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Latencies to first interictal epileptiform discharges in different seizure types during video-EEG monitoring

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ABSTRACT

Purpose: Interictal epileptiform discharges (IEDs) have high diagnostic value concerning patients with epilepsy and the instances of obtaining IEDs increase with longer recording times. However, the merit of a single, extended electroencephalography (EEG) recording in detecting IEDs has not been substantiated. We aimed to determine the optimal duration of an EEG required to diagnose epilepsy in different seizure types.

Methods: Overall, 84 patients—29 with generalised onset epilepsy and 55 with focal onset epilepsy—were evaluated. Long-term video electroencephalographic monitoring (VEM) was analysed to find the first definite IED besides assessing the first seizure and latency.

Results: The median latency of the first IED (12 min, ranging from 1 to 440 min vs. 55 min, ranging from 2 to 7500 min; $p = 0.014$) and the median duration of a VEM recording (2 d, ranging from 1 to 10 d vs. 3 d, ranging from 1 to 10 d; $p = 0.012$) were found significantly lower in the generalised epilepsy group compared with that in the focal epilepsy group.

Conclusions: Generalised onset epilepsy showed a significantly shorter latency to IED and VEM duration compared with focal onset epilepsy. In our data set, all the patients with generalised onset epilepsy had interictal IED within 10 h, but the patients with focal onset epilepsy required monitoring for three days to obtain IED.

1. Introduction

Electroencephalography (EEG) is the gold standard electrophysiological test that is routinely used for presurgical evaluation and differential diagnosis and prognosis of epilepsy [1]. However, it is a dynamic test and specific EEG abnormalities, such as interictal spike waves, sharp waves, which can be combined as interictal epileptiform discharges (IEDs), may not be obtained initially because only 29%–56% of patients with epilepsy have IED during the initial recording [1,2]. Therefore, an EEG needs to be repeated to obtain diagnostic data because the detection of IED can increase to 92% by the fourth EEG recording [2]. However, the significance of using a long-term EEG recording to detect IED is not well known [3]. Notably, video electroencephalographic monitoring (VEM) is the ultimate tool for the differential diagnosis of epilepsy and other paroxysmal events, such as psychogenic nonepileptic seizures (PNES) [4]. Approximately 26% of patients referred with epilepsy are misdiagnosed with epilepsy because of incomplete history-taking and EEG misinterpretation [5]. Notably, the high diagnostic value of VEM in patients with epilepsy has been confirmed [6,7].

However, the use of long-term inpatient VEM is limited because of the cost, duration, the need for trained personnel and a significant amount of equipment required [1]. Several studies investigated the required duration of VEM in terms of efficacy and the ability to obtain the necessary data [1,4,6,8,9]. Additionally, studies investigated latency to the first IED to predict the recording duration required for an optimal diagnostic yield [3,10,11]. However, some of these studies focused only on the generalised seizure type and others did not record the time of the first IED or only evaluated outpatient recordings [3,11,12]. Only a few studies have made comparisons between different

Abbreviations: EEG, electroencephalography; VEM, video-EEG monitoring; IED, interictal epileptiform discharge; AED, antiepileptic drug; ILAE, International league against epilepsy; SPSS, statistical Package for the Social Sciences; MRI, magnetic resonance imaging

