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

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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*

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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