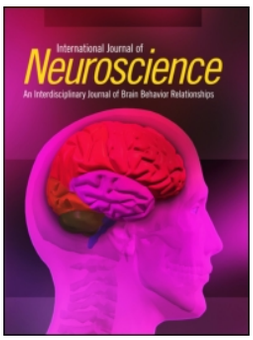

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ORIGINAL ARTICLE

The investigation of EEG specificity in epileptic children during Depakine therapy

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Background: Antiepileptic drug (AED) therapy in epileptic children can be optimized via an anticipation of AED efficacy during early stages of therapy. We hypothesize that the comprehensive electroencephalography (EEG) evaluation can determine AED efficacy in epileptic children. Thus, this study aimed to investigate the alteration of characteristics of interictal EEG during the AED therapy. *Methods*: Forty-three children aged 3–9 were investigated. EEGs were recorded three times: prior to valproic acid-Depakine (Dep) monotherapy and twice under the Dep therapy (at three and six/eight months). Baseline EEG was analyzed for quantitative characteristics of interictal EEG, such as absolute values of the power (AVP) spectra and EEG topography/brain mapping. The study involved epileptiform EEG and clinical condition assessments. *Results*: Dep decreased AVP spectra in a low-frequency range, suppressed spontaneous epileptic discharge, and spike-wave complex 3/s. Dep partially decreased spikes-polyspikes, sharp waves, and generalized paroxysmal bursts during functional trials. Dep did not diminish rhythmic monomorphic theta-waves (RMT) of tempo-parietal localization observed by brain mapping. The presence of RMT correlated with the reocurrence of seizures if Dep was withdrawn. *Conclusions*: The findings of this study suggest that the presence of RMT with tempo-parietal localization on the interictal EEG can anticipate reocurrence of seizures if Dep dose will be reduced or withdrawn. The efficacy of the AED therapy can be revealed via reduction of low-frequency waves and suppression of epileptiform EEG elements parallel to clinical improvement. Thus, optimal treatment strategies can be tailored based on the evaluation of background EEG characteristics using spectral analysis, EEG mapping, and the quantitative EEG approach.

KEYWORDS: EEG power spectra, pediatric epilepsy, treatment, RMT

Introduction

Valproic acid (VPA) and its derivatives are one of the widely used basic, antiepileptic drugs (AED) [1,2]. According to the International League Against Epilepsy (ILAE) recommendations, VPA has been considered the first choice of AED in the treatment of epileptic seizures [3,4]. One of the reasons is that VPA enhances the gamma amino butiric acid (GABA)-energic inhibition in the neuronal networks of the central neural system (CNS) [5]. VPA-derivative Depakine (Dep) [6] exerts a combined influence on the brain neurons. It increases the GABA content in neurons through GABA-transferase (GABA-transaminase) inhibition and in the synapse through reducing of GABA reuptake that results in the activation of GABA receptors in the neuronal membrane [5]. In turn, it decreases the excitation and readiness to seizure activity in cortical areas contributing to the motor behavior.

The EEG examination of the patients under the Dep therapy suggests that treatment should be tailored with regard to the epilepsy type, individual EEG pattern and dynamics, and clinical manifestations [7]. Thus, the interictal EEG analysis under the Dep therapy can offer better treatment strategy as well as a predict possibility of recurrent seizures in epileptic children [8–10]. Evaluation of the EEG dynamics during the treatment is especially important for the pediatric epileptology, because the brain and EEG (basic rhythm) are not fully matured and this makes children more vulnerable to environmental insults [11–13]. Lack of the systemic analysis of EEG characteristics during pharmacotherapy

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also hinders our understanding if EEG can be an early predictor of beneficial/adverse effect of the AED therapy [14]. Moreover, up to now, alterations of EEG characteristics are mostly studied with respect to qualitative aspects of epileptic activity (spikes, sharp waves, etc.), whereas the data on quantitative characteristics of baseline activity in interictal period are less [15–17].