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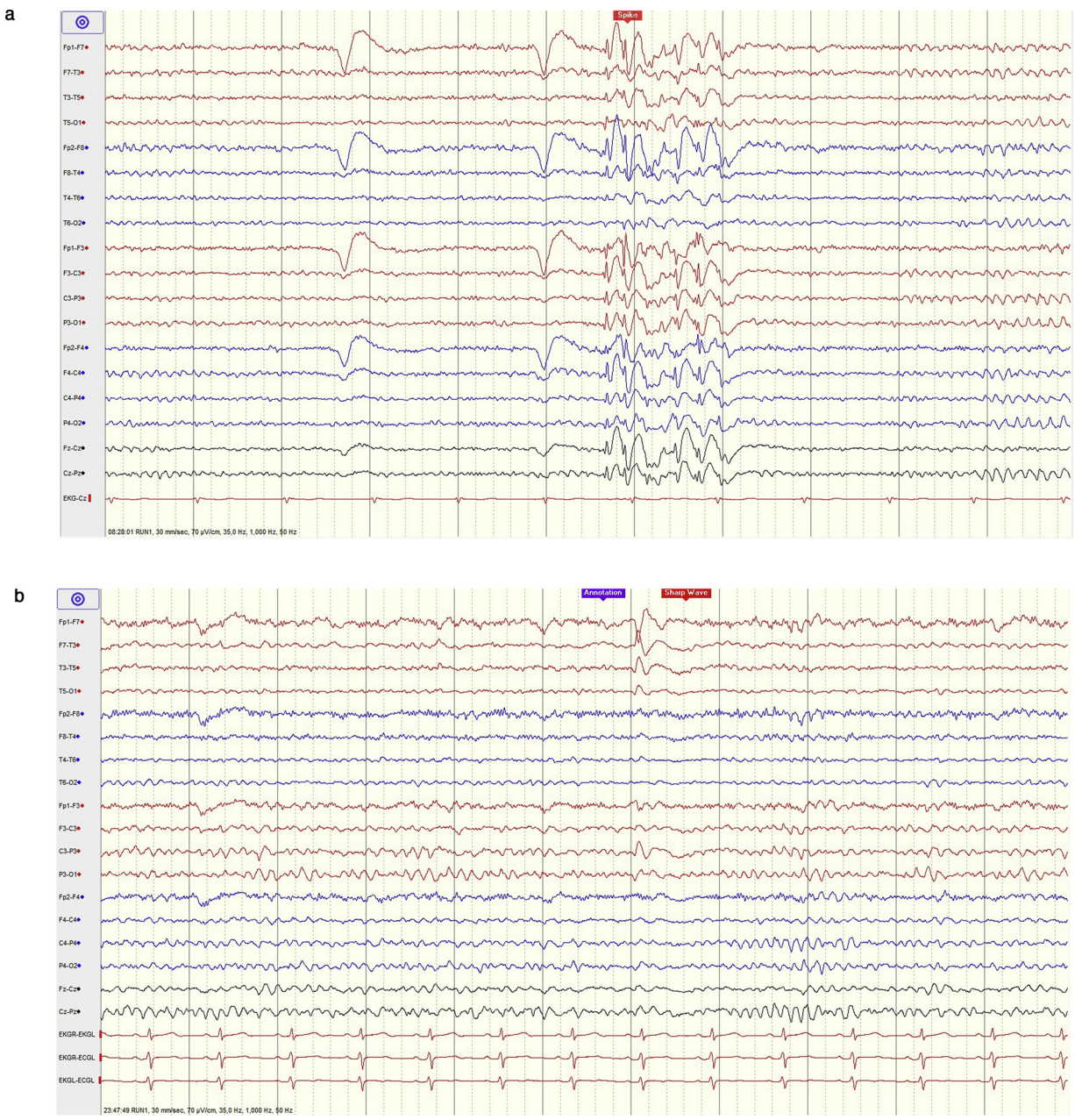

Fig. 1. Initial interictal epileptiform discharge observed after 15 min of recording in patient with generalised epilepsy (a) and after 867 min of recording in patient with focal epilepsy (b).

seizure types regarding latency to first IED [1,10].

We endeavoured to predict the optimal duration of VEM required for making the diagnosis in focal and generalised onset epilepsy on the basis of the first IED by evaluating the data from 123 long-term, in-patient VEM recordings of patients who underwent VEM recording for presurgical evaluation, seizure control and diagnosis or differential diagnosis of epilepsy. We evaluated a database of the different seizure types and estimated specific durations of EEG recordings for generalised and focal onset epilepsy.

