Epilepsy & Behavior xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Duration of focal complex, secondarily generalized tonic–clonic, and primarily generalized tonic–clonic seizures — A video-EEG analysis

Judith Dobesberger [a,b,*,1], Aleksandar J. Ristić [c,1], Gerald Walser [a], Giorgi Kuchukhidze [a,b], Iris Unterberger [a], Julia Höfler [a,b], Edda Amann [d], Eugen Trinka [a,b]

[a] Department of Neurology, Paracelsus Medical University, Centre for Cognitive Neuroscience, Salzburg, Austria
[b] Department of Neurology, Medical Innsbruck University, Innsbruck, Austria
[c] Clinical Centre of Serbia, Institute of Neurology, Department of Epileptology, Belgrade, Serbia
[d] Medical University Innsbruck, Department for Medical Statistics, Informatics and Health Economy, Innsbruck, Austria

ARTICLE INFO

Article history:
Accepted 22 March 2015
Available online xxxx

Keywords:
Seizure duration
Predictors
Video-EEG monitoring
Status epilepticus
Antiepileptic drugs

ABSTRACT

Introduction: Identifying seizures with prolonged duration during video-electroencephalographic (EEG) monitoring is of importance to inform clinicians when to start emergency treatment of seizures to prevent status epilepticus. The aims of this study were to assess the clinical and EEG seizure duration (SD) in consecutive patients with epilepsy who underwent prolonged video-EEG monitoring and to identify a seizure type-dependent time point to start emergency treatment based on the likelihood that seizures will not stop spontaneously. Furthermore, we sought to determine predictors of SD and explored the relationship between antiepileptic drug (AED) serum levels and SD.
Material and methods: We retrospectively analyzed 1796 seizures in 200 patients undergoing video-EEG monitoring between January 2006 and March 2008.
Results: Focal simple seizures lasted significantly shorter (clinical SD: 28 s, EEG SD: 42 s) compared with focal complex seizures (clinical SD: 64 s, EEG SD: 62 s), and both seizure types lasted significantly shorter compared with secondarily generalized tonic–clonic seizures (GTCSs; clinical SD: 90 s, EEG SD: 96 s). There was no difference between the duration of the convulsive phase of primary GTCSs (defined as nonfocal) and that of secondarily GTCSs (each 65 s). Cumulative clinical SD (99%) was 7 min in focal complex seizures and 11 min in focal simple seizures. Mixed linear regression model demonstrated that history of status epilepticus ($P = 0.034$), temporal lobe seizure onset ($P = 0.040$), and MRI lesions ($P = 0.013$) were significantly associated with logarithmic EEG SD in focal epilepsies recorded with scalp electrodes. We found significant negative correlations between the AED serum level and the EEG SD in patients treated with monotherapy: carbamazepine ($P < 0.001$), levetiracetam ($P = 0.001$), oxcarbazepine ($P = 0.001$), and valproic acid ($P = 0.038$) but not with lamotrigine monotherapy and EEG SD.
Discussion: Based on the results of this study, we propose 2 min of convulsive seizure activity (irrespective of focal or generalized onset) as a prolonged seizure, which could serve as a time point to consider treatment to prevent status epilepticus. In focal complex seizures, we suggest an upper limit of 7 min, and in focal simple seizures 11 min, as definition of prolonged seizures. History of status epilepticus, temporal seizure onset, and lesional MRI findings are factors associated with significantly longer SD. Negative correlations of carbamazepine, levetiracetam, oxcarbazepine, and valproic acid serum levels and SD suggest a prolonging effect on seizures during withdrawal of these AEDs during video-EEG monitoring sessions.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

The current definition of an epileptic seizure as proposed by the ILAE is "*a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain*" [1]. This definition implies that seizures are self-limited. Status epilepticus as the most extreme form of epileptic seizure was defined as "*the failure of the natural homeostatic seizure-suppressing mechanisms responsible for*

* Corresponding author at: Department of Neurology, Paracelsus Medical University, Ignaz Harrer Straße 79, A-5020 Salzburg, Austria. Tel.: +43 662 4483 56004; fax: +43 662 4483 3004.
E-mail address: j.dobesberger@salk.at (J. Dobesberger).
[1] These authors contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.yebeh.2015.03.023
1525-5050/

seizure termination" [2], resulting in seizure duration (SD) of more than 5 min of ongoing convulsive activity, or convulsions, without recovery between the attacks [3]. Although, this operational definition matches the almost universal practice in emergency rooms to treat patients with ongoing seizure activity of more than 5 min, there is limited support from studies in humans.

Video-electroencephalographic (EEG) monitoring is the gold standard for objective assessment of behavioral and EEG duration of seizures. Thus, it offers the possibility to define the upper limits of the usual range of SD based on descriptive analysis. Up to now, only a few published studies dealt with clinical and EEG SD and in selected patient groups [4–6]. These studies differed in their patient selection and definition of SD. Furthermore, they did not analyze the clinical determinants of SD, especially the influence of decreasing serum levels of antiepileptic drugs (AEDs), which is the case during video-EEG monitoring, where controlled withdrawal of AEDs is a standard procedure. Decreasing serum levels may have a significant influence on SD and, eventually, progression into status epilepticus, which is a well-recognized adverse event during video-EEG monitoring [7]. This assumption is also supported by population-based studies, which consistently reported low AED levels in patients with epilepsy who had status epilepticus [8,9].

