Recurrence rate of seizure following discontinuation of anti-epileptic drugs in patients with normal long term electroencephalography

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Abstract

Background: The usefulness of electroencephalography (EEG) in predicting seizure recurrence after antiepileptic drugs (AED) tapering is a controversial subject. There have been no studies which tested the additional yield of long-term over routine EEG recordings in predicting seizure recurrence after AED withdrawal. Objective: The primary objective of our study is to determine the recurrence rate of seizure following AED withdrawal in patients with focal epilepsy, unknown cause who had normal long-term electroencephalography (LTEEG) and secondary objective is to analyze the variables that would predict seizure recurrence. Materials and Methods: This was a prospective observational study. A total of 91 patients were included. 62 patients who had normal routine and LTEEG entered the final phase of the study were followed-up regularly for 1 year or until seizure recurrence whichever was earlier. Results: A total number of 91 patients were enrolled for the first phase of the study. Of these, 13 (14.29%) patients had an abnormal routine EEG. Of the remaining patients, another 16 (17.58%) had abnormal LTEEG. The remaining 62 patients with normal routine and long-term EEG entered the final phase of the study. Of these, 17 patients (27.41%) had seizure recurrence during the follow-up while 45 (72.58%) remained seizure free until the end of the 1 year follow-up. The significant variables associated with a higher risk of seizure relapse were a positive past history of seizure recurrence on prior drug withdrawal (relative risk: 2.19, confidence interval: 1.01-4.74, P < 0.05) and the duration of epilepsy until seizure control was achieved (P < 0.009). Conclusions: The recurrence rate of seizure in patients with a normal LTEEG is 27.41%. A positive past history of seizure recurrence and a longer time to achieve seizure freedom with AED increased the risk of seizure recurrence.

Key Words
Antiepileptic drugs, electroencephalography, epilepsy

Introduction

The usefulness of electroencephalography (EEG) in predicting seizure recurrence after antiepileptic drug (AED) tapering is a controversial subject. The presence of electroencephalographic abnormalities, both slowing and epileptiform, correlates with a higher rate of seizure recurrence after AED withdrawal, in children or in epilepsies with onset in childhood. The results of a large randomized study of AED withdrawal in 873 adult patients in remission were insufficient to conclude the importance of any electroencephalographic abnormality in the entry EEG. In a group of patients with epilepsy of relatively short duration and 2 years of seizure freedom on their first AED, an abnormal EEG before treatment and unchanged EEG before withdrawal carried the worst prognosis. A meta-analysis revealed an increased risk of relapse in patients with abnormal versus normal EEGs, but failed to obtain reliable data on the importance of specific EEG features. Another longitudinal study in adult patients with partial epilepsies with multiple EEG studies before and at various time points during and after AED withdrawal confirmed the generally accepted view that an EEG should not be considered in the decision to withdraw an AED in patients with partial epilepsies. However the role of long-term electroencephalography (LTEEG) recordings in predicting seizure recurrence has not been adequately studied. One study which employed prolonged 5-h video/EEG monitoring following secobarbital-induced sleep was found not helpful in predicting relapse. Another study aimed to test the prognostic value of long-term ambulatory electroencephalography in AED reduction found a positive
association between abnormal EEG and seizure recurrence but, the study subjects were adults with learning disability and epilepsy.[9] There have been no studies which tested the additional yield of long-term over routine LTEEG recordings in predicting seizure recurrence after AED withdrawal in otherwise normal epileptics.

The aim of our study was to determine the recurrence rate of seizure following AED withdrawal in patients with idiopathic focal epilepsy who had normal LTEEG including natural overnight sleep and to analyze the variables that would predict seizure recurrence.

