Chapter

The Dynamic of EEG Characteristics in Epileptic Children during the Treatment with Valproic Acid

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Abstract

Anticonvulsant drug (AED) treatment in epileptic children should be optimized through the anticipation of AED effectiveness at the beginning of the treatment. Researchers thought that the complex EEG analysis should identify the AED treatment's output in children with epilepsy. The research purpose is to study the different EEG pattern bases on AED treatment. A total of 43 patients with ages of 3–9 years were studied. Three EEGs' registration took place: before valproic acid-depakin (Dep) treatment, second (3 months), and third (6 months) after treatment. The background EEG pattern was investigated as a quantitative [absolute power spectra (APs)] and brain mapping. In addition, epileptiform EEG and the clinical characteristics of patients were evaluated. Valproic acid reduces Aps in high-amplitude slow waves and spontaneous epileptic patterns decrease and spike-wave complex (3/s) reduces; spikes-polyspikes, sharp waves, and generalized paroxysms during functional tests decreased. The rhythmic monomorphic theta waves (RMT) of tempo-parietal region were studied using brain mapping. The RMT correlated with the recurrence of seizures if Dep was withdrawn. The AED treatment effectiveness had been shown by decreases of slow waves and suppression of epileptiform EEG pattern and clinical improvement. The effective AED therapy should consider the analysis of the base EEG pattern, power spectra, and EEG mapping.

Keywords: EEG pattern, epileptic children, therapy

1. Introduction

Depakin is an anticonvulsant drug (AED) [1, 2] according to the International League Against Epilepsy (ILAE) recommendations [3, 4]. Depakin increases the GABA-ergic inhibition in the neuronal networks of the CNS [5]. VPA derivative depakine (Dep) [6] exerts a combined influence on the brain's neurons. It increases the GABA content through GABA transfers inhibition, reducing the reuptake of GABA in the brain tissue and activating the GABA receptors. [5].

The EEG study during Dep treatment depends on the form of epilepsy [7]. EEG investigation in pediatric population during Dep treatment should be considered as a better approach [8–10] as brain malination is not completed [11–13].

Moreover, nowadays no data base analysis is done to study the correlation between EEG and AED treatment [14]. Another problem is that there are more data on the EEG morphology compared to the quantitative EEG analysis [15–18].

A quantitative analysis of the EEG should reflect the effectiveness of the AED treatment since the EEG disorders are connected with clinical exacerbation [14, 19–21]. Thus, this work's purpose is to investigate the alteration of EEG in epileptic children during AED treatment.

2. Materials and methods

2.1 Epileptic children

Forty-three patients with ages of 3–9 years and with different forms of epilepsy were recruited. Three EEGs' registration took place: before treatment, second (3 months), and third (6 months) after treatment with valproic acid-depakin (Dep), 30–50 mg/kg treatment. They appealed at the Center of Experimental Biomedicene.

The diagnosis was done based on the International Classification of Epilepsy and Syndromes [4], clinical history, and neurological and MRI investigations. Classification of patients by seizure types and epileptic syndromes accurately identified the patients at risk for Dep-exacerbated epilepsy [22, 23]. Study involved both EEG and clinical analyses. Patients were characterized for the Dep dose, type and frequency of seizures, and EEG and Dep plasma levels [24, 25], both before and during the treatment. Out of 45 patients who received treatment, three of them developed undesirable effects. Although the physician adjusted the Dep dose, it did not improve the clinical outcome in two patients. Thus, these patients were excluded from the study. In summary, the present study included only 43 children of 3–9 years of age (**Table 1**).

The EEG investigation followed international performance standards [26] as part of the prescribed therapy plan. This plan was also approved by the parents and institutional ethics committee.

2.2 The EEG recording and methods of analysis

All patients underwent EEG recording three times: once—before administration of Dep (first visit) and twice—during Dep treatment, (i) 3–4 months later (the second visit) and (ii) 6–8 months later (the third visit).

The EEG registration was done with closed and open eyes. Functional test was performed with rhythmic photostimulation; hyperventilation and registration were ended with closed eyes. The duration of registration was 35–55 min.

The EEG signals were digitally recorded using a set of 19 scalp electrodes according to the International 10–20 system [26] and ENCEPHALAN 131–03, professional version "MEDICOM."