Therefore, we aimed to assess the clinical and EEG SD (median value per patient) in a large nonselected group of patients with epilepsy who underwent video-EEG monitoring and compare the duration of different seizure types. We investigated the likelihood that seizures stop spontaneously and propose a seizure type-dependent working definition of impending status epilepticus to guide the clinical decision when to start with intravenous treatment. We tried to determine predictors of SD and further aimed to explore the relationship between SD and decreasing serum AED levels.

2. Material and methods

2.1. Patients and clinical data

We retrospectively analyzed the video and EEG recordings of 274 consecutive patients with epilepsy, who were admitted for presurgical or diagnostic evaluation to the video-EEG monitoring unit of the Department of Neurology, Medical University Innsbruck, Austria, from January 2006 to March 2008. A definite epilepsy diagnosis was established in all patients after obtaining detailed history, neurological examination, long-term video-EEG monitoring, high-resolution MRI (1.5-Tesla scanner, Sonata, Siemens, Erlangen, Germany), and neuropsychological testing. Additional investigations like F18-FDG-PET, interictal and ictal [^{99m}Tc] HMPAO-SPECT and their coregistration subtraction, and Wada test were performed, as needed in the context of presurgical evaluation. Clinical variables such as age, duration of the disease, epilepsy syndrome (focal or generalized), etiology (idiopathic/genetic, cryptogenic/unknown, symptomatic/structural, or metabolic), and localization of seizure onset; MRI findings; as well as history of status epilepticus or febrile seizures were extracted from the clinical charts after presurgical evaluation.

2.2. Video-EEG monitoring

Long-term video-EEG was performed on two 64-channel and two 128-channel video-EEGs (Schwarzer® Epas acquisition system and EEG software Harmony by Stellate Systems®). Two hundred and sixty-two monitoring sessions with clinical events were performed in a total of 227 patients (249 surface EEG recordings of 220 patients; 12 intracranial recordings of 12 patients, 6 of them had surface EEG recording before analyzed period; and 1 surface EEG recording with foramen ovale electrodes). In 26/227 patients, video-EEG monitoring was repeated, and 8/26 patients were monitored three times. Seizures were classified according to the ILAE terminology [10]. Psychogenic nonepileptic seizures (87 events in 27 patients) were excluded, but one patient had both psychogenic nonepileptic and epileptic seizures and entered analysis, so 26 patients were excluded from 227. In total, 1810 seizures in 201 patients entered further analysis (134/201 presurgical evaluations and 67/201 diagnostic procedures). Fourteen out of 1810 seizures in 11 patients were interrupted by intravenous benzodiazepines according to the clinical decision of the treating neurologist and were excluded from analysis of uninterrupted seizures — in these patients, only uninterrupted seizures were analyzed; one of the patients had only one seizure during recording interrupted by intravenous AEDs and, therefore, was excluded. Hence, 1796 seizures (1472 clinical seizures and 324 subclinical, i.e., electroencephalographic seizures) in 200 patients were analyzed.

The clinical and EEG SD of seizures as well as the duration of the convulsive phase of primary (i.e., nonfocal) and secondarily generalized tonic–clonic seizures (GTCSs) were independently determined by visual analysis of the onset and end of the seizures on video and EEG by three of the authors (JD, AJR, and GW). The overall interobserver agreement was excellent, with a kappa index of 1.0. Clinical SD was considered as the time between first clinical sign or patient report of aura (indicated by a "push button event") and clinical end of motor activity or end of behavioral changes. Electroencephalographic SD was defined as the time between the earliest sustained local or regional onset of ictal EEG pattern and the end of the ictal discharge. According to previous definitions, we designated the clinical onset of generalization of the primary or secondarily GTCSs with versive head or body movement or by vocalization [5]. The duration of the convulsive phase of primary or secondarily GTCSs was defined as the time between generalization onset and last clonic movement. In 59/1472 (4%) clinical seizures, we were unable to determine clinical end by abovementioned criteria. These seizures were excluded from further analysis of clinical parameters.

Sleep or awake states were determined during 30 s of the recording that preceded seizure onset.

2.3. Antiepileptic drugs

Withdrawal of AEDs during monitoring sessions was based on an individual clinical decision of the attending neurologist. In nearly all patients, except those with daily seizures, withdrawal of the AED started from the first day of the monitoring session. Blood samples for AED serum levels were obtained in the early morning hours (6 a.m. to 7 a.m.), i.e., before intake of the morning dose (which roughly corresponds to the trough levels). Values of drug levels on the day when epileptic seizures occurred were available in 61.7% (1109/1796) seizures in 158 patients (daily measurements started in January 2007). Most patients took two AEDs on the day when seizures were recorded (51.5%, 81/158), 20.7% (33/158) took three or more AEDs, and 27.8% (44/158) were on monotherapy.