2. Methods

2.1. Procedure

This retrospective study included the long-term VEM recordings of patients with epilepsy or with the prediagnosis of epilepsy performed between September 2014 and November 2018. Patients had the VEM recording for presurgical evaluation, diagnosis of epilepsy or classification and control of seizures. At least three seizure recordings were obtained for presurgical evaluation. For differential diagnosis, at least one recording from the different seizure types was obtained. Reduction or discontinuation of the antiepileptic drug (AED) occurred on an individual basis according to the purpose of VEM, history and clinical situation of patients. If the patient had frequent seizures, AED treatment was not changed. An as-needed dosage-reduction or discontinuation of AED was implemented using the following protocol: half of the AEDs were reduced to a half dose on the first day; if no event was noted, the AEDs were stopped, whereas the other half of AEDs was reduced to a half dose on the second day; if no event was noted, all the AEDs were stopped on the third day. None of our patients had status epilepticus during the VEM recording. The dosages of AEDs during the VEM were documented. Once the required number and kind of seizures were obtained, VEM evaluation was terminated. The patients in whom the AED treatment was decreased or stopped during VEM were monitored in the

hospital for at least one day to ensure safety after restarting the AEDs after VEM. Patients who had symptomatic seizures or a seizure one day before evaluation were not included in the study because of IED possibly increasing the postictal period [10,13]. Seizures were classified according to the International League against Epilepsy (ILAE) 2017 classification. Patients who could not be classified as either focal or generalised onset epilepsy were excluded from the evaluation [14]. The study was approved by the local Ethical Committee and was accordant with the Declaration of Helsinki ethical standards.

2.2. VEM recording and analysis

The patients underwent continuous VEM recording using 32-channel digital video-EEG systems (Nicolet v32, Natus Neurology Incorporated, Middleton, WI, USA). EEG and video data were stored on a hard disc. The recordings were performed before noon, between 8 am and 12 pm. Routine EEG procedures were performed, including eyes opening, eyes closing, hyperventilation and photic stimulation during the initial 20–30 min of the recording. This study did not use triggers. The electrodes were placed per the international 10–20 system, which included anterior temporal electrodes (T1 and T2). Ten20 Conductive Paste (Weaver and Company, Aurora, CO, USA) was used for conduction, and Collodion Adhesive (Bilkosis Ltd., İstanbul, TR) was used for sticking the electrodes.

The EEG data was visually reviewed daily by three neurologists, and the latency to the first IED and the first clinical event was recorded [1]. An activity was considered an IED if it met four of the following five conditions: (1) asymmetric morphology with a steeper rise to the peak than fall to the baseline and a potential field; (2) a slow after wave following the spike; (3) biphasic or triphasic morphology; (4) spike having a different wave duration than the ongoing background activity and (5) background activity surrounding the epileptiform wave disturbed by the presence of slow waves of a frequency range below that of the predominant background rhythm [10,15,16]. The EEG was visually analysed to detect the first, definite epileptiform activity, and the latency was calculated. The next four consecutive spikes or sharp waves were also observed to confirm the epileptiform morphology [10]. If the transients did not meet these criteria, they were considered sharp transients and not IED. The duration of VEM was within the range of 24 h to 10 d. All neurologists discussed the identified IED and recorded seizures in a weekly conference, and the latency to the first IED and seizure was evaluated (Figs. 1a and b, 2 a and b). All the neurologists arrived at a unanimous final decision based on the seizure history, results of the examination, VEM findings and other laboratory results.

2.3. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 23.0 (IBM Corporation, Armonk, NY, USA). Visual (histograms) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) were used to determine whether the variables were normally distributed. Descriptive analyses were presented using medians and minimum-maximum range for the non-normally distributed data. The MannWhitney U-test was used for nonparametric data, the chi-squared test was used for ratios and the Pearson correlation test was used to evaluate correlation. A p value of less than 0.05 was considered statistically significant. Figures were obtained using Microsoft Excel 2010 and SPSS.

