Medical Sciences

Current Evidence on Optimal Time Interval for Performing an Initial EEG in Patients with Presumed New-Onset Unprovoked Seizures

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Electroencephalogram (EEG) has played an important role in the diagnosis, classification and management of seizures. As with any neurodiagnostic evaluation tool, it is imperative to study it under various conditions in order to obtain optimal working parameters. Current guidelines on the ideal time frame in which to perform an initial EEG following an unprovoked seizure have been vague, and it is acknowledged that further studies are needed. This review aims to analyze studies with time recorded between seizure episode and EEG, and summarize the updated evidence on an optimal time frame for performing EEGs following the first unprovoked seizure.

New onset seizure | EEG | Epileptiform discharges

Introduction

It is estimated that 150,000 people experience an unprovoked first seizure every year in the United States [1]. Globally, the annual incidence rate of unprovoked seizures is 73–86 cases per 100,000 [2]. According to the latest figures from the Centers for Disease Control and Prevention (CDC) about 5.1 million people in the United States have a diagnosis of epilepsy or a seizure disorder. A seizure is a harrowing and distressing event and has real life consequences in peoples' lives. Restriction in driving privileges, increased insurance premiums, and job restrictions have financial and practical implications [3]. The total indirect and direct financial cost of epilepsy translates to an estimated $15.5 billion annually in the United States [4].

What is an "unprovoked seizure"?

Unprovoked seizures are defined as "seizures occurring in the absence of a potentially responsible clinical condition or beyond the interval estimated for the occurrence of acute symptomatic seizures" [5]. Epilepsy is diagnosed by the occurrence of two or more unprovoked seizures or a single seizure with the possibility for recurrence comparable to that following two unprovoked seizures (at least 60% in the next 10 years) [6].

Multiple publications and current guidelines have testified to the importance of an electroencephalogram (EEG) in the evaluation of an initial unprovoked seizure [7-10]. According to King *et al.,* the proportion of patients diagnosed with epilepsy increased from 47% to 77% when EEG data were considered [9]. In a review of one Class I and ten Class II articles assessing the yield of EEG, EEGs were reported to exhibit epileptiform activity in 12% to 73% and significantly abnormal epileptiform activity in 8% to 50% (average 29%). Epileptiform activity in this study was defined as "spikes or sharp waves as interpreted by the local or reading electroencephalographer" [8].

While approximately half of subjects clinically diagnosed with seizure might have a normal EEG [8] and up to 10% of patients with epilepsy might never show any epileptiform discharges [11], an epileptiform abnormality might be the most significant EEG finding when a diagnosis of a first-ever seizure is suspected. In fact, multiple meta-analyses in adults and children have shown that individuals with epileptiform abnormalities were about twice as likely to have a seizure recurrence [8, 12], with most of the recurrences occurring within the first 1 to 2 years following the initial seizure [13]. Further, Goodin and Aminoff in their analysis demonstrated that when a strong suspicion for epilepsy was involved, epileptiform activity in the EEG almost conclusively established the diagnosis [14]. The EEG is particularly useful in diagnosing younger patients and those with seizures of unknown origin [15].

Effect of timely diagnosis on patient management

As mentioned earlier, the new International League Against Epilepsy (ILAE) definition of epilepsy now includes a single seizure with a recurrence risk similar to that after 2 unprovoked seizures [6]. It is left to the judgement of the clinician managing the epilepsy to decide what constitutes a 60% risk. The decision to initiate Anti-Epileptic Drug (AED) treatment after a first unprovoked seizure is made after weighing seizure etiology, recurrence risk, and risk-benefit assessment of potential adverse effects [16, 17]. The American Academy of Neurology (AAN) practice parameter on evaluating a first nonfebrile seizure in children examined several Class I and Class II studies and concluded that the EEG was vital for determining seizure or epilepsy type and risk of recurrence, and hence had an important role in guiding management decisions [18]. The 2016 Journal of the American Medical Association (JAMA) Clinical Guideline and the 2015 AAN guideline noted that the epileptiform EEG pattern was among the most consistently noted factors associated with an increased risk of seizure recurrence [13, 17].

Timely diagnosis is also of paramount importance on account of its implications in treatment. A random-effects meta-analysis included in the recent AAN guideline on the management of an unprovoked first seizure in adults shows an absolute risk reduction in seizure recurrence of 35% (95% CI 23%–46%) in a comparison of immediate and delayed AED treatment for pooled 2-year data, even though it did not affect the long term prognosis ie. seizure remission rate [13]. The European Multicenter Epilepsy and Single Seizure Study (MESS) by Marson and colleagues, showed that immediate AED therapy increased the time to first seizure (after the initial seizure), second seizure, and first tonic-clonic seizure, as well as considerably reduced the time to attain a 2-year remission of seizures [16, 19].

