up till then not diagnosed seizure symptoms (such as vacant spells, muscle twitches or isolated *déjà vu* / brief epigastric sensations). However, we pragmatically included patients who first noticed such seizure symptoms around the time of the index seizure and were uncertain of their exact onset in relation to the latter. Finally, we did not consider patients presenting with a first focal seizure, myoclonic jerks or absences that are far less likely to bring patients to the emergency department; indeed, during the period of this hospital-based study, only a handful of patients attended our emergency department with focal seizures, myoclonic jerks or absences, which were usually the most severe but not the first in life.

We focused on TC seizures which are of utmost concern for people with epilepsy and typically easy to recognize and accurately study. We did not factor into the estimation of risk of seizure recurrence absences, myoclonic, or focal seizures that many of our patients subsequently developed. Such seizures define syndromes but do not always occur (genetic epilepsy with GTC seizures only and epilepsy with exclusively nocturnal BTC seizures are notable examples) and may be difficult to clinically identify when mild, potentially leading to underestimation of the recurrence rate. The long-term course of absences and myoclonic seizures and their responsiveness to AEDs is well known to be syndrome-related (Baykan *et al*., 2008; Vorderwülbecke *et al*., 2017).

Written informed consent from the patients was not required because the study was not interventional and involved retrospective analysis of anonymised data (IRAS ID 101321 approved by HRA).

Setting and design of the FSC with four time points of contact with patients

Our FSC is part of the epilepsy and EEG section of the neurology department with rapid access to routine and sleep EEG after partial sleep deprivation (SDEEG) and imaging. Electronic referrals to the FSC are generated at the emergency department on the day of the index seizure (*first point of contact*) and patients are seen at the FSC by the authors, typically within two weeks (FSC1: *second point of contact*).

At FSC1, medical summaries, general and neurological examination, and results of tests undertaken at the emergency department on the day of the index seizure, including ECG and variably brain imaging (usually brain CT), are accessible through the electronic patient records (EPR) system of the hospital. As a rule, patients with a single index seizure are at this stage untreated, while those with multiple seizures at first presentation or a second TC seizure before they attend FSC1 (known from a second visit to the emergency department that is also registered on EPR) are on a starting dose of an AED. Therefore, patient recruitment and prospective follow-up effectively start from the day of the index seizure when patients attend the emergency department.

Interviews at FSC1 include pre- and post-index seizure symptoms and their time course, time, circumstances, and possible modulators and triggers, such as sleep deprivation, stress, exposure to environmental lights or reading, and descriptions by observers. For unaccompanied patients, possible witnesses are contacted by phone or invited to patients' EEG or to the second clinical appointment at the FSC (FSC2). Medical and neurological history includes possible earlier non-convulsive seizures and their onset in relation to the index seizure, prior brain insults, and co-morbidities with the relevant treatments. Social circumstances, intake of alcohol or illicit substances, and sleep habits are noted. Patients are physically and neurologically examined, and brain MRI and video-EEG are requested. Patients with clinically suspected other diagnoses are referred for tilt-table test or ECG monitoring, as appropriate; those with suspected psychogenic non-epileptic seizures have video-EEG.

The *third point of contact* with patients, and witnesses of the index seizure when appropriate, is the diagnostic EEG, performed before FSC2, using dedicated weekly "first seizure" EEG slots. We typically opt for SDEEG, tailored according to the clinical information obtained at FSC1 to assist epilepsy classification (Leach *et al*., 2006). Our EEG methodology is described elsewhere (Koutroumanidis *et al*., 2008). Using this strategy, all patients have EEG within the first three to four weeks and before FSC2. All EEGs are interpreted by the authors in formal clinical-EEG reporting sessions when the clinical evidence is also reviewed, and therefore a combined clinical-EEG impression for each patient is formed before they are reviewed at FSC2 (*fourth point of contact*), typically within four weeks from the index seizure.

At FSC2, the possible cause, the type or syndrome of epilepsy (when identified), and the likely long-term prognosis are discussed with the patients and appropriate advice about possible seizure modulators and lifestyle is offered; decisions about immediate or deferred treatment are made according to the national guidelines (National Institute for Health and Clinical Excellence, 2016), taking into account patients' individual preferences and circumstances, and implemented with their fully informed consent.

Depending on aetiology and clinical needs, patients are subsequently reviewed every 3-6 months for the first 12-18 months, and annually thereafter. The clinical data, including updates on seizure recurrence and initial and repeat EEG and MRI data of all patients are prospectively entered into a password-protected database at FSC1, FSC2, and each follow-up visit.