For an individual patient, a 10 s, artifact-free EEG pattern was analyzed.

A qualitative assessment of the EEG characteristics was performed in accordance of the age standards [27].

A quantitative EEG pattern of signal processing and the power spectrum was obtained for each lead. The spectral analysis was used to calculate the absolute value [28] of power (AVP, μV^2s) within six frequency bands: delta (0.5–4.0 Hz), theta-1 (4.0–6.0 Hz), theta-2 (6.0–8.0 Hz), alpha (8–13 Hz), beta-1 (13–24 Hz), and beta-2 (24–50.8 Hz) (**Figure 1**).

Number of patients	43 (26 male, 17 female)
Age (year)	
Mean ± SD	5.3 ± 1.23
Range	2.11–8.10
Onset of epilepsy	
Age (year)	4.3 ± 1.1
Range	2.00–5.37
Interval from the first to second seizures	
<1 week	3
1 week–1 month	14
1 month–1 year	21
>1 year	3
Unknown	2
Seizure types	
GS	
ABS	14
TN	5
CL	7
TN-CL	8
PS	
SPS	2
CPS	3
PSG	4
Etiology	
Post-traumatic	2
Perinatal	18
Neonatal	5
Febrile	8
Unknown	10
EEG findings	
Generalize	20
ABS	13
Focal (sharp waves, spikes, SW, etc.)	5
PSG	5

GS: generalize seizure; ABS: absence; SPS: simple partial seizure; CPS: complex partial Seizure; and PSG: partial, sometimes with secondarily generalization.

Table 1.
Characteristic of patients.

Alpha, beta, delta, and theta frequency bands were characterized by the wave amplitude, stability, and domination area.

Brain topography was conducted for the quantitative study.

