DOI 10.25789/YMJ.2024.85.04

UDC 616.853

GREBENYUK Oleg V. – PhD, Associate Professor of the Department of Neurology and Neurosurgery of the Federal State Budgetary Educational Institution of Higher Professional Education "Siberian State Medical University" of the Ministry of Health of the Russian Federation, ; e-mail: oleg129129@mail.ru. ORCID iD: 0000-0002-4740-0162; **KAZENNYKH Tatiana V.** – MD, Deputy Director for Scientific and Medical Work of Mental Health Research Institute of Tomsk National Research Medical Center, Professor of the Department of Psychiatry, Narcology and Psychotherapy of the Federal State Budgetary Educational Institution of Higher Professional Education Siberian State Medical University MH RF; e-mail: tvk151@yandex.ru. ORCID iD: 0000-0002-6253-4644; **SVETLIK Mikhail V.** – PhD, Associate Professor of the Department of Human and Animal Physiology of the Biological Institute of the Federal State Autonomous Educational Institution of Higher Education National Research Tomsk State University, e-mail: mihasv@mail.tsu.ru. ORCID iD: 0000-0003-0990-2580; **PUGACHENKO Natalia V.** – Associate Professor of the Department of Neurology and Neurosurgery of the Federal State Budgetary Educational Institution of Higher Professional Education Siberian State Medical University of the Ministry of Health of the Russian Federation, Cand.Sc. (Medicine), e-mail: nv_pugachenko@mail.ru. ORCID iD: 0000-0002-3878-1725; **AVKHIMENKO Viktor A.** – PhD, General Director of the Federal State Budgetary Institution of the Siberian Federal Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia, e-mail: kb81@med.tomsk.ru. ORCID iD: 0000-0002-2178-601X; **LEVKO Alena N.** – PhD, Vice-Rector for Interaction with Regions of the Federal State Budgetary Educational Institution of Higher Professional Education Siberian State Medical University of the Ministry of Health of the Russian Federation, e-mail: alenalevko@mail.ru. ORCID iD: 0000-0003-0313-0698; **ALIFIROVA Valentina M.** – MD, Head of the Department of Neurology and Neurosurgery of the Federal State Budgetary Educational Institution of Higher Professional Education Siberian State Medical University of the Ministry of Health of the Russian Federation, Professor, e-mail: v_alifirova@mail.ru. ORCID iD: 0000-0002-4140-3223; **BOKHAN Nikolay A.** – MD, Director of Mental Health Research Institute of Tomsk National Research Medical Center, psychiatrist of the highest category, Professor, academician of the Russian Academy of Sciences, Honored Scientist of the Russian Federation, Head of the Department of Psychiatry, Narcology and Psychotherapy of the Federal State Budgetary Educational Institution of Higher Professional Education Siberian State Medical University of the Ministry of Health of the Russian Federation, e-mail: mental@tnimc.ru. ORCID iD: 0000-0002-1052-855X

O.V. Grebenyuk, T.V. Kazennykh, M.V. Svetlik, N.V. Pugachenko, V.A. Avkhimenko, A.N. Levko, V.M. Alifirova, N.A. Bohan

SLEEP STRUCTURE IN ADULTS WITH RECURRENT EPILEPTIC SEIZURES OF REMOTE SYMPTOMATIC ETIOLOGY

A video-polysomnographic study of the structural characteristics of night sleep was carried out in 157 patients with a first-time unprovoked tonic-clonic seizure. The main group included patients with remote symptomatic seizure (RSS). Over the course of three years, 60 individuals had recurrent attacks; 38 patients had no recurrence of attacks during the observation period. The comparison group included 59 MRI- and EEG-negative patients. Patients with recurrent RSS had lower sleep efficiency, longer rapid eye movement phase, sleep fragmentation, wake after sleep onset, and more frequent awakenings from sleep (number of awakenings) versus patients with a single RSS and the comparison group. The identified changes demonstrate deeper disturbances in sleep architecture in patients with recurrent RSS and can be taken into account in prognostic counseling of this category of patients.

