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COMPARATIVE EFFICACY OF PHARMACOLOGICAL TREATMENT OF ABSENCE EPILEPSY WITH TYPICAL AND DEVIATING (COMPLEX) EEG PATTERNS

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In a group of 96 children and teenagers suffering from absence epilepsy, we compared the efficacy of treatment with a valproic acid derivative, Depakin (D). In 72 patients of group 1, EEGs contained bursts of typical absence seizure phenomena, generalized 3–4 Hz spike/wave complexes, SWCs. In 24 patients of group 2, these EEG phenomena were combined with other types of epileptiform elements (generalized and focal irregular peak/wave complexes, single and grouped sharp waves, spikes, polyspikes, etc.). It was found that pharmacotherapy with D effectively eliminated SWCs generated in the resting state of the patients; epileptiform phenomena provoked by hyperventilation and rhythmic photostimulation were noticeably more resistant from this aspect. The efficacy of treatment with D was considerably higher in group 1 (patients with the EEG patterns including only SWCs) than in group 2 (patients with deviating EEG patterns containing, together with SWCs, epileptiform elements of other types). Six months after the D therapy initiation, complete elimination of typical 3-4 Hz SWCs was observed in 63.9% of group-1 patients and in 41.7% of group-2 patients.

Keywords: absence epilepsy, EEG, generalized 3–4 Hz spike/wave complexes (SWCs), deviating epileptiform EEG elements, combination of different EEG phenomena, valproic acid, Depakin.

INTRODUCTION

According to the statements of the International League Against Epilepsy (ILAE) Commission on Classification and Terminology, absence epilepsy can be manifested in (i) typical or atypical absence seizures and (ii) seizures with special features [1]. Pathognomonic EEG correlates of typical absence seizures (TASs) look as generalized spike/slow wave complexes (SWCs, 3-4 Hz). In clinical practice, however, many deviating cases are encountered where the EEG pattern containing TASs is combined with other types of epileptiform phenomena, namely irregular peak/wave complexes, sharp waves, spikes, polyspikes, etc. [2-11].

According to the ILAE recommendations, a first-line choice for the treatment of TASs is valproic acid and its derivatives [12]. The existence of absence epilepsy cases with dissimilar EEG patterns should, apparently, be taken into consideration when selecting an adequate strategy of treatment. In the accessible literature we, however, have not met publications devoted to the dynamics of combined EEG patterns at TASs during monotherapy with valproic acid and its derivatives.

In this regard, it seemed expedient to carry out a comparative study of the dynamics of epileptiform discharges in patients suffering from absence epilepsy with typical and deviating EEG patterns under conditions of monotherapy with one of the valproic acid-based drugs, Depakin (D). The results of such study were assumed to be useful in selecting an adequate treatment strategy with respect to TASs characterized by different EEG patterns. It should be emphasized, that the term “typical absence,” or “TAS,” used within this context refers rather to the EEG pattern, than to the clinical (behavioral) type of epileptic seizures.

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METHODS

In total, 96 patients with the clinical diagnosis of TAS, who were treated against absence epilepsy, were examined. These were 4- to 16-year-old children; they underwent routine EEG examination in the David Tatishvili Medical Center (Tbilisi, Georgia) within the period of 2005–2012. The main requirement of the selection consisted in that the patient had at least three consecutive registrations of EEG: at the first visit to the physician (prior to the treatment) and three and six months after the start of monotherapy with D. The dosage for each patient was standard, and the treatment was carried out under constant control of the drug level in the blood plasma.

The EEG examination in all patients was performed using standard techniques, in the morning against the background of quiet wakefulness. The patients were in a sound- and light-attenuated room, at a controlled ambient temperature of 22°C. The mean duration of EEG recording was 30-35 min.

The EEG signals were digitally recorded using an EEG analyzer, Encephalan 131-03 (Medicom MTD, Russia) and 19 scalp electrodes located according to the international 10–20 system with a linked ear contact as a reference. The amplifier bandpass was 0.5 to 100 Hz, with a 50 Hz notch filter (outputs being 3 db down at these frequencies). The signals from each electrode were digitized with the sampling rate 256 sec^{-1} and resolution of 12 bits. The specific resistance of Ag/AgCl electrodes was between 5 and 1 kΩ. The EEG samples were stored on a hard disk for off-line analysis.