Definitions and classifications

Diagnosis of aetiology and epilepsy type / syndrome classification was based on clinical, EEG and brain imaging information that was available at FSC2, according to the ILAE classification criteria (Scheffer *et al*., 2017).

We used the combined term "*genetic (idiopathic) generalised epilepsy*" (GGE/IGE) to also account for possibly genetic syndromes that are not currently included in the ILAE classification (Koutroumanidis *et*

al., 2017), such as absence status epilepsy (Genton *et al*., 2008) and epilepsy with phantom absences (Panayiotopoulos *et al*., 1997). *Genetic / possibly genetic focal epilepsies* (GF) included photosensitive occipital (Koutroumanidis *et al*., 2015) and reading epilepsy.

We classified non-genetic focal epilepsies into *structural focal* when initial brain imaging showed a focal lesion, and *focal of unknown aetiology* when imaging was normal, and sub-classified them into specific lobar syndromes according to the seizure symptoms and the topography of the initial EEG and brain imaging findings.

At FSC2, patients with cerebrovascular disease (CVD), but without localizing clinical, EEG or imaging evidence to suggest a certain lobar origin, were classified with *possible* CVD-related *undetermined focal epilepsy* (UF). Similarly, patients with both focal/multifocal and diffuse ED on their first EEG, but normal imaging and no sufficient clinical evidence to indicate a certain epilepsy type (focal or generalized), were initially grouped as *possible unclassified epilepsy* (UE). We considered the *possibility* rather than the diagnosis of epilepsy in patients within these two groups who had no other seizure during the observation period, because our follow-up was too short to apply the new definition of epilepsy (Fisher *et al*., 2014). Patients with a single index seizure but no other clinical, EEG or imaging evidence of epilepsy were initially categorized as having a first unprovoked TC seizure.

After epilepsy type / syndrome diagnosis, recurrent TC seizures were recognized as GTC, BTC or TC seizures of unknown onset (Fisher *et al*., 2017). The term "seizure recurrence" (SR) is henceforth applied to these seizures.

Statistical analysis

We used the t-test for comparisons between groups, analysis of variance for normally distributed data, and the chi-square test for categorical data. Time to SR was analysed using Kaplan-Meier curves and statistical significance was calculated using a weighted log-rank statistic (generalized Wilcoxon test), to account for unbalanced distribution of confounders. Data were censored at 2,000 days from the index seizure. To identify independent predictors of SR, univariate and multivariate analyses were performed using Cox's proportional hazards model. All the variables with $p<0.10$ based on the univariate analysis were simultaneously entered in the multivariate analysis. Age, sex and AED therapy were considered *a-priori* confounders and were included in the model. The likelihood ratio test was used to determine independent variables to be removed. Ninety-five percent confidence intervals (95% CI) for hazard risks (HRs) were calculated. The level of significance was set at $p<0.05$ (two-tailed test). Predictors of SR were also separately analysed for idiopathic and symptomatic epilepsies. For factors showing statistical significance, interaction and possible additive effects were estimated through an interaction analysis under the Cox's proportional hazards model. Each variable was split into two categories and multiplicative interaction terms were created. An additive effect was considered present if the level of risk for the new interaction term was significantly greater than the risk for either factor taken separately. Data were analysed using STATA 14.0 software packages (StataCorp, 2015).

Table 1. Initial diagnosis and epilepsy classification in 150 patients with a first unprovoked tonic-clonic seizure (TC).

A. EPILEPSY (TYPE / SYNDROME)	
1. GENETIC (POSSIBLY GENETIC)	
1.1 Generalized	47 (31.3%)
Epilepsy with GTC alone	29
Juvenile myoclonic epilepsy	9
Juvenile absence epilepsy	4
Epilepsy with phantom absences	3
Absence status epilepsy	2
1.2 Focal	6 (4.0%)
Photosensitive occipital epilepsy	5
Reading epilepsy	1
2. NON-GENETIC	
2.1 Generalized	0
2.2 Focal (structural / unknown aetiology)	**85 (56.7%)**
2.2.1. Specific types	
- Temporal lobe epilepsy	39
- Frontal lobe epilepsy	17
2.2.2. CVD-related, of undetermined origin†	29
3. UNCLASSIFIED†	1‡ (0.67%)
B. FIRST UNPROVOKED TONIC-CLONIC	11# (7.3)

CVD: cerebrovascular disease;
†possible, pending a second seizure (*see Definitions and Classifications in the Methods section*); Seventeen of these patients (58.6%) had a second focal to bilateral tonic-clonic seizure during follow up;
‡the patient with focal and generalized EEG discharges and normal MRI had further TC of unknown onset and remained unclassified until the end of the observation period;
#patients without further clinical evidence of epilepsy and initially normal EEG and brain MRI; one was later diagnosed with TLE and five had SR but their epilepsy remained unclassified.