Clinical improvement in epileptic children due to the AED therapy is not always accompanied by the improvement in EEG pattern. On the contrary, the improvement of EEG pattern due to AED not always indicates remission [14,18,19]. As a result, it is difficult to determine the efficacy of the AED therapy; selection of an appropriate AED and its dose, and a timely replacement of ineffective AED also affect the evaluation of the AED therapy efficacy, especially in children [14]. Thus, the evaluation of interictal EEG using quantitative analysis might determine the efficacy of the AED therapy [9,13,20]. Such investigation is also very important because the characteristics of EEG abnormalities may sometimes signal the aggravation of clinical signs [14,21]. The study aims to evaluate alterations of the EEG characteristics under the Dep therapy.

Materials and methods

A group of children was studied for both epileptiform EEG correlates and background EEG. The EEG recording was evaluated for quantitative and qualitative aspects of interictal EEG in parallel to clinical assessment.

Patients

Forty-five patients with different types of seizures were referred to the I.Beritashvili Center of Experimental Biomedicine, Tbilisi and Tatishvili Medical Center, Tbilisi, Georgia. The patients received the Dep monotherapy with a daily dose of 30–50 mg/kg. They had epilepsy with at least two seizures in six months prior to enrollment into the study.

The patients were diagnosed according to the International Classification of Epilepsy and Epileptic Syndromes [4], based on the clinical history, neurological examination, and detailed investigation including neuroimaging (MRI) and blood studies. These investigations, besides classification of patients by seizure types and epileptic syndromes, gave us the opportunity to accurately identify the patients at risk for adverse effects of the Dep therapy [22,23]. The study involved both EEG and clinical analysis. Patients were characterized for Dep dose, the type and frequency of seizures, EEG and Dep plasma levels [24,25] both before and during the treatment.

Table 1. Characteristic of patients.

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 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, s/w, etc.)	5
PSG	5

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

Parents and family members were asked for improvement or worsening of the patient's condition before and during the Dep treatment. In addition, clinical signs on the skin, the digestive tract dysfunctions, and associated abnormalities neurological (nystagmus, ataxia, headache, and tremor) were assessed at each visit. Out of 45 patients who received treatment, 3 of them developed undesirable effects. The most common side effects were the disturbances of the digestive tract, the most extended side effect of Dep – pancreatitis and the disturbance of the function of the liver (hepatomegaly, vomiting and of others). The dose correction had no effect on persistent side-effects in two patients. The Dep treatment was canceled in a month. Therefore, these patients with a drug-induced intoxication were excluded from the study. In summary, this study included only 43 children of 3–9 years old (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. The research was approved by the local Bioethics Committee – The Bioethics Committee of I.Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia, and research was carried out in accordance with the World Medical Association Helsinki Declaration. The parents gave informed written consent.

The EEG recording and methods of analysis

All patients underwent EEG recording three times: once – before the administration of Dep (first visit) and twice – during the Dep treatment, (1) 3–4 months later (the second visit) and (2) 6–8 months (the third visit). The EEG recording was performed at the same time of the day, in the morning. An EEG trial without functional load preceded the EEG recording with a functional load. The Dep dose was reduced in 12 patients with absence seizures after 8 months due to clinical and EEG improvement.

The EEG without functional trials was recorded with eyes closed (3 minutes), with eyes open (2 minutes) and once again with the eyes closed (3 minutes). Functional trials were performed with rhythmic photostimulation, at frequencies 3–5–10–15–20 Hz; hyperventilation (3 minutes) – with open, closed eyes, and the breath hold (15–25 sec); recording was finished with closed eyes. The mean duration of EEG recording was 35–55 minutes.

The ENCEPHALAN 131-03 software "MEDICOM" (Russia) digitally recorded 19 scalp electrodes, according to the International 10-20 system [26]. The band pass of the amplifiers was 0.5–100 Hz and notch filter was 50 Hz. The signals from each input electrode were digitized with the sampling rate of 256 Hz with the resolution of 16 bits. Electrode (Ag/AgCl) specific resistance was not higher than 5 kΩ

For each patient, 10 sec artifact-free EEG epochs were selected (at rest, with open and closed eyes). Total of 10–15 fragments for each patient was analyzed.

The quantitative analysis was conducted on eight EEG fragments without epileptiform elements in each patient and their number was constant. However, EEG fragments for spike counts varied (2–7), since the number of spikes varied among patients.