The EEG recording started with the eyes closed (5 min, background activity), continued with the eyes open (5 min), and once again with eyes closed (3 min). During EEG recording, standard activation procedures, namely rhythmic photic stimulation (RPS) and hyperventilation (HpV) were used. The former was carried out with the eyes closed, the flash lamp was positioned approximately 30 cm in front of the eyes. The procedure started with three flashes per second, and the frequency was gradually increased to the rate of 27 sec^{-1}. Each flash rate was presented for about 10 sec. The pV procedure lasted 3-5 min with the eyes open and closed, and with the breath hold (25-30 sec after HpV termination.

RESULTS

The entire examined contingent of 96 patients was divided into two groups (Table 1). Group 1 involved 72 subjects (75% of the total number); in EEGs of these patients only SWC (3-4 Hz) bursts were observed. Group 2 included 24 patients (25% of the total number) who, along with 3-4 Hz SWCs, showed epileptiform elements of various morphology; these were focal or generalized single and grouped peak/wave complexes, sharp waves, EEG spikes, polyspikes, etc.

Most patients of groups 1 and 2 (62.5 and 54.2%, respectively) were 4 to 8 years old. Much smaller proportions of the patients (12.5% in both groups) included teenagers (13 to 16 years). Girls prevailed in most above-mentioned age subgroups; three 13- to

T a b l e 1. Characteristics of the studied sampling. 1 and 2) Groups of patients with a typical TAS EEG pattern containing exclusively SWCs (1) and those who, along with the TAS pattern demonstrated epileptiform phenomena of different morphologies (2, see the text); *n* is number of patients; a and b are percentages in the total sampling and in the given group, respectively

Т а б л и ц я. 1. Характеристики обстеженої групи

Contingent	Group					
	1			2		
	N	a	B	N	a	b
4-8 years	45	46.9%	62.5%	13	13.5%	54.2%
M	14	14.6%	19.4%	4	4.2%	16.7%
F	31	32.3%	43.0%	9	9.4%	37.5%
9-12 years	18	18.7%	25.0%	8	8.3%	33.3%
M	7	7.3%	9.7%	3	3.1%	12.5%
F	11	11.5%	15.3%	5	5.2%	20.8%
13-6 years	9	9.4%	12.5%	3	3.1%	12.5%
M	3	3.1%	4.21%	2	2.1%	8.3%
F	6	6.2%	8.31%	1	1.1%	4.2%

16-year-old patients of group 2 were two boys and one girl.

Efficacy of Treatment in Group 1. The analysis of results of D-based treatment in group 1 is presented in Table 2. In this group, the greatest subgroup (51.4%) of TAS patients was characterized by the EEG pattern, with included generalized 3-4 Hz SWCs observed in both background state and after the action of HpV (subgroup A). In 31.9% of the cases, SWCs were absent in the resting state but could be provoked by HpV (subgroup B). In 9.7% of subjects of group 1, such bursts arose spontaneously and could be induced by both HpV and RPS procedures (subgroup C). In 6.9% of group-1 patients, 3-4 Hz SWCs were not generated spontaneously, but could be induced by both Hpv and RPS (subgroup D).

The analysis of EEGs, recorded three and six months after initiation of the treatment with D, showed that such treatment provided almost complete suppression of generation of spontaneous background SWC bursts in all above-mentioned subgroups.. The SWC bursts initiated by activation procedures were noticeably more resistant to the treatment used. In this regard, it should be emphasized that, after 3- and 6-month-long treatment, only 3-4 Hz SWCs provoked by activation procedures continued to be recorded (Table 2).

We also should note that clinical improvement (i.e., suppression of clinical seizure attacks) did not always coincide with EEG findings. In 11 patients of group 1 (15.3%) with full elimination of clinical attacks, SWC bursts induced by activation procedures continued to be recorded in EEGs.

Table 2 also illustrates the percentage of patients who demonstrated complete elimination of the SWCs in EEGs six months after initiation of the D treatment. In group 1 in general, the number of such successful cases made up 63.9%; this figure agrees with the data reported by other authors [12-14]. It seems that the best results (69.6%) were observed in patients of subgroup B (in which EEG SWC bursts arose only against HpV), but the difference from subgroup A in this respect is probably insignificant. Subgroup D, in which 3-4 Hz SWCs were not generated spontaneously but could be provoked by both HpV and RPS, demonstrated the greatest resistivity to the influence of D (the treatment was successful in only 40%).

