COMORBID DISORDERS IN POSTTRAUMATIC AND POST-SUCCESS EPILEPSY. POSSIBILITIES OF THERAPY

A. O. Kaptalan, T. O. Andreeva, O. M. Stoyanov, I. O. Ostapenko, S. M. Oliinyk

Ukrainian Research Institute of Transport Medicine, Odessa
*Odessa National Medical University

Abstract

In the article, the authors substantiate the methods of treatment of the most common cause of symptomatic epilepsy in adults, namely traumatic and ischemic. The complexity of treatment is the need to take into account the location and magnitude of brain damage, the severity of the pathological process, risk factors for the most symptomatic epilepsy, the presence of comorbid pathology. Also, the large number of side effects from taking antiepileptic drugs, encourages the discovery of new treatments.

A method of treating post-traumatic epilepsy (PTE), in which, in addition to standard anticonvulsant therapy, other drugs were prescribed, such as: ethylmethylhydroxypyridine succinate, nootropic heptapeptide ACTH 4-10, Magnerot, ethylmethylhydroxypyridine succinate, Semax 0.1% solution.

Fifteen patients with PTE and 19 patients with post-stroke epilepsy (PIE) were examined. In the process of examination of patients with PTE, the main neurological syndromes that accompany epilepsy are identified and are often combined with each other. At PIE in the anamnesis all patients had various cardiovascular pathology: cerebral atherosclerosis, arterial hypertension, diabetes mellitus, ischemic heart disease, etc.

During treatment, in addition to controlling seizures, the number of complaints of cephalgia decreased, the signs of clinical depression and subjective experiences decreased.
Positive changes in bioelectrogenesis have been registered. The state of short-term and long-term memory, stability of attention has improved. A positive effect was obtained from the treatment of seizures and comorbid pathology.

The alternating effect of the proposed drugs on the background of anticonvulsant therapy leads to a significant reduction in the number and duration of epileptic seizures.

**Key words: symptomatic epilepsy; comorbid diseases; traumatic brain injury; stroke; treatment**

**КОМОРБІДНІ ПОРУШЕННЯ ПРИ ПОСТТРАВМАТИЧНОЇ ТА ПОСТИНСУЛЬТНОЇ ЕПІЛЕПСІЇ. МОЖЛИВОСТІ ТЕРАПІЇ**

А. О. Капталан, Т. О. Андрєєва, О. М. Стоянов, І. О. Остапенко, С. М. Олійник

Український науково-дослідний інститут медицини транспорту, Одеса

*Одеський національний медичний університет

В статті автори обґрунтовують методи лікування найпоширенішої причини виникнення симптоматичної епілепсії у дорослих, а саме травматичної та ішемічної. Складність лікування полягає в необхідності враховувати локалізацію і величину пошкодження мозку, тяжкість патологічного процесу, фактори ризику виникнення самої симптоматичної епілепсії, наявність коморбідної патології. Також, велика кількість побічних ефектів від прийому противоепілептичних препаратів, спонукає знаходити нові методи лікування.

Метод лікування посттравматичної епілепсії (ПТЕ), в якому, крім стандартної протисудомної терапії призначали і інші препарати, такі як: етилметилгідроксипіридину сукцинат, ноотропний гептапептид АКТГ 4-10, Магнерот, етилметилгідроксипіридин сукцинат, Семаке 0,1% розчин.

Було обстежено 15 хворих з ПТЕ та 19 хворих з постінсультною епілепсією (ПІЕ). В процесі обстеження хворих на ПТЕ виділено основні неврологічні синдроми, що супроводжують епілепсію, та часто поєднуються між собою. При ПІЕ в анамнезі всі пацієнти мали різноманітну серцево-судинну патологію: церебральний атеросклероз, артеріальну гіпертензію, цукровий діабет, ішемічну хворобу серця та ін.

Протягом лікування, окрім контролю над судомами, знизилася кількість скарг на цефалгії, скоротилися ознаки клінічної депресії і суб’єктивні переживання.
The relevance of treatment of symptomatic epilepsy is due to the fact that traumatic and ischemic brain injuries (TIBI) make up the vast majority of this type of epilepsy and is a multidisciplinary problem, which involves a large number of medical specialties. In addition to etiological reasons, the complexity of treatment is that it is necessary to take into account the location and magnitude of ischemic or traumatic brain injury, severity of the pathological process, risk factors for symptomatic epilepsy, comorbid pathology, and similar pathophysiological mechanisms of TIBI, which are largely similar. This is primarily due to the activation of lipoperoxidation, inhibition of antioxidant protection, excitotoxicity, membrane damage, lack of energy resources, as well as hyperproduction of proinflammatory cytokines, inflammation, apoptosis [1, 2].

All of the above encourages the development of universal comprehensive treatment methods TIBI, as well as their consequences in the form of symptomatic epilepsy, which is the result of summary CNS damage (vascular, posttraumatic, maladaptive factors) with the progression of cognitive, intellectual and mental disorders [3, 4].

It is also known that taking antiepileptic drugs (AEDs) can lead to toxic and other side effects, affect biological processes, often inhibit mental activity, especially given the existing cognitive and intellectual disorders as a result of encephalopathy in trauma, vascular pathology CNS and comorbid support of this pathology.

Based on the data on ischemic lesions characteristic of TIBI, reduction of antioxidant activity against the background of oxidative stress, which is the leading mechanism of epileptogenesis, a number of treatment approaches have been developed that affect these processes.