Materials and Methods

This is a prospective observational study conducted in the Department of Neurology, Calicut Medical College and a tertiary care hospital in South India from January 2011 to February 2012. The study was conducted among patients attending the Epilepsy Clinic of our department over a 1 year period. Inclusion criteria were (1) diagnosis of epilepsy, (2) normal neurological examination and overall intelligence (3) a seizure-free period of at least 3 years while on AEDs. We excluded patients who had symptomatic epilepsy and idiopathic generalized epilepsy; children <6 years and patients on more than 2 AEDs. Diagnosis of epilepsy was made by clinical, EEG and neuroradiologic examination. Seizures were classified according to the International Classification of seizures in persons with epilepsy. After getting the approval of the study protocol by the institutional review board, we recruited 91 patients who satisfied the inclusion criteria and were willing to give a written informed consent. After recruitment, all patients entered the first phase of the study and underwent a routine EEG. The routine EEG was a 20-min recording using a range of bipolar and average reference montages; electrodes were positioned in accordance with the International 10-20 System. Hyperventilation (3 min in duration) and photic stimulation (frequency range: 1-60 Hz) were used in all patients. 13 patients were found to have an abnormal routine EEG and were excluded from further studies.

Those who had normal routine EEGs entered the second phase and underwent LTEEG recording. The long-term EEG studies were performed using a 16-channel digital recorder (Nihon Kohden) using the International 10-20 system of electrode placement. All studies included periods of wakefulness and natural sleep and average duration of recording was 21½ h. All recorded data were reviewed by two neurologists independently. For each recording the following was considered: Presence of alpha rhythm, presence of theta + delta activity, presence of spikes and sharp waves and localization and symmetry of these features. Only spikes, spike-and-waves, sharp waves, sharp slow waves and paroxysmal slow wave abnormalities were considered as unequivocal epileptiform features. 16 patients had abnormal LTEEGs and they were excluded from the next level of the study.

Thus, 62 patients who had normal routine and LTEEG entered the third and final phase. In these patients AEDs were tapered over 3-6 months. If the patients were receiving more than one AED, the AEDs were withdrawn sequentially with each AED being withdrawn over at least 3 months. Phenobarbital was usually the last AED to be withdrawn. After total drug withdrawal, the study subjects were followed-up regularly for 1 year or until seizure recurrence whichever was earlier. Statistical analysis for significance was performed with Chi-square analysis for qualitative and Mann-Whitney test for quantitative variables.

Results

A total number of 91 patients were enrolled for the first phase of the study. (14.29%) patients had an abnormal routine EEG and were excluded from entering the second phase. Of the remaining patients, another 16 (17.58%) had abnormal LTEEG and they did not enter the third phase. Hence a total of 29 out of 91 (31.87%) patients had abnormal EEG. The remaining 62 patients with normal routine and long-term EEG entered the final phase of the study. There were 34 men and 28 women. The mean age was 26.40 years (range 12-55). Of these, 17 patients (27.41%) had seizure recurrence during the follow-up while 45 (72.58%) remained seizure free till the end of the 1 year follow-up.

We performed a subgroup analysis to know whether there were any variables that was significantly associated with the risk of recurrence. For this we divided the patients as relapsers and non-relapsers [Table 1]. There was no significant difference (P = 0.994) in mean age of the patients between the two groups; 25.12 years (range 12-55, standard deviation [SD]: 4.99) in relapsers and 27.69 years (range 17-34, SD: 12.13) in non relapsers. The gender ratio was almost similar in both groups. There were 9 men and 8 women among relapsers (M:F ratio = 1.1:1) and 25 men and 20 women among non relapsers (M:F ratio = 1.25:1). Even though, there was slight male excess in both the groups, no significant difference was found with regard to gender between the two groups (relative risk [RR]: 0.90 confidence interval [CI]: 0.41-2.08; P: 0.85). Mean total duration of epilepsy was 8.5 years (range 4-15, SD: 3.59) in relapsers and 8.2 years (range 3-23 SD: 5.65) in non relapsers (P: 0.291). The average years of seizure freedom was 4.24 (SD: 0.664) in relapsers and 4.47 (2.56) in non relapsers (P: 0.536). Total number of seizure episode was 4.06 (SD: 1.92) in relapsers and 6.69 (SD: 3.35) in non-relapsers (P: 0.482).

| Variable                                         | Relapsers | Non-relapsers | P value |
|--------------------------------------------------|-----------|---------------|---------|
| No.                                              | 17        | 45            |         |
| M/F                                              | 9/8       | 25/20         | 0.85    |
| Mean age (years)                                 | 25.12     | 27.69         | 0.994   |
| Mean total duration of epilepsy (years)          | 8.5       | 8.2           | 0.291   |
| Average years of seizure freedom                 | 4.24      | 4.47          | 0.536   |
| Total number of epileptic attacks                | 4.06      | 6.69          | 0.482   |
| Positive past history of seizure recurrence on prior drug withdrawal | 7/17 | 8/37 | 0.05 |
| Duration of epilepsy until seizure control was achieved (years) | 3.76 | 1.95 | 0.009 |