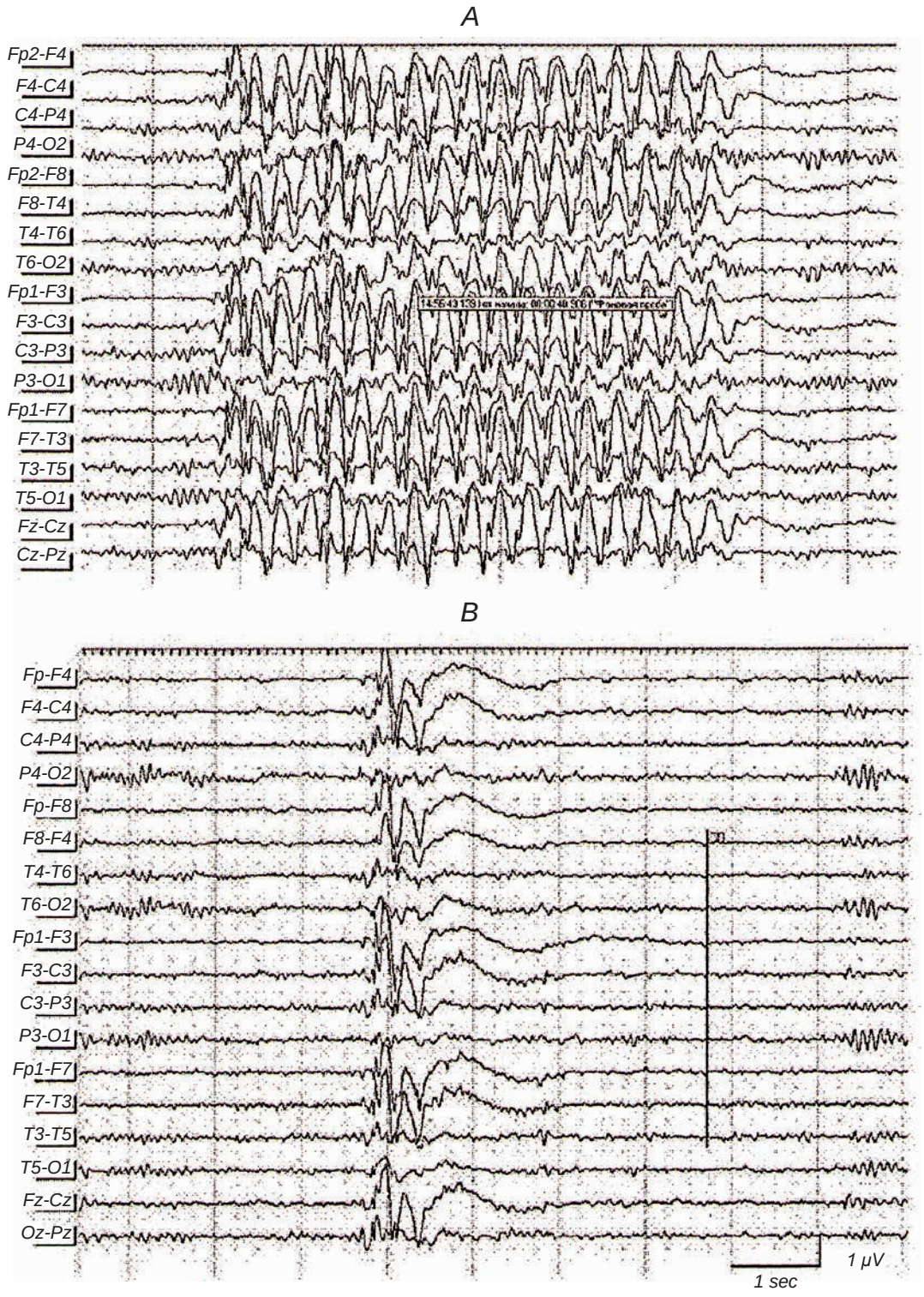
Efficacy of Treatment in Group 2. In patients of this group, EEG patterns contained both SWCs and epileptiform elements of differing morphology. Most frequently, SWC bursts were combined with focal epileptiform elements (19 cases, 79.2%), less frequently (5 cases, 20.8%), such elements were generalized (Fig. 1).