A qualitative assessment of the EEG characteristics was performed in accordance with age standards [27,28]. EEG was analyzed for abnormal epileptiform EEG activity: (1) spike discharges, sharp waves, and paroxysmal burst; (2) the spike density within 10 sec; and (3) the number of paroxysmal discharges of 15 sec long.

A quantitative analysis of the EEG epochs was conducted using a fast Fourier transformation (FFT) algorithm. The spectral analysis was used to calculate absolute value 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), Beta-2 (24–50.8 Hz).

A relative contribution of various frequencies to an overall signal was calculated by FFT for power at a given frequency. Alpha, beta, delta, and theta frequency bands were characterized by the wave amplitude, stability, and domination area. AVP was used as an indirect measure of the wave amplitude. Stability was assessed by the coefficient of variation $< 33\%$. The dominant area was defined in accordance of maximum AVP. Since alpha, delta, and theta waves are synchronized, the rhythmicity and degree of synchronization was also evaluated visually. The gradient was quantified only for the alpha frequency band because of its modulation due to the ongoing brain maturation.

Features of the response in functional trials (photostimulation and hyperventilation) were also assessed.

Brain mapping, that is the topography of the EEG spectral characteristics, such as a spatial distribution of the activity of the separated frequency ranges over the brain surface was also examined. The topography was analyzed for EEG epochs used for the quantitative analysis.

Statistical analysis

Statistical significance for each end-point measures was assessed using Mann–Whitney U-test (BIOSTAT). The data obtained before treatment served as a baseline for assessing the dynamics of EEG characteristic 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 $p < 0.05$.

Since all patients underwent EEG recording three times: once – before administration of Dep (first visit) and twice – during the Dep treatment, 3–4 months later (the second visit) and 6–8 months (the third visit) multiple comparison was conducted. Dennett's test was used to compare the second and third visit to the first visit. Paired *t*-test was used for the second and third visit.

Results

The baseline EEG pattern before starting the Dep therapy had been decelerated due to the presence of low-frequency high-amplitude poly- or monomorphic waves. Quantitative spectral analysis (brain mapping) of interictal EEG revealed that in the total EEG spectrum, the