2.4. Statistical analysis

We used nonparametric statistical methods, and except from convulsive phase of GTCSs, the data were not normally distributed. Descriptive statistics of clinical SD and EEG SD were presented as median and the convulsive phase of GTCSs as mean. For a direct comparison of clinical SD and EEG SD, values with both measures available were selected and evaluated with a two-tailed Wilcoxon signed-rank test. Median clinical SD and EEG SD per patient of different seizure types were calculated with the Kruskal–Wallis H test or the Mann–Whitney *U* test. Comparison of EEG SD between different seizure types in the group with invasive EEG recordings was not performed because of low statistical power. We used 99% cumulative clinical SD and EEG SD of most frequent seizure types recorded with surface EEG at the time when 99% of the recorded seizures ended spontaneously (focal simple seizures, focal complex seizures, secondarily GTCSs, and primary GTCSs). The EEG SD and AED serum levels were correlated using the Spearman correlation coefficient. To adjust for the unbalanced repeated measures

Please cite this article as: Dobesberger J, et al, Duration of focal complex, secondarily generalized tonic–clonic, and primarily generalized tonic–clonic seizures — A video-EEG analysis, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.03.023

(i.e., number of seizures per patient), we used a mixed linear regression model with EEG SD as dependent variable, which was logarithmized to obtain normality. Prior to mixed linear regression, we used one-way analysis of variance (ANOVA) to test for applicability of potential candidates as factors for the mixed linear regression model among clinically salient features such as gender, state of sleep or awake at the beginning of the seizure, presence of abnormal finding on MRI, temporal or frontal seizure onset, and left or right side of epilepsy on dependent variable logarithmical EEG SD. Variables showing statistically significant association were tested for potential interaction (ANOVA) subsequently. Because of nonsignificant differences between logarithmic EEG SD of left and right sides of seizure origin and EEG SD of the seizures of subjects with or without a positive history of febrile seizures, these variables were not included in the subsequent model. There were no significant correlations between continuous variables. Univariate analysis of variance did not show significant interactions between the variables. The Mann–Whitney *U* test was used to analyze the variable history of SE and FS on the dependent variable EEG SD.

Statistical analysis was performed with SPSS version 15.0 for Windows. The level of significance was set at alpha = 0.05. According to the Austrian law on retrospective research, this study did not require the approval of the ethics committee.

3. Results

3.1. Demographic data

We included 1796 uninterrupted seizure of 200 patients (822 seizures of 91 women; 45.5%), with mean age of 34.4 ± 12.9 years (range: 13–75) and mean disease duration of 17.4 ± 13 years (range: 0.1–50). Further demographic data are shown in Table 1.

3.2. Clinical and electroencephalographic seizure duration of different seizure types

Clinically identifiable ictal behavioral changes providing clinical SD were observed in 1416/1796 seizures; EEG SD could be identified in 1664/1796 seizures; and, in 1293/1796 seizures, both clinical SD and EEG SD were determined (Table 2).

Clinical SD and EEG SD of different seizures types recorded by surface or intracranial electrodes are presented in Table 3. The duration of intracranial EEG was significantly longer in subclinical seizures, focal complex seizures, and secondarily GTCSs but not in focal simple seizures (Table 3).

Table 2
Available data of clinical and electroencephalographic seizure duration according to seizure type are revealed.

Clinical and electroencephalographic seizure duration		
Seizure type	Clinical SD	EEG SD
SC Sz.	–	289/289
FSSs	289/324	217/324
FCSs	707/752	734/752
SGTCs	157/157	157/157
PGTCSs	31/31	31/31
ASs	77/86	86/86
MSs	24/24	21/24
TSs	91/91	91/91
Astatic Sz.	3/3	3/3
TAAs	33/35	31/35
Atypical absences	4/4	4/4
Available data for SD	1416/1796	1664/1796

Abbreviations: EEG — electroencephalographic; FCSs — focal complex seizures; FSSs — focal simple seizures; MSs — myoclonic seizures; PGTCSs — primarily generalized tonic–clonic seizures; pts. — patients; SC — subclinical; SD — seizure duration; Sz./sz. — Seizure(s)/seizure(s); SGTCSs — secondarily generalized tonic–clonic seizures; TAAs — tonic automatic attacks; TSs — tonic seizures.

Clinical SD and EEG SD of focal simple seizures, focal complex seizures, secondarily GTCSs, and primary GTCSs are shown in Table 4. Cumulative (99%) clinical and EEG SD did not differ in focal simple seizures (11 min versus 10.5 min) and primary GTCSs (both 2 min and 40 s) but differed clearly in focal complex seizures (99% cumulative clinical SD: 7 min, EEG SD: 12 min, $P < 0.001$) and secondarily GTCSs (99% cumulative clinical SD: nearly 6 min, EEG SD: about 9 min, $P < 0.001$). The distribution of the EEG SD in focal complex seizures and the clinical duration of the convulsive phase of secondarily GTCSs are given in Fig. 1. The EEG SD of focal complex seizures follows an exponential distribution, whereas the duration of the convulsive phase of secondarily GTCSs has a normal Gaussian distribution.

3.3. Seizure duration in focal and generalized epilepsies recorded by surface electroencephalography

The clinical SD and the ictal EEG duration differed significantly in the 1293/1796 seizures, in which both values were available ($P < 0.001$). Therefore, for further analysis, we used EEG SD, expecting a more robust

Table 1
Demographic characteristics of patients analyzed (n = 200) are given.