Deviating epileptiform elements were most frequently recorded in the fronto-central and fronto-temporo-central sites (66%). In most cases, such epileptiform elements looked as irregular single or grouped spike/wave or sharp wave/slow wave complexes (18 patients, 75%). Less frequently, spike and polyspike discharges were observed (6 patients, 25%). These elements occurred spontaneously in the background EEG, but more frequently they were provoked by HpV. In two patients, specific epileptiform discharges were provoked only by RPS,

T a b l e 2. Dynamics of the EEG patterns in group 1. A-D) Subgroups of group 1; 1) before the treatment; 2 and 3) three and six months after the start of the treatment with Depakin. The last column shows the percentage of successful cases, revealed six months after initiation of the treatment (see the text)

Т а б л и ц я. 2. Динаміка змін патернів ЕЕГ у групі 1

Subgroups	Registration			
	1	2	3	Positive effect (%)
A Spontaneous and activated by HPV	37 (51.4%)	24	13	64.9%
B Activated only by HPV	23 (31.9%)	16	7	69.6%
C Activated by HPV and RPS	7 (9.7%)	5	3	57.1%
D Spontaneous and activated by HPV and RPS	5 (6.9%)	3	3	40.0%
Total	72	48	26	63.9%



Example of a combination of spike/wave complexes (SWCs, 3-4 Hz) with generalized epileptiform discharges provoked by activation procedures (before the start of the treatment). A) Typical absence SWCs provoked by hyperventilation; B) generalized epileptiform discharges provoked by repetitive photostimulation.

Приклад комбінації комплексів пік/хвиля (SWC, 3-4 Гц) з генералізованими епілептиформними розрядами, провокованими активаційними процедурами (перед початком лікування).

and in two cases they were induced by both RPS and HpV (Table 3).

Similarly to what was observed in patients of group 1, the D-based treatment was considered successful at complete elimination of epileptiform elements in EEG. In other words, the cases, where introduction of D eliminated generation of 3-4 Hz SWCs, but other types of epileptiform EEG elements continued to be generated, were not interpreted as successful.

The number of patients in subgroups of group 2 is limited; this is why we do not present the percentage of successful and unsuccessful cases for each subgroup separately. At the same time, it should be emphasized that, in general, the percentage of successful treatment cases six months after the beginning of pharmacotherapy with D was 41.7%, i.e., significantly smaller than the respective index in group 1.

Patients with deviating epileptiform discharges provoked by both RPS and HpV and accompanying SWCs appeared to be more resistant to the D treatment. It should be noted that intensification of concomitant deviating epileptiform discharges was observed in a parallel manner with complete elimination of SWCs in three patients of group 2. Suppression of SWC bursts under the influence of D in this group was noticeably slower than in patients of group 1. Three months after the start of treatment with D, bursts of SWCs continued to be recorded in 48 patients (65.3%) of group 1 and in 21 patients (87.5%) of group 2 (Tables 1 and 2).

DISCUSSION

The characteristics of group-1 patients (Table 1) are mostly compliant with the existing statistical data. In this group, the largest part (62.5%) was represented by 4- to 8-year-old patients, i.e., their age was commonly viewed as a peak of TAS manifestations [15-18]. Age groups of 9-12 and 13-16 years made up 25% and 12.5% of general sampling, respectively. Some doubts in respect to the manifestation of TAS in children elder than 10 years were expressed [15-18]. Other authors reported that absence epilepsy was diagnosed in 10- to 15-year-old patients and those over 15 years in 17.8 and 2.8% of the cases, respectively [19]. Comparable results were presented by Hauser [20]. Granieri et al. [21] reported TASs could be observed

T a b l e 3. Occurrence of EEG deviating epileptiform elements in patients of group 2 treated with Depakin. Other designations are similar to those in Table 2. Detailed explanations are presented in the text

Т а б л и ц я. 3. Наявність девіантних епілептиформних ЕЕГ-феноменів у пацієнтів групи 2, підданих лікуванню депакіном

SWCs (3–4 Hz) and other epileptiform elements	Registration		
	1	2	3
A. Spontaneous in background EEG			
focal	3	3	2
generalized	1	1	0
B. Provoked by HPV			
focal	5	4	2
generalized	1	1	1
C. Provoked by RPS			
focal	1	1	1
generalized	1	1	1
D. Provoked by HPV+RPS			
focal	2	2	2
generalized	0	0	0
E. Spontaneous + HPV			
focal	7	5	3
generalized	2	2	1
F. Spontaneous + HPV + RPS			
focal	1	1	1
generalized	0	0	0

rather frequently in 10-19-year-old patients and, sometimes, in 20- to 39-year-old subjects. Such discrepancies between the data of various authors can be accounted for differences in the diagnostic criteria used by different researchers [15-18, 22].

