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EFFICIENCY OF THE TREATMENT OF EPILEPSY IN ADOLESCENT CHILDREN ACCORDING TO INDICATORS OF EVOKED POTENTIALS

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Abstract

The aim: to identify the peculiarities of the indicators of evoked potentials in epileptic children against the background of anticonvulsant treatment. **Methods:** auditory long-latency, visual flash-evoked potentials. Epileptic children were divided into two groups. The first group received monotherapy, the second group received polytherapy. **Results:** The study of average values of latencies showed that children with polytherapy had a more pronounced lengthening of latencies compared to those of the first group. According to the latencies analysis in the group of monotherapeutic children there were no ties between various anticonvulsant drugs and results of examination. There was a tendency towards normalization of latencies, mainly for visual evoked potentials in the group of children with a positive response to treatment. **Conclusion:** It is advisable to use the method of evoked potentials to assess the functional state of sensory systems in children with epilepsy, in order to predict the course of the disease and assess the effectiveness of treatment.

Key words: **children with epilepsy; visual evoked potential on flash; long-latency auditory evoked potential.**

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Introduction

Childhood is an important period of a person's life cycle, during which the foundation for a long, fruitful, full-fledged social life is formed [1]. Today, there is a significant increase in neurological diseases among children, including epilepsy (E). The disease has an important social significance. In the structure of neurological diseases E occupies the third place. The disease results in high degree of disability, risk of sudden death, social stigmatization of patients [2-4, 5-6], in addition 30% of patients are unable to control their attacks. Worldwide, about 65 million people suffer from E. In 70-75% of cases [7-8] the disease begins in childhood or adolescence

The development of new approaches to the diagnosis and treatment of E, as well as the prediction of the course of this pathology, remain relevant.

Along with such a method as encephalography (EEG), which is the main and undisputed method for E diagnosis, recently the method of evoked potentials (EVP) has been used. Registration of EVP is an objective and non-invasive method of central nervous system functions testing.

EVP examination is important for determination of the functions of such sensory systems as vision, hearing, and touch and the degree of their impairment. Thus, visual, auditory, somatosensory and other EVPs, related to the modality of the presented stimulus, are distinguished [9-10].

Long-latency auditory evoked potentials (LLAEVPs) are a superposition of near-field potentials from the zones of the primary auditory cortex, which gives the maximum response in the vertex region. This is the late component of the auditory response. Active electrodes are placed above points T5, T6 of the international electrode location scheme "10-20". The so-called V-wave is distinguished: a negative-positive complex with peak latencies N from 70 to 90 ms and P from 150 to 200 ms [11-13].

Evaluation at different levels of the visual system is possible with the help of EVP, in particular visual for flash. Active electrodes are placed over the occipital region in leads O1 and O2. Visual EVPs for flash can be divided into primary or early components of the response up to 100 ms and secondary or late components above 100 ms. Most authors consider the pronounced P2 peak with a latency of 103±15 ms [11, 12, 14, 15]. Peak P2 is the result of generation in the cortex of the striatum - the 17th-18th field according to Brodmann [14].

The aim of the study. To evaluate the effectiveness of E treatment in teens using the EVP method.

Object and research methods. 51 children with a diagnosis of E who received anticonvulsant therapy took part in the study. The examination was conducted in accordance with the principles of the Helsinki Declaration on the Protection of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, and the provisions of the relevant laws of Ukraine. Informed consent of the children's parents was obtained for the examination, as well as the collection and processing of patient data. Various forms of E were diagnosed: structural, infectious, genetic, metabolic, immune, and the forms with an unknown etiologic factor. Seizures with a focal onset, generalized and unknown, motor and non-motor, with preserved or disturbed awareness [16] were noted:.

During the research, the following methods were used: clinical and anamnestic, clinical and neurological, neurophysiological (EEG), evoked potentials method - visual flash (VF) and long-latency auditory evoked potentials (LLAEVP), neuroimaging (MRI), analytical and statistical.

Statistical analysis packages SPSSStatistics 19.0, Statistica 10 (StatSoftInc., USA), Microsoft Excel for Windows were used for statistical processing of the results obtained. The Shapiro-Wilk (W) test was used to check the distribution of signs for normality. The distribution was considered normal at $p>0.05$. Continuous variables are given as mean (M) and standard deviation or median (Me), first and third quartiles, minimum and maximum, depending on whether the sample follows a normal distribution. Differences in group means were tested using Student's t-test and Mann-Whitney U-test. A value of $p<0.05$ was considered statistically significant.

The electroencephalographic 16-channel computer complex "BRAINTEST", produced by research and production enterprise "DX-systems" (Kharkiv) was used to conduct an EEG study. The same device was used in the research process of EVPs, but the calculation of indicators was performed on a separate program.

Epileptic children underwent brain MRI with a magnetic field strength (H) of at least 1.5 T to detect structural changes in the brain.