		Number of patients (%)	Number of seizures (%)	Median of seizures (range)
Epileptic syndrome	Generalized	28 (14)	276 (15.3)	5 (1–37)
	Focal	172 (86)	1520 (84.7)	7 (1–48)
Epilepsy etiology	Undetermined	1 (0.5)	5 (0.3)	
	Idiopathic[a]	18 (9)	123 (6.8)	5 (1–23)
	Cryptogenic[a]	56 (28)	653 (36.4)	7 (1–48)
	Symptomatic[a]	125 (62.5)	1015 (56.5)	5 (1–43)
Brain MRI findings	Normal	71 (35.5)	735 (40.9)	7 (1–48)
	AHS	32 (16)	269 (15)	5 (1–43)
	FCD	17 (8.5)	131 (7.3)	4 (1–17)
	Other MCDs	14 (7)	83 (4.6)	4 (1–14)
	Tumors	6 (3)	93 (5.2)	6 (1–35)
	Vascular malformations	8 (4)	82 (4.6)	5.5 (1–33)
	Other vascular causes	5 (2.5)	31 (1.7)	6 (1–21)
	Dual pathologies	8 (4)	120 (6.7)	10 (1–34)
	Nonspecific gliosis	17 (8.5)[b]	118 (6.6)	5 (1–28)
	Other lesion types including atrophy and gliosis after encephalitis, brain trauma or postoperative	22 (11)	134 (7.5)	4 (1–26)

Abbreviations: AHS — ammons horn sclerosis; FCD — focal cortical dysplasia; MCDs — malformations of cortical development.
[a] Idiopathic/genetic, cryptogenic/unknown, or symptomatic/structural/metabolic.
[b] One patient with cryptogenic/unknown and 2 patients with idiopathic/genetic epilepsy had nonspecific gliosis estimated as unrelated to their epilepsy.

Please cite this article as: Dobesberger J, et al, Duration of focal complex, secondarily generalized tonic–clonic, and primarily generalized tonic–clonic seizures — A video-EEG analysis, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.03.023

Table 3
Median clinical and electroencephalographic seizure duration of different seizure types is given (in seconds).

Seizure duration in focal epilepsies			
Sz. type	Surface EEG SD (158 pts)	Intracranial EEG SD (12 pts)	Clinical SD (157 pts)[a–c]
SC Sz.[d]	36.5 (range: 8–147); 135 sz. in 37 pts. (median sz.: 2, range: 1–21)	75.5 (range: 10–257); 127 sz. in 10 pts. (median sz.: 12.5, range: 1–30)	
FSSs[d]	42 (range: 3.5–681); 180 sz. in 41 pts. (median sz.: 2, range: 1–41)	38.5 (range: 16–61); 32 sz. in 2 pts. (median sz.: 16, range: 11–21)	28 (range: 5–3805); 264 sz. in 55 pts. (median sz.: 3, range: 1–41)
FCSs[d]	61.5 (range: 12–1245); 657 sz. in 106 pts. (median sz.: 4, range: 1–42)	97 (range: 55–447); 66 sz. in 9 pts. (median sz.: 7, range: 1–14)	64 (range: 14–1620); 635 sz. in 106 pts. (median sz.: 3.5, range: 1–42)
SGTCSs	96.25 (range: 51–649); 152 sz. in 68 pts. (median sz.: 2, range: 1–10)	135 (range: 87.5–500); 5 sz. in 3 pts. (median sz.: 2, range: 1–2)	90.25 (range: 52–381); 152 sz. in 68 pts. (median sz.: 2, range: 1–10)
Sz. with available values/total number of Sz.	1124/1256	230/230	1051/1256

Seizure duration in generalized epilepsies according to etiology				
Sz. type	Surface EEG SD		Clinical SD	
	Idiopathic (18 pts.)	Symptomatic/cryptogenic (10 pts.)[c]	Idiopathic (18 pts.)	Symptomatic/cryptogenic (10 pts.)[c]
MSs	3 (range: 1–4.5); 16 sz. in 3 pts. (median sz.: 7, range: 1–8)	1 (range: 1–21.5); 5 sz. in 3 pts. (median sz.: 2, range: 1–2)	3 (range: 1–5); 16 sz. in 3 pts. (median sz.: 7, range: 1–8)	4 (range: 1–21.5); 8 sz. in 3 pts. (median sz.: 2, range: 1–2)
ASs	8.25 (range: 1.5–85); 86 sz. in 12 pts. (median sz.: 3.5, range: 1–23)		8.5 (range: 1.5–85); 77 sz. in 13 pts. (median sz.: 3, range: 1–22)	
TSs		14.5 (range: 5–35); 91 sz. in 5 pts. (median sz.: 13, range: 1–37)		16 (range: 4–35); 91 sz. in 6 pts. (median sz.: 21, range: 1–37)
PGTCSs	75.5 (range: 50–305); 21 sz. in 3 pts. (median sz.: 1, range: 1–2)	59.5 (range: 58–76); 10 sz. in 5 pts. (median sz.: 2, range: 1–5)	74 (range: 50–227.5); 21 sz. in 13 pts. (median sz.: 1, range: 1–3)	56.5 (range: 2–63); 10 sz. in 5 pts. (median sz.: 2, range: 1–3)
Sz. with available values/total number of Sz.	123/123	153/160	114/123	149/160