3. Results

3.1. Patients

The VEM recordings of 125 patients were evaluated. Of these, 30 patients had generalised onset epilepsy, 58 ha d focal onset epilepsy, 22 ha d psychogenic nonepileptic seizures, 2 ha d syncope and 13 were unclassified. One patient with generalised epilepsy and three patients with focal epilepsy were excluded because they were under six years of age and a history of epileptic seizures could not be confirmed.

Finally, we evaluated the records of 84 patients who had epilepsy and were classified according to ILAE 2017 classification as having generalised onset epilepsy (n = 29) and focal onset epilepsy (n = 55) [14]. The focal epilepsy group had three patients who had no IEDs even though they had seizures and four patients had no seizures, but they had IEDs. One patient in the generalised epilepsy group had no seizures but had frequent generalised spike waves.

3.2. Latencies to initial typical epileptiform discharge and seizure

The latency data were not normally distributed, and the median latency of first IEDs, first seizure and duration of VEM are shown in Table 1. The latency of the first IED in the generalised epilepsy group was significantly lower than that of the focal onset epilepsy group ($p = 0.014$). There was no intergroup difference regarding the latency of the first seizure ($p = 0.085$) (Fig. 3). In the generalised epilepsy group, 79.3% of the patients had IEDs in the first 60 min and 100% of the patients had IEDs within 10 h. In the focal onset epilepsy group, only 55.81% of patients had IEDs in 60 min and 98.1% had IEDs within the first three days (Fig. 4). During the first day, 78.6% of patients with generalised epilepsy and 74.5% of patients with focal onset epilepsy had a seizure (Fig. 5). The number of seizures was statistically higher in the generalised epilepsy group ($p = 0.005$).

3.3. Antiepileptic drug treatment during monitoring and other clinical conditions

No intergroup differences were noted regarding sex, neurological examination, brain magnetic resonance imaging (MRI) or vigilance state at the time of first IED and seizure, or the number of AEDs and AED use during VEM. The generalised epilepsy group had patients with lower current age and first seizure age (Table 1). When evaluating the vigilance state difference between latency to first IED and seizure, the ratio of the first seizure in the sleep state was significantly higher than the first IED in sleep overall ($p = 0.003$).

3.4. Duration of VEM

The duration of VEM was lower in the generalised epilepsy group compared with the focal epilepsy group ($p = 0.012$). The focal epilepsy group showed a positive correlation between the latency of the first IED and the latency of first seizure and also the duration of VEM ($r = 0.591$, $p < 0.001$; $r = 0.604$, $p < 0.001$ respectively). A positive correlation was noted between the latency of first IED and the latency of first seizure in the generalised epilepsy group ($r = 0.425$, $p = 0.024$). However, no correlation was observed between the latency of first IED and the duration of VEM in the generalised epilepsy group ($r = 0.127$, $p = 0.510$). The percentage of patients who completed VEM on the first day was 9.1% in the focal epilepsy group and 34.5% in the generalised epilepsy group. This percentage increased to 60% vs. 75.9% on the third day, 74.5% vs. 89.79% on the fourth day and 89.1% vs. 93.1% on the fifth day for the focal and generalised epilepsy groups, respectively (Fig. 6).

4. Discussion

The main finding of our study was that patients with generalised onset epilepsy had a shorter latency to the first IED compared with patients with focal onset epilepsy. This study revealed a statistically significant difference of latencies to the first IED between generalised and focal onset epilepsy. The results demonstrated that a shorter recording duration was sufficient to capture the first IED in generalised onset epilepsy compared with the recording duration required for focal