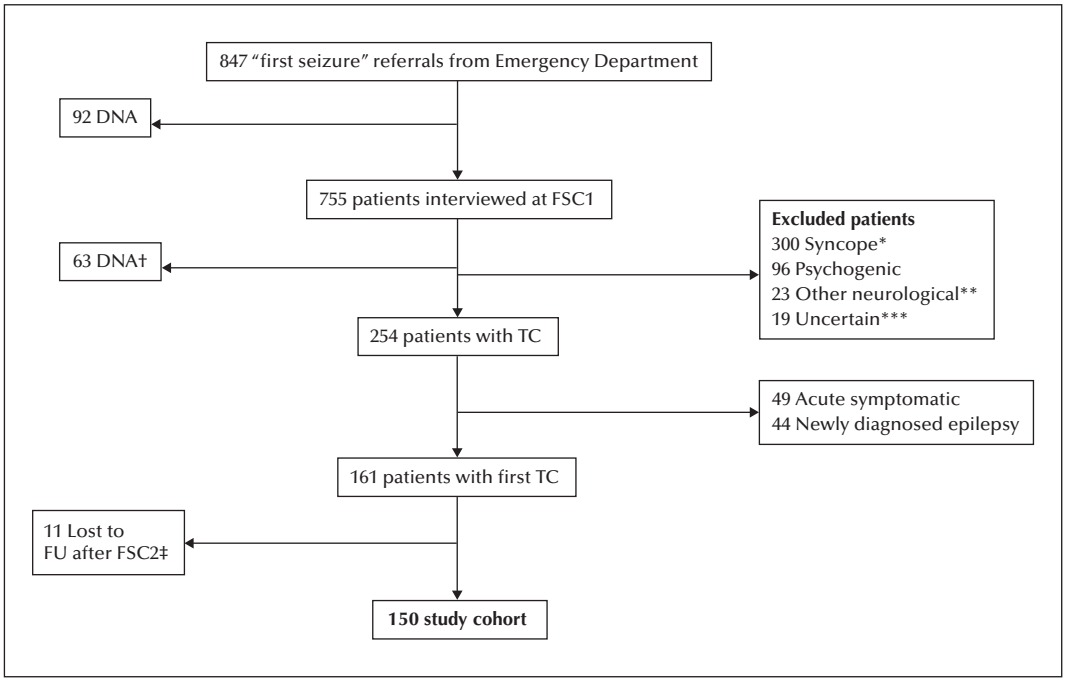

Figure 1. Flowchart of the study.
DNA: patients who did not attend FSC1 (within the first two weeks from the index seizure. DNA†: patients who did not attend appointments for initial diagnostic investigations (EEG, brain scan, tilt table) and FSC2.
‡Patients with a diagnosed first TC seizure but who were lost to follow-up after FSC2 (without a second TC seizure).
*Mostly convulsive neurally mediated (cardiogenic in 24 patients).
**Migraine, intermittent central obstruction (such as Chiari malformation), sudden naps/cataplexy, transient ischaemic attack.
***No clinical pointers of TC seizures and unremarkable extensive neurological, autonomic and cardiological investigations.
TC: tonic-clonic seizure of initially unknown onset.

Results

Our study cohort included 150 patients (*figure 1*). The mean duration of follow-up was 3.1 (±2.1) years. At FSC2, we were able to classify 109 patients (72.7%) into specific epilepsy types and syndromes, including GGE/IGE, temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE), and genetic focal syndromes (*table 1*). Of the 29 patients with possible CVD-associated UF, the first EEG showed typically bilateral, variably lateralized frontotemporal slow activity in 14 and was unremarkable in 15, and initial imaging with MRI (17 patients) and CT (12 patients) showed mostly multiple areas of old infarcts or watershed ischaemic areas in eight, diffuse small vessel disease in 19, and was unremarkable in two patients. The latter and other eight had a history of stroke (remote symptomatic aetiology). The aetiology of the non-genetic epilepsies is shown in *supplementary table 1*.