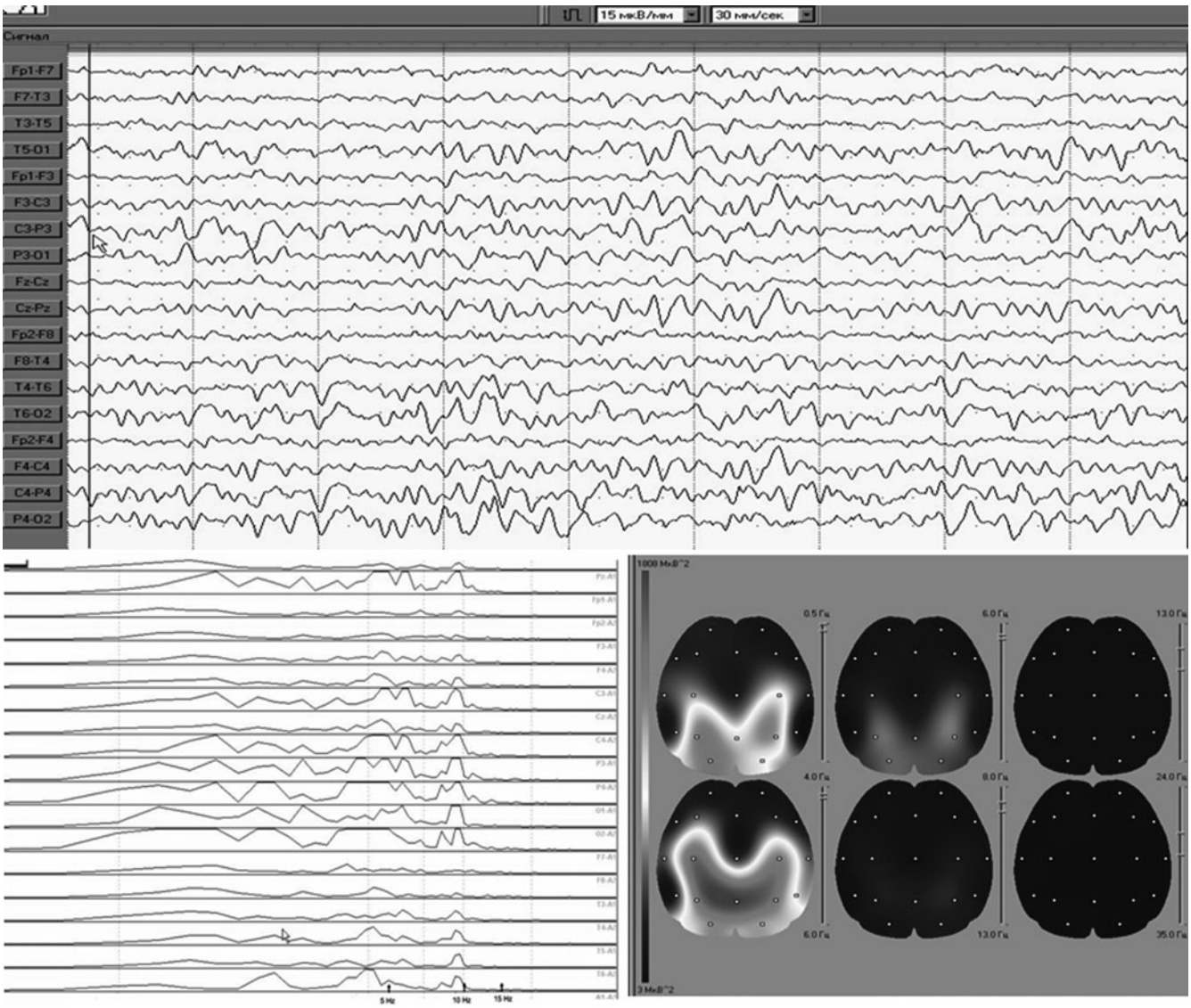

Figure 1. Mapping of the EEG spectral characteristics. Spatial distribution of the activity of the separated frequency ranges over the brain convexital surface. Sample picture of power spectra in patient (female, 5 year). Oscillations of 3–8 Hz with prevalent amplitude of 60–120 μV.

most dominant are the oscillations of 3–8 Hz with the prevalent amplitude of 60–120 μv (Figure 1).

Qualitative EEG evaluation during the Dep treatment

The qualitative analysis revealed that spontaneous paroxysms reduced by 76% (in average the paroxysm observed were 1.1 ± 0.5) in the resting EEG. Dep suppressed primarily 3 Hz SW (spike-wave complexes) in a typical absence seizure. Dep has the most beneficial effect in patients with absence epilepsy.

The Dep therapy tended to reduce the incidence of irregular single spike-waves complexes, sharp waves, spikes-polyspikes, as well as on generalized paroxysmal bursts provoked by functional tests, but the Dep therapy-induced changes did not reach statistically significant level.

Quantitative EEG evaluation during the Dep treatment

The quantitative analysis of total AVP revealed a significant reduction in all frequency bands through the cortex ($p < 0.05$). Figure 2 shows total AVP and its dynamics at the third and sixth months of the Dep treatment.

The spectral analysis of AVP dynamics (in separate frequency range) revealed that the Dep therapy-induced

