Epilepsy

Accuracy of Patient Seizure Counts

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Objective: To evaluate the effects of a daily patient reminder on seizure documentation accuracy.

Design: Randomized controlled trial.

Setting: Monitoring unit of an academic department of epileptology.

Patients: Consecutive sample of 91 adult inpatients with focal epilepsies undergoing video-electroencephalographic monitoring.

Intervention: While all patients were asked to document seizures at the beginning of the monitoring period, patients from the experimental group were reminded each day to document seizures.

Main Outcome Measure: Documentation accuracy (percentage of documented seizures).

Results: A total of 582 partial seizures were recorded. Patients failed to document 55.5% of all recorded seizures, 73.2% of complex partial seizures, 26.2% of simple partial seizures, 41.7% of secondarily generalized tonic-clonic seizures, 85.8% of all seizures during sleeping, and 32.0% of all seizures during the awake state. The group medians of individual documentation accuracies for overall seizures, simple partial seizures, complex partial seizures, and secondarily generalized tonic-clonic seizures were 33.3%, 66.7%, 0%, and 83.3%, respectively. Neither the patient reminder nor cognitive performance affected documentation accuracy. A left-sided electroencephalographic focus or lesion, but not the site (frontal or temporal), contributed to documentation failure.

Conclusions: Patient seizure counts do not provide valid information. Documentation failures result from postictal seizure unawareness, which cannot be avoided by reminders. Unchanged documentation accuracy is a prerequisite for the use of patient seizure counts in clinical trials and has to be demonstrated in a subsample of patients undergoing electroencephalographic monitoring.

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SEIZURES ARE THE MAIN SYMPTOM of epilepsy and the major target of its treatment. Accordingly, seizure frequency is the primary outcome measure for individual treatment and for clinical trials. Epileptic seizures can be detected objectively by video-electroencephalographic (EEG) monitoring according to international classifications.[1] However, because of the high costs, video-based telemetry is only applied in a few patients for a limited period. The adequacy of ambulatory EEG recording is under debate.[2-5] According to the present criterion standard, patients are asked to maintain seizure diaries. Thus, modern epileptology, to a large extent, depends on the assumption that patient seizure data provide reliable and valid information. Two studies[6,7] confirmed the reliability of patient seizure memory. However, seizure counts are no subjective measure and have to be compared with objective data as derived from EEG monitoring. Former studies[8-11] revealed that most patients fail to document about half of their seizures.

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This study aims at an analysis of the impact of seizure type, vigilance state, side and site of lesion or EEG focus, antiepileptic medication, and cognitive performance on patient seizure documentation failure. Furthermore, to evaluate the role of postictal seizure unawareness vs subsequent documentation failure (eg, because of carelessness), we conducted a randomized controlled trial to test the effects of a daily reminder to document seizures.

METHODS

STUDY DESIGN

This was a prospective study with a consecutive sample of adult inpatients in a video-EEG monitoring unit at an academic department of

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Table 1. Characteristics of the 91 Patients

Characteristic	Value[a]
Male to female ratio	52:39
Age, mean±SD, y	39.5±12.3
RCT "reminder," yes to no ratio	42:49
Monitoring period, mean±SD, d	4.5±3.0
Break during monitoring[b]	4
Presurgical workup	71
Intracranial EEG	20
Former epilepsy surgery	6
TLE to FLE ratio	49:25
Lesion or MRI	55
Hippocampal sclerosis	25
EEG focus or lesion, left to right ratio	39:20
AED (0/1/2/3/4/5)[c]	8/24/28/24/6/1
AED withdrawn during monitoring (0/1/2/3)[c]	50/27/10/4
Low intelligence level (IQ<85)[d]	13
School education, ordinary to advanced level ratio	45:46
Self-reported seizure awareness, median, %	80

Abbreviations: AED, antiepileptic drug; EEG, electroencephalography; FLE, frontal lobe epilepsy; MRI, magnetic resonance imaging; RCT, randomized controlled trial; TLE, temporal lobe epilepsy.
[a] Data are given as number of patients unless otherwise indicated.
[b] Break for 2, 4, 12, and 110 days.
[c] Numbers in parentheses indicate the number of AEDs. Numbers in the right column indicate the number of patients taking the respective number of AEDs.
[d] Intelligence tests were administered in 64 patients.

epileptology (single units). A nonblind, randomized controlled trial on the effects of daily reminding patients to document seizures was embedded. The random allocation to the experimental groups (reminder yes vs no) was done weekly (odd or even calendar weeks).

PATIENTS

All patients referred to the monitoring unit from October 1, 2004, to July 31, 2005, were considered to participate in the study. The inclusion criteria were adult age, diagnosis of epilepsy, recording of at least 1 epileptic seizure during the monitoring period, and written informed consent according to the Declaration of Helsinki. Exclusion criteria were history or recording of pseudoseizures and long-lasting subclinical seizure patterns and generalized epilepsy. The study was restricted to epileptic seizures to exclude unpredictable effects of unclassifiable or psychogenic seizures on seizure documentation.

