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FREQUENCY OF INTERICTAL EPILEPTIFORM DISCHARGES IN SLOW SLEEP WITH RELAPSE OF TONIC-CONICAL SEIZURES IN ADULTS WITH GENERALIZED EPILEPSY AFTER WITHDRAWAL OF ANTIEPILEPTIC DRUGS

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Interictal epileptiform discharge rates (IED) were studied in slow-wave sleep phases (NREM) with recurrent tonic-clonic seizures with generalized onset (GTCS) in adults after withdrawal from antiepileptic drugs (AED) with the debut of idiopathic generalized epilepsy (IGE) before the onset of adult age (group A). The control group consisted of IGE patients with non-drug-induced remission of GTCS for more than 5 years (group B). Patients who had presented information on myoclonic seizures in adolescence constituted group 1, patients with isolated GTCS - group of probable IGE GTCS (group 2). Patients with febrile and absence seizures in the disease history, structural alterations on MRT, myoclonic, and absence seizures at the time of the study were excluded. All patients underwent polysomnographic investigation (PSG) on the device "Neuron-Spectr-4VP" of the firm "Neurosoft" in the period of physiological nocturnal sleep. Visual identification of sleep phases was carried out in accordance with the guidelines of the American Academy of Sleep Medicine. IEDs were revealed during visual evaluation of the native EEG, and manual counting of the absolute number of discharges in NREM was performed. The IED generation rates were calculated as a ratio of the absolute number of IED to the summarized duration of every phase in the parts without artefacts. The comparison of the rates of IED in NREM in study groups was conducted. Statistical processing was performed with the Statistica 6.0 toolkit. The study used parametric and nonparametric methods of comparison. For the entire period of registration of the slow wave sleep phase, the absolute number and rates of IED per hour of recording were higher in patients with recurrent GTCS and myoclonic seizures in the illness history compared to other groups. In patients with recurrent GTCS and myoclonic seizures in the history of the disease, the persistent increase in IED rates per hour to the deep wave sleep phase was observed compared to the other group of patients with IGE. The evaluation of the IED rates in the slow wave sleep phase can be performed in patients with IGE for the prediction of recurrent GTCS and the solution of the question of withdrawal from the AED.

Keywords: interictal epileptiform discharges, slow wave sleep phases, generalized tonic-clonic seizures, idiopathic generalized epilepsy.

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Introduction. The literature accumulated sufficient data comprising long-term follow-ups of electroclinical dynamics with some syndromes of idiopathic generalized epilepsy (IGE) with a variable phenotype, however, rates of interictal epileptiform discharges (IED) in slow wave sleep phases (NREM) with recurrent tonic-clonic seizures with a generalized onset (GTCS) in patients with IEG debut prior to onset of the adult age after withdrawal from AED were studied inadequately. GTCS are of major medico-social importance in adults with idiopathic generalized epilepsy (IGE) with a variable phenotype [1, 2]. The continuum of IGE is characterized by variety of generalized seizures and comprises juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with isolated GTCS (IGE GTCS) [3,4]. Favorable prediction of IGE is associated with reduction in rates and duration of IED, however, methodological heterogeneity of the studies explains contradictory character of results, which are reported about predictive value of the EEG in IGE and is in need of further research [5]. As a whole, type of the seizure and registration of IED after withdrawal from AED is considered as a predictor of the recurrent seizures into the remission of an unspecified syndrome of IGE [6]. In its turn, a higher density and major duration of IED may be retrospectively associated with a shorter remission which supposes potential possibility of the use of EEG as a biomarker of the prediction in IGE and makes clinical research in this direction relevant [7].

The purpose of the study was to investigate the rates of IED in NREM with recurrent GTCS in adults after withdrawal from AED with the IGE debut prior to the onset of adult age.