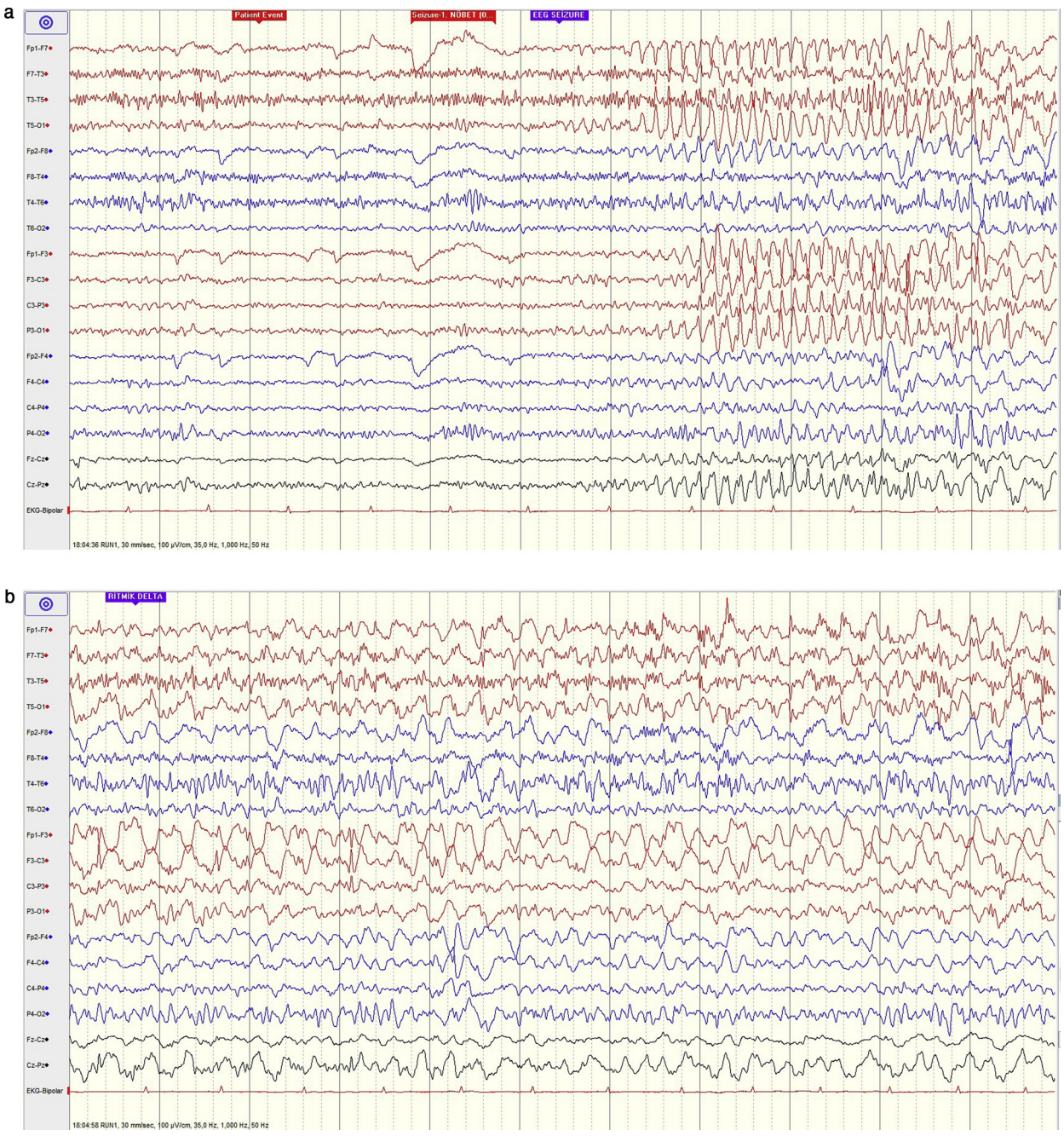

Fig. 2. Ictal electroencephalography activity observed after 1804 min of recording in patient with focal epilepsy, initial (a) and after 20 s (b).

onset epilepsy. All IEDs were obtained within 10 h in generalised onset epilepsy group. However, in the focal onset epilepsy group, IEDs may not be obtained even if the patients had seizures, such as that observed in three patients of our study sample.