Keywords: remote symptomatic seizure, sleep structure.

Introduction. Remote symptomatic seizures (RSS) refer to unprovoked epileptic seizures that occur in the setting of previous structural brain injury [14]. The risk of relapse of RSS is often high, but the clinical indicator of the onset of epilepsy in adults continues to be a repeated epileptic seizure [28]. According to various researchers, the likelihood of relapse of RSS depends on the etiology and concomitant diseases [4, 7, 19], significantly increasing when epileptiform activity is detected [10]. It is well known that the probability of recording epileptiform discharges increases when recording the bioelectrical activity of the brain during sleep [2, 11]. Sleep and epilepsy are pathogenetically interrelated cyclic processes [12]. Epileptiform activity alters sleep structure, and sleep disturbance is one of the main risk factors for recurrent seizures [15]. According to recent data, epilepsy is characterized by a characteristic change in polysomnographic (PSG) indicators in the form of a reduction in the REM sleep phase and an increase in the number of spontaneous awakenings during sleep [26]. The study of PSG sleep indicators, potential markers of epileptogenesis that can predict the recurrence of epileptic seizures and influence treatment tactics in patients with remote symptomatic etiology is a relevant task, currently underrepresented in the available literature.

The study aim was to study the macro-architecture of night sleep during relapse of RSS in adults.

Materials and Methods. The study included 157 patients with a first-time unprovoked tonic-clonic seizure who were followed up by an epileptologist from 2008 to 2020. Neurophysiological investigation was carried out in the laboratory of video-EEG monitoring of the Department of Neurology and Neurosurgery of the Federal State Budgetary Educational Institution "Siberian State Medical University". The main group included patients with a first-time epileptic seizure with a focal onset, classified as RSS. Clinical inclusion criteria: anamnestic evidence of previous neurological diseases or traumatic brain injury confirmed by neurological examination, structural changes on MRI, age from 18 to 55 years, follow-up for three years, absence of epileptic seizures within 10 days before the study. Clinical exclusion criteria: repeated epileptic seizure, antiepileptic therapy [27], acute neurological pathology, acute physical conditions and exacerbations of chronic physical diseases [27], gravidity period and lactation, mental disorders, epileptiform activity on the EEG. During the observation period, 60 persons had recurrent seizures and, in accordance with the criteria [1], the onset of epilepsy was diagnosed. These patients made up group A. In 38 patients, attacks did not recur during the observation period (group B). The comparison group included 59 MRI- and EEG-negative patients with a first-time epileptic seizure with an unspecified onset (group B).

The characteristics of the individuals included in the study are presented in Table 1. The study groups were comparable in sex, age and lobar localization of epileptogenic damage to the cerebral cortex.

Neurophysiological study protocol. All patients underwent a video-polysomnographic study, including electroencephalography (in leads F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2 using the standard arrangement of electrodes according to the 10–20 system), electrooculography (2 channels), electrocardiography (1 lead), electromyography from the mentalis (2 channels), using the Neuron-Spectrum-4VP device from Neurosoft during physiological night sleep. Visual determination of sleep stages was performed according to the standard criteria of the American Academy of Sleep Medicine [8]. After identifying the stages and phases of sleep, the generally accepted parameters characterizing the structure of sleep were calculated [3]: total recording time (TIB - time in bed), total sleep duration (TST - total sleep time) - the total duration of all stages and phases of sleep, sleep latency (SOL – sleep onset latency) – time from turning off the light to the onset of the first period of sleep in minutes, sleep efficiency (SE – sleep efficiency) – percentage of TST from TIB, REM sleep latency (RL – rapid eye movement sleep latency) – time from falling asleep before the onset of the first epoch of rapid eye movement (R) in minutes, the relative duration of each stage of slow-wave sleep (nREM): the first stage - N1, the second stage - N2, the third stage - N3 and R in relation to TST as a percentage, the relative duration of wakefulness within sleep (WASO – wake after sleep onset) – in the interval from falling asleep to morning awakening (TIB-SOL) as a percentage, the number of spontaneous awakenings from sleep (NWake – number of awakenings) and overall sleep fragmentation (SSI – stage shift index) [13] in terms of 1 hour of sleep in absolute units. To estimate the number of awakenings in the nREM stages, we counted the number of actual transitions from N1, N2 and N3 to the wakefulness stage (W) [17] in the period from falling asleep to morning awakening. The normalized frequency of awakenings was calculated in relation to the sum of all transitions in W as a percentage [16]. Statistical processing was performed using the Statistica 6.0 package. The study used nonparametric comparison methods (Mann–Whitney, Kruskal-Wallis test), for evaluation of inter-group differences in the case of multiple comparisons we used Bonferroni correction [27]. A significance level of $p<0.05$ was accepted as reliable. Data are presented as medians (Me) and quartiles (q1; q3) – Me (q1; q2).

