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Original article

Analysis of EEG dynamics in epileptic children during carbamazepine therapy

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Background: The analysis of the dynamics of background EEG characteristics on the different stages of CBZ-therapy is very important for revealing the possible early predictors of benefit/adverse effects of the treatment and optimizing the anti-epileptic therapy.

Objective: Evaluate the carbamazepine (CBZ) effect on the dynamics of EEG pattern in epileptic children at different stages of CBZ-monotherapy.

Methods: Forty-five children (aged 3-9) with partial epilepsy were investigated. The EEG was recorded at rest and during functional tests prior to CBZ administration and three and six months after the initiation of CBZ-therapy. Epileptiform graphoelements and baseline EEG activities were analyzed.

Results: Following three months of CBZ-therapy an absolute power value in the low frequency bands of EEG spectrum increased while an average frequency of alpha waves decreased. During rest, CBZ reduced density of spontaneous epileptiform graphoelements and generalized epileptiform bursts. Generalized paroxysmal bursts decreased under functional tests. The EEG pattern maintained the same characteristics for six months. Deterioration of EEG pattern and clinical signs was observed in four children.

Conclusion: Elevation of indices of low frequency bands, especially in occipital and parietal regions, concomitant with reduction of epileptiform elements and seizure frequency three months after initiation of therapy suggests that CBZ in appropriate doses might be continued. Otherwise, the strategy of antiepileptic therapy should be revised.

Keywords: Carbamazepine, children, EEG power value, epilepsy

According to the ILAE recommendations, Carbamazepine (CBZ) has been considered the first choice AED in treatment of partial epileptic seizures, including the fits with secondary generalization [1]. Taking into account the prevalence of partial (localization-dependent) seizures present in up to 60% of all forms of epilepsy in children and about 80%-in adults [2], CBZ and its derivatives are used in approximately 50% of cases [3]. Nevertheless, provocation of certain types of epileptic paroxysms after CBZ administration in primarily generalized seizures with atonic, myoclonic, and absence fits was also reported [4, 5]. Genton and colleagues found exacerbation of seizures in juvenile myoclonic epilepsy following CBZ [6]. A tendency to increase secondary generalized tonic-clonic seizures was found after withdrawal of CBZ, following therapeutic intensive seizure analysis [7]. Risk of aggravation was found for benign partial epilepsy (BECTS) [8], during syndromes of Lennox-Gastaut [9] and Landay-Kleffner [10, 11].

The CBZ antiepileptic action is achieved via Na^+ channels inactivation. Delay in the recovery of their activity results in the suppression of high frequency firing of the neurons [12]. The CBZ reduces the conductivity of Ca^{2+} channels, influences the synaptic transmission, partly blocks the action of aspartate and

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glutamate, slows down binding of catecholamines, enhances the GABAergic inhibition [13], acts on the aminergic processes, and inhibits the dopaminergic system [14,15].

The EEG examination of the patients under CBZ-therapy suggests that CBZ should be scheduled with regard to the epilepsy type, individual EEG pattern and dynamics, and clinical manifestations [16-19]. Studies of the CBZ-effects on EEG are few [20-24], especially in the children with epilepsy [25-28]. Evaluation of the EEG dynamics is important for pediatric epileptology, because the brain and EEG (basic rhythmicity) maturation is not completed in childhood that makes them more labile to different influences. Nevertheless, no systemic analysis was performed to evaluate the dynamics of EEG characteristics throughout therapy or to determine the possible early predictors for benefit/adverse effect of CBZ-therapy. Moreover, alterations of EEG-characteristics are mostly studied with respect to quantitative and qualitative aspects of epileptic activity but not to baseline activity. Complex changes in EEG such as the baseline activity in parallel to reduction of epileptiform activity and improvement of clinical signs might benefit assessment of CBZ-therapy efficacy. Thus, the aim of the present study was to evaluate dynamics of EEG characteristics at different stages of CBZ-monotherapy in epileptic children. Such investigation is very important, because characteristics of EEG abnormalities may sometimes signal clinical signs of aggravation [4].

Materials and methods

The group of children was analyzed for both epileptiform graphoelements and baseline EEG prior to, and after three and six months of CBZ-monotherapy. The EEG recording was evaluated for quantitative and qualitative aspects of EEG-characteristics in parallel to clinical assessment. The influence of CBZ on ictal and interictal EEG parameters was evaluated as well.