Werhahn et al. investigated 210 consecutive patients with active epilepsy, and found that IEDs were absent in 21.4% of patients, but if present, IEDs occurred during the first 72 h of long-term video—EEG recording in most epilepsy patients [17]. Oehl et al. studied 39 patients with generalised epilepsy and found that the mean latency of the first typical IED was 853 min, ranging from a minimum of 3 to a maximum of 7305 min [11]. Our study observed a median latency of the first IED to be 12 min in the generalised epilepsy group. The main difference between these two study results is that we evaluated the median latency because the data were not normally distributed, but Oehl et al. evaluated the mean latency. Oehl et al. also found that 38.5% of patients had IEDs during the first hour and 87.2% of patients had IEDs during the first day [11], whereas we found that all of the patients had IEDs during the first 10 h. Park et al. investigated 55 patients with juvenile myoclonic epilepsy within the range of one to six days and found that 88% of the patients had an EEG abnormality and 57% of them had seizures. They found the mean duration of VEM to be 1.8 d and made a suggestion that one or two days of VEM is appropriate for juvenile myoclonic epilepsy [12]. The conventional activation methods such as photic stimulation may affect the latency to the first IED, particularly in the generalised epilepsy group. However, the inclusion of activation methods to the investigation enabled us to evaluate daily practice. Lee et al. used hyperventilation and photic stimulation methods in the patients and found that the latency to the first epileptiform discharge was shorter in patients with generalised epilepsy compared with localisation-related epilepsy [1]. Faulkner et al. also found that the latencies to the first IED with generalised epilepsy were shorter compared with focal epilepsy but they did not mention whether they used activation

Table 1
EEG and patient data summary.

	Focal onset epilepsy	Generalised onset epilepsy	P value
Sex (F/M) (N)	27/28	11/18	0.329
Age	29 (6–55)	19 (6–53)	< ***0.001***
Age of first seizure	11 (1 month–50 years)	7 (3 months–35 years)	***0.045***
Seizure frequency (monthly)	5 (0.5–60)	10 (1–1500)	0.130
Neurological examination (Normal/Abnormal) (N)	45/10	20/9	0.181
Brain MRI (Normal/Abnormal) (N)	33/22	22/7	0.146
Number of AED	2 (0–5)	2 (0–4)	0.953
Drug use during VEM (N)	Tapered 25	Tapered 15	0.342
	Stopped 18	Stopped 5	
	Unchanged 11	Unchanged 7	
	Not using 1	Not using 2	
Reason for VEM (N)	Presurgical evaluation 44	Presurgical evaluation 11	< ***0.001***
	Diagnosis 8	Diagnosis 4	
	Seizure control 3	Seizure control 14	
Duration of VEM (day)	3 (1–10)	2 (1–10)	***0.012***
Median latency to first epileptiform activity (minute)	55 (2–7500)	12 (1–440)	***0.014***
Median latency to first seizure (minute)	940 (20–10080)	476 (9–7320)	0.085
Vigilance at first epileptiform activity (Awake/Asleep) (N)	43/8	26/2	0.275
Vigilance state at first seizure (Awake/Asleep) (N)	34/17	19/9	0.914
Number of seizures	4 (0–150)	9.5 (0–119)	***0.005***

Footnotes: EEG, electroencephalogram; F, female; M, male; N, number; AED, antiepileptic drug; VEM, video-EEG monitoring; *p* value less than 0.05 was considered statistically significant.

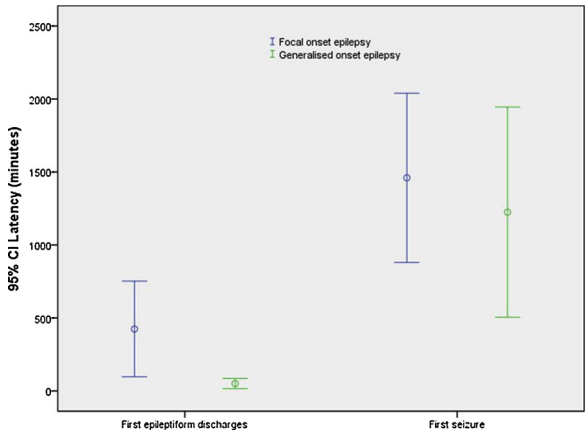

Fig. 3. Comparisons of latency to first epileptiform discharges and seizures between generalised and focal onset epilepsies.