Results. Indicators characterizing the night sleep macrostructure are shown in Table 2. In patients from group A, the duration of TST was statistically significantly [27] reduced compared to group C, and the onset time R was increased, but these indicators did not differ among patients with focal seizures. The total recording time, sleep latency and nREM structure were comparable in the study groups, however, the relative duration of the REM sleep phase in group A was statistically significantly less than in group C. The duration of R in group B was also longer than in group A, however the differences did not reach the level of significance.

SE values in patients from group A were statistically significantly lower than the corresponding indicator in groups B and C (Figure 1).

The decrease in sleep efficiency among subjects of this group was accompanied by a significant increase in the relative duration of WASO.

Patients in group A had higher sleep fragmentation compared to the other groups (Table 3). The number of spontaneous awakenings per hour of sleep in patients from group A also statistically significantly exceeded the values of the corresponding indicators in the other groups.

When comparing the number of awakenings per hour in the stages of

Table 1

Clinical characteristics of individuals included in the study

Indicator	A (n=60)	B (n=38)	C (n=59)	p K-W test
Age, years (Me(q1; q2))	37.5(26;45)	34(26;50)	29(25;41)	0.2
Sex, f (m) - abs. numbers	15/45	10 /28	19 /40	0.6
Localization (MRI) according to the lobes of the brain - abs. numbers (%)				
Frontal	27 (45.0)	17 (44.74)		0.7
Temporal	24 (40.0)	14 (36.84)		
Parietal	7 (11.67)	5 (13.16)		
Occipital	2 (3.33)	2 (5.26)		
Note. K-W test – Kruskal-Wallis test				

Table 2

Commonly accepted polysomnographic indicators in the study groups

Indicator	Groups			p K-W test
	A	B	C	
TIB, min	397.43 (357.21;433.02)	396.26 (346.32;428.23)	406.26 (365.1;439.89)	pA-B 0.483
TST, min	333.08 (271.64;380.81)	355.14 (304.4;393.72)	374.92 (321.18;399.68)	pA-B 0.024 pA,B 0.008
SOL, min	7.67 (3.73;19.68)	6.18 (2.53;20.47)	7.37 (3.38;21.07)	pA-B 0.56
RL, min	86.57 (66.69;125.77)	85.23 (63.78;119.45)	73.28 (56.2;102.52)	pA-B 0.074
N1, %	21.3 (13.41;28.67)	17.8 (11.79;24.56)	17.02 (13.17;25.17)	pA-B 0.243
N2, %	42.85 (35.85;48.37)	41.02 (33.64;44.94)	43.84 (33.93;49.56)	pA-B 0.681
N3, %	22.56 (15.93;27.24)	24.12 (18.41;30.66)	20.52 (14.66;28)	pA-B 0.166
R, %	13.2 (10.56;15.47)	16.24 (10.95;18.28)	17.37 (16.2;19.9)	pA-B 0.0001 pA,B 0.00001

Note. The values of sleep indicators are given in minutes as medians (Me) and quartiles (q1; q3) – Me (q1; q2); K-W test – Kruskal-Wallis test pA-C – differences between all compared groups, pA-B – differences between groups A and B, pB-C – differences between groups B and C, pA-C – differences between groups A and C

slow sleep (Figure 2), a statistically significant increase in these indicators was revealed in the stages [21] of slow sleep in group A compared to group B, in [22] N1, N2 compared to group C. The relative number of transitions to the waking stage from N3 in group A exceeded the value of the corresponding indicators in groups B and C, but the differences did not reach the level of significance.