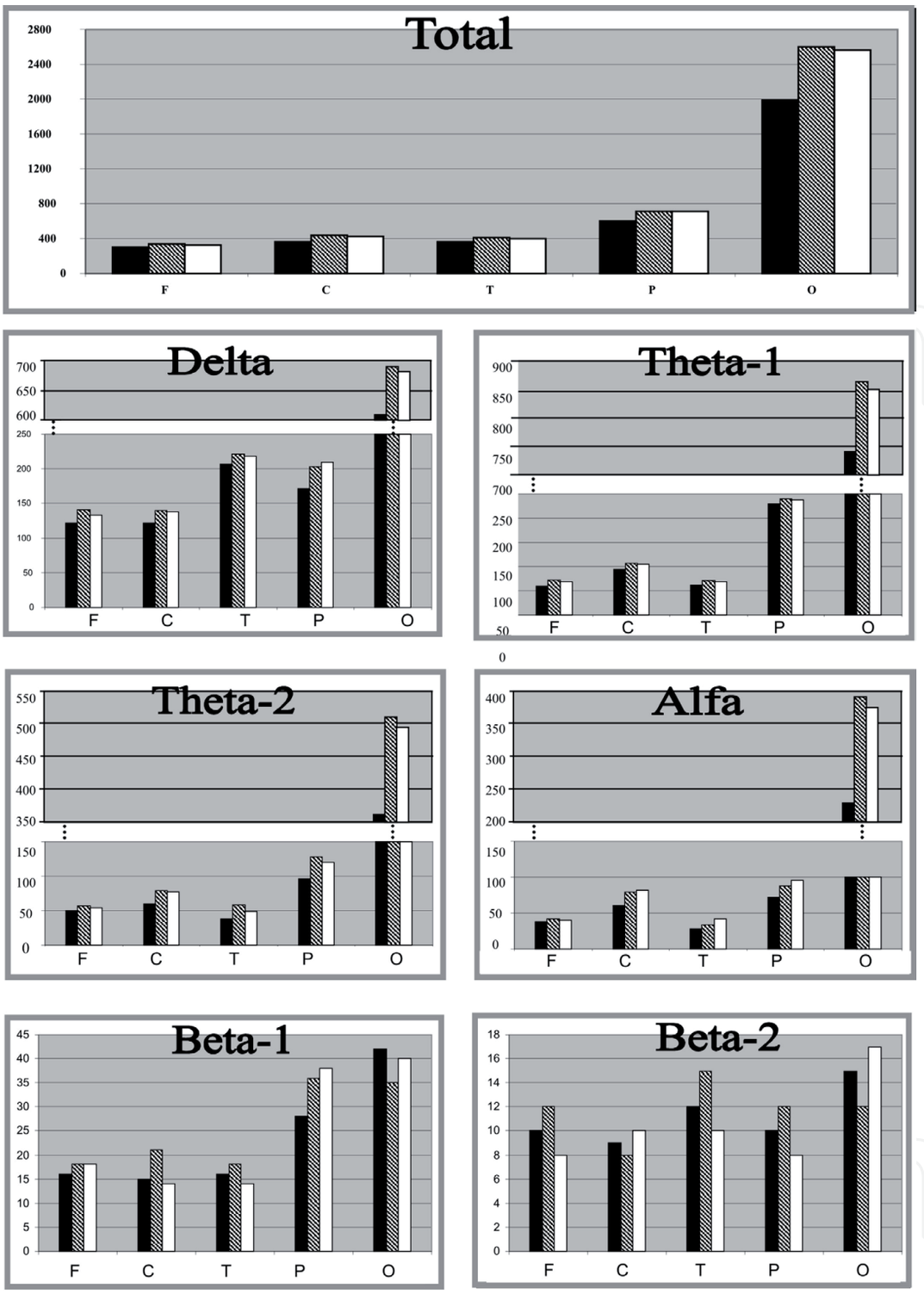

Figure 1.
Dynamics of absolute values of power spectra (AVP) at different stages of treatment. Summarizes results obtained from the quantitative analysis of the EEG dynamics, total of AVP (TAVP), and below the AVP of different frequency bands. X-line: F-frontal, C-central, T-temporal, O-occipital, and P-parietal regions of the brain cortex. Black columns—before treatment, shaded columns—3 months, and white columns—6 months after the initiation of Dep treatment. Y-line: power value—μV^2s.

2.3 Statistical analysis

Statistical significance for each endpoint measures was assessed using Mann–Whitney U-test (BIOSTAT). The data obtained before treatment served as a baseline for assessing the dynamics of EEG characteristics during treatment. Thus, each subject served as its own control in the evaluation of EEG during treatment.

The changes in the EEG characteristics were assessed using Wilcoxon signed-ranks test [29]. The significance was set at $p < 0.05$.

3. Results

EEG before administration of Dep can be described as the deceleration of the background EEG due to augmentation of the high-amplitude poly- and monomorphic waves within the low-frequency range. Quantitative spectral analysis (brain mapping) of interictal EEG revealed that, in the total EEG spectrum, the most dominant are the oscillations of 3–8 Hz with a prevalent amplitude of 60–120 μv.

Dep reduced the amplitude in the low-frequency range ($p < 0.05$).

3.1 Qualitative EEG study

The qualitative analysis revealed that the Dep therapy reduced the number of spontaneous paroxysmal discharge (by 76%) in the resting EEG and suppressed primarily the typical epileptiform complexes of spike-waves (SW) (3/s) (absence) [30, 31].

3.2 Quantitative EEG study

The quantitative analysis showed reduction of frequency ($p < 0.05$).

The Aps dynamics revealed the reduction of the incidence of low-frequency waves ($p < 0.05$), especially this effect was more prominent for the theta range.

Following the initial reduction of APs' alpha activity, especially in the occipital region ($p < 0.05$), this index did not show any further decline ($p < 0.05$).

Dep treatment produced a decreased brain activity within the range of beta ($p < 0.05$) [32].

The presence of a rhythmic monomorphic mid–/high-amplitude theta waves despite clinical improvements (seizure-free and no epileptiform EEG correlates) can provoke seizures after the Dep withdrawal. Seizures recurred due to not only Dep withdrawal but also due to dose reduction in patients. This aggravation of epilepsy was found in 64% of patients [33–35]. The rhythmic monomorphic mid–/high-amplitude theta waves can be observed using brain mapping and power spectra. Such a pattern is not visible in the visual EEG observation.

Dep therapy did not show a EEG clinical aggravation that was diagnosed with the criteria of Genton and McMenamin [33].