Table 1: Characteristics of relapsers and non-relapsers
The significant variables associated with a higher risk of seizure relapse were a positive past history of seizure recurrence on prior drug withdrawal and the duration of epilepsy until seizure control was achieved. While 7 out of 17 relapers had a history of failed withdrawal in the past, only 8 out of the 37 non-relapers had past relapse (RR: 2.19, CI: 1.01-4.74, \( P = 0.05 \)). Likewise, a shorter duration of epilepsy until seizure control was achieved also had a significant association with a favorable long-term outcome. The mean duration of seizure before seizure freedom was 3.76 years in relapers and 1.95 years in non relapers (\( P = 0.009 \)).

**Discussion**

In this prospective observational study, we investigated the recurrence rate of seizure following withdrawal of AEDs, in patients who had normal routine and long-term EEGs. To the best of our knowledge, this is the first study to examine the usefulness of long-term EEG, with regard to identifying the incidence of seizure recurrence following AED withdrawal in otherwise normal patients with epilepsy.

In accordance with previous studies, LTEEG including an overnight recording increased the yield in detecting epileptiform abnormalities compared with routine EEG.[12] Routine EEGs performed in our patients who have remained seizure free at least for 3 years, were abnormal in 14.29%. When the remaining patients were submitted for LTEEG abnormalities were detected in another 17.58%, thus almost doubling the yield.

The poor sensitivity of routine EEG in detecting epileptiform activity may be due to the intermittent occurrence of interictal epileptiform discharges. Subclinical EEG discharges occur anytime within a 24-h period, but random 20-min EEGs sample only a small fraction of the activity occurring during a 24-h period.[13] It is known that this pattern is frequently modulated by extrinsic or intrinsic factors, which influence the overall discharge probability.[14,15] This fluctuating nature of interictal discharges explains why they are not observed in random EEGs in individual patients.[16,17] Failure of a single routine EEG to detect relevant epileptiform EEG abnormalities is most likely due to limited sampling time. The circadian pattern and day-to-day variability of interictal discharges are relevant to the use of LTEEG recording as a means of assessing therapy. Hence, repeated or prolonged EEG recordings are more reliable in determining the frequency of discharges in patients with epilepsy.

The most remarkable finding of our study was that, even after excluding those patients with abnormal routine and LTEEGs, there was a 27.41% recurrence of seizures within 1 year of AED withdrawal. The risk of seizure relapse after withdrawal of AEDs has been estimated at from 10% to 70% depending on the method and design of the studies.[18] Based on a meta-analysis of the literature, the risk of relapse after drug withdrawal was 25% at 1 year and 29% at 2 years.[19] Hence, our study shows that, though LTEEG had a higher sensitivity in detecting epileptiform abnormalities than a routine EEG, the recurrence rate of seizure in this cohort of patients with a normal LTEEG was comparable to that of the existing literature.

Nearly half of our patients (47%) relapsed during tapering and the rest (53%) relapsed after complete AED withdrawal. A positive past history of seizure recurrence on prior drug withdrawal was significantly associated with seizure relapse in this study (\( P = 0.05 \)). Our results also show that the time to reach seizure freedom is a significant predictor of the long-term seizure outcome (\( P = 0.009 \)), suggesting that the chance of long-term seizure freedom decreases with the time of ineffective AED treatment. Similar finding was observed in another study in a cohort of patients with juvenile myoclonic epilepsy.[20]

In summary, our data showed that, LTEEG had a higher yield in detecting IEDs which is almost double compared with routine 20 min EEG before AED withdrawal. However, even in patients with a normal routine and LTEEG prior to AED withdrawal, the recurrence rate of seizure is 27.41% during a 1 year follow-up. Currently, there are no studies which have utilized LTEEG before AED withdrawal in otherwise normal patients with epilepsy and therefore, this data might provide a base on which further studies could be carried out. In addition, our study also demonstrated that, a positive past history of recurrence and a longer time to achieve seizure freedom with AED increased the risk of seizure recurrence.

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