Discussion. Sleep is a complex neurodynamic self-regulating process and its changes in patients with new-onset RSS may be associated with subclinical epileptogenic restructuring of neural networks and, according to [23], analysis of patients with epileptic seizures who are not taking antiepileptic therapy can reveal changes in sleep architecture, associated to a greater extent with the influence of the pathogenesis of the disease.

In patients with recurrent RSS, there was a decrease in the total duration and efficiency of sleep, but the latency and structure of slow-wave sleep did not differ in the study groups. In general, sleep efficiency is an integral indicator that depends on the time of falling asleep and the duration of wakefulness during sleep. In the group of patients with recurrence of focal attacks, the relative duration of wakefulness within sleep and the overall fragmentation of sleep were higher, which characterizes the instability of sleep maintenance processes in this group of patients. The findings echo the changes identified [9] in sleep macro-architecture in adult patients with the onset of focal epilepsy and, according to the authors, can be explained by neurotransmitter disorders caused by epileptogenesis, leading to disruption of sleep regulation.

Clinical studies carried-out to date have shown that patients with epilepsy are characterized by an increase in the time of onset of the REM sleep phase, and the duration of this phase becomes shorter [25].

In the cohort of patients with the debut of focal epilepsy, a reduction in REM sleep was observed, however, latency values of this phase did not differ in the groups of comparison

A number of studies demonstrate variability in the duration of REM sleep depending on drug control of seizures and the effectiveness of surgical treatment of focal epilepsy [21, 27]. In patients with a follow-up onset of epilepsy, the duration of the REM sleep phase was shorter compared to patients with a single RSS, but the differences did not reach a statistically significant level.

It is now known that neurodynamic processes occurring in slow-wave sleep can promote the propagation of epileptiform activity, on the contrary, suppress the REM sleep phase [22].

It is assumed that the persistently detected phenomenon of REM sleep reduction in patients with epilepsy is not directly pathophysiologically related to the epileptic process, but is probably secondary to the disturbance in the dynamics of the change and duration of slow-wave sleep stages caused by epileptogenesis, which is manifested by increased fragmentation and frequent awakenings [18].

The overall fragmentation and the number of spontaneous awakenings during sleep in patients with recurrent RSS were higher compared to other groups, which from a modern point of view can be considered as a potential neurophysiological marker of an increased risk of recurrent epileptic seizures in this group of patients with unprovoked seizures.

Table 3

Number of spontaneous awakenings during sleep and overall sleep fragmentation in the study groups

Indicator (number of events an hour)	Groups			p K-W test	p M-W U Test
	A	B	C		
SSI	8.55 (6.5;12.71)	6.35 (4.34;9.07)	6.51 (4.27;9.03)	0.002	A>Б* A>B*
N of awakenings	1.75 (0.95;2.94)	0.82 (0.42;1.52)	0.88 (0.37;1.87)	0.001	A1>Б** A>B*

Note. Sleep indicators values are presented as medians (Me) and quartiles (q1; q3) – Me (q1; q2); K-W test – Kruskal-Wallis test; M-W U Test – Mann-Whitney U Test; **p< 0.001 and *p< 0.01 (Mann-Whitney U Test).