VIDEO-EEG MONITORING

The EEG examination took place with adhesive electrodes (10-20 system), with additional temporal electrodes. Patients were under permanent video monitoring and were asked to push a warning button to summon the nurse when they felt a seizure coming. In case of seizures, hospital staff came to assist the patient. Ictal and postictal testing of motor, verbal, and memory function was performed.

INSTRUCTIONS AND MEASURES

At the beginning of the monitoring period, all patients were asked to estimate their level of seizure awareness (rating scale: 0% indicates "unaware of all seizures"; and 100%, "recognize all seizures"). All patients received a seizure diary and were asked to carefully document every seizure event. Only the patients from the "reminder" group were reminded every morning to document all seizures during the monitoring period. The number of objective seizures was determined by analysis of the video-EEG monitoring files. Seizure types (simple partial seizures [SPS], complex partial seizures [CPS], secondarily generalized tonic-clonic seizures [sGTCS], and pseudoseizures) and preictal vigilance states (wakefulness or sleep) were classified by an experienced senior neurologist (A.P.) according to international classifications.[1,12] To adjust for the varying duration of the monitoring periods, individual seizure frequencies per month were calculated from patient seizure counts and video-EEG data. Seizure documentation accuracy was defined as the percentage of patient-documented seizures. Patients were classified as "perfect documenters" in cases of a 100% rate of documented seizures. Only patients who experienced a respective seizure event were included in group analyses on documentation accuracies for different seizure types and vigilance states. Comprehensive neuropsychological profiles and intelligence-level estimates were available for two-thirds of the patients.[13]

STATISTICAL ANALYSIS

Normal distribution was tested by the Kolmogorov-Smirnov goodness-of-fit test. Nonparametric statistical testing was applied when required (Mann-Whitney test, Wilcoxon signed rank test, χ^2 test, or Spearman rank correlation). Analysis of variance was applied to explore data for possible interaction effects. All statistical analyses were performed using a commercially available software program (SPSS 12.0G for Windows; SPSS Inc, Chicago, Illinois).

RESULTS

All eligible patients agreed to participate in the study. **Table 1** shows the patient characteristics.

Table 2 shows the patient seizure documentation statistics by different seizure types and vigilance states. Of 582 classifiable seizures, 323 were not documented by the patients. The documentation rate clearly depended on preictal vigilance state and seizure type. Seizures occurring during sleep were not documented in 85.8% of all cases in contrast to 32.0% of undocumented seizures in the awake state. The documentation rate for CPS was clearly less than that for SPS, resulting in a different frequency distribution of seizure types depending on how seizures were documented (video-EEG: CPS, 59.6%; SPS, 32.1%; and sGTCS, 8.2%; and patient counts: SPS, 53.3%; CPS, 35.9%; and sGTCS, 10.8%). Of the seizures, 43.6% actually occurred from sleep, while the patient data suggested a far lower portion of 13.9%. Seizure frequencies per month, as projected from the monitoring period, differed significantly depending on whether they were calculated from patient or video-EEG data. Patients activated the push-button alarm ahead of 51 seizures (8.8%) but failed to document 17 (33.3%) of these seizures.

The group medians of the individual documentation accuracies are shown in **Table 3** (nonnormal distribution Kolmogorov-Smirnov goodness-of-fit test, $P<.01$ for all measures).

More than half of the patients failed to document any CPS (51%), any seizure during sleep (66%), any CPS during sleep (73%), and any SPS during sleep (75%). The rate of perfect documenters is given in Table 3. Perfect documenters experienced more SPS (4.0 vs 0.8; $P=.03$,

Table 2. Documentation Quality: Seizure Level

Type of Seizure	Total No. of Seizures (Video-EEG)	No. (%) Undocumented by Patient	SFPM[a]		*P* Value[b]
			Video-EEG	Patient	
Total	**582**	**323** (55.5)	28.4	7.1	<.001
Awake state	328	105 (32.0)	18.9	8.0	<.001
Sleep	254	218 (85.8)	22.4	0	<.05
SPS	**187**	**49** (26.2)	16.6	4.2	<.001
Awake state	150	17 (11.3)	14.1	6.7	<.01
Sleep	37	32 (86.5)	19.9	0	<.01
CPS	**347**	**254** (73.2)	22.0	0	<.001
Awake state	150	79 (52.7)	15.9	6.5	<.001
Sleep	197	175 (88.8)	16.8	0	<.001
sGTCS	**48**	**20** (41.7)	10.4	6.3	<.01
Awake state	28	9 (32.1)	7.3	6.2	<.01
Sleep	20	11 (55.0)	9.4	4.0	<.05

Abbreviations: CPS, complex partial seizures; EEG, electroencephalography; SFPM, seizure frequency per month; sGTCS, secondarily generalized tonic-clonic seizures; SPS, simple partial seizures.
[a] Data are given as group medians. The SFPM was calculated as follows: SFPM = number of seizures/duration of monitoring (in days) × 30 (days). Only patients with the respective video-EEG seizure events were included (the varying sample sizes are given in Table 3).
[b] Wilcoxon signed rank tests.