Values for clinical SD and EEG SD represent median of the median value per patient.
Abbreviations: EEG — electroencephalographic; FCSs — focal complex seizures; FSSs — focal simple seizures; MSs — myoclonic seizures; PGTCSs —primary generalized tonic–clonic seizures; pts. — patients; SC — subclinical; SD — seizure duration; Sz./sz. — Seizure(s)/seizure(s); SGTCSs — secondarily generalized tonic–clonic seizures; TAAs — tonic automatic attacks; TSs — tonic seizures.
[a] Data refer to the group recorded by surface EEG.
[b] Clinical SD values for 93 seizures recorded by intracranial EEG (22 FSSs, 67 FCSs, and 4 SGTCSs) and 9 seizures recorded by surface EEG in combination with foramen ovale electrodes (3 FSSs and 6 FCSs) are not shown; in a single patient recorded with foramen ovale electrodes, 32/34 seizures with EEG SD values were recorded (23/32 subclinical seizures), clinical SD values available in 9/34 seizures in the same patient.
[c] For better representation EEG SD values for 4 SC seizures in 2 pts.; 5 FCSs in 1 patient, 3 astatic seizures in 3 pts.; 4 atypical absences in 1 patient; 31 TAAs in 3 pts. (all in symptomatic group) are not showed in the table. Clinical SD values for 3 astatic seizures in 3 pts., 4 atypical absences in 1 patient, and 33 TAAs in 3 pts. (all in the symptomatic group) were left out from the table.
[d] EEG SD values for 23 SC seizures, 5 FSSs, and 6 FCSs recorded by surface EEG in combination with foramen ovale electrodes are not shown.

value of interrater reliability compared with ictal clinical behavioral changes, which may show a more gradual start and end.

The duration of the ictal EEG differed according to the seizure types in focal epilepsies (chi-square: 68.523; df: 3; $P < 0.001$; results are presented in Table 3). Focal simple seizures were shorter compared with focal complex seizures (U: 1777.5; $P = 0.007$) and secondarily GTCSs (U: 1998.5; $P < 0.001$). Focal complex seizures were also shorter compared with secondarily GTCSs (U: 629.0; $P < 0.001$). Subclinical seizures and focal complex seizures had different EEG SD when recorded by surface or intracranial EEG (U: 249.0; $P = 0.018$) (U: 101.5; $P = 0.028$) but not secondarily GTCSs. Tonic seizures were the shortest of all seizure types; they were shorter compared with subclinical seizures (U: 46.5; $P = 0.009$). The total duration of primary GTCSs was shorter than the duration of secondarily GTCSs (U: 306.5; $P = 0.001$). However, there was no difference (U: 2268; $P = 0.55$) between the convulsive phase of primary GTCSs (65.1 ± 18.9 s; range: 20–110) and that of secondarily GTCSs (64.8 ± 16.3 s; range: 15–140).

3.4. Clinical features and independent predictors of electroencephalographic seizure duration in focal epilepsies recorded by surface electroencephalography

In a mixed linear regression model with age and duration of disease as covariates and gender, state of sleep or awake at seizure onset, lobar localization of seizure-onset zone, and MRI lesion as predictors, we found history of status epilepticus ($F = 4.576$; $P = 0.034$), temporal lobe of seizure onset ($F = 4.271$; $P = 0.040$), and MRI lesions ($F = 6.265$; $P = 0.013$) to be associated with the logarithmic EEG SD in focal seizures (Table 5). The same analysis applied in the subgroup of focal complex seizures demonstrated that gender ($F = 4.983$; $P = 0.027$), lobe of seizure onset ($F = 21.208$; $P < 0.001$), and MRI lesions ($F = 9.088$; $P = 0.003$) were predictors of logarithmic EEG SD. However, in the subgroup of secondarily GTCSs, only history of status epilepticus ($F = 10.652$; $P = 0.002$) and MRI findings ($F = 5.266$; $P = 0.026$) showed significant relations to logarithmic EEG SD when tested in a mixed linear model.

Table 4
99% cumulative electroencephalographic and clinical seizure duration values for most frequent seizure types recorded with surface EEG are shown.

Seizure type	FSSs	FCSs	SGTCSs	PGTCSs
99% cumulative EEG SD	623 s (10 min, 23 s)	712 (11 min, 52 s)	556 s (9 min, 16 s)	160 s (2 min, 40 s)
Number of seizures (EEG SD in seconds) above the 99% limit	2 (634, 681)	7 (805, 810, 939, 1245, 1366, 1877, 3640)	2 (695, 742)	1 (435)
99% cumulative clinical SD	656 (10 min, 56 s)	407 (6 min, 57 s)	347 (5 min, 47 s)	160 s (2 min, 40 s)
Number of seizures (clinical SD in seconds) above the 99% limit	3 (699, 904, 3807)	7 (428, 492, 619, 637, 1237, 1620, 1795)	2 (381, 686)	1 (435)

Abbreviations: EEG — electroencephalographic/electroencephalography; FCSs — focal complex seizures; FSSs — focal simple seizures; min — minutes; PGTCs — primary generalized tonic–clonic seizures; s — seconds; SD — seizure duration; SGTCs — secondarily generalized tonic–clonic seizures.

