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Original article

Quantitative EEG findings and response to treatment with antiepileptic medications in children with epilepsy

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Abstract

Background: Epilepsy is a common chronic disorder in pediatric neurology. Nowadays, a variety of antiepileptic drugs (AEDs) are available. A scientific method designed to evaluate the effectiveness of AEDs in the early stage of treatment has not been reported.

Purpose: In this study, we try to use quantitative EEG (QEEG) analysis as a biomarker to evaluate therapeutic effectiveness.

Methods: 20 epileptic children were enrolled in this study. Participants were classified as effective if they achieved a reduction in seizure frequency over 50%. Ineffective was defined as a reduction in seizure frequency less than 50%. Eleven participants were placed in the effective group, the remaining 9 participants were placed in the ineffective group. EEG segments before and after 1–3 months of antiepileptic drugs start/change were analyzed and compared by QEEG analysis. The follow-up EEG segments after the 2nd examinations were used to test the accuracy of the analytic results.

Results: Six crucial EEG feature descriptors were selected for classifying the effective and ineffective groups. Significantly increased RelPowAlpha_avg_AVG, RelPowAlpha_snr_AVG, HjorthM_avg_AVG, and DecorrTime_snr_AVG values were found in the effective group as compared to the ineffective group. On the contrary, there were significantly decreases in DecorrTime_std_AVG, and Wavelet_db4_EnergyBand_5_avg_AVG values in the effective group as compared to the ineffective group. The analyses yielded a precision rate of 100%. When the follow-up EEG segments were used to test the analytic results, the accuracy was 83.3%.

Conclusion: The developed method is a useful tool in analyzing the effectiveness of antiepileptic drugs. This method may assist pediatric neurologists in evaluating the efficacy of AEDs and making antiepileptic drug adjustments when managing epileptic patients in the early stage.

Keywords: Effectiveness; Antiepileptic drugs; QEEG; Epilepsy

1. Introduction

Epilepsy is the most common chronic disease in pediatric neurology. The prevalence ranges from 0.5% to 1%

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of the population [1]. Antiepileptic drugs (AED) are the mainstay of treatment for epilepsy. Sixty to seventy percent of those diagnosed with epilepsy can achieve good control of seizures with AED therapy [2]. However, 30–40% of the patients will continue to have seizures in spite of using a range of AEDs in adequate doses and even in various combinations [3]. Although many factors need to be considered in the selection of AEDs in the treatment of epilepsy, including its relative efficacy, serious toxicity, tolerability, ease of use, the presence of comorbid conditions, and cost of treatment, effectiveness of the drug in controlling seizures is the first priority of concern [4]. Currently, the effectiveness of AEDs is evaluated by observing long-term reductions in seizure frequencies. The unpredictability of seizures makes observations in clinical settings unreliable. Until now, there has been a lack of scientific biomarkers useful in evaluating the efficacy of AEDs.

In the past, pediatric neurologists have interpreted electroencephalogram (EEG) by visual inspection. Although quantitative EEG is more frequently used for research purposes in patients with epilepsy, nowadays, in clinical settings, most pediatric neurologists still analyze EEG data with the naked eye. In some epileptic syndromes, visual analysis of background EEG activity has been described as normal. However, the background EEG shows significant differences in EEG features when computer analysis is used. For examples, Santiago-Rodrıguez reports that patients with juvenile myoclonic epilepsy had an increase in absolute power delta, alpha, and beta bands when compared with EEGs from normal subjects [5]. Another quantitative EEG (QEEG) study of AEDs revealed that carbamazepine caused an absolute theta power increase and alpha mean frequency decrease. Oxcarbazepine caused an alpha mean frequency decrease. Valproate and lamotrigine did not decrease alpha mean frequency, but reduced broadband power [6]. The increase of absolute theta power may be associated with a sedative effect or neurotoxicity [7]. Accordingly, QEEG analysis is a useful tool to evaluate background EEG activity. In the present study, we used QEEG analysis as a biomarker to evaluate the therapeutic effectiveness of AEDs in patients with epilepsy.

2. Methods

2.1. Subjects

Twenty epileptic children (10 boys and 10 girls) were enrolled in this study. The diagnosis of epilepsy was made according to the criteria established by the International League Against Epilepsy (ILAE). The participants were divided into two epilepsy groups, effective and ineffective. A seizure diary was given to parents or guardian to record seizure frequency. Participants were classified as effective if they achieved a reduction in seizure frequency over 50% compared with the baseline following the start/change of an AED [8]. Ineffective was defined as a reduction in seizure frequency less than 50% compared with the baseline. The numbers of patients in the effective and ineffective classes were 11 and 9, respectively. The observation period for AED effectiveness in each patient was 6 months without a change of AED. The mean age of seizure onset in the effective group was 10 years 5 months $\pm$ 2 years 3 months and in the ineffective was 10 years 11 months $\pm$ 3 years 4 months. A written informed consent was given by a family member or legal guardian in each case. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUIRB-20120095).

2.2. EEG recordings

The same equipment and procedures were used for all patients when EEGs were recorded during the interictal state. Subjects were tested in a quiet air conditioned room with the experimenter and recording equipment present. All recordings were performed during the daytime (8:00 am to 5:00 pm). EEG data were digitally obtained by 21 electrodes at a sampling rate of 256 Hz (EBNeuro Mizar 33, Florence, Italy). Amplifier characteristics were bandpass filtered between 0.5 Hz and 60 Hz with 10,000 times gain. Electrodes were arranged based on the International 10–20 System.

2.3. EEG classification analysis

In this study, a classification analysis-based approach composed of a training phase and a classification phase, as shown in Fig. 1, was developed to determine whether the patient's AED treatment would be effective or ineffective. The training phase comprised four steps, namely EEG segment acquisition, global feature difference extraction, discriminative feature selection, and support vector machine (SVM) model training. First, two classes of EEG segments were acquired from EEG recordings of the effective and ineffective groups respectively. For each patient, several artifact-free EEG segments were acquired, in which the first was taken from the EEG recording before AED start/change (EEG1) and the second EEG was obtained from an EEG recording after 1–3 months of AED start/change (EEG2). Others were taken from EEG recordings after 6, 12 months of AED start/change (EEG3, EEG4...). Second, 216 EEG global features were extracted from each EEG segment to describe the statistical distributions of 24 quantitative univariate features of the EEG segment across channels as well as over time [9]. To represent the variation of each EEG global feature during the AED treatment process, the corresponding value before AED start/change was then subtracted from each of the corresponding values after AED start/change, resulting in a