Gender distinctions in the patients of group 1 also corresponded to the conventional statistical data. TASs were more frequently encountered in girls than in boys making up 66.7 and 33.3%, respectively [15-19, 23-25]. Interestingly, practically the same ratio between girls and boys was also observed in all selected age subgroups, namely 68.9 and 31.1% in the 4-8-year subgroup, 61.1 and 38.9% in the 9-12-year subgroup, and 66.7 and 33.3% in the 13-16-year subgroup.

In agreement with the existing literature data [23, 26, 27], HpV provoked TASs in all patients of group 1. In most cases (51.4%), the TAS EEG pattern was manifested as short (4-7 sec) spontaneous SWC bursts in the background EEG and as longer (6-12 sec) trains at the HpV action. In a part of cases (9.7%), 3-4 Hz SWCs were provoked not only by HpV but also by RPS. Probably, special attention should be paid to these cases because the ILAE Commission did not consider EEG reactions to RPS as an adequate EEG-sign of TAS [15-18, 25, 28,]. Some authors admitted the possibility of high photosensitivity in TAS [26, 29].

The absence of video monitoring of seizures is a noticeable drawback of our study. This procedure may allow us to reveal certain specificity of behavioral manifestations of the attacks developing in patients under HpV and RPS influences. Our study was exceptionally based on the analysis of EEG phenomena; nonetheless, we decided to include such patients in group 1 as a separate subgroup. 3-4 Hz SWCs induced by RPS met all criteria of the TAS EEG pattern and morphologically did not differ from the bursts provoked in the same patients by HpV. Considering the same grounds, we differentiated a small subgroup of patients (6.9%) in whom SWC bursts were recorded under all three conditions, in the resting state and during both RPS and HpV.

The highest index of successfulness of D monotherapy (69.6%) was observed in patients with the EEG pattern of TAS recorded under background conditions and at HpV. This index was slightly lower (64.9%) in the cases where this pattern was also recorded as spontaneous bursts in the resting state. In the subgroup of patients with the SWC pattern provoked by both HpV and RPS the effectiveness of the therapy made up 57.1%. The lowest effectiveness of the treatment (40%) was observed in group 1 in the patients with the EEG pattern of TAS recorded both at rest and during HpV and RPS.

The number of patients responding to RPS was rather limited; such reaction was observed in 12 patients (Table 2, subgroups D and E); the respective subgroups constituted 12.5% of group 1. It should be taken into account that HpV and RPS exert fundamentally different effects on the CNS; thus, it cannot be ruled out that high photosensitivity in these patients reflects certain specificity of the intimate mechanisms of epileptogenesis in such cases. The appearance of spontaneous and RPS- and HpV-provoked SWCs can apparently reflect a higher level of hyperexcitability in thalamic and/or cortical neuronal pools triggering this epileptiform EEG pattern. A high resistance of such patients to D monotherapy, as compared to that in patients from other subgroups, should surely be taken into consideration while choosing the strategy of anticonvulsive therapy in such patients.

Group 2. Cases where EEG of one and the same patient included 3-4 Hz SWCs and epileptiform phenomena of other types have been described by a few authors. The EEG pattern of TAS in a combination with single regional sharp wave/slow wave complexes was encountered in 1.5% of patients [4]. According to other authors [30], a typical absence EEG pattern with additional other generalized seizures and slow irregular spike-and-wave activity in the EEG was observed in 10.1% of cases. Epileptiform elements in TAS EEGs looking as centrotemporal sharp waves [25] or persistent focal disorders [7] were described by a number of authors [12].