Patients with genetic epilepsies were younger and reported more seizure modulators that included sleep deprivation and sensitivity to light and reading, while those with non-genetic focal epilepsies reported more nocturnal seizures. Follow-up lengths were comparable (*table 2*).

AED treatment was started in 85 patients (56.7%) before SR, without any difference between the genetic and non-genetic groups (p=0.3). The treated and untreated groups were also balanced for age (p=0.8) and gender (p=0.8). More patients in the non-genetic group were still on treatment at their last follow-up visit compared to those in the genetic group (p=0.001) (*table 2*).

The first EEG showed ED in 103 (68.7%) patients. SDEEG, performed for 116 patients, showed ED in 92 (79.3%) of them; in all 42 with genetic epilepsies and in 50 of 74 (67.5%) with non-genetic focal epilepsies (*table 2*).

Risk of seizure recurrence (SR)

SR occurred in 100 (66.7%) patients during the study period. The risk was highest within the first year (52.7%; 95% CI: 44.9-60.8), particularly in the first six months (*figure 2A*, *supplementary table 2*).

SR was noted in 62.3% of patients with genetic and in 69.1% of patients with non-genetic epilepsies after a mean time of 306.8 (±376.0) and 226.6 (±257.5) days, respectively (*figure 2B*). The risk was lower in patients with genetic epilepsies throughout the observation period (p=0.04), with a major difference observed at six months (26.4% for genetic *vs* 44.3% for non-genetic).

Table 2. Patients and index seizure characteristics (*n*=150).

Characteristics	***n* (%)**		
	Genetic ***n*=53**	**Non-genetic** ***n*=97**	**Total** ***n*=150**
Sex			
Male	31 (58.5)	68 (70.1)	99 (66.0)
Female	22 (41.5)	29 (29.9)	51 (34.0)
Age at index seizure†	26.3 ± 8.7	43.1 ± 19.1	37.2 ± 18.0
(mean ± SD) (median, IR, range)	(24, 20-30, 15-55)	(40, 25-58, 16-84)	(31, 23-49, 15-84)
Age range†			
17 to <30	39 (73.6)	30 (30.9)	69 (46.0)
30 to <60	14 (26.4)	44 (45.4)	58 (38.7)
≥ 60	-	23 (23.7)	23 (15.3)
Family history of epilepsy			
No	44 (83.0)	88 (90.7)	132 (88.0)
Yes	5 (9.4)	7 (7.2)	12 (8.0)
Unknown	4 (7.6)	2 (2.1)	6 (4.0)
Febrile convulsions			
No	41 (77.4)	94 (97.0)	135 (90.0)
Yes	8 (15.1)	1 (1.0)	9 (6.0)
Unknown	4 (7.5)	2 (2.0)	6 (4.0)
Neurological deficit			
No	53 (100)	94 (97.0)	147 (98.0)
Yes	-	3 (3.0)	3 (2.0)
History of remote aetiology			
No	53 (100)	81 (84.5)	134 (89.3)
Yes	-	16 (16.5)	16 (10.7)
Multiple seizures at first presentation			
No	49 (92.5)	84 (86.6)	133 (88.7)
Yes	4 (7.5)	13 (13.4)	17 (11.3)
State of arousal at index seizure†			
Awake	46(86.8)	75 (77.3)	121 (80.7)
On awakening (within first hour)	6 (11.3)	1 (1.0)	7 (4.7)
Out of sleep	1 (1.9)	21 (21.7)	22 (14.6)
Modulators of index seizure†			
None	34 (64.1)	86 (88.7)	120 (80.0)
Yes	19 (35.9)	11 (11.3)	30 (20.0)
Sleep deprivation	7 (36.8)	7 (63.6)	14 (46.7)
Alcohol	1 (5.3)	1 (9.1)	2 (6.7)
Sleep deprivation and alcohol	5 (26.3)	1 (9.1)	6 (20.0)
Lights	5 (26.3)	-	5 (16.7)
Infection	-	2 (18.2)	2 (6.7)
Reading	1 (5.3)	-	1 (3.2)

Table 2. Patients and index seizure characteristics (*n*=150) (*Continued*).

