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Can electroencephalograms provide guidance for the withdrawal of antiepileptic drugs: A meta-analysis

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HIGHLIGHTS

- Abnormal EEG recordings prior to AED withdrawal predicted a high risk of relapse.
- Paroxysmal, slowing, spike and wave activities on EEG indicated an increased risk of relapse.
- Nonparoxysmal, spike and focal abnormalities on EEG showed lower predictive values.

ABSTRACT

Objective: The discontinuation of antiepileptic drugs (AEDs) is an important treatment decision for epilepsy patients who have been seizure-free for 2 years or longer. Some patients experience seizures relapse after AED withdrawal. The prognostic value of electroencephalograms (EEGs) for seizure relapse following AED withdrawal is controversial. To our knowledge, this is the first meta-analysis to address whether EEG data can be used to guide the discontinuation of AEDs.
Method: We performed a meta-analysis of cohort studies that reported original EEG data from before AED withdrawal and recurrence after AED-withdrawal. The quality of each study was assessed using the Newcastle–Ottawa Scale.
Results: Fifteen studies including a total of 2349 participants were included in this meta-analysis. This meta-analysis of 15 studies demonstrates that an abnormal electroencephalogram was a predictor of the risk of relapse. Additionally, paroxysmal, slowing, spike and wave activities on electroencephalograms were associated with increased risk of relapse.
Conclusion: We reveal that abnormal EEG records, particularly paroxysmal abnormalities, before AED withdrawal predicted a high risk of relapse. Slowing and spike and wave activities also exhibited moderate predictive values.
Significance: Our findings suggest that, EEGs might be an important prognostic tool for antiepileptic drug reduction.

1. Introduction

Epilepsy is a very common chronic neurological disorder, and antiepileptic drugs (AEDs) remain a primary method of epilepsy control. Approximately 60–70% of patients become seizure-free after the commencement of antiepileptic drug therapy (Brodie and Kwan, 2002; Cockerell et al., 1995; Kwan and Brodie, 2000). However, the ideal timing for the withdrawal of medication remains unknown. For seizure-free patients, the issue of whether medication should be continued is controversial due to the side effects, costs and the inconveniences associated with antiepileptic drug therapy. The identification of a point at which the risk of epilepsy relapse is minimal is urgently needed. Electroencephalography (EEG) plays an important role in the diagnosis, treatment and management of epilepsy. However, the prognostic value of EEG for antiepileptic drug reduction is debatable. In an early trial, Juul-Jensen found that patients with abnormal EEGs exhibited a higher recurrence rate following AED withdrawal (Juul-Jensen, 1968). Similar outcomes have been reported in some subsequent studies (Donati et al., 1995; Emerson et al., 1981; Geerts et al., 2005; Koepp et al., 2008; Pavlovic et al., 2012; Shafer et al., 1988; Specchio and Beghi, 2004; Todt, 1984). However, other

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studies have observed negative correlations. The authors of these later studies have proposed that abnormal EEGs are not a risk factor for relapse (Galimberti et al., 1993; Lossius et al., 2008; Pavlovic et al., 2011; Thurston et al., 1982). Therefore, we performed a meta-analysis to determine the relative risk of recurrence in terms of EEG data collected prior to AED withdrawal.

2. Materials and methods

2.1. Data sources and searches

We performed an electronic literature search of the PubMed and EMBASE databases from 1981 to 2015. The reference lists of the identified articles were reviewed to select any supplementary studies that could strengthen our study. Two authors independently assessed the articles retrieved by the search by screening the titles, abstracts and full-texts. All disagreements were resolved by discussion or by the third author.

2.2. Keyword searches

The following terms were included in the keyword searches: epilepsy, withdrawal, discontinuing, electroencephalogram, EEG, anticonvulsants, and antiepileptic.

2.3. Study selection

We included the articles that met the following criteria: (1) studies designed to address the question of relapse following AED withdrawal, (2) EEG data collected prior to the discontinuation of AEDs were available, and (3) the article was published in English. We excluded studies that restricted their patients to highly selective subpopulations, such as convulsive status epilepticus, surgical epilepsy treatment or vagus nerve stimulation. Reports that lacked original EEG data were also excluded.