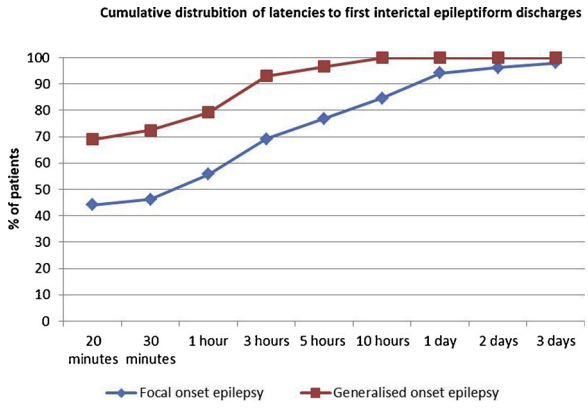

Fig. 4. Time to the first epileptiform discharge and cumulative percentage of patients in video-electroencephalography monitoring.

methods or not [18]. Lee et al. evaluated subgroups of focal epilepsy group and they did not find a statistically significant difference between temporal lobe epilepsy, frontal lobe epilepsy and other epilepsies or complex partial seizures of uncertain origins [1].

We also found that the median duration time of VEM was two days

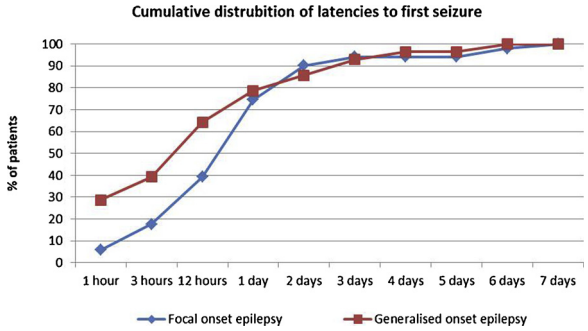

Fig. 5. Time to the first seizure and cumulative percentage of patients in video-electroencephalography monitoring.

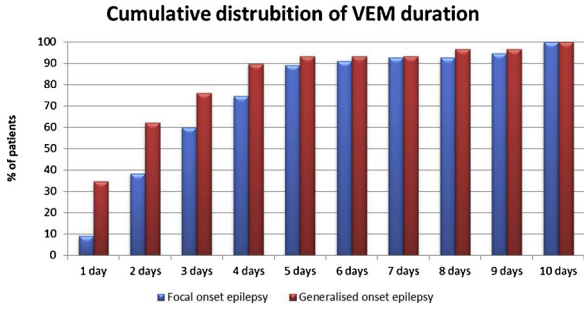

Fig. 6. Percentage of patients who completed video-electroencephalography monitoring evaluation within different intervals of time.

in generalised epilepsy—concordant with the suggestion of Park et al. Faulkner et al. investigated 180 patients with epilepsy, who had undergone 96 h of outpatient ambulatory EEGs, and found that the median latency to the first IED was 316 min (ranging from 1 to 4569 min), and 95% of the patients had IED within 48 h. They did not evaluate the latency to seizures [18]. Badry looked at the first IED in 200 patients and found that IED was detected in 45.45% of the patients in the first 20 min and this percentage increased to 85.45% after 24 h [16]. Badry also found there was a higher chance to obtain IEDs in patients with generalised epilepsy (n = 51/200, including primary and symptomatic generalised epilepsy syndromes) in the first 20 min, which is concordant with our findings. However, no statistical comparison was