Materials and Methods. During the elaboration of the research protocol, a 'case-control' design was used to compare records of patients with IGE and recurrent GTCS (group A) and patients with a remission duration of more than 5 years (group B). The duration of remission was evaluated based on the clinical questionnaire according to guidelines [8]. Seizures were defined as GTCS according to the guidelines [9]. The reconstruction of IGE syndrome was conducted based on illness history information (detection of other types of generalized attacks in the debut of the disease) in the accordance with the guidelines [10]. Patients who gave the information on their myoc-

lonic attacks at adolescence constituted the group of probable JME (group 1), patients with isolated GTCS – the group of probable IGE GTCS (group 2). All patients underwent EEG monitoring in the period of physiological sleep in the laboratory Video-EEG-monitoring of the Department of Neurology and Neurosurgery of SibSMU. Criteria of inclusion: observation in the outpatient network with the diagnosis IGE; age from 18 to 50 years, absence of epileptic attacks during 10 days prior to investigation, withdrawal from AED not less than 12 months prior to the study. Criteria of exclusion: actual physical and neurological pathology, febrile and absence attacks in the history of the disease, structural alterations in MRT, gravida period and lactation, mental disorders, myoclonic (including myoclonus of eyelids with absences) and absence attacks at the time of study, documented GTCS during neurophysiological investigation. The study included 78 patients with IGE. Of them, 54 women and 24 men aged 18 to 51 years. The mean age was 25.07±6.05 and 24.83±7.15, respectively (p= 0.87). The main group (group A) included 60 patients, complaining of recurrent GTCS within 1 to 8 years. The average duration of the previous remission was 2.46±1.44 years. The control group (group B) included 18 patients with remission of attacks from 5 to 8 years. The average duration of remission was 6.2±1.1 years. The myoclonic attacks in the illness history were revealed in 40 patients (group 1), the remaining patients entered group 2. The comparison was carried out in homogeneous groups formed according to sex and age among patients with IGE with variable phenotype with myoclonic attacks in the history of the disease and isolated GTCS after withdrawal from AED in the subgroups according to the course of the disease.

Protocol of neurophysiological investigation. All patients underwent polysomnographic investigation (PSG), including electroencephalography (in leads F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, 2 with the use of the standard position of the electrodes according to the system 10–20), electro-oculography (2 channels), electrocardiography (1 lead), electromyography of the mental muscles (2 channels), on the device “Neuron-Spektr-4VP” of the firm “Neurosoft” in the period of physiological nocturnal sleep. Visual determination of sleep phases was performed according to the guidelines of the American Academy of Sleep Medicine [31]. Some IEDs (complexes peak-wave, polypeak-wave) were revealed during visual evaluation of the native EEG according to the conventional classification [32]. In patients with documented IEDs in the first, second and third NREM of the first cycle of the sleep, a manual counting of the absolute number of discharges was conducted. The description of the quantity of IEDs was carried out according to the guidelines [33]. The rates of generation of IEDs were calculated as a ratio of the absolute number of the IEDs to the summarized duration of every phase in the parts without artefacts in all cycles of the sleep. Comparison of IED rates in NREM was conducted in the study groups. Statistical processing was performed with the use of the Statistica 6.0 toolkit. The study used parametric and nonparametric methods of the comparison, Mann-Whitney, Freedman, Kruskal-Wallis test, Shapiro-Wilk, t-test (Student). For the reliable level, the level of significance $p<0.05$ was accepted. Data were presented as mean and standard deviation (M±SD), median (Me) and quartiles (q1; q3) – Me (q1; q2).

Results and Discussion. In the structure of IGE, recurrent GTCS in adults can be observed in IGE GTCS and JME. Both IGE syndromes are not referred to as self-resolved, but may have a tendency to a benign course, including spontaneous long-term remissions irrespective of AED intake [19]. In the formed sample of patients with IGE, illness history information on the presence of myoclonic attacks at adolescence did not allow concluding about prediction of recurrent GTCS: breakage of remission was documented in 72.5% of patients with myoclonic attacks in the illness history and in 81.6% with isolated seizures (p=0.34148).