Patients

Patients with partial seizures were referred to the Tbilisi Institute of Physiology and Medical Center. They had partial epilepsy with at least two seizures in six months prior to enrollment into the study. The Diagnosis was made according to the International Classification of Epilepsy and Epileptic Syndromes [29], and determined by clinical history, neurological examination, and detailed investigations including neuroimaging (MRI) and blood studies. Classification of patients by seizure types and epileptic syndromes gave accurate identification of patients at risk for CBZ-exacerbated epilepsy and opportunity for correct prescription. Study was performed by careful EEG data analysis and clinical pictures. Factors relative to CBZ-therapy reviewed for their status before and during the treatment, were dosing, seizure type frequency, EEG results, and CBZ plasma levels.

Patients and their families were questioned about changes for better or worse before and during CBZ treatment. In addition, clinical signs in the skin, the digestive tract dysfunctions, and associated neurological abnormalities (nystagmus, ataxia, headache, and tremor) were assessed at each visit. Out of 48 patients who received treatment, seven developed undesirable effects. The most common side effects were the following: drowsiness, digestive disorders (nausea, and vomiting); Most patients were associated with high doses and/or plasma levels of CBZ. The dose correction had no effect on persistent side-effects in three patients (persisting seizures in one and rash in two cases). They discontinued treatment after less than one month. Patients with drug-induced intoxication were excluded from the study to avoid any possible effect of drug dose modification and drug withdrawal/alteration on the EEG. As a result, the number of analyzed patients became less than examined at the beginning of the study.

The present study included 45 children whose age ranged 3-9 years old (**Table 1**). The CBZ monotherapy daily dose was 20mg/kg body weight.

The EEG investigations were conducted using international performance standards as part of the prescribed therapy plan, approved by the parents and by our institutional ethics committee.

The EEG recording and methods of analysis

All patients underwent EEG recording three times as follows. At the first visit before administration of CBZ, 3-4 months later (the 2nd visit) and 6-8 months (the 3rd visit) after initiation of CBZ-treatment. The EEG recording was always made at the same time - in the morning. Trial without functional load (background activity) preceded the EEG recording with functional load.

The EEG without functional trials was recorded with eyes closed (three minutes), with open eyes (two minutes) and once again with closed eyes (three

Table 1. Characteristics of patients.

Number of patients	45 (21 males, 24 females)
Age (year)	
mean ± SD	5.74 ± 1.23
range	3.50 - 8.42
Onset of epilepsy	
age (year)	4.3 ± 1.1
range	3.00 -7.67
Interval from 1st to 2nd seizures	
< 1 week	2
1 week - 1 month	17
1 month -1 year	21
> 1 year	3
unknown	2
Seizure types	
SPS 12	
SPS + US	3
CPS 17	
CPS + US	4
PSG 9	
Etiology	
post-Traumatic	4
perinatal	14
neonatal	7
febrile	11
unknown	9
EEG findings	
focal (sharp waves, spike waves, spike-and-wave, spike and sharp waves)	28
generalized	6
abnormal	11

minutes). Functional trials were performed with rhythmic photostimulation, frequencies 3-5-10-15-20Hz; hyperventilation (three minutes)- with open, closed eyes and the breath hold (15-25sec); recording was finished with closed eyes. Total duration of EEG recording was 35-55minutes.

The EEG signals were digitally recorded using a set of 19 scalp electrodes according to the International 10-20 system [30] and ENCEPHALAN 131-03, professional version "MEDICOM". The band pass of the amplifiers was 0.5-100Hz, and notch filter was 50Hz. The signals from each input electrode were digitized with sampling rate of 256Hz with the resolution of 12 bits. Electrode (Ag/AgCl) specific resistance was not higher than 5kΩ.

For each patient, 10 second artifact-free EEG epochs were selected (at rest, with open and closed eyes, during functional exertion). Total of 10-15 fragments for each patient were selected.

Visual analysis of EEG for evaluation of the specificity of the background activity (focal and/or generalized, slow waves, morphology of epileptiform elements, the spike density and the number of paroxysmal burst discharges) was done before the quantitative assessment.

A fast Fourier transformation algorithm of signal processing was used to obtain the power spectrum for each lead. The spectral analysis was used to calculate absolute value of power [31]. For the statistical evaluation of the EEG, the phenomena were calculated within six frequency bands: delta (0.5-4 Hz), theta-1 (4-6Hz), theta-2 (6-8Hz), alpha (8-13Hz), beta-1 (13-24Hz) and beta-2 (24-50.8Hz).