performed between the seizure types; the recording ended in 24 h, and only IED was evaluated not seizures [16]. Losey et al. found that the mean duration to the first IED was 56 min in patients with temporal discharges (n = 20) and 22 min in patients with generalised discharges (n = 14) ($p = 0.053$), with an outpatient recording in the range of 65–384 min [3]. Our study had a higher number of patients with long-term VEM recording within the range of 1–10 d. We found no inter-group difference regarding latency to first seizure. However, we found that duration of VEM recording was shorter in generalised epilepsy compared with focal epilepsy, which implied that even if the latency to first seizure was not different, the total evaluation time was different between groups.

The significance and variabilities of VEM duration have been stressed repeatedly [1,4,7,8,19–23]. The duration of VEM was found to be 2.54–3.9 d, ranging from 4 h to 14 d [7,8,11]. We found the median duration of VEM to be two days (ranging from 1 to 10 d) in the generalised onset epilepsy group, three days (ranging from 1 to 10 d) in the focal onset epilepsy group and three days (ranging from 1 to 10 d) overall. Furthermore, in our study, approximately 75% of the patients completed VEM evaluation in four days in the focal onset epilepsy and three days in the generalised onset epilepsy. Foong et al. suggested that five days are sufficient to obtain seizures because they found 98% of all clinical events were obtained on the fifth day [8]. However, they did not evaluate the duration of VEM according to seizure onset. Notably, we found that 94.1% and 96.4% of all first seizures in the focal and generalised onset epilepsy groups, respectively, occurred on the fourth day. We also found that 80% of first seizures were obtained during 1632 and 1861 min in the focal and generalised onset epilepsy groups, respectively—consistent with the literature [8,21,24]. We did not find a higher ratio of the first IED in the sleep state. Our recording began before noon, and the initial part of the recording was awake EEG with long duration, after which we obtained the sleep EEG—the probable reason for not finding any difference between sleep and awake states. Nonetheless, the ratio of first seizure in sleep is higher than the first IED in sleep, which suggests the advantage of sleep to obtain seizures.

One of the limitations of this study was that we did not make a strict drug reducing or withdrawal protocol and drug adjustment was performed on an individual basis per the patients' needs. Therefore, the effect of drugs on the first IEDs and seizures was not accurately evaluated. However, our primary aim was to evaluate the latency to the first IED and first seizure and the duration of VEM. We combined the focal and generalised onset epilepsy subtypes to obtain enough patients to compare the seizure types. Nonetheless, future studies with even more number of patients representing an adequate sample of different seizure subtypes can thereby facilitate better correlation of latency to the first IED besides the seizure and VEM duration.

5. Conclusions

A significant strength of this study is that it compares generalised and focal onset epilepsy based on the latencies to the first IED and seizure besides the duration of VEM with long-term VEM recording. To the best of our knowledge, this is the first study to show the differences in latency to the first IED between generalised and focal onset epilepsy by recording inpatient long-term VEM. Generalised onset epilepsy had a significantly shorter latency to the first IED compared with focal onset epilepsy. In our data set, all patients with generalised onset epilepsy had IED within 10 h, but the patients with focal onset epilepsy needed to be monitored for up to three days because 98.1% of them had IED during that time. Both IED and VEM duration was significantly shorter in generalised onset epilepsy compared with focal onset epilepsy. Our results suggest that with a duration of four days for focal onset epilepsy and three days for generalised onset epilepsy, three-quarters of VEM evaluation can be completed. Therefore, before planning VEM, an evaluation of the patient's history, routine EEG, brain MRI findings should be performed. If the prediagnosis of the patient is consistent with generalised epilepsy, then a shorter duration of VEM evaluation may be scheduled. These data can be helpful to predict the VEM duration in different seizure types and to plan the start time for the next patient, thereby facilitating effortless planning of VEM appointments, particularly in immensely busy epilepsy centres.

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Disclosure of conflict of interest

Authors have no conflicts of interest to disclose.

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