2.4. Data extraction and quality assessment

The eligible studies were assessed by two authors. Disagreements were resolved by consensus. The following data were extracted from the studies: first author, year of publication, characteristics of the study population (i.e., gender and age at withdrawal), number of subjects, antiepileptic drug treatment project, follow-up period, recurrence rate, and original EEG data. Some of the studies contained subgroup data regarding the characteristics of the abnormal EEG data (i.e., spike, slowing, spike and wave, focal, paroxysmal and nonparoxysmal abnormalities). These data were also extracted for analysis. We assessed the risk of bias using the Newcastle–Ottawa Scale (NOS), which contains selection, comparability, and outcome components (Wells et al., 2000). The NOS scores were divided into groups of 1–3, 4–6, and 7–9, which represented low, medium, and high methodological quality levels, respectively (Table 1).

2.5. Statistical analyses

We assessed statistical heterogeneity using the *I*-squared (I^2) value. An $I^2 > 75\%$ was considered indicative of significant heterogeneity. Different modes of analysis were chosen according to the heterogeneity findings. Fixed-effect models were used in the analyses of samples without significant heterogeneity. Random-effects models were applied to the samples with significant heterogeneity. The risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to express the results using the Mantel–Haenszel statistical method. All analyses were performed using Review Manager 5.3 and SPSS 22.0.

3. Results

3.1. Search results

We identified 836 publications in the electronic databases. Due to irrelevancy and duplications, a total of 761 publications were excluded based on reading the titles and abstracts. Of the 75 remaining articles, 62 full-text articles were excluded due to the absence of original data or to the other exclusion criteria, leaving 13 eligible trials. Two studies were identified by browsing the reference lists. In total, 15 full-text studies satisfied our inclusion criteria.

A total of 2349 epileptic patients were included in our analysis. The main characteristics and outcomes of the 15 included articles are summarized in Table 2. In most studies, the participants were enrolled after at least two seizure-free years (Donati et al., 1995; Emerson et al., 1981; Galimberti et al., 1993; Li et al., 2014; Murakami et al., 1995; Pavlovic et al., 2011, 2012; Shinnar et al., 1985; Su et al., 2013; Thurston et al., 1982; Tinuper et al., 1996). Shlomo Shinnar's experiment included patients who were seizure-free for 1 or more years, and 60 of these participants had been seizure-free for less than 2 years (Shinnar et al., 1994). The study by Todt enrolled 59 children who were seizure-free for at least 1 year (Todt, 1984). The other two studies did not mention the seizure-free period (Andersson et al., 1997; Olmez et al., 2009).

Table 1
Methodological quality assessment using the Newcastle–Ottawa quality assessment scale for cohort studies.

Author	Selection				Comparability		Outcome			Total
	1	2	3	4	1	2	1	2	3	
Emerson et al. (1981)	1	1	1	1	0	0	1	1	0	6
Thurston et al. (1982)	1	1	1	1	0	0	1	1	1	7
Todt (1984)	1	1	1	1	0	0	1	1	1	7
Shinnar et al. (1985)	1	1	1	1	0	1	1	1	0	7
Galimberti et al. (1993)	1	1	1	1	0	1	1	1	1	8
Shinnar et al. (1994)	1	1	1	1	0	1	1	1	0	7
Donati et al. (1995)	1	1	1	1	0	0	1	1	1	7
Murakami et al. (1995)	1	1	1	1	0	0	1	1	1	7
Tinuper et al. (1996)	1	1	1	1	0	1	1	1	1	8
Andersson et al. (1997)	0	1	1	1	0	0	1	1	0	5
Olmez et al. (2009)	1	1	1	1	0	0	1	1	0	6
Pavlovic et al. (2011)	1	1	1	1	0	0	1	1	0	6
Pavlovic et al. (2012)	1	1	1	1	0	0	1	1	1	7
Su et al. (2013)	1	1	1	1	0	0	1	1	0	6
Li et al. (2014)	1	1	1	1	0	0	1	1	1	7