Mann-Whitney tests), fewer CPS (1.0 vs 5.6; $P<.001$), and fewer seizures during sleep (0.7 vs 4.1; $P<.001$). The patient self-reported seizure awareness was weakly correlated with the percentage of documented CPS (Spearman rank correlation, $r=0.28$, $P=.02$ [n=71]) and, in a nonsignificant trend, with the overall documentation accuracy ($r=0.20$, $P=.06$). Only 11 of 36 patients who self-reported to be perfectly aware of their seizures actually were perfect documenters.

The embedded randomized controlled trial on the effect of a daily reminder failed to reveal group differences in documentation accuracy measures. However, a near-significant difference regarding the group mean percentage of patient-documented SPS from the awake state (n=22), which was lower in the group of regularly reminded patients (reminder group, 49%; and no reminder group, 80%; $P=.07$, Mann-Whitney test), was revealed. In addition, reminding patients did not affect the rate of perfect documenters in either group ($P=.95$, χ^2 test). This finding indicates that reminding the patient to document seizures is unlikely to improve the documentation accuracy.

The seizure documentation accuracy was independent of the number of antiepileptic drugs (AEDs) at the beginning of the monitoring period and of the number of drugs withdrawn during monitoring. Patients with typical add-on drugs, such as lamotrigine (n=35), levetiracetam (n=37), or pregabalin (n=18), received more AEDs at the beginning of the monitoring period, but no other differences were identified (eg, overall seizure count). In patients receiving levetiracetam, but not lamotrigine or pregabalin, the number of CPS during the awake state was significantly increased (1.9 vs 1.4; $P=.048$, Mann-Whitney test). Furthermore, the percentage of documented overall CPS and CPS from the awake state was significantly higher in levetiracetam-treated patients than in patients receiving other medication (CPS, 47% vs 27% [$P=.04$]; CPS from the awake state, 60% vs 35% [$P=.048$]; Mann-Whitney tests), but documentation accuracy was unchanged in 4 patients with levetiracetam withdrawal during the monitoring period. Because levetiracetam was not experimentally controlled for, this finding may be because of a random sample effect. However, it may also indicate a differential impact of AEDs on seizure awareness (eg, by affecting seizure types or shifting seizures to other vigilance states).

Table 3. Documentation Quality: Patient Level

Type of Seizure	Patients[a]	No. (%) of Perfect Documenters	Undocumented Seizures per Patient, %[b]
Total	91	35 (38.5)	67
Awake state	71	28 (39.4)	33
Sleep	53	11 (20.8)	100
SPS	32	13 (40.6)	33
Awake state	23	11 (47.8)	0
Sleep	12	3 (25.0)	100
CPS	71	18 (25.4)	100
Awake state	50	19 (38.0)	50
Sleep	44	6 (13.6)	100
sGTCS	28	14 (50.0)	17
Awake state	22	13 (59.1)	0
Sleep	14	7 (50.0)	25

Abbreviations: See Table 2.
[a] Data are given as medians for the group of patients with respective seizure events.
[b] Data are given as group medians.

The accuracy of seizure documentation was not correlated with neuropsychological performance, including verbal or nonverbal memory, verbal fluency, and intelligence level, nor was it correlated with academic achievement. However, in a group comparison, perfect seizure documenters had better verbal memory performance (delayed free recall, group mean ± SD *t* score, 44 ± 9 vs 40 ± 10; $P=.04$, Mann-Whitney test) and higher school education (advanced level: 23 of 35 vs 23 of 56; $\chi^2_1=5.2$, $P=.02$) than did nonperfect documenters.

Table 4. Effects of Side and Site of EEG Focus or Lesion on Documentation Accuracy[a]

Type of Epilepsy	Side		Total
	Left	Right	
Temporal lobe	50 (49±43) [n=31]	100 (65±47) [n=14]	67 (54±45) [n=45]
Frontal lobe	0 (29±45) [n=8]	100 (73±44) [n=6]	35 (48±48) [n=14]
Total	33 (45±44) [n=39]	100 (67±45) [n=20]	57 (53±45) [n=59]

Abbreviation: EEG, electroencephalography.
[a]Data are given as group median, which provides documentation accuracy (group arithmetic mean±SD) [number of patients affected].