The quantitative characteristics of EEGs were analyzed as follows. 1) The pattern of native EEG with monopolar, bipolar and common average reference montage recordings for evaluation of the specificity of the background activity (focal and/or

generalized slow waves); 2) Absolute values of the power spectra (AVP, μV^2s) – the area below the corresponding plot on the spectrogram of the separated frequency ranges; 3) Relative values of the power; 4) The spectrum frequency limits - the utmost values of the frequencies within the spectrum of the EEG segment analyzed; 5) Mapping of the EEG spectral characteristics (topography) - spatial distribution of the activity of the separated frequency ranges over the brain surface (see **Fig. 1**)

Considering the corresponding age standards of EEG patterns [32, 33], qualitative assessment of the EEG characteristics was performed as follows. 1) Interictal epileptiform abnormalities: presence of epileptiform activity (spike discharges, sharp waves, paroxysmal burst). The spike density (within three seconds) and the number of paroxysmal discharges (15 seconds), indicating abnormal EEG activity, were measured; 2) Characteristics of alpha activity: a) expression regularity of the rhythm, frequency stability; b) distribution pattern over the brain convexital surface (gradients, domination area, symmetry of the amplitude and frequency); 3) Characteristics of beta activity: a) the amplitude and topography b) limits and stability; 4) characteristics of low frequency range activity: a) wave amplitude, correspondence of the indices and topography of given age group, area of predominance; b) type of low frequency oscillations, their regularity, availability or absence of the rhythmicity, the degree of synchronization and stability.

Features of the response in functional trials were also assessed. At photostimulation, Attention was paid to the range and character of rhythm adoption, and at hyperventilation, to the following: 1) time from the start of loading until the appearance of changes on the EEG; 2) time of EEG indices restoration.

Statistical analysis

After preliminary evaluation of selected fragments of EEG, the tables and figures for the changes in EEG characteristics (dynamics), from each of 16 standard recording electrodes, were organized for each patient. The data obtained during the first visit served as a baseline for the data collected (compare) on the second and third visit for each patient. Assessing the dynamics of EEG characteristics, each subject served as its own control. The data obtained on the1st, 2nd and 3rd visits were compared between each other.

Statistical significance for the difference in variables registered at different stages of investigation was assessed using Mann-Whitney U-test (BIOSTAT). The changes in the EEG characteristics for the whole group were assessed using Wilcoxon rank sum test [34]. The $p<0.05$ was considered significantly different.

Results

Figure 1 shows sample picture of power spectra.

Figure 2 summarizes results obtained from the quantitative analysis of the EEG dynamics at the different stages of CBZ administration.

As indicated by Total in **Fig. 2,** the analysis of total TAVP dynamics reveal a reliable elevation of this index in parietal ($p<0.05$) and, especially, occipital recordings three months after beginning of the treatment. The TAVP showed a similar picture at six months after the therapy initiation ($p<0.05$). At all the stages of the treatment, the TAVP indices preserved higher level compared to the 1st TAVP.

As indicated by Theta-1 and -2 in **Fig. 2**, the spectral analysis of AVP dynamics, showed that the increase of this index is caused mainly by the growth of specific number of low frequency waves in the EEG pattern. The CBZ-induced elevation of AVP at three and six months after CBZ-therapy compared to the 1st visit was found due to the increase of AVP in the low frequency wave ranges. Statistically significant increase in both delta ($p<0.05$) and theta ($p<0.05$) activities were observed, being most pronounced in the theta range. Dynamics in the theta sub-ranges revealed rise of the quantity of waves in both sub-ranges ($p<0.05$). No significant difference ($p>0.5$) between the EEG records at three and six months after CBZ-therapy was found.

Alpha activity, indicated by Alfa in **Fig. 2,** was elevated after CBZ-therapy. Significantly - in occipital region ($p<0.05$), and reached maximal values at the 3rd month of CBZ treatment.

It should be emphasized that along with increase of AVP in alpha range there was also a decrease in mean frequency of alpha rhythm at three months after initiation of CBZ-therapy. Individual changes of the power and average-frequency alpha activity were rather variable. In 71% of examined patients, the changes in mean frequency of alpha were observed. Decrease in the average alpha frequency ($\Delta alpha_{3month}$) was more than ~0.5Hz; this was revealed in 31.3% of the patients; in the rest of the patients this deceleration did not exceed 0.5Hz. The effect was maintained during the course of investigation.