Characteristics	*n* (%)		
	Genetic ***n*=53**	**Non-genetic** ***n*=97**	**Total** ***n*=150**
Associated other seizure types*			
No	36 (67.9)	81 (83.5)	117 (78.0)
Yes	17 (32.1)	16 (16.5)	33 (22.0)
Absence	9 (53.0)	-	9 (27.3)
Myoclonic jerks	8 (47.0)	-	8 (24.2)
Simple motor	-	2 (12.5)	2 (6.1)
Complex motor	-	6 (37.5)	6 (18.2)
Déjà vu	-	5 (31.3)	5 (15.1)
Gustative	-	2 (12.5)	2 (6.1)
Epigastric discomfort	-	1 (6.2)	1 (3.0)
Brain imaging after index seizure†			
Normal	46 (86.8)	43 (44.3)	89 (59.3)
Abnormal (non-acute)	-	54 (55.7)	54 (36.0)
Focal	-	35 (64.8)	35 (64.8)
Diffuse	-	19 (35.2)	19 (35.2)
Not performed	7 (13.2)	-	7 (4.7)
EEG after index seizure			
Routine	11 (20.7)	23 (23.7)	34 (22.7)
Sleep deprived	42 (79.3)	74 (76.3)	116 (77.3)
EEG findings			
Normal	-	33 (34.0)	33 (22.0)
ED	53 (100)	50 (51.6)	103 (68.7)
GSWDs	42 (79.2)	-	42 (40.8)
Focal	11 (20.8)	50 (100)	61 (59.2)
Focal slow activity only	-	14 (14.4)	14 (9.3)
Treatment started before second TC seizure			
No	20 (37.7)	45 (46.4)	65 (43.3)
Yes	33 (62.3)	52 (53.6)	85 (56.7)
On treatment at the last follow-up visit†			
No	24 (45.3)	16 (16.5)	40 (26.7)
Yes	29 (54.7)	81 (83.5)	110 (73.3)
Total follow-up time (days; mean ± SD)	1,174.1±816.5	1,092.8±726.3	1,121.5±757.7

†$p<0.05$; *absences, myoclonic or focal seizures presented concurrently with or subsequently to the index seizure; ED: epileptiform discharges; SR: seizure recurrence.

In the genetic group (*figure 2C*), absences or myoclonic seizures concurrent with the index seizure or presenting subsequently significantly increased the risk for SR (p=0.05).

In the non-genetic group, diagnosis of a localized focal epilepsy (*i.e.* TLE or FLE) was associated with significantly higher risk of SR compared to UF (*figure 2D*) (p=0.000). At six months, the risk of SR amounted to 64.7% for FLE, 57.5% for TLE, and only 7.2% for the possible CVD-related UF.

Predictors of seizure recurrence

Multivariate analysis performed on the entire cohort of patients (*supplementary table 3*) indicated that non-genetic aetiology is an independent predictor of SR, with a 2.4-fold increased risk (95% CI: 1.1-6.4) compared with genetic. The presence of a focal structural abnormality on brain imaging was also an independent risk factor (HR: 2.1; 95% CI: 1.2-3.5; p=0.006).

On the other hand, identifiable seizure modulators or triggers and AED treatment after the index seizure