The incidence rates of IED in NREM in study groups of patients with IGE depending on the course of the disease are presented in Figure 1. In adult patients with IGE, very frequent (more often than 1 per 10 seconds) IEDs were not documented. The frequent (more frequent than 1 per one minute but more rarely than 1 per 10 seconds) ones were predominantly documented in group A1, whereas in groups A2 and B, rare (more rarely than once an hour) IEDs. The presented data correspond to the formed in the literature notions about major rates of IED in patients with JME in comparison with IGE GTCS and higher risk of recurrent JME during frequent IEDs [7,11].

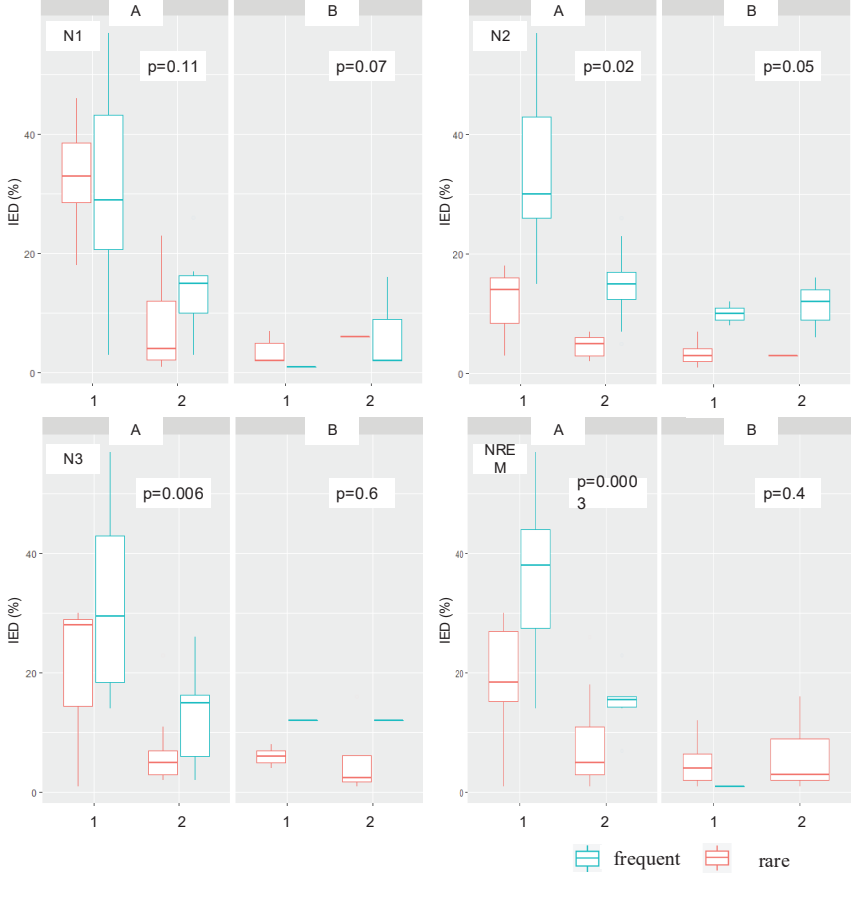

Fig. 1. IED incidence rates in NREM in study groups of patients with IGE
Note: IED – interictal epileptiform discharges: frequent rare
N1 – stage 1 of NREM, N2 – stage 2 of NREM, N3 – stage 3 of NREM, NREM – stages 1-3 of NREM

As a whole, despite of that in the adult patients with IGE, rare IED were documented more often, diagnostically relevant duration of EEG monitoring corresponded to data [14].

The frequency of documenting the IEDs in NREM in study groups of patients with IGE taking AED is presented in table 1. Duration of parts of the EEG without artefacts in NREM did not differ in the study groups.