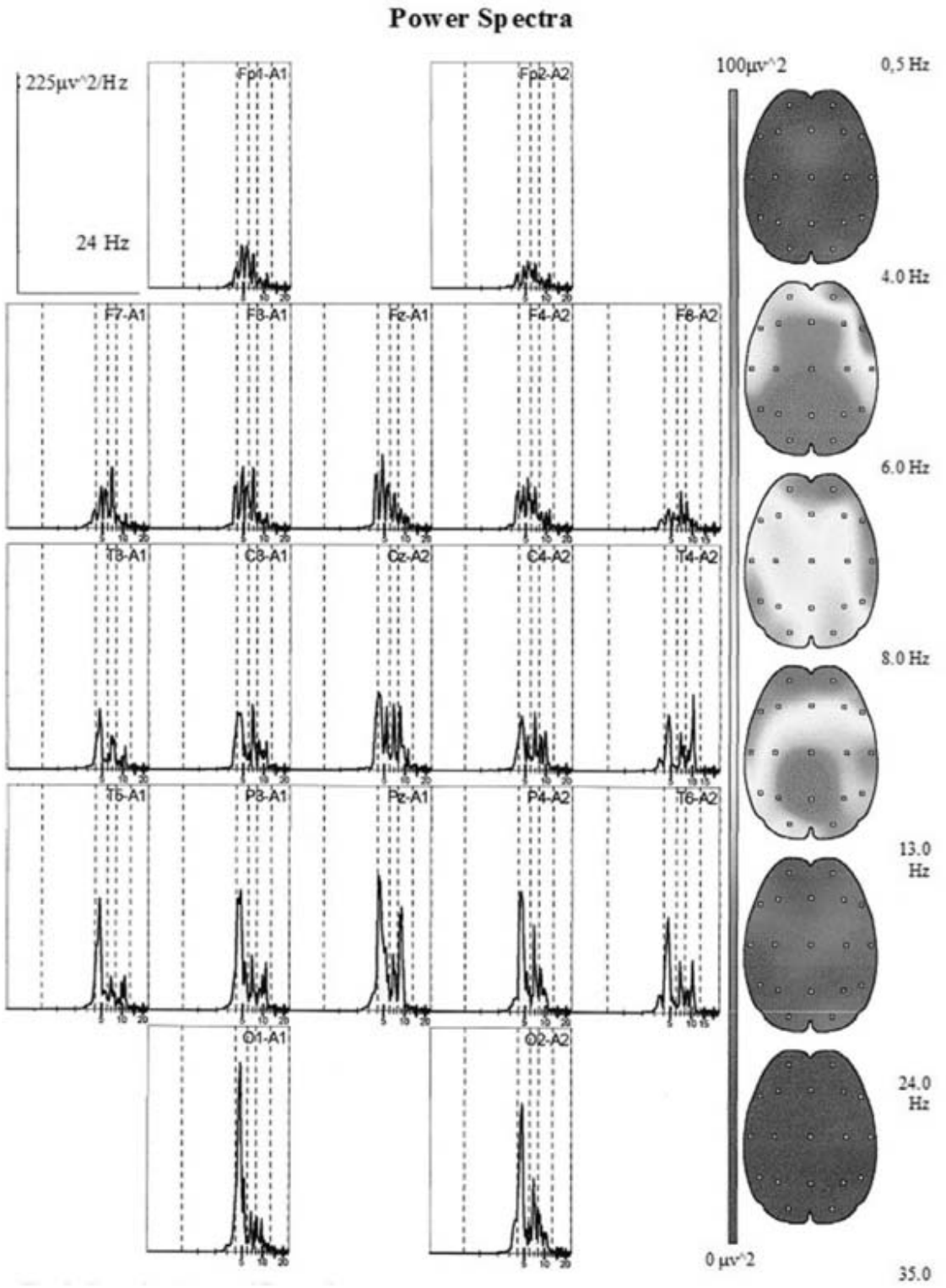

Fig. 1 Mapping of the EEG spectral charactersistics Sample picture of power spectra in Patient 1 (female, 5 years). Spatial distribution of the activity of the separated frequency ranges over the brain convexital surface.