Please cite this article as: Dobesberger J, et al, Duration of focal complex, secondarily generalized tonic–clonic, and primarily generalized tonic–clonic seizures — A video-EEG analysis, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.03.023

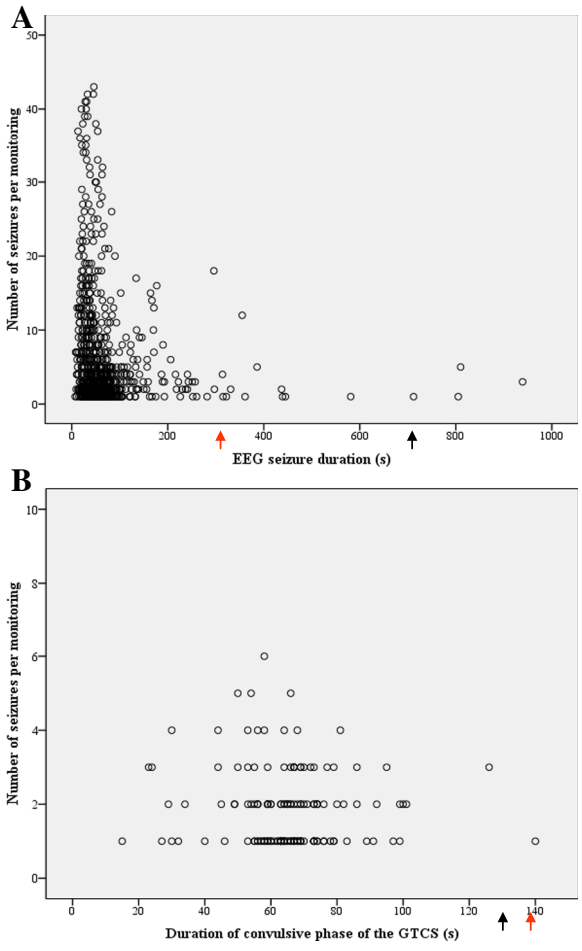

Fig. 1. A) Distribution of electroencephalographic seizure duration of focal complex seizures (4 seizures that last longer than 1000 s were left out of the graph); black arrow represents cumulative 99% of duration of focal complex seizures; red arrow represents median for EEG seizure duration of focal complex seizures. B) Distribution of the duration of the convulsive phase of secondarily generalized tonic–clonic seizures; black arrow represents mean duration ± 4 SD (130 s); red arrow represents mean for duration of empirically interrupted convulsive seizures (decision by treating physician in the monitoring unit).

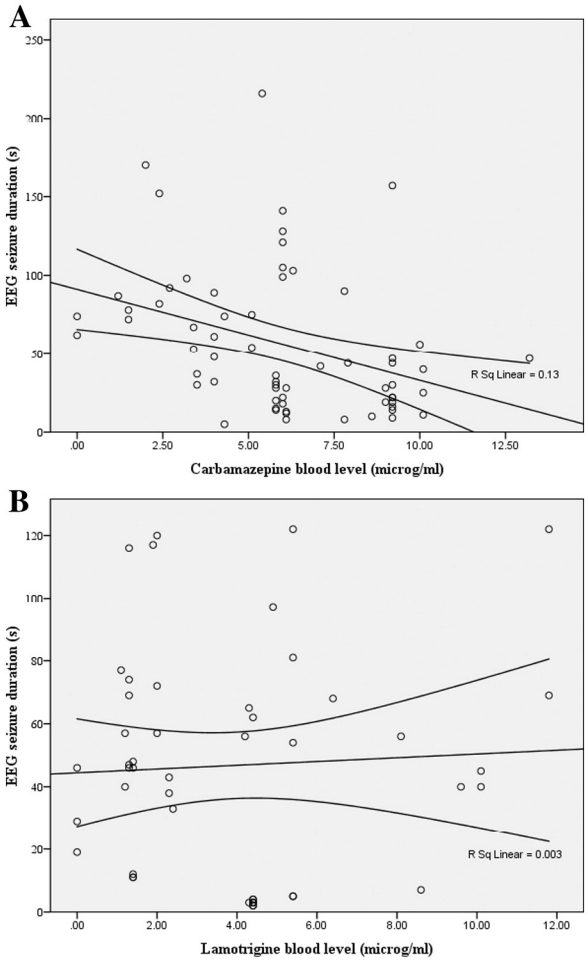

Fig. 2. Scatterplot of patients with monotherapy. A) Significant negative correlation between electroencephalographic seizure duration and corresponding blood levels of carbamazepine and B) absence of correlation between electroencephalographic seizure duration and corresponding blood levels of lamotrigine.

Table 5
Medians and statistical analysis of potential candidates for predictors of electroencephalographic seizure duration in patients with focal epilepsies recorded by surface electroencephalography are stated.