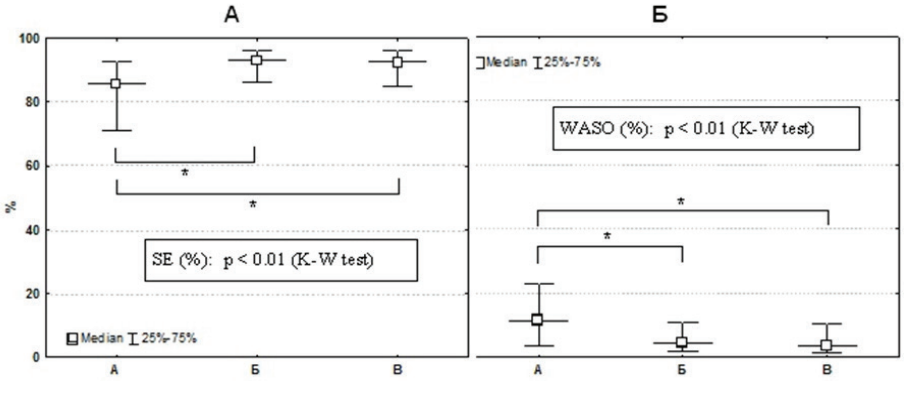

Fig. 1. Note. Sleep indicators values are presented in % as medians (Me) and quartiles (q1; q3); K-W test – Kruskal-Wallis test; p – level of reliability of differences; *p< 0.01 (Mann-Whitney U Test); А – SE (%): TST / TIB in %, И – WASO (%): WASO/(TIB-SOL) in %.
Sleep efficiency and duration of wakefulness during sleep in the study groups.

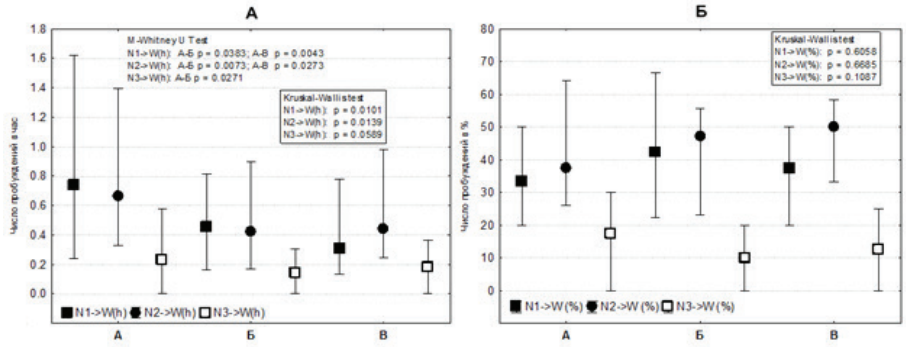

Fig. 2. Absolute (per hour) and relative (in %) number of awakenings at the stages of slow-wave sleep in the study groups: A – number of awakenings per hour: N1->W(h) - out of stage N1, N2->W(h) – out of stage N2, N3->W(h) – out of stage N3; B – relative number of transitions into the stage W out of definite stage of slow sleep in % in relation to the sum of all awakenings: N1->W(%) – out of stage N1, N2->W(%) – out of stage N2, N3->W(%) – out of stage N3.

Recent experimental model-based analysis of post-traumatic epilepsy in rats has demonstrated the need for stage differentiation when assessing PSG indicators characterizing sleep continuity [6]. According to the authors, a higher frequency of transitions from delta sleep to wakefulness can be considered a prognostic marker of post-traumatic epileptogenesis.

In patients with recurrent RSS, the absolute and relative frequency of awakenings from the deep stage of slow-wave sleep tended to exceed the value of the corresponding indicator compared to other groups.

According to the modern clinical paradigm, timely initiation of antiepileptic therapy is a necessary condition for achieving disease remission [25], and freedom from seizures correlates with normalization of sleep architecture [24].

According to J.L. Moore, D.Z. Carvalho, E.K. St. Louis, C. Bazil [20], the systematic study of two inextricably interacting neurodynamic processes of sleep and epilepsy is an urgent clinical task. The data obtained in the present study indicate that in patients with recurrent RSS, sleep consolidation and continuity are more affected, which is manifested by more frequent awakenings and sleep fragmentation.

Conclusion. The identified changes may characterize the disruption of chronobiological sleep regulation associated with subclinical epileptogenesis and be taken into account in prognostic counseling of patients with remote symptomatic seizures when assessing the prognosis of the disease and developing programs for personalized rehabilitation and prevention of relapse of epileptic seizures in this category of patients.