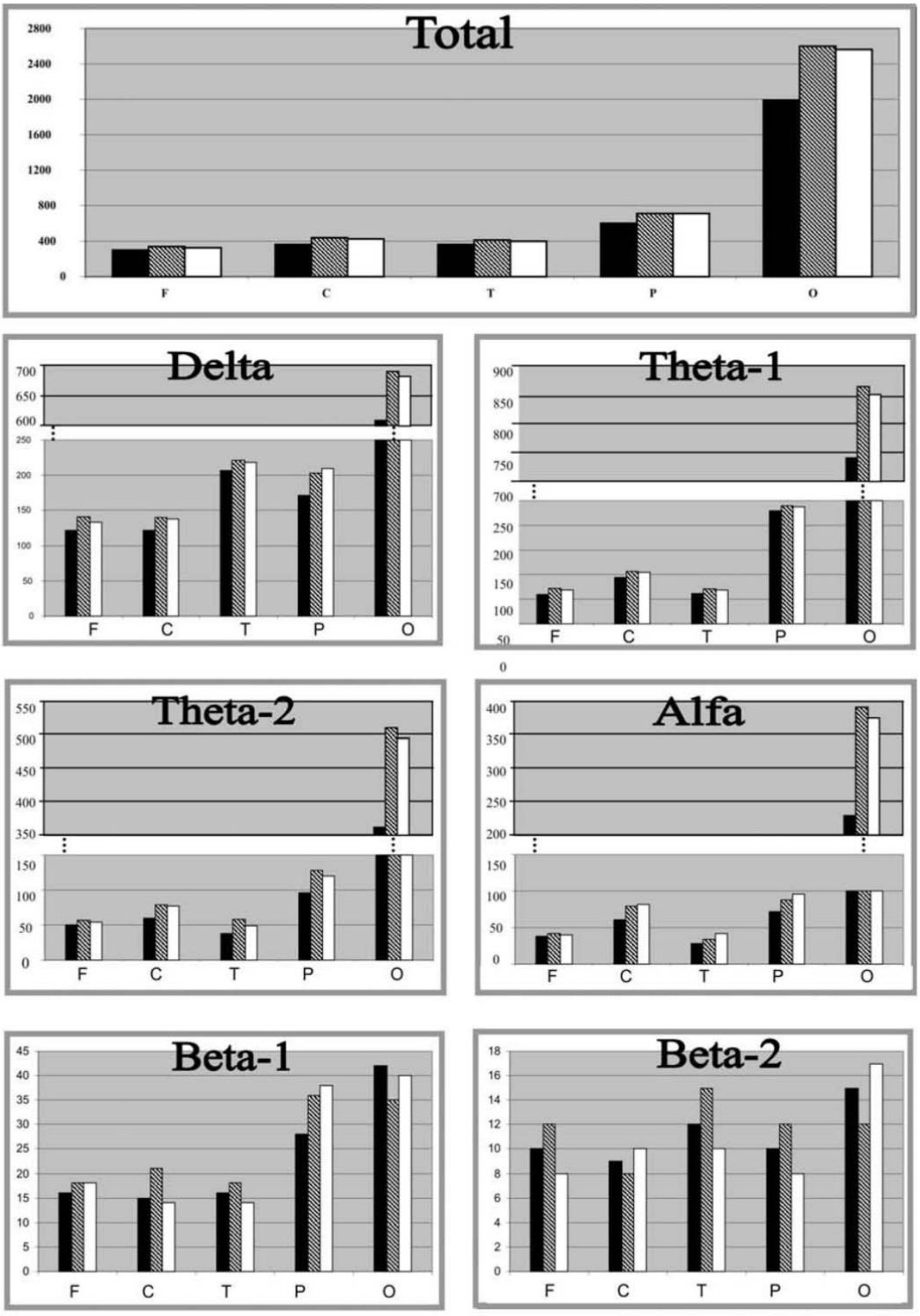

Fig. 2 Dynamics of absolute values of power spectra (AVP) at different stages of treatment. Total of AVP (TAVP), below the AVP of different frequency bands, is shown. Black columns: before treatment (21st visit), shaded columns: three months (2nd visit),white columns: six months (3rd visit) after the initiation of CBZ treatment. F-frontal, C-central, T-temporal, O-occipital, P-pariental regions of the brains of the brain cortex. Y-line: power value (μV^2s).