For the entire period of documenting the slow wave sleep, the absolute quantity and rates of IED per hour were higher in patients with recurrent GTCS and myoclonic attacks in the illness history compared to other groups. The effect of the pronounced reduction in absolute amount and IED rates per hour in patients with JME remission is shown during the outpatient EEG with long-term accumulation of pathological graph elements [11]. According to common notions, a stable decrease in rates and the absence of epileptiform patterns with JME may be considered as a neurophysiological predictor of remission of the disease [5]. However, alongside with increase of the duration of documenting the EEG, in literature there is another trend based on the evaluation of the interaction of the physiological and pathological activity in IGE. In IGE during slow wave sleep and specifically in the second phase of NREM, conditions are created for synergy of physiological and pathological activity that leads to increased frequency of IEDs [5, 15]. It is shown that variants of the correlations between physiological patterns of the sleep and IEDs may be considered during prediction of the JME remission [16]. In patients with recurrent GTCS and myoclonic attacks in the history of the illness, the absolute number and IED rates per hour of recording in phase 2 of NREM exceeded the corresponding values in other study groups, which is consistent with the available data in the literature.

In recent years, the diagnostic significance of the documenting the IED in delta-sleep is studied [17]. In patients with recurrent GTCS and myoclonic attacks in the history of the disease, the absolute number and IED rates per hour of recording in deep-wave sleep exceeded the corresponding values in other study groups, which can be considered as a neurophysiological indicator of unstable IGE remission. It should be agreed with the proposition [17], that despite the patterns of distribution of IEDs with different courses of IGE revealed in many works, the attitude towards the practical application of the findings of EEG investigations remains sceptic due to the heterogeneity of the groups and methods used. In the next stage of the work, the evaluation of the dynamics of IEDs in NREM in study groups of patients with IGE (Figure 2).

In patients with recurrent GTCS and myoclonic attacks in the history of the illness, a persistent increase in IED rates per hour to deep-wave sleep phases was documented compared to other groups of patients with IGE.

Quantity of interictal epileptiform discharges in slow wave sleep in study groups of patients with IGE - (q1; Me; q2) n

Studied indicators		A1	A2	B1	B2	Level of reliability of differences (p)
Stage 1	Duration of the documenting (without artefacts, hour)	(0.17;0.51;0.71) 29	(0.37;0.7;1.08) 31	(0.14;0.29;0.76) 11	(0.08;0.37;1.25) 7	0.094078
	Quantity of IED	(1;2;4) 23	(1;2;3) 18	(1;1;1) 6	(1;1.5;3) 4	0.336655
	Rates (incidence rates) of IED (number per hour)	(3.33;5.88;12.94) 23	(2.16;2.485;5.56) 18	(1.72;2.17;3.45) 6	(1;1.5;3) 4	0.139856
Stage 2	Duration of the documenting (without artefacts, hour)	(0.61;1.89;3.54) 29	(0.64;2.18;3.71) 31	(0.84;0.99;3.66) 11	(0.79;1.38;2.12) 7	0.729974
	Quantity of IED	(6.5;13;23.5) 28*.**	(2;5.5;8) 24*	(1;2;5) 10**	(3.5;6;7.5) 4	0.001424* 0.000590**
	Rates (incidence rates) of IED (number per hour)	(3.2;6.85;20.09) 28*.**	(1.53;3.445;7.025) 24*	(1.01;1.175;2.19) 10**	(3.025;4.37;5.35) 4	0.003899* 0.003282**
Delta-sleep	Duration of the documenting (without artefacts, hour)	(0.32;0.5;1.02) 26	(0.5;0.75;1.27) 27	(0.31;0.71;1.22) 8	(0.47;0.95;1.35) 6	0.430172
	Quantity of IED	(4;9;14) 25*	(1;2;7) 23*	(2;3;4) 3	(1;1;4) 5	0.001053*
	Rates (incidence rates) of IED (number per hour)	(8.82;16.05;26.92) 25*	(2;3.23;6.18) 23*	(1.47;1.91;3.13) 3	(2.13;2.45;3.03) 5	0.000387*
All stages	Duration of the documenting (without artefacts, hour)	(1.31;2.67;5.53) 29	(1.32;4.43;5.55) 31	(1.48;1.56;5.66) 11	(1.34;2.1;4.75) 7	0.678822
	Quantity of IED	(18;29;43) 29*.**.***	(3;7;15) 31*	(2;4;7) 11**	(2;3;12) 7***	0.000149* 0.000149** 0.000150**
	Rates (incidence rates) of IED (number per hour)	(4.66;10.69;22.31) 29*.**.***	(1.07;2.59;4.55) 31*	(1;1.28;2.01) 11**	(0.75;2.11;2.86) 7***	0.000151* 0.000211** 0.001618***