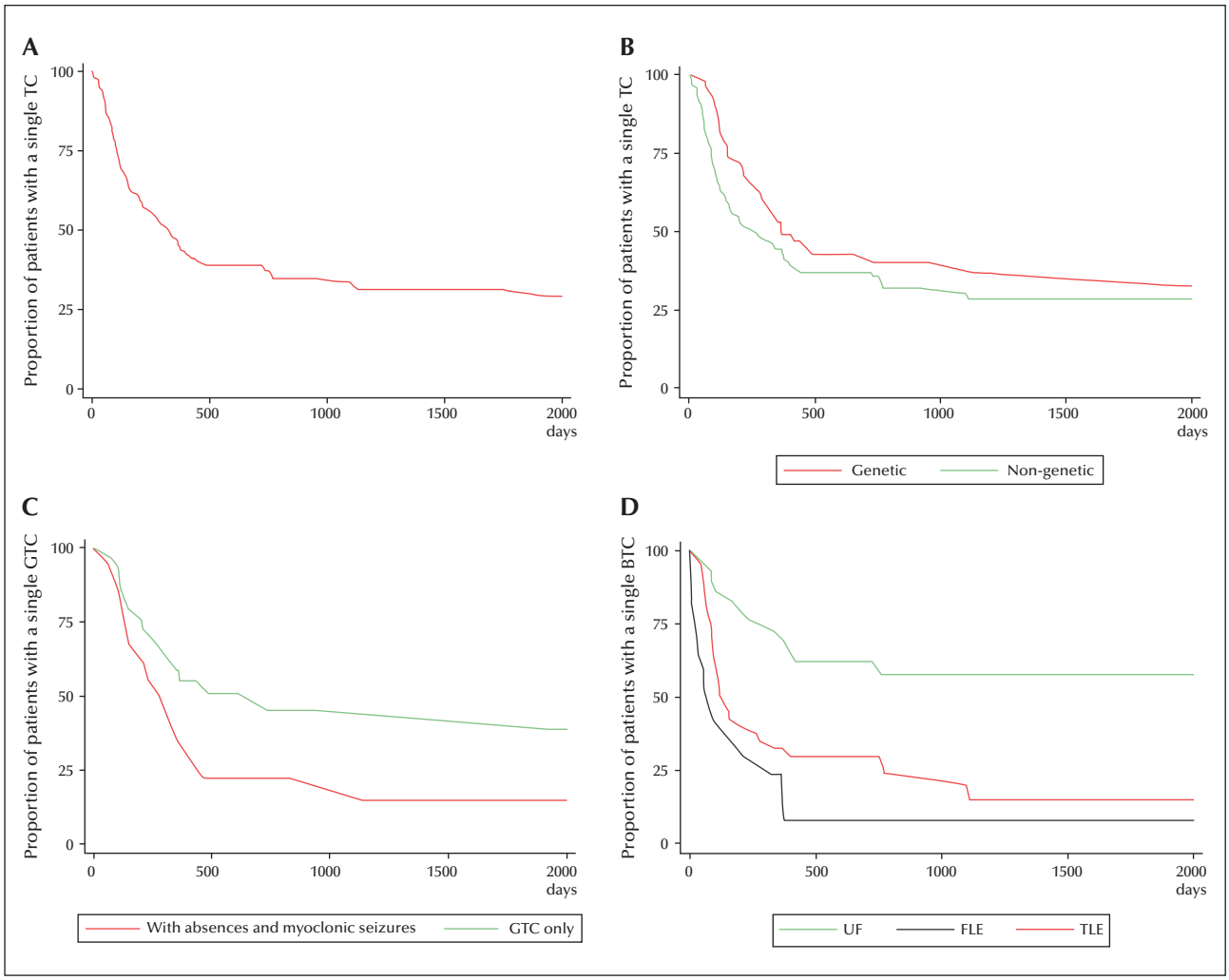

Figure 2. Kaplan-Meier plots: (A) time to second tonic-clonic (TC) seizure in the total population (*n*=150); (B) time to second TC seizure according to epilepsy aetiology (*p*=0.04); (C) time to second generalized tonic-clonic (GTC) seizure for genetic (idiopathic) generalized epilepsy (GGE/IGE) according to seizure type (*p*=0.05); and (D) time to second focal to bilateral tonic-clonic (BTC) seizure for non-genetic focal epilepsies according to localization to brain region (*p*=0.000).
FLE: frontal lobe epilepsy; TLE: temporal lobe epilepsy; UF: undetermined focal epilepsy.

significantly reduced the risk of recurrence (*p*=0.05 and 0.02, respectively).
A history of remote symptomatic cause, the state of arousal at the time of the index seizure, and the occurrence of ED on the first EEG, including when ED were analysed as binary variables (irrespective of whether they were focal or generalized), did not influence the risk for SR (HR: 1.3; 95% CI: 0.8-2.0; *p*=0.2).

Patients with genetic epilepsies (n=53)
Multivariate analysis (*supplementary table 4*) showed that absences or myoclonic seizures presented concurrently with or subsequently to the index seizure (HR: 1.8; 95% CI: 1.1-4.0; *p*=0.05) and occurrence of the index seizure within an hour after awakening (HR: 2.7; 95% CI: 1.1-6.7; *p*=0.03) were independent predictors of SR. Early treatment and the presence of generalized spike-and-wave discharges (GSWD) on the EEG did not affect the risk of SR. No additive effect was demonstrated for these variables combined.

Patients with non-genetic epilepsies (n=97)
Multivariate analysis (*supplementary table 5*) showed that diagnosis of TLE had a 5.7-fold increased risk (95% CI: 1.2-26.6; *p*=0.03) and FLE a 7.4-fold increased risk (95% CI: 1.7-31.2; *p*=0.006), compared with that of UF.
Focal ED (HR: 1.8; 95% CI: 1.1-3.0; *p*=0.05) and a change on focal imaging (HR: 1.9; 95% CI: 1.1-3.7; *p*=0.06) were

independent risk factors for SR. Conversely, age at index seizure >60 (HR: 0.3; 95% CI: 0.1-0.9; p=0.03) and early treatment (HR: 0.3; 95% CI: 0.2-0.6; p=0.001) had significant inverse association.
The risk of SR was no different between patients with structural focal and those with focal of unknown aetiology (p=0.4).
The presence of two or more independent risk factors was associated with a significant higher risk of SR compared to the risk incurred by any individual factor (*table 3*).