LLAEP and VF for the flash were performed twice (before and during treatment, at least after 6 months of therapy) in order to assess the functional state of the central links of auditory and visual analyzers.

To evaluate the results of EVP, an analysis of latencies was performed, especially that of P2 peak, the amplitude and shape of the curve, the interaural and interocular difference of EVP.

In the available sources, data regarding changes in EVP indicators in the course of E pharmacotherapy are contradictory, there is no analysis comparing the effectiveness of treatment and the presence/absence of structural changes on the part of the brain, which are recorded during neuroimaging [17]. The case is still up whether it is possible to use the EVP method to further confirm the effectiveness of treatment and predict the course of E in adolescent children.

Research results and their discussion

There were 51 children with a diagnosis of E. 30 children formed a monotherapeutic group (group1), 21 children (group 2) received two or more anticonvulsant drugs, that is, they were on polytherapy. In the first (monotherateutic group), positive dynamics, i.e. when the latencies during the study of EVP tended to normal values, were noted in 21 children, while in 9 children there was a prolongation of latencies, and 20 children were free from seizures. From the group of children who received polytherapy, on the contrary, there were more children with indicators of latencies that exceeded normal (13 patients with E) and positive dynamics were noted in 8 children (Table 1).

Table 1 – Influence of treatment features on treatment dynamics

Dynamics Treatment	Features of treatment		Total, (Abs. quantity, n)
	Monotherapy, (Abs. amount, n)	Polytherapy, (Abs. quantity, n)	
Positive	21	8	29
Missing dynamics	9	13	22
Total	30	21	51

In 8 patients the attacks persisted against the background of polytherapy. Calculated Pearson's test χ^2, p=0.0236; Yates' corrected value, χ^2=3.91, p=0.0481, $V_{Kramer's}$ =0,3170; Fisher's exact test (one-sided area) p=0.0238, less than the level of statistical significance (p=0.05). This indicates a statistically significant difference in treatment outcomes when using two types of treatment (monotherapy and polytherapy). The results obtained indicate that monotherapeutic treatment of E is more effective than the use of a combination of several anticonvulsant drugs (polytherapy).

The calculation of the odds ratio (OR) gives the value of OR=3.7917 for the 95% confidence interval (1.169; 12.3). In other words, the probability of having positive dynamics in treatment using monotherapy is 3.7917 times higher than in treatment with polytherapy and with a 95% probability is in the range of 1.169-12.3.

The assessment of the difference in the latencies of LLAEVP and VF between the group of monotherapeutic children and the group of children who received two or more anticonvulsant drugs ("polytherapy") was performed using the Mann-Whitney U-test (Table 2).

Thus, an assessment by each lead shows that in the study of LLAEVPs with stimulation on the right and on the left, a more pronounced lengthening of the average values of latencies in the polytherapeutic group takes place.

Similar data for all leads were obtained in the study of VFs for a flash in polytherapeutic group in comparison with children who received treatment with one drug.

Table 2 – Differences in indicators of LLAEVP and VF in the groups with monotherapy (Group 1) and polytherapy (Group 2)

Indicator		Group 1- monotherapy, n = 30, ms	Group 2 – polytherapy, n = 21, ms	z	p
Leads	Right-T5	185 (180; 208) [138; 234]	198 (187; 209) [154; 224]	-0.88095	0.378351
	Right-T6	193.5 (183; 202) [160; 243]	205 (194; 210) [150; 246]	-1.94357	0.051956
	Left –T5	190.5 (176; 210) [125; 260]	194 (185; 208) [174; 313]	-1.12034	0.262577
	Left – T6	187 (178; 199) [153; 234]	196 (188; 205) [170; 234]	-1.72407	0.084705
	Right –O1	107 (94; 118) [82; 176]	113 (106; 150) [85; 194]	-1.42634	0.153781
	Right – O2	101.5 (94; 119) [81; 182]	116 (101; 132) [85; 201]	-1.78134	0.074867
	Left – O1	107 (98; 116) [81; 178]	125 (112; 185) [85; 199]	-2.34601	0.018982
	Left-O2	103 (96; 117) [81; 187]	112 (105; 140) [84; 224]	-1.97185	0.048635

Note: Right T5, T6 – leads T5, T6 during stimulation from the right; Left T5, T6 – during stimulation from the left during the study of LLAEVPs. Right O1, O2 leads O1, O2 during stimulation from the right; Left O1, O2 - during stimulation from the left during the study of VF. *Monotherapy* – a group of children receiving treatment with one drug; *Polytherapy* – a group of children receiving two or more anticonvulsant drugs; z – z-value; p - the probability.

Thus, when investigating the indicators of latencies at LLAEVPs and VF, unidirectional results were recorded - an increase in the average values of the indicators in epileptic polytherapeutic children in comparison with the group of children who received monotherapy.