Variable y	Groups (number of seizures)	Median (s)	*F* value (df)/U	*P*
Gender	Male (594)	49	4.400 (1–1126)	0.034
	Female (534)	62.5		
History of FS	No (1028)	55	2654	0.331
	Yes (56)	68.5		
History of SE	No (1025)	53	2316	<0.001
	Yes (75)	91		
Sleep vs. awake	Sleep (592)	47	33.887 (1–1126)	<0.001
	Awake (536)	65		
Lobe of seizure onset	Frontal (295)	38	38.956 (1–942)	<0.001
	Temporal (469)	62		
Normal vs. lesional MRI	Normal (392)	41.5	34.743 (1–1126)	<0.001
	Lesional (736)	63		
Epilepsy side	Left (452)	59	1.416 (1–989)	0.234
	Right (539)	50		

Abbreviations: EEG — electroencephalographic; FSs — febrile seizures; *P* — *P*-value; s — seconds; SE — status epilepticus; vs. — versus.

3.5. Correlations of the serum level of antiepileptic drugs and electroencephalographic seizure duration

Patients on monotherapy in whom serum AED levels were measured on the day of the index seizure (n = 44 patients) were used for this analysis. There was a negative correlation between the AED serum level and the EEG SD with carbamazepine (63 seizures in 13/44 patients; $r = -0.433$; $P < 0.001$), levetiracetam (37 seizures in 12/44 patients; $r = -0.567$; $P = 0.001$), oxcarbazepine (27 seizures in 5/44 patients; $r = -0.603$; $P = 0.001$), and valproic acid (23 seizures in 6/44 patients; $r = -0.353$; $P = 0.038$) but not with lamotrigine (41 seizures in 8/44 patients; $r = -0.063$; $P = 0.670$) (Fig. 2). There were significant negative correlations between EEG SD of 192 seizures with serum levels of carbamazepine ($r = -0.377$; $P < 0.001$) and levetiracetam ($r = -0.554$; $P < 0.001$) in 29 patients treated with dual therapy of these two drugs.

4. Discussion

This study assessed the clinical and EEG SD in a large group of consecutive patients undergoing video-EEG monitoring and defined an upper limit of what is a prolonged seizure, which could aid in developing a new definition of status epilepticus. The mean (+4 SD) clinical SD of GTCSs was 130 s. The 99% cumulative duration of focal complex

Please cite this article as: Dobesberger J, et al, Duration of focal complex, secondarily generalized tonic–clonic, and primarily generalized tonic–clonic seizures — A video-EEG analysis, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.03.023

seizures was 11 min and 52 s. Predictors of longer SD were history of status epilepticus, lobe of seizure onset, and a lesional MRI. Decreasing serum levels of carbamazepine, levetiracetam, and valproate correlated with an increase in EEG SD.

4.1. Comparison of seizure duration between seizure types

Secondarily GTCSs lasted significantly longer compared with primary GTCSs and focal complex seizures, and the latter lasted significantly longer compared with focal simple seizures. This confirmed previous findings in terms of overall SD per seizure type [4]. However, previous studies did not further delineate the seizure-onset zone. In our patients, temporal seizure onset was associated with a significant longer SD.

Furthermore, we also included invasively recorded seizures in our analysis. The median values of EEG SD were longer in intracranial EEG than in surface EEG recordings. This is concordant with the results of an earlier study on 53 invasively recorded patients [6], which compared median duration of focal complex seizures with mesial or neocortical temporal origin to neocortical extratemporal origin but did not compare the findings with noninvasively recorded seizures.

4.2. Seizure duration and impact on treatment

Up to now, there have been two studies analyzing the duration of secondarily GTCSs (Jenssen et al.: 70 seizures in 34 patients; Theodore et al.: 120 seizures in 47 patients) during AED withdrawal. The duration of the convulsive phase in GTCSs recorded with surface electrodes provided in previous studies (median: 74 s; mean: 62 s) is similar to our results [4,5]. Furthermore, our data confirm previous findings that the duration of the convulsive phase of primary and secondarily GTCSs is not significantly different [4]. There are only 2 seizures in our study (126 s and 140 s) and none in previously published studies that are out of this limit, reflecting a chance of error of 0.6%. We suggest this time limit of 2 min of convulsive activity, after which intravenous treatment in video-EEG monitoring units should be considered.

Estimating a cutoff value for the focal seizures without secondary generalization, which shows a skewed distribution, is more difficult. We applied the 99% cumulative EEG SD and clinical SD to better define the time frame that determines a therapeutic decision. According to these data, only 1% of patients present with ongoing seizure activity beyond the 99% cumulative EEG SD and which eventually ended spontaneously. Two seizures of the 2 patients in this group of self-limiting prolonged focal complex seizures lasted 1 h or 30 min of EEG and clinical SD. Therefore, we suggest a 99% cumulative clinical SD as a cutoff value for a prolonged seizure and operational definition of status epilepticus. This would mean that focal complex seizures lasting longer than 7 min and focal simple seizures lasting longer than 11 min should be considered as prolonged, and treatment should be started in order to prevent established status epilepticus. Because of the large intergroup variability and the selected patient group (only patients with drug-resistant epilepsy undergoing video-EEG with AED withdrawal were included), the interpretation of these data must be considered with caution.