As indicated by Beta-1 and -2 in **Fig. 2**, alteration of AVP and frequency characteristics of the activity in beta range did not show any steady dynamics, revealing different features at a particular recording. The beta-1 range in frontal central and temporal zones showed growth of the activity power after three months of CBZ-therapy. Nevertheless, AVP decreased after six months of the therapy and reached initial level, occasionally being even lower. The CBZ-induced changes in parietal and occipital zones differed from frontal central and temporal zones. Dynamics of beta-2 range activity in frontal, central and temporal zones coincided with beta-1 range, whereas a significant decrease of AVP in the parietal zone at six months of the observation was found.

The described AVP dynamics was analogous in both hemispheres. No inter-hemispheric specificity was seen in the dynamics of the frequency ranges analyzed.

The qualitative analysis revealed that CBZ-therapy reduces density of spontaneous epileptiform graphoelements (78%, at an average), compared to first recording, as well as spontaneous generalized epileptiform bursts (82%, at average) in the EEGs recorded at rest with the eyes closed. Complete normalization of the EEG at rest was recorded in 39% of patients after three months and in 47% of patients after six months of the initiation of the treatment.

The CBZ-therapy reduced the number of generalized paroxysmal bursts of interictal and especially ictal type under rhythmic photostimulation and hyperventilation at three and six months after therapy compared to primary EEG recordings. There was no significant difference ($p>0.5$) between the EEG recordings obtained at three and six months.

During the CBZ-therapy, the worsening of EEG and clinical signs of aggravation were observed in four cases (age ratio: 3-7 years; one with temporal lobe epilepsy, two with frontal-, and one with rolandic epilepsy (BECTS)) - new appearance or worsening of generalized, paroxysmal EEG discharges and their correlation with seizure exacerbation, more frequent seizures, myoclonus, onset of new types of seizures, sometimes appearance of fits with secondary generalization. Aggravation of epilepsy by AED was diagnosed with the criteria of Genton and McMenamin [35]. The presence at the first EEG recordings of periodic spontaneous diffuse sharp and spike-wave abnormalities after the CBZ-therapy, secondary generalized paroxysms did occur. The EEG became more abnormal and the new generalized spike wave and polyspike-and-wave discharges were evident. Withholding of CBZ was required in these patients.

The investigations were carried out in 45 patients, based upon which the patient's reports and EEG-recordings within the last six months, the complete documentation of CBZ-therapy were performed. The clinical outcomes and EEG findings are described in **Table 2**. In 38 patients, reduction in seizure frequency was revealed. Twenty-nine of these showed both clinical and EEG improvement. In 9 patients, decrease in seizure frequency (50%), without any change in the EEG-records, were found. No clinical changes were found in three patients (though the two patients had tendency to decrease duration of individual seizures), and four patients had increased frequency and onset of new seizure types. The characteristics by seizure type of rest 41 patients during CBZ-therapy are listed in **Table 3.**

Table 2. Clinical outcome and EEG records in 45 patients.

EEG / Clinical follow-up	Complete normalization	Improved	No change	Worse	Total
Clinical improvement Number (%)	21 (47%)	8 (17%)	9 (20%)		38 (84%)
No clinical change Number (%)			2 (4%)	1 (2%)	3 (7%)
Clinical aggravation Number (%)				4 (9%)	4 (9%)
Total Number (%)	21 (47%)	8 (17%)	11 (24%)	5 (12%)	45

Table 3. Clinical Data of 41 patients on the CBZ treatment. Clinical improvement was seen with a decrease in seizure frequency (50-75%) during six months of follow-up.

Sizure types	Number of patients	In 3 months		In 6 months	
		Improved	No change	Improved	No change
SPS	12	7	5	12	0
SPS-US	3	2	1	3	0
CPS	16	7	9	15	1
CPS-US	4	1	3	4	0
PSG	6	2	4	4	2

SPS: Simple partial seizure, US: Unilateral seizure, CPS: Complex partial seizure, PSG: Partial sometimes with secondarily generalization.

Discussion

Our studies showed that during the CBZ-treatment, EEG undergoes a number of regular changes. Most important are: 1) Deceleration of the background EEG rhythmicity at the expense of the augmentation of high amplitude activity of the low frequency range, predominantly in parietal and occipital regions of the brain cortex; 2) Decrease in the mean frequency of the alpha-rhythm, 3) Decrease in the frequency of clinical fits and epileptiform graphoelements in the EEG ($p<0.001$), 4) No interhemi-spheric differences, 5) Absence of reliable differences in the effect following three and six months, and 6) Exacerbation of the state in four patients.