Dep treatment decreased the number of seizures. The clinical signs and EEG pattern are described in **Table 2**.

Clinical follow-up	**EEG**				
	Complete normalization EEG	**Improve EEG**	**No EEG change**	**EEG worse**	**Total**
Clinical improvement number (%)	33 (80%)	8 (18%)	1 (2%)		42
No clinical change number (%)			1 (2%)		1
Clinical aggravation number (%)					
Total number (%)	33 (80%)	8 (18%)	2 (3%)		43

Table 2.
Clinical outcome and EEG record in 46 patients.

4. Discussion

Antiepileptic therapy in children can be optimized via the anticipation of the efficacy of AED during the early stages of therapy. Since EEG provides rich information about the brain activity, we hypothesized that the comprehensive EEG evaluation during Dep therapy in the children with epilepsy can be a sensitive indicator of the efficacy of the treatment.

Dep therapy induced decreases of APs of low-frequency waves, which is an indicator of reducing of CNS excitation. Dep reduces beta bends in the posterior lobes, which is related with the CNS dysfunction [32].

Dep reduces spike-waves (3/s), which is related to the absence of epilepsy that is triggered from the thalamocortical pathway. Dep was considered as an effective drug in such cases [31, 36, 37].

Dep does not have an effect on irregular single spike-wave complexes, sharp waves, spikes-polyspikes, and paroxysmal bursts provoked by functional trials. These cases reflect certain specificity of epileptogenesis [7, 38]. Dep differently acts on the generation of epileptiform elements with various morphologies—particularly, it suppresses SW complexes (3/s) but does not have a good effect on irregular single spike-wave complexes, sharp waves, and spikes. Such a picture allows us to suggest the differences in the morphology of epileptiform elements that may reflect different neurophysiological and neurochemical mechanisms [3, 7, 39]. Revealing of selectivity represents certain theoretical and practical interests as it can serve as an indirect evidence of assumptions in the genesis of various epileptiform EEG elements and accordingly different types of epileptic attacks [39, 40]. Other researchers like Truccolo et al. [41] apparently pay attention to the morphological pictures of background EEG [13].

VPA was shown different activity and is not effective of any type of epilepsy [38]. The possibility of Dep treatment of non-epileptic paroxysmal conditions in children and adolescents [42–45] and the investigation of children with partial epilepsy during carbamazepine (CBZ) treatment were described in our previous investigation [46].

Brain mapping revealed the essential prognostic value of morphology of the theta waves and its distribution upon the cortical surface. The EEG pattern was revealed before treatment initiation and was persistent during Dep therapy. The presence of rhythmic monomorphic mid-/high-amplitude theta waves on the EEG, especially of the temporoparietal regions, despite clinical improvements (seizure-free and no epileptiform EEG correlates) may suggest the possible recurrence of seizures after withdrawal of Dep. Not only withdrawal but even reduction of doses can lead to a recommencement of the attacks in this group of patients. Such a feature of VPA suggests that its antiepileptic effect is achieved via neurophysiological and molecular mechanisms, which partly differ from the action mechanisms of other AEDs [33, 34]. Analysis of basic characteristics of EEG during the treatment suggests that the rhythmic monomorphic mid–/high-amplitude theta waves are predicting signs of aggravation. Such an EEG pattern is revealed based on the evaluation of background EEG characteristics, spectral analysis, and EEG mapping using a quantitative EEG approach.

AED treatment should be done under a regular EEG control due to aggravation of the EEG pattern, which sometimes predicts the clinical signs of exacerbation [47, 48].

Reduction of slow wave concomitant with decreases of epileptiform pattern and clinical signs at 3 months after DEP treatment suggests that the treatment is effective in these cases [49].

5. Conclusions

The EEG study suggests that the presence of rhythmic monomorphic theta waves with the tempo-parietal region should anticipate the recurrence of epilepsy in children with epilepsy, if the Dep dose would be reduced or if the Dep therapy would be withdrawn. The efficacy of Dep treatment should be correlated with decreases of high amplitude, low frequency, and suppression of epileptiform EEG parallel to the clinical improvement. Thus, optimal therapy suggests of evaluation of baseline EEG, power spectra, and brain topography mapping using EEG methods.

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