The article was published as part of the complex research topic “Biopsychosocial mechanisms of pathogenesis and clinical polymorphism, adaptive potential and predictors of treatment effectiveness in patients with mental and behavioral disorders in the Siberian region”, state registration number 122020200054-8, topic code FGWM-2022-0025.

References

1. Avakyan G.N., Blinov D.V., Lebedeva A.V., Burd S.G., Avakyan G.G. Klassifikatsiya epilepsii Mezhdunarodnoy Protivoepilepticheskoy Ligi: peresmotr i obnovlenie 2017 goda. Epilepsiya i paroksizmal'nye sostoyaniya. [ILAE Classification of the epilepsies: the 2017 revision and update. Epilepsy and Paroxysmal Conditions. 2017;9(1):6-25 (In Russ.).] https://doi.org/10.17749/2077-8333.2017.9.1.006-025

2. Karlov V.A., Vlasov P.N., Azhigova A.M., Kozhokaru A.B., Orlova A.S. Fenomen farmakodinamicheskoy aggravatsii pri primenenii blokatorov natrievykh kanalov u patsientov s vpervye vyyavlennoy fokal'noy epilepsiey. Nevrologiya, neyropsikhiatriya, psikhosomatika [Pharmacodynamic sodium channel blockers-induced seizure aggravation in patients with newly diagnosed focal epilepsy. Neurology, Neuropsychiatry, Psychosomatics. 2021;13(4):43-51. (In Russ.).]. https://doi.org/10.14412/2074-2711-2021-4-43-51

3. Levin Ya.I., Kovrov G.V., Poluektov M.G., Korabel'nikova E.A., Strygin K.N., Tarasov B.A., Posokhov S.I. Insomniya, sovremennye diagnosticheskie i lechebnye podkhody [Insomnia, modern diagnostic and treatment approaches. M: Medpraktika-M, 2005.116 p. (In Russ.).]

4. Naumova G.I. Organizatsiya meditsinskoy pomoshchi patsientam s vpervye razvivshimsya sudorozhnym pripadkom. Nevrologiya, neyropsikhiatriya, psikhosomatika. 2009;1 (2):37-41. [Organization of health care to patients with new-onset convulsive seizure. Neurology, Neuropsychiatry, Psychosomatics. 2009; 1 (2):37-41 (In Russ.)] doi.org/10.14412/2074-2711-2009-36

5. Ob effektivnosti, bezopasnosti i otsenke rezul'tatov lekarstvennoy terapii bol'nykh epilepsiey. Epilepsiya i paroksizmal'nye sostoyaniya [Effectiveness, safety and assessing the results of drug therapy in patients with epilepsy. Epilepsy and Paroxysmal Conditions 2021;13(3):306-310. (In Russ.)]. https://doi.org/10.17749/2077-8333/epi.par.con.2021.093

6. Andrade P, Lara-Valderrábano L, Manninen E et al. Seizure susceptibility and sleep disturbance as biomarkers of epileptogenesis after experimental TBI. Biomedicines. 2022;10(5):1138. Published 2022 May 14. https://doi.org/10.3390/biomedicines10051138

7. Berg Anne T. Risk of recurrence after a first unprovoked seizure. Epilepsia 2008;49(Suppl. 1):13-8.

8. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, Troester MT, & Vaughn BV. AASM scoring manual updates for 2017 (version 2.4). Journal of Clinical Sleep Medicine. 2017; 13(5), 665-666. https://doi.org/10.5664/jcsm.6576

9. Calvello C, Fernandes M, Lupo C et al. Sleep architecture in drug-naïve adult patients with epilepsy: Comparison between focal and generalized epilepsy. Epilepsia Open. 2023;8(1):165-172. https://doi.org/10.1002/epi4.12687

10. Debicki DB. Electroencephalography after a single unprovoked seizure. Seizure. 2017;49:69-73. doi:10.1016/j.seizure.2017.03.001

11. Delil S, Senel GB, Demiray DY, Yeni N. The role of sleep electroencephalography in patients with new onset epilepsy. Seizure. 2015;31:80-83. https://doi.org/10.1016/j.seizure.2015.07.011