The differences in the average values for the two leads O1 and O2 during stimulation from the left are statistically significant at the p=0.05 level. For lead T6 with stimulation from the left and right, and for lead O2 with stimulation from the right, the differences in mean values are for the level of significance p=0.1.

30 monotherapeutic patients received the following treatment: 16 – valproic acid, 3 – carbamazepine, 8 – levetiracetam and 3 children got oxcarbazepine.

The analysis carried out in 4 groups of patients taking different drugs as monotherapy with the use of Kruskel-Wallis's H-criterion, showed that there is no statistically significant difference in the average values in the groups for each of the 8 leads ($p>0.05$).

In order to find out whether there are statistically significant changes in the study of indicators in the dynamics, the data of children with a positive response to treatment were used. That is, there are 21 monotherapeutic patients and 8 polytherapeutic children.

The study of differences in latencies in groups was conducted using the Student's t-test for paired samples and the Wilcoxon T-test for the level of statistical significance $p=0.05$ (Table 3)

Table 3 – Indicators of EVP in dynamics, during the treatment of children with anticonvulsant drugs

Indicator		Subgroup 1- before treatment, n = 29, ms	Subgroup 2 – during treatment, n = 29, ms	z	p
Leads	Right-T5	195 (183.5; 225) [172; 307]	185 (175; 207.5) [138; 234]	2.5167	0.01185
	Right-T6	202 (183.0; 219.5) [166; 253]	200 (184.5; 204.5) [160; 240]	1.0022	0.31625
	Left –T5	196 (190; 217.5) [150; 251]	189 (176; 201) [125; 260]	1.4602	0.14423
	Left – T6	205 (189; 223) [162; 290]	188 (183.5; 204) [153; 234]	2.8222	0.00477
	Right –O1	115 (102; 131) [82; 207]	100 (90.5; 110.5) [82; 126]	2.8929	0.01087
	Right – O2	107 (98.5; 122) [84; 187]	98 (93; 107) [81; 119]	2.8929	0.00382
	Left – O1	106 (95; 127) [77; 190]	106 (95.5; 110.5) [85; 125]	1.5947	0.11079
	Left-O2	112 (100.5; 121) [77; 191]	100 (94; 109.5) [81; 117]	3.0831	0.00205

Note. Subgroup 1 – a group of children at the beginning of treatment with mono- or polytherapy; Subgroup 2 – a group of children observed in dynamics against the background of treatment with one or two or more drugs; z – z-value; p - the probability.

It can be seen from Table 3 that for almost all leads there is a tendency towards normalization of latencies in the second group. In addition, there are differences for five leads, namely, during the LLAEVP with right stimulation in T5 lead, with left stimulation in T6 lead, during VF with right stimulation in O1 and O2 leads, and with left stimulation in O2 lead. Differences in groups of patients before and after treatment are statistically significant ($p<0.05$).

Conclusions

1. The results obtained showed that the method of examination with the help of EVP of adolescents with E can be applied not only to confirm the effectiveness of the treatment, but also to visualize the preservation/restoration of the functioning of brain structures, in particular, hearing and vision.

2. It was established that the use of polytherapy compared to monotherapy, more pronounced lengthening of latencies was observed during the study of DSVP and ZVP. This may indicate an adverse effect of polytherapy on brain functions.

3. It has been proven that monotherapy did not influence on the results of E treatment as well as on improvement of brain functions, especially visual one. The effect did not depend on the active substance of the antiepileptic drugs that were used.

4. In the course of treatment, children with a positive response had a tendency to normalize the latencies, mostly this related to visual evoked potentials.

5. In our opinion, visual evoked potentials are more sensitive for use in practical activities with the aim of recording the dynamics of the course of E during treatment.

Prospects for further research

There are still unclarified questions regarding the influence on the EVP indicators of anti-epileptic drugs different in mechanism of their action in the treatment of epileptic children. Our further researches will be devoted to the investigation of this problem.

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Authors' Contribution

Conceptualization (Gekova M. V., Tantsura L. M.),; methodology (Gekova M. V., Tantsura L. M.); formal analysis (Gekova M. V., Tantsura L. M.); data management (Gekova M. V.),

writing an article (Hekova M.V., Tantsura L.M.); statistical processing of materials (Gekova M. V.). All authors have read and approved the published version of the manuscript.

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State institution "Institute of Neurology, Psychiatry and Narcology named after P.V. Voloshyn of the National Academy of Medical Sciences of Ukraine" (Kharkiv, Ukraine) (protocol No. 10 dated 13.10.2023), the basic moral and ethical principles of the Helsinki Declaration of the World Medical Association for Biomedical Research were observed.

Informed Consent Statement

Written informed consent for the processing of personal data and their further use was obtained from the patients.

Conflict of interest

The authors declare no conflict of interest