Note. Duration of registration – the total duration of non-abstract EEG sections in the studied nREM stage per hour; number of IER – the absolute number of IER in the studied nREM stage; frequency of IER – the number (occurrence) IER per hour; pairs of signs with statistically significant differences were marked with the same number of asterisks.

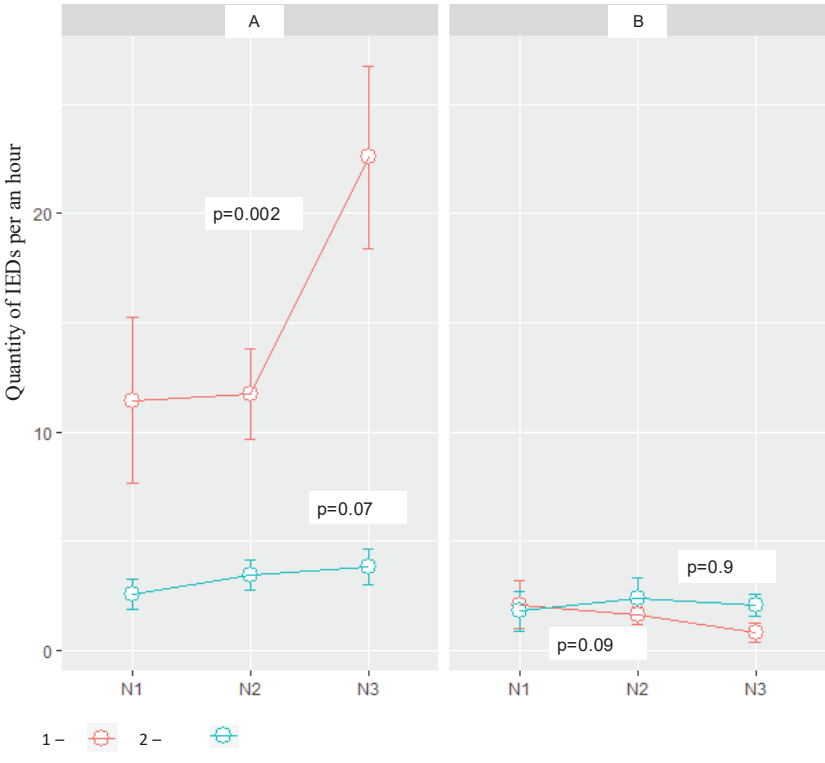

Fig. 2. Dynamics of IED rates in NREM in study groups of patients with IGE
Note: N1 – stage 1 of NREM, N2 – stage 2 of NREM, N3 – stage 3 of NREM, NREM – stages 1-3 of NREM

Conclusions However, the clinical importance of the findings is in need of further sophistication with the accumulation of data; the following is practically applicable: during the registration of frequent IEDs in patients with remission of IGE in combination with myoclonic attacks in the history of the disease, the question of withdrawal from AED should be solved regardless of the duration of the remission taking into account the dynamics of reduction of pathological activity in the EEG; the increase in the rates of IEDs per hour in the deep-wave sleep phases may be considered as an unfavorable predictive factor of recurrent GTCS in the individual clinical case.

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