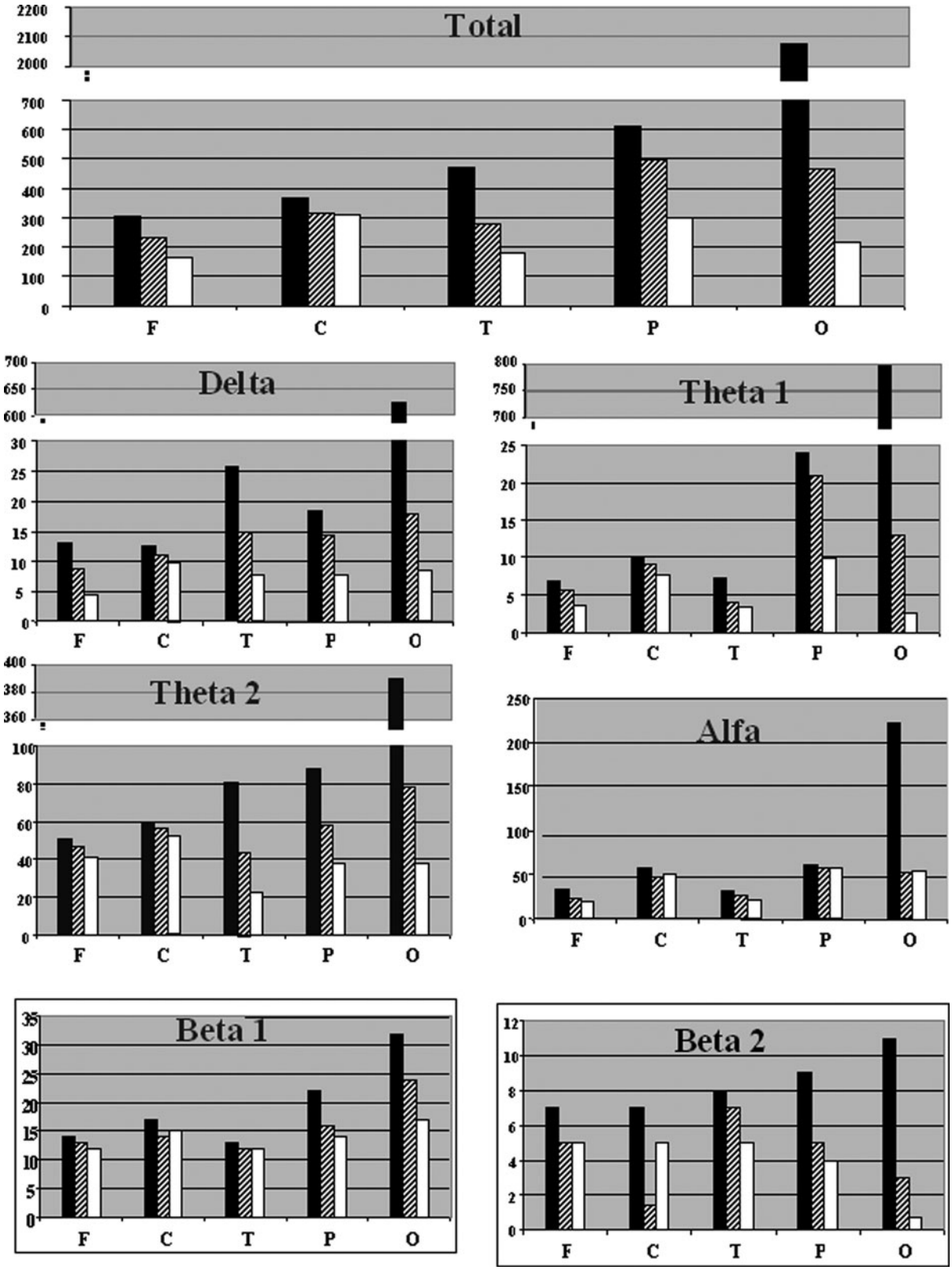

Figure 2. Dynamics of absolute values of power spectra (AVP) at different stages of treatment summarizes results obtained from the quantitative analysis of the EEG dynamics, total of AVP (TAVP); below the AVP of different frequency bands. X-line: F-frontal, C-central, T-temporal, O-occipital, P-parietal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