These complex changes in EEG were already observed at three months after initiation of the CBZ-therapy and were associated with improvement of clinical conditions of the patients. The effect was permanent across six-month period.

In the present study, the CBZ-monotherapy produced deceleration of the baseline EEG rhythmicity and decrease in the mean frequency of the alpha-rhythm [36, 37]. The CBZ is the only medication, among currently used AEDs, to decelerate the baseline EEG rhythmicity concomitantly with reduction of epileptic activity [38, 39]. The neurophysiological mechanisms of such CBZ-effect are not known [40]. A special feature of CBZ suggests that its anti-epileptic effect is achieved via neurophysiological and molecular mechanisms that partly differ from the action mechanisms of other AEDs, especially from valproate derivatives [38, 41]. The findings by Liu and colleagues [42] that at the thalamic level CBZ can activate GABA-A receptors of neuronal membranes, in contrast to other anti-epileptic drugs, support our suggestion. The different mechanism of action of lamotrigine, carbamazepine, and phenytoin on extracellular levels of 5-hydroxytryptamine, dopamine, and amino acids was reported as well [43].

In agreement with the present opinion on genesis of basic EEG rhythm, the effect of CBZ might be suggested as achieving mainly via cortical neuronal activity. The indirect support of our suggestion comes from the findings by Goyal et al. [44]. It was shown that during Transcranial Magnetic Stimulation, CBZ depresses excitability of the cortical motoneurons in epileptic patients.

Beta spectrum did not show any steady dynamics. The functional meaning of this type dynamics is not quite clear. Only in some cases of frontal epilepsy, the rapid beta (gamma) activity was found.

Exacerbation of the epilepsy was observed in 8.8% of the patients. It is supposed that in the absence seizures, with the thalamic pacemaker, CBZ might be capable to act on neuronal structures of the thalamic ventro-basal nucleus leading to elevation of seizure activities. In this respect, we have to emphasize the worsening we observed in the patients with partial frontal and temporal seizures. Kochen et al. [45] doubt that this mechanism explains exacerbation of the fits in some cases of CBZ-therapy. The authors report that increment of intensity of the fits not only in the patients with generalized forms of epilepsy but also in adults and children suffering the partial fits, parallels our results. Thus, in cryptogenic frontal epilepsy with spike-wave discharges there is a risk of negative effect of CBZ. Talwar et al. [46] reported that in children with symptomatic partial epilepsy, seizure worsening was induced by add-on of CBZ, preceded by appearance of generalized spike-wave discharges. The issue that the negative effect of CBZ is largely

related to the type of seizures, or depends on the morphology of dominating epileptiform elements, still remains important [47]. Thereupon, children with BECTS and diffuse interictal sharp and spike-wave discharges are likely to be at risk of aggravation of the epileptic attacks. In fact, new appearance of generalized paroxysmal discharges during treatment was correlated with seizure exacerbation and adverse outcome.

It should be considered that exacerbation of disease is observed not only with CBZ-therapy: in an approximately comparable number of cases this effect was described in treatment with all currently used, AEDs [4], mostly of the first generation [48]. Identification of true aggravation during epilepsy treatment in the absence of over dosage or drug toxicity is a common and clinically important problem for both well-established and newly-designed AEDs, the biologic mechanisms of which remain unknown.

Conclusion

EEG data as predictors of seizure exacerbation in children with newly developed epilepsy and prescribed CBZ-therapy are revealing. Amplification of slow-wave activity is observed during the CBZ-therapy, which might be an index for the excitation decrease in the thalamo-cortical pathways. Elevation of indices of high amplitude low frequency activity in the occipital and parietal regions, concomitant to reduction of frequency and amplitude of epileptiform elements and parallel decrease of seizure frequency by three months after initiation of CBZ-therapy, suggests that CBZ-therapy at appropriate doses might be continued in the specific patient and is effective AED. Otherwise, the strategy of antiepileptic therapy should be revised. New occurrence of generalized paroxysmal discharges during the CBZ-therapy correlated with seizure aggravation. Antiepileptic therapy should be applied with caution and under regular EEG-control. Worsening of the EEG-characteristics, in some cases, precedes exacerbation of the patient's state. Careful follow-up EEG, including repeated EEG recordings, will be useful to identify changes of seizure aggravation after initiation of treatment. The necessity of regular EEG control throughout treatment period is recommended no less than once in three months. Such control is more important in children with recent onset seizures. Incomplete myelination may induce incorrect EEG features.

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