Discussion

The findings of this exclusively hospital-based study demonstrate that early recognition of new epilepsy after a first TC seizure can lead to the identification of syndrome-specific risk factors of GTC or BTC seizure recurrence, and therefore to the refinement of management and treatment in clinically distinctive groups of patients. The main strengths of the study are the systematic and timely diagnostic work-up including SDEEG and the prospective ascertainment of SR from the day of the index seizure. The relatively limited total number of patients and the unavoidable loss of further possible patients with TC seizures amongst the 155 who were not seen at FSC at all (92 patients) or further investigated (63 patients) (*figure 1*) may have affected the degree of accuracy of our results, but would not be expected to substantially modify our key findings. The relatively brief follow-up is another limitation, however, a longer period might not be significantly more contributory given the high rate of recurrence.

Incident epilepsy

Diagnosis and classification of new epilepsy was possible in 72.7% of patients at four weeks from the index seizure. Previous first seizure epileptology studies (King *et al*., 1998; Jallon *et al*., 2001) reported classification of new epilepsy in up to 77% of patients (King *et al*., 1998), but comparisons with ours are hindered by different populations that included children and adults with other types of first seizure. The superior diagnostic capability of SDEEG may have also contributed to a high percentage found in our study. Notwithstanding these methodological differences, the evidence from these studies and ours appears in keeping with the rationale of the new definition of epilepsy (Beretta *et al*., 2017; Fisher *et al*., 2017) and indicates that the hitherto reported recurrence rates after a first seizure may have significantly under-estimated the actual incidence of new epilepsy.

SR and risk factors

Our approach is conceptually different to that of other "first seizure" studies, which considered new epilepsy only when a second seizure occurred and used two mutually exclusive aetiologies, "remote symptomatic" and "unknown". The latter, interchangeably described as "idiopathic" (Jallon *et al*., 2001) or "cryptogenic" (Hauser *et al*., 1990), inevitably contained patients with GGE/IGE *and* focal epilepsies of clinically occult causes (*e.g*. cortical dysplasia), or of unknown aetiology (also known as cryptogenic). Still, when our entire cohort is considered as a homogenous "first seizure" group, our results appear in keeping with existing well-established evidence (Krumholz *et al*., 2015); the risk of SR was higher in the first year and was significantly reduced by early AED treatment, while a focal abnormality on imaging was a major risk factor for SR. Our cumulative risk of SR over a >three-year mean observation period is high (66.7%), and as it concerns only TC seizures cannot be directly compared with

Table 3. Non-idiopathic epilepsies of structural and unknown aetiology (n=97): additive effects of risk factors.

Risk factors	HR	95% CI	
Focal ED on EEG	1.8	1.1	3
Age 17-60	2.2	1.2	4.3
Change on focal imaging	2.7	1.6	4.6
Localized focal epilepsy*	3.5	1.8	6.6
Age 17-60 + focal ED on EEG	2.9	1.3	6.2
Change on focal imaging + focal ED on EEG	3.2	1.6	6.3
Age 17-60 + Change on focal imaging	4.8	2.1	10.7
Localized focal epilepsy + Change on focal imaging	5.1	2.5	10.5

*Temporal lobe and frontal lobe epilepsies; HR: hazard risk; CI: confidence interval.

similarly high risks reported by others; 56% by five years (Annegers *et al*., 1986), above 60% by three years (Lawn *et al*., 2014), and 71% by 3-4 years (Elwes *et al*., 1985). Possible explanations for such a high risk include our strict clinical criteria for the first TC seizure and that most of our patients had epilepsy instead of a "first seizure". A recent retrospective study in patients diagnosed with the new definition of epilepsy reported 83.6% recurrence at 10 years and 89% at 15 years (Beretta *et al*., 2017). A new finding from our study is that identified seizure modulators and specific triggers significantly protected against SR, implying that lifestyle advice might moderate or even defer an otherwise advisable early AED treatment and its consequences that can affect quality of life (Perucca, 2008).