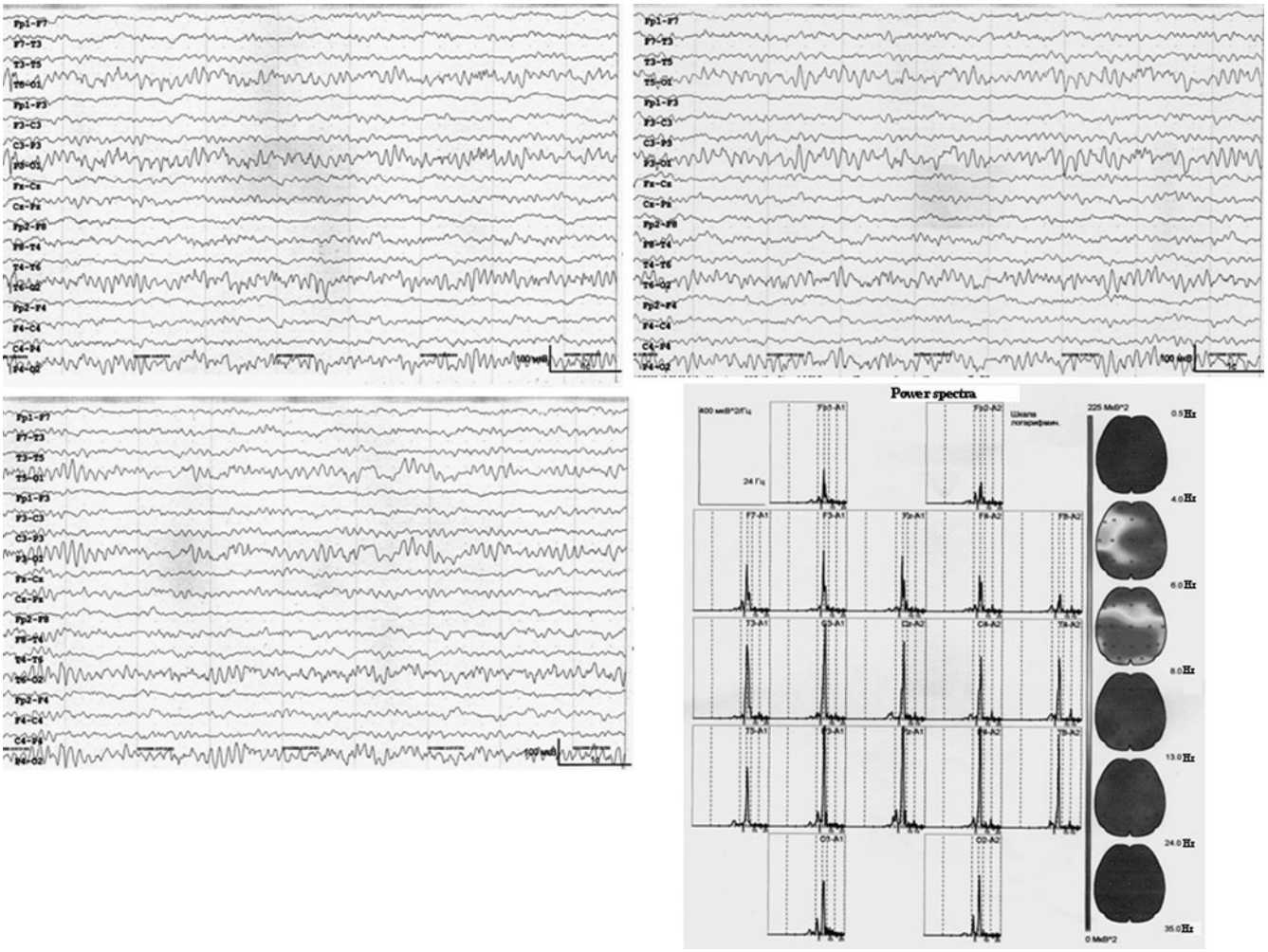

Figure 3. The rhythmic monomorphic mid/high amplitude theta-waves can be observed using brain mapping and power spectra. This activity is not obvious during the visual inspection of EEG.

decreases of AVP stemmed from the reduction of the incidence of low-frequency waves ($p < 0.05$), especially this effect was more prominent in the theta range.

The DEP therapy significantly reduced AVP of alpha rhythm especially in the occipital region at the third and the sixth months of treatment compared with the first visit ($p < 0.05$). However, following the initial reduction of AVP alpha activity especially in the occipital region ($p < 0.05$), this index did not show any further declined at the sixth month of the Dep treatment compared to the index measured at the third month of the Dep treatment.

Brain activity within the Beta-1 and Beta-2 range in the parietal and occipital areas revealed reduction ($p < 0.05$).

AVP dynamics was analogous in both hemispheres. No interhemispheric specificity was seen in the dynamics of the frequency ranges analyzed.

Rhythmic monomorphic mid/high amplitude theta-waves (RMT) in temporo-parietal regions were revealed before the Dep treatment using brain mapping. The activity was persistent during the Dep therapy**.** After the improvement of EEG and clinical signs, showed in Dep-treated patients ($n = 12$) with absence epilepsy, the Dep dose was reduced at the eighth month. Seizures reoccured in 64% of these patients ($n = 7$). All of them had RMT on EEG.