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Table 1. Studies with measured time between seizure and EEG

Study Author	No. of patients/ Nature of Study	Age Range [years]	Seizure criteria	Mean time interval between seizure and EEG/admission to hospital	EEG showing epileptiform discharge
Van Donselaar, Schimsheimer et al. 1992 [21]	157 - Prospective	15-85	Idiopathic first seizure	6.7 days (53% presented within 24 hours)	19/157 (12.1%)
Tardy, Lafond et al. 1995 [22]	247 -Retrospective	15->60	First generalized tonic-clonic seizure	Seizure Less than 24 hours prior to admission	67/209 (32%)
King, Newton et al. 1998 [9]	300 -Prospective	5-83	First Unprovoked Seizure	Within 12 hours- 89 patients Between 12-24 hours- 67 patients More than 24 hours- 144	<24 hours- 80/156 (51%) >24 hours- 49/144 (34%)
Neufeld, Chistik et al. 2000 [15]	91 -Retrospective	15-87	First Unprovoked Seizure	Less than 48 hours after admission	19/91 (21%)
Hui, Tang et al. 2001 [23]	132 - Retrospective	13-86	First Unprovoked generalized tonic-clonic seizure	15.7 days (range 1–36 days)	39/132 (29.5%)
Schreiner and Pohlmann-Eden 2003 [24]	157 - Prospective	17-84	First unprovoked seizures	<48 hours (95% within 24 hours)	42/157 (26.7%)
Sofat, Teter et al. 2016 [25]	270- Retrospective	1-91	First Unprovoked Seizure	Within 12 hours- 32 patients Between 12-48 hours- 118 patients More than 48 hours- 120 patients	17/32 (53.1%) 27/118 (22.9%) 30/120 (25%)

Current EEG Time-frame Recommendations

Various guidelines have been proposed by various professional bodies regarding EEG timeframe recommendations. For instance, the widely cited study by King *et al* showed that investigation within 24 hours of a seizure revealed Interictal Epileptiform Discharge (IED) in 51%, compared with 34% of those who had EEGs later [9]. Review from Beghi *et al* regarding diagnosis and treatment options for a first epileptic seizure used King's study as evidence that "an EEG should be performed within 24 hours after a seizure, particularly in children", classifying it as Class III evidence and a Level B recommendation, but cautioned that "slowing of the EEG background activity at 24–48 h after the seizure may be transient and should be interpreted with caution" [2].

Wilden and Cohen-Gadol advised that "Ideally, EEG should be obtained 24–48 hours after the seizure, should be performed using hyperventilation or photic stimulation, and should capture sleep and awake states because these measures increase the likelihood of detecting abnormalities" [20]. Therefore, it is imperative to examine the effect that time interval between the first seizure and EEG recording has on EEG yield, considering the repercussions it has on diagnosis and treatment.

Currently available studies

In order to evaluate the optimal timeframe during which an initial EEG yields the highest value, we analyzed various studies that have been performed and compared the time frames at which EEG had been performed.

We searched Pubmed with the term "first unprovoked seizure" until October 30, 2016. Articles were included if EEGs were obtained as part of the evaluation. Only published papers containing the data showing the time frame or time limits within which EEGs were performed and EEG results were considered. While some of the examined studies included both initial and sleep-deprived EEG, wherever discernment was possible, only the initial EEG results were included in order to ensure uniformity (Table 1).

Discussion

Diagnostic tests are most beneficial when they yield defined, reliable, unprejudiced, clinically important results that support medical decision making. While the interval between the first seizure and EEG recording might have significant impact on the sensitivity of the EEG recording [24], a stratified time dependent breakdown of the effectiveness of EEG as a diagnostic tool has not been studied extensively. The Practice parameter posed by AAN lamented that one of the "limitations" of currently available studies was due to the "variability in the timing of the EEG" following the initial seizure [8].

The studies in Table 1 show a wide range of figures for the detection of epileptiform discharges on EEG. As a meta-analysis of EEG test performance has shown, the variance could be partly attributed to the differences in the interpretation-threshold of the

EEG readers [26]. However, it is interesting to note the similarities in the findings of King *et al* and our findings. It is worthwhile noting that these are the only two studies that compare the results of the EEGs based on a timeframe stratification, and hence warrant deeper scrutiny and analysis.

While the study by King *et al* was a prospective study, ours was a retrospective analysis. Both included a substantial number of patients and examined unprovoked first seizures. The minor yet noteworthy difference in their inclusion/exclusion criteria is that while King et al included patients who had a history of prior seizures, so long as they had no previous diagnosis or treatment, we considered a known seizure history as an exclusion criterion. While King stratified their findings into <24 and >24 hours showing a statistically significant difference of 51% Vs 34%, we went a step further stratifying them into time-blocks of 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 and >96 hours showing epileptiform discharges in 67%, 52%, 24%, 25%, 22%, 18% and 27% respectively [9, 25].

In spite of an early EEG not being considered a priority in the work up previously, based on their findings, King et al suggested that the EEG should be done within 24 hours. We have shown that the most sensitive time frame to detect epileptiform patterns is even earlier and recommended that EEGs be performed in the first 12 hours. Both studies demonstrate an increased detection of epileptiform abnormalities among children than among adults, which was also affirmed by the study by Neufeld et al [9, 15, 25].

There are several possible factors that prevent an EEG from being performed within the first 12 hours. The difficulty of access to EEG equipment is an important cause that precludes the performance of an EEG following an initial unprovoked seizure, particularly in non-urban centers. The performance of an EEG requires certified EEG technologists for the preparation and initiation of the procedure. Further, trained epileptologists are required for interpretation. Lack of readily available trained personnel is a significant contributing factor for delayed performance of an EEG [27].

While further studies on a larger scale with an increased number of subjects in each time interval are warranted to confirm the findings, based on current evidence, we recommend that the optimal time for performing an EEG following a first unprovoked seizure, is within the first 12 hours. We believe this will lead to maximizing the efficiency of an EEG test, increase its reliability and lead to better clinical judgement enabling an accurate early diagnosis and appropriate treatment.

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