In our study, the proportion of patients with the deviating combined EEG pattern was equal to 25% of the examined patient sampling. Probably, it is reasonable to emphasize that such a ratio cannot be considered completely adequately reflecting the real situation. The patients whose EEGs were analyzed, were selected according to certain special requirements (see Methods); therefore, the examined sampling cannot be regarded as statistically representative. In general, comparison of the findings made by the authors mentioned above suggests that the deviating combined EEG pattern containing SWCs and other generalized and/or focal epileptiform phenomena can be found in approximately 10% of subjects manifesting TASs.

As Table 3 shows, elimination of typical SVC bursts and concurrent varying epileptiform elements was observed after three and six months of D therapy in

10 out of 24 group-2 patients, i.e., in 41.7% of cases. Thus, the effect of such therapy in this group was much worse that in group 1 where it was 63.9% (Table 2). It should be again noted that such a low percentage of the treatment efficacy in group 1 was found only in patients with SWCs arising both spontaneously and provoked by RPS and HpV.

Even more demonstrative is the fact related to the difference in the treatment efficacy observed three months after beginning of D introduction. Successful complete elimination of EEG paroxysms was observed in 24 patients of group 1 (33.3%), while in group 2, similar results were observed only in two patients (8.3%; Tables 2 and 3).

The question on the existence of any pathogenetic relation between typical 3–4 Hz SWSs and other types of epileptiform discharges in EEG of the same patient remains unclear. In this connection, it is interesting that, in three patients of group 2, 3-4 Hz SWCs were completely suppressed, while other epileptyform phenomena of different types remained clearly manifested or even were intensified.

Of a special interest is the fact that the dynamics of D-provided elimination of TAS phenomena in EEGs three and six months after the start of treatment was markedly slower in patients of group 2 than in those of group 1. In other words, the patients of group 2 exhibited noticeably higher resistivity of typical SWC bursts to the action of D. Similar situation was described by Massa et al. [31] in patients with idiopathic Rolandic epilepsy. Possible neurophysiological background for this fact remains at present unclear. We can only state that a combination of the typical TAS pattern with other types of epileptiform phenomena in EEG of the same patients clearly correlates with a higher resistivity of seizures to the treatment with D. This situation, no doubt should be considered while planning the strategy of anticonvulsant therapy in such patients.

All participants were informed in detail about the experimental process. The ethical protocol of this study was based on the Declaration of Helsinki and respective international ethical norms. The written informed consent was signed by all participants and/or their parents.

The authors, V. I. Maloletnev, M. L. Gugushvili, and I. O. Khachidze, declare that there were no conflicts of any kind relating to commercial or financial relations, relations with organizations or persons, which could in any way be associated with the investigation, and to the interrelationship of the co-authors of the article.

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ПОРІВНЯЛЬНА ЕФЕКТИВНІСТЬ ФАРМАКОЛОГІЧНОГО ЛІКУВАННЯ АБСАНСНОЇ ЕПІЛЕПСІЇ З ТИПОВИМИ ТА ДЕВІАНТНИМИ (СКЛАДНИМИ) ПАТЕРНАМИ ЕЕГ

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Р е з ю м е

У групі з 96 дітей та підлітків, що страждали на абсансну епілепсію, ми порівнювали ефективність лікування з використанням похідного вальпроєвої кислоти депакіну (Д). У 72 пацієнтів групи 1 в ЕЕГ були присутні типові феномени абсансної судомної активності – генералізовані комплекси пік/хвиля (SWC, 3–4 Гц). У 24 пацієнтів такі ЕЕГ-феномени комбінувалися з епілептиформними елементами інших типів (генералізованими та фокальними нерегулярними комплексами пік/хвиля, поодинокими та груповими гострими хвилями, ЕЕГ-піками, множинними піками і т. д.). Як виявилося, фармакотерапія з використанням Д ефективно усувала SWC, генеровані в спокійному стані пацієнтів; епілептиформні ЕЕГ-феномени, провоковані гіпервентиляцією та ритмічною фотостимуляцією, були помітно більш опірними в цьому аспекті. Ефективність лікування за допомогою Д в групі 1 (пацієнти з наявністю виключно SWC у складі ЕЕГ) була істотно вищою, ніж у групі 2 (пацієнти з девіантними ЕЕГ-патернами, котрі містили в собі комбінації епілептиформних елементів інших типів із SWC). Через шість місяців після початку прийому Д типові SWC (3–4 Гц) повністю зникали з ЕЕГ 63.9 % пацієнтів групи 1 та 41.7 % пацієнтів групи 2.

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