The presence of an RMT despite the clinical improvements (seizures free and no epileptiform EEG correlates) can provoke seizures after the Dep withdrawal. In all patients (100%) with RMT on the EEG, reoccurrence of seizure after Dep withdrawal was observed. Seizures occurred not only after the Dep withdrawal, but the even administration of lower doses. Figure 3 shows that RMT can be observed using brain mapping and power spectra. This activity is not obvious during the visual inspection of EEG.

The Dep therapy reduced the number of high-amplitude (>100 μV) poly-morph waves in a low-frequency range. In turn, it reduced disorganized and

Table 2. Clinical outcome and EEG record in 43 patients.

	EEG				
Clinical follow-up	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

excessive synchronization of basic EEG. The effect was most apparent in 4–6-year-old children.

The Dep therapy did not worsen EEG and/or clinical signs of epilepsy. Aggravation of epilepsy by AED was diagnosed with the criteria of Genton and McMenamin [30].

The Dep therapy reduced the seizure frequency. The clinical outcomes and EEG findings are described in Table 2. Forty-one patients showed both clinical and EEG improvement. One patient showed a 50% decline in seizure frequency (without any change in the EEGs). No clinical and EEG changes were found in one patient, however, the Dep therapy tends to decrease the duration of individual seizures.

Discussion

It is essential to determine the efficacy of the AED therapy in children with epilepsy at the early stage of the treatment. Since EEG provides rich information about brain activity, we hypothesized that the comprehensive EEG evaluation during the Dep therapy in the children with epilepsy can be a sensitive indicator of the efficacy of the treatment.

Dep reduced the degree of disorganization of basic EEG rhythmicity of high-amplitude waves in low-frequency range, suppressed a spike-wave complex and decreased total AVP spectra, especially in parietal/occipital cortex. The Dep therapy decreased the beta activity in the parieto-occipital lobes, the regions where its presence is conventionally accounted for the CNS regulatory mechanisms dysfunction [31]

Dep suppresses the first of the typical epileptiform complexes SW 3/s which is characteristic for absence epilepsy generated by thalamo-cortical structures. This effect was observed as early as three months after the beginning of the treatment and Dep was evaluated as successful at complete elimination of epileptiform elements in EEG [32–34].

Dep reveals less effect on the irregular single spike-waves complexes, sharp waves, spikes-polyspikes, and as well as on generalized paroxysmal bursts provoked by functional trials, and Dep was not considered as fully successful. These cases reflect the certain specificity of epileptogenesis [35,36]. Dep differently acts on the generation of epileptiform elements with various morphologies – particularly, suppresses SW complexes 3/sec, but only partially reduces irregular single spikes, sharp waves, etc. Such picture allows us to suggest that the differences in the morphology of epileptiform elements may reflect different neurophysiological and neurochemical mechanisms [3,37]. Localization of the zone of initiation of epileptic activity might help better understand the intimate mechanisms of epileptogenesis [38–40]. The different types of epileptic attacks are accorded with various epileptiform EEG elements that could suppose the mechanism of epileptogenesis [41,42]. On the other hand, by Truccolo et al. [43], differences in the activity of neurons in the epileptic focus may be reflected in the morphology of epileptiform elements of the total EEG. In clinical epileptology, apparently, should be paying more attention to the morphological characteristics of epileptiform elements and baseline activity [13,39].

VPA revealed a broad spectrum of activity and is not contraindicated in any seizure type [3,35,44]. The results have shown that VPA and drugs from this group reduced the degree of disorganization of basic rhythmicity of EEG due to decreasing of low-frequency range within the total spectra of bioelectric activity. This indicates that Dep reduces (32–45%), in the first of all, the signs of excessive disorganization and synchronization of resting EEG, which is indicative of the decrease in the CNS threshold of seizure readiness [16,45,46]. According to the present opinion on the genesis of basic EEG rhythm, the effect of Dep probably involves the changes in cortical neuronal activity [38,41]. The possibility of using Dep in the management of non-epileptic paroxysmal conditions in children and adolescents for determining the response to the therapy was investigated by our previous studies [45,47]. The decrease of interictal discharges with the Dep treatment occurred in primary generalized epilepsy more than for focal epilepsies, that was confirmed by our research [48] and studies of other authors [16,36]. EEG investigation and study of patients with partial epilepsy during the carbamazepin (CBZ) therapy was discussed in our studies [49]. CBZ suggests that its anti-epileptic effect is achieved via neurophysiological and pharmacological effect that partly differ from the action mechanisms of other AEDs, especially from valproate derivatives [42,44,46]