However, adults presenting with a first seizure hardly form a homogenous group. The risk of SR was significantly lower in genetic epilepsies (mostly GGE/IGE) than in the non-genetic (mostly focal) epilepsies, and a clear protective role of early treatment was evident only in the latter. GTC/BTC seizure remission was similar in the two groups, but more patients with non-genetic epilepsies were on AEDs at the end of the follow-up period. The incidence of adult-onset GGE/IGE in cohorts of first seizure patients has been consistently shown to be sizable, ranging from 22.3% and 24.6% (King *et al*., 1998; Jallon *et al*., 2001) to 31.3% in our series. Although remission is high, both in large community-based studies and incidence series (Annegers *et al*., 1979; Mohanraj and Brodie, 2007), early diagnosis of GGE/IGE is important to avoid use of inappropriate AEDs that can exacerbate seizures (Benbadis *et al*., 2003) and, also, to offer specific lifestyle advice.

We also recognised risk factors specific for different types of epilepsy; other concurrent seizure types (myoclonic and absences) were a risk factor for GGE/IGE, which include specific syndromes, such as juvenile myoclonic epilepsy (JME). This difference appears in keeping with the generally higher frequency of GTC seizures in JME compared to the better outcome and the lower seizure frequency in epilepsy with GTC seizures only (Baykan *et al*., 2008; Camfield and Camfield, 2009; Camfield and Camfield, 2010; Vorderwülbecke *et al*., 2017).

Amongst the non-genetic focal epilepsies, diagnosis of a localized type (TLE or FLE) incurred a very high risk of SR, compared to CVD-associated UF. The latter were also associated with older age, which emerged as an independent protective factor. New epilepsy in the elderly commonly relates to CVD and decisions about treatment should take into account the frequent comorbidities and complex drug interactions in this age group (Krämer, 2001). Our findings are in keeping with the high remission of new and newly diagnosed focal epilepsies in patients with CVD (Mohanraj and Brodie, 2005) and in those over 60-65 (Lühdorf *et al*., 1986; Stephen *et al*., 2006), and suggest that modest doses of AEDs may suffice in such patients.

Our approach has also led to the identification of hitherto elusive additive effects of independent risk factors, though only for non-genetic focal epilepsies.

The role of the EEG

We mostly used SDEEG in preference to routine EEG, at variance with all previous studies on patients with a first seizure. The yield of ED based on SDEEG was maximal in patients with TLE and FLE, including those with a first seizure while asleep. Routine EEG was equally helpful in patients with GGE/IGE, as previously reported (King *et al*., 1998; Baldin *et al*., 2014; Delil *et al*., 2015), but neither type of EEG showed clear ED in older patients with CVD-related seizures (Krämer, 2001; Stephen *et al*., 2006).

The officially advocated routine EEG within the first 24-48 hours from the first seizure (Krumholz *et al*., 2015) provides earlier information but has shown inferior diagnostic yield; for instance, ED have been reported in 19% (Paliwal *et al*., 2015), 21% (Neufeld *et al*., 2000), 26.8% (Schreiner and Pohlmann-Eden, 2003), and 39% of adults (King *et al*., 1998). Within a slightly more lenient time window (Baldin *et al*., 2014), routine EEG after a median time of three days showed ED in 39.1% of 141 adults and children with a first unprovoked seizure, and after a median of four days in 52.7% of 478 with new epilepsy, with highest yield for GGE/IGE. It is also worth noting that EEG after the first 48 hours and even later outpatient routine EEG in adults do not appear to show any difference in yield of ED compared to early recordings (27% [Hopkins *et al*., 1988] and 34% [Bora *et al*., 1995]).

Our findings suggest that SDEEG within the first three to four weeks is preferable to early routine EEG when the primary objective is to diagnose and classify new epilepsy. However, its pragmatic use depends on the design of the service and the available resources. In the absence of direct comparative evidence between the two EEG methodologies, either from any of the previous studies (Hopkins *et al*., 1988; Bora *et al*., 1995; King *et al*., 1998; Schreiner and Pohlmann-Eden, 2003; Baldin *et al*., 2014; Paliwal *et al*., 2015) or ours, the question of optimal EEG strategy remains open and can be conclusively addressed only by prospective comparative studies. □

Supplementary data.

Summary didactic slides and supplementary tables are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What is an "acute symptomatic seizure"?

(2) What are the most robust clinical criteria to diagnose a tonic-clonic seizure and distinguish it from a convulsive vasovagal syncope (VVS) or a psychogenic non-epileptic seizure (PNES)?

(3) Why might a sleep EEG after partial sleep deprivation (SDEEG) be considered more diagnostic than a routine recording (REEG) in patients with epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".