No effects of age, sex, or duration of epilepsy on overall documentation accuracy were obtained. However, the rate of documented sGTCS, but not of other types, was correlated with age at seizure onset ($r=0.47$, $P=.01$ [n=27]), indicating more accurate documentation in patients who were older at seizure onset.

Table 4 shows the data separately for patients with left- and right-sided frontal and temporal lobe epilepsy. No main effect of the site of lesion or EEG focus (temporal vs frontal) was obtained. The group mean documentation accuracy was slightly, but not significantly, lower in patients with left-sided than in patients with right-sided lesions or EEG focus (left vs right, 45% vs 67%; $P=.06$, Mann-Whitney test); this group difference was significant for seizures from sleeping (left vs right, 26% vs 71%; $P=.04$). Of 20 patients with right-sided temporal or frontal lobe epilepsy, 13 (65.0%) were perfect documenters, vs 13 of 39 patients (33.3%) with left-sided temporal or frontal lobe epilepsy ($\chi^2_1=5.4$, $P=.02$) (nonclassified data: $P=.06$, Mann-Whitney test). The effects of the factor site (temporal vs frontal lobe) and side (left vs right) on documentation accuracy were tested by an explorative 2-factorial analysis of variance that revealed a main effect for side but not for site and no interaction effect. No effect was obtained when the side of the epileptic focus was defined relatively to the speech-dominant hemisphere (Wada test, 15 patients; functional magnetic resonance imaging, 2 patients; results: 10 left sided, 5 bilateral, and 2 right dominant). This finding indicates a role of left hemisphere functional disturbance for seizure unawareness that may be more pronounced if the left frontal lobe is involved.

COMMENT

Former studies[8-10] and the findings of the present study give evidence that patient seizure counts do not reflect the objective seizure and risk burden. Only a few patients (38.5%) were able to document all seizures accurately, whereas most of the patients fail to document the major part of their seizures (total rate of undocumented seizures, 55%). The low documentation accuracy is unlikely to result from the specific conditions of video-EEG monitoring (eg, lying in bed)[8,14] because under ambulatory conditions quite similar findings were obtained.[11]

Underreporting may be a misleading term because it implies that patients could have reported the correct figures if they had put more effort into it. However, the embedded randomized controlled trial on the effects of a patient reminder could not reveal any evidence that urging patients to document and supporting their memory increases documentation accuracy. No effect of cognitive performance on documentation accuracy was obtained. Finally, former studies[6,7] already demonstrated the reliability of patient seizure memory. Thus, it is unlikely that patients are careless or forget to document. Underreporting is, rather, caused by processes that are out of the patient's control. For example, seizures occurring during sleeping (85.8%) and CPS (73.2%) are at the highest risk of not being documented. Seizure-induced seizure unawareness is a frequent, but rather unrecognized, postictal symptom particularly associated with seizures from sleeping and with CPS.

The mechanisms underlying seizure unawareness are not yet clear. In our sample, besides the vigilance state and the seizure type, the left-sided focus or lesion, but not the site, of the epileptic focus or lesion (temporal or frontal lobe) contributed moderately to seizure unawareness, which is in accord with former studies.[9,10] In contrast to the study by Blum et al,[8] sGTCS were recognized and documented even more often than CPS. From neurocognitive studies[15,16] of the ictal state and from the definition of CPS, including impaired consciousness, it is clear that the patient is dependent on unambiguous postictal bodily signs (eg, muscle pain, tongue bite, or enuresis), environmental changes (eg, broken glass), or social reactions (eg, caring proxies) to become aware that a seizure had occurred.

Our study revealed a possible interaction of seizure awareness with anticonvulsant medication, such that patients receiving levetiracetam had better documentation accuracy than did patients receiving another AED. This explorative finding may result from a random sample effect but may also indicate specific effects of AEDs on seizure awareness and documentation accuracy. However, true seizure efficacy can be calculated from patient data only under the assumption that documentation accuracy is unaffected by the treatment.

This study was restricted to adult patients with partial seizures. Findings and conclusions may not be applicable to patients with primarily generalized seizures or to pediatric patients under all-day observation. Furthermore, most of our patients underwent video-EEG monitoring for presurgical workup, which may also have biased the pattern of results.

In conclusion, patient seizure counts are not valid and reports of complete seizure freedom may need objective evaluation (eg, regarding a driver's license).

Seizure underreporting is a consequence of postictal seizure unawareness, rather than of careless documentation. Reminding the patient to document seizures will, therefore, not improve documentation accuracy. For premarket evaluation of new treatments for partial seizures (drugs and devices), additional EEG-based seizure data are required. An unambiguous demonstration of unchanged seizure awareness (documentation accuracy) under the new treatment based on EEG monitoring is a prerequisite of calculating valid seizure frequency reduction (percentage) from (invalid) patient seizure counts. Alternative designs for clinical trials, including video-EEG monitoring, have been proposed by Bien and Elger.[17]

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