Brain mapping revealed the essential prognostic value of morphology, the theta-waves, and its distribution upon the cortical surface. The RMT pattern was revealed before treatment initiation and was persistent during the Dep therapy. In those patients with typical absence seizures, who showed the improvement of EEG and clinical signs of epilepsy, the Dep dose was reduced after eight months of the treatment. Patients with RMT on the EEG started having the reoccurrence of seizure. The presence of RMT on the EEG especially of the temporo-parietal regions despite clinical improvements (seizures free and no epileptiform EEG correlates), may suggest possible reoccurrence of seizures after withdrawal of Dep. Not only withdrawal but even an administration of lower doses can lead to a recommencement of the attacks in this group of patients. The fact that Dep could control absence seizures but failed to suppress RMT suggests that RMT likely is caused by neurophysiological and molecular mechanisms different from those absence seizures. Thus, we could speculate that either these patients should remain on Dep; or polytherapy would be more efficient to suppress both absence seizures and RMT.

The inefficiency of Dep in the children with the absence seizures with RMT could be also associated to maturational processes of the brain [50]. In this study, the rhythmic theta activity is co-existed with the absence seizures. Guilhoto et al. reported that the occipital intermittent rhythmic delta activity (OIRDA) is in association with absence epilepsy in the comparable age group [51]. Therefore, rhythmic monomorphic activities of slow activity co-existing with absence seizures can be specific for childhood epilepsy.

Based on our observation, we cannot reach any conclusion on the origin and mechanisms of RMT. As we argue in the manuscript, RMT activity could not be considered as a subclinical ictal activity because RMT was not suppressed by the Dep therapy. Alternatively, Guilhoto et al. considered the rhythmic delta activity as an epileptiform because AEDs controlled both absence seizures and rhythmic delta activity.

Analysis of basic characteristics of EEG during the Dep treatment suggests that the RMT are predicting signs of aggravation of seizure. Our finding is in line with the previous observation on prognostic features OIRDA for typical absence epilepsy in children [51]. Although OIRDA was considered as epileptiform EEG patter [51], the origin and mechanisms of RMT are not obvious from this study and needs further investigation.

In another study (case report – non-paraneoplastic limbic encephalitis characterized by mesio-temporal seizures and extratemporal lesions), EEG monitoring showed seizure pattern consisting of temporo-parietal, rhythmic theta waves followed by spiking activity [52].

Characteristics of EEG abnormalities have become evident (sometimes triggered) by prescription of incorrect treatment [14]. Our data highlight the importance of detail analysis of EEG during the AED therapy to identify changes predicting a possible aggravation of the epileptic disease. The AED therapy should be performed with maximal caution and under regular EEG control, because worsening of EEG characteristics, in some cases, precedes the onset of clinical signs of exacerbation of the patients [50,53,54].

The necessity of regular EEG control throughout the treatment period is recommended no less than once in three months [12]. Such control is more important in children with recent onset seizures [26]. Incomplete myelination may induce incorrect EEG feature [13]. Reduction of high-amplitude low-frequency wave concomitant with suppression of epileptiform elements and seizure fit at the three months after initiation of the DEP therapy suggests that current treatment is effective enough to be continued in the particular patients.

Conclusions

The findings of this study suggest that the presence of rhythmic monomorphic theta-waves with tempo-parietal localization on the interictal EEG can anticipate recurrence of seizures if Dep dose will be reduced or the Dep therapy will be withdrawn in these patients. The efficacy of the Dep therapy can be identified via reduction of high-amplitude low-frequency waves and suppression of epileptiform EEG elements parallel to clinical improvement. Thus, optimal treatment strategies can be tailored based on the evaluation of background EEG characteristics, spectral analysis, and EEG mapping using the qEEG approach.

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Declaration of Interest

The authors have no conflict of interest to declare.

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