4.3. Predictors of seizure duration

Mixed linear model of regression analysis showed that history of status epilepticus, temporal seizure onset, and lesional MRI findings are significantly associated with a longer SD. Separate analysis according to seizure types further revealed that history of status epilepticus was also a significant predictor for longer SD in secondarily GTCSs. A lesional MRI was a predictor for longer SD in both complex partial seizures and secondarily GTCSs in our study. A temporal seizure onset was associated with a longer SD in the whole group as well as the subgroup with focal complex seizures. Our results suggest that ictal EEG discharges of focal complex seizures seem to remain regional for a longer time in temporal lobe epilepsies than in frontal lobe epilepsies. This is also supported by invasive EEG studies in focal seizures of different origin [6]. Another predictor for longer EEG SD in focal complex seizures was female sex. Hormonal influence during anovulatory and ovulatory cycles on the frequency of focal complex seizures in female patients who had temporal lobe epilepsy was already demonstrated in a prospective study [11].

4.4. Impact of withdrawal of antiepileptic drugs on seizure duration

It is well recognized that withdrawal of AEDs may lead to an increase in seizure frequency, but only a few studies have investigated the seizure duration during withdrawal. A previous study found only a nonsignificant trend toward a longer duration of the last focal complex seizure in a monitoring session compared with the first seizure but did not correlate the SD with the serum AED levels [4]. Our data suggest an effect of decreasing serum levels of AEDs (levetiracetam, oxcarbazepine, and valproic acid) on SD. Lamotrigine is the only AED that showed no correlation to SD. However, this could be due to different mechanisms of action not directly related to serum drug levels.

5. Conclusions

Based on the results of this study, we propose definitions of prolonged seizure duration, heralding impending status epilepticus, which could help in determining the point of time for medical intervention: 2 min of convulsive seizure activity (focal onset or generalized onset), 7 min in focal complex seizures, and 11 min in focal simple seizures. History of status epilepticus, temporal seizure onset, and lesional MRI findings were associated with a prolonged SD. We also found longer SD during rapid withdrawal of AEDs in the monitoring unit.

The results of our study might be limited by the fact that it was performed mainly in patients with drug-resistant epilepsies undergoing presurgical evaluation. Whether these findings can also be applied to patients with nonrefractory epilepsies remains to be shown.

Conflicts of interest

Judith Dobesberger has received honoraria from UCB Pharma, Gerot-Lanach, Eisai, and GlaxoSmithKline.

Aleksandar J. Ristić received honoraria from UCB Pharma and GlaxoSmithKline.

Gerald Walser has no conflicts of interest.

Giorgi Kuchukhidze has no conflicts of interest.

Iris Unterberger has received advisory board/speaker honoraria from UCB Pharma, Eisai, GlaxoSmithKline, and GL Lannacher.

Julia Höfler received speaker honoraria from UCB Pharma and travel support from Eisai and UCB Pharma.

Edda Amann has no conflicts of interest.

Eugen Trinka has acted as a paid consultant to Eisai, Ever Neuropharma, Biogen Idec, Medtronics, Bial, and UCB and has received speaker honoraria from Bial, Eisai, GL Lannacher, GlaxoSmithKline, Boehringer, Viropharma, Actavis, and UCB Pharma. He has received research funding from UCB Pharma, Biogen Idec, Red Bull, Merck, the European Union, FWF (Österreichischer Fond zur Wissenschaftsförderung), and Bundesministerium für Wissenschaft und Forschung.

References

[1] Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46:470–2.

[2] Wasterlain CG, Treiman DM, editors. Status epilepticus: mechanisms and management. Boston: MIT Press; 2006.

Please cite this article as: Dobesberger J, et al, Duration of focal complex, secondarily generalized tonic–clonic, and primarily generalized tonic–clonic seizures — A video-EEG analysis, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.03.023

[3] Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999;40:120–2.
[4] Jenssen S, Gracely JE, Sperling MR. How long do most seizures last? A systematic comparison of seizures recorded in the epilepsy monitoring unit. Epilepsia 2006; 47:1499–503.
[5] Theodore WH, Porter RJ, Albert P, Kelley K, Bromfield E, Devinsky O, et al. The secondary generalized tonic–clonic seizures: a videotape analysis. Neurology 1994; 44:1403–7.
[6] Afra P, Jouny CC, Bergey GK. Duration of complex partial seizures: an intracranial EEG study. Epilepsia 2008;49:677–84.
[7] Dobesberger J, Walser G, Unterberger I, Seppi K, Kuchukhidze G, Larch J, et al. Video-EEG monitoring: safety and adverse events in 507 consecutive patients. Epilepsia 2011;52:443–52.
[8] DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46:1029–35.
[9] Knake S, Rosenow F, Vescovi M, Oertel WH, Mueller HH, Wirbatz A, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 2001;42:714–8.
[10] Commission of Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489–501.
[11] Bauer J, Burr W, Elger CE. Seizure occurrence during ovulatory and anovulatory cycles in patients with temporal lobe epilepsy: a prospective study. Eur J Neurol 1998;5:83–8.

Please cite this article as: Dobesberger J, et al, Duration of focal complex, secondarily generalized tonic–clonic, and primarily generalized tonic–clonic seizures — A video-EEG analysis, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.03.023