12. Grigg-Damberger M, Foldvary-Schaefer N. Bidirectional relationships of sleep and epilepsy in adults with epilepsy. Epilepsy Behav. 2021;116:107735. https://doi.org/10.1016/j.yebeh.2020.107735

13. Haba-Rubio J, Ibanez V, Sforza E. An alternative measure of sleep fragmentation in clinical practice: the sleep fragmentation index. Sleep Med. 2004;5(6):577-581. https://doi.org/10.1016/j.sleep.2004.06.007

14. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. Epilepsia. 2008;49 Suppl 1:8-12. https://doi.org/10.1111/j.1528-1167.2008.01443.x

15. Kataria L, Vaughn BV. Sleep and epilepsy. Sleep Med Clin. (2016) 11:25–38. https://doi.org/10.1016/j.jsmc.2015.10.008

16. Kishi A, Struzik ZR, Natelson BH, Togo F, Yamamoto Y. Dynamics of sleep stage transitions in healthy humans and patients with chronic fatigue syndrome. Am J Physiol Regul Integr Comp Physiol. 2008; 294:1980-7.

17. Laffan A, Caffo B, Swihart BJ, Punjabi NM. Utility of sleep stage transitions in a ssessing sleep continuity. SLEEP. 2010;33(12):1681-1686.

18. Liguori C, Spanetta M, Fernandes M, Izzi F, Placidi F, Mercuri NB. More than sleep and wake disturbances: An actigraphic study showing the sleep-wake pattern dysregulation in epilepsy. Seizure. 2022;94:95–99.

19. Maksimova M.Yu., Shalimanova E.V., Brutyan A.G. Post-stroke seizures and epilepsy after stroke. Consilium Medicum. 2020; 22 (9): 38–45. https://doi.org/10.26442/20751753.2020.9.200273

20. Moore JL, Carvalho DZ, St Louis EK, Bazil C. Sleep and Epilepsy: a Focused Review of Pathophysiology, Clinical Syndromes, Co-morbidities, and Therapy [published correction appears in Neurotherapeutics. 2021 Apr 13;:]. Neurotherapeutics. 2021;18(1):170-180. https://doi.org/10.1007/s13311-021-01021-w

21. Serafini A, Kuate C, Gelisse P, et al. Sleep before and after temporal lobe epilepsy surgery. Seizure. 2012;21(4):260–5.

22. Shouse MN, Farber PR, Staba RJ. Physiological basis: how NREM sleep components can promote and REM sleep components can suppress seizure discharge propagation. Clin Neurophysiol. 2000;111(Suppl 2):S9–18.

23. Sudbrack-Oliveira P, Lima Najar L, Foldvary-Schaefer N, da Mota Gomes M. Sleep architecture in adults with epilepsy: a systematic review. Sleep Med. 2019;53:22-27. https://doi.org/10.1016/j.sleep.2018.09.004].

24. Tork, M.A., Rashed, H.R., Elnabil, L. et al. Sleep pattern in epilepsy patients: a polysomnographic study. Egypt J Neurol Psychiatry Neurosurg. 2020; 56, 5. https://doi.org/10.1186/s41983-019-0141-4

25. Yeh WC, Lai CL, Wu MN, et al. Rapid eye movement sleep disturbance in patients with refractory epilepsy: A polysomnographic study. Sleep Med. 2021;81:101–8.

26. Yeh WC, Lin HJ, Li YS, et al. Rapid eye movement sleep reduction in patients with epilepsy: A systematic review and meta-analysis. Seizure. 2022;96:46-58. https://doi.org/10.1016/j.seizure.2022.01.014

27. Zanzmera P, Shukla G, Gupta A, et al. Markedly disturbed sleep in medically refractory compared to controlled epilepsy - a clinical and polysomnography study. Seizure. 2012;21(7):487–90.

28. Zelano J. Recurrence risk after a first remote symptomatic seizure in adults: Epilepsy or not? Epilepsia Open. 2021;6(4):634-644. https://doi.org/10.1002/epi4.12543