Treatment of post-traumatic epilepsy (PTE) is used, in which, in addition to standard anticonvulsant therapy, ethylmethylhydroxyperidine succinate was prescribed, drip daily in a daily dose of 100 mg, for a course of 10-15 days [5]. The disadvantages of this method are the low dosage of ethylmethylhydroxyperidine succinate, in the presence of a known dose-
dependent effect of the drug [6, 7], a short course that does not achieve sufficient antioxidant protection for prolonged and progressive oxidative stress and deprives the ability to conduct adequate neurotherapy on epileptogenesis, which complicates, increases the duration and number of epiparoxysms, has a minimal effect on comorbidity and somatic pathology. This is especially true of the restoration of cognitive functions, as well as the correction of all levels of the autonomic nervous system (ANS), which actively controls epileptogenesis.

In addition to the above, the treatment of symptomatic partial epilepsy with the nootropic heptapeptide ACTH 4-10, which includes a peptide group - methionyl-glutamyl-histidyl-phenylalanyl-proyl-glycyl-proline for complex anticonvulsant monotherapy [8]. It affects only the cognitive sphere, while there is no pronounced antioxidant effect, energy deficiency is not restored, as well as the therapeutic effect on comorbid diseases characteristic of epilepsy; in addition, there may be over excitation, which should be considered in the elderly as the main group of patients with post-stroke epilepsy (PIE) and psychoorganic syndrome as a comorbid condition of residual TBI along with PTE.

We analyzed the literature and selected drugs to influence the main links of TIBI, induced and related epileptogenesis. As a result, prescribed against the background of anticonvulsant monotherapy in addition Magnerot 1 table. 3 times a day for a month, ethylimethyhydroxypyridine succinate intravenously drip 300 mg 1-2 times a day for 10 days, then - 200 mg intramuscularly once, 10 days, and then 125 mg 2-3 times for 4-6 weeks; simultaneously with intramuscular administration appoint Semax 0.1% solution of 2-3 drops in each nasal passage 2-3 times a day.

**Materials and methods.** 15 patients were examined. The mean age was 31.1 ± 5.9 years. The average term of PTE formation reached 13.2 ± 2.5 years, and the frequency of attacks was 2.1 ± 0.7 per month. Focal seizures predominated (60.0%).

There were 19 patients with epilepsy that developed after an ischemic stroke - PIE. The mean age of patients was 56.2 ± 6.7%. The average term of PIE formation was 11.5 ± 3.1 years, and the frequency of attacks was 1.8 ± 0.9 per month. Focal seizures dominated in 73.7% of cases, ischemic injuries in the middle cerebral artery were 68.4%.

In the process of examination of patients with PTE identified the main neurological syndromes that accompany it, which are often combined with each other: the syndrome of autonomic dystonia (73.3%); cerebral-focal (33.3%), asthenic (33.3%), psychoorganic (26.6%), vestibular (13.3%).

MRI analysis of PTE history revealed CNS damage: bone defects (6.7%), scar-atrophic injuries (26.7%), post-traumatic cysts (20.0%) and hematomas (13.3%), dilation of
subarachnoid spaces (60.0%), ventricular system (20.0%) external (26.7%) and internal hydrocephalus (40.0%), increased or decreased density of brain matter of different localization (33.3%).

According to HADS, depressive strata were registered in 46.7% of patients with PTE, and anxiety in 33.3% of cases.

The productivity of random memorization of verbal material in PTE was significantly reduced in comparison with the normative data, the volume of direct reproduction in these patients was 4.6 ± 0.5 in the first presentation, delayed - 5.6 ± 0.7 words.

In the anamnesis all patients had various cardiovascular pathologies: cerebral atherosclerosis, arterial hypertension, diabetes mellitus, coronary heart disease and others.

In the group with seizures that developed after a stroke - PIE registered organic neurological symptoms, in 31.6% of cases there were compatible disorders of cerebral circulation in the carotid and vertebrobasilar basins - in 31.6% of cases. Atherothrombotic subtype of stroke - 52.6%, cardioembolic - 47.4%. Focal seizures dominated (75.6%). On MRI or CT, the cortical localization of brain damage was 78.9%, less often it was subcortical or mixed, lesions of the basal ganglia - 15.7%, dilatation of the cerebrospinal fluid was registered in 57.9%, the presence of leukoareosis 73.7%. According to ultrasound, stenoses of the main arteries, decreased cerebrovascular reactivity in carotid (57.9%), vertebrobasilar (63.1%) basins were detected.

The EEG recorded foci of pathological (47.3%), epileptoform (15.7%) activity, its generalization 21.0%, and slow waves (73.6%).

According to the indicators of psychometric research, there was an increase in the insufficiency of intellectual operations, among which the leading place was occupied by a decrease in the level of generalization. Various dysmnestic disorders were noted. The presence of attention disorders, as well as quantitative indicators of switching indicated a significant (P <0.05) increase in the duration of processing Schulte tables (1.7 times).

The productivity of random memorization of verbal material and the state of short-term and long-term memory, according to the test for memorizing 10 words on the Luria test was significantly reduced compared to the normative data, the volume of direct reproduction in these patients was 3.73 words, and delayed - 3.59 words.

**Research results and their discussion**

In the course of PTE therapy, control of seizures was registered for more than 24 weeks in 80.0% (P <0.05). The number of complaints of cephalgia decreased by 46.7% (P <0.05). Similar positive dynamics was registered in relation to other complaints and
subjective experiences. Positive changes in bioelectrogenesis (more than 40.0%, P <0.05) were observed in all major subgroups.

The number of people with clinically significant depression decreased 1.7 times (P <0.05). The number of anxious experiences decreased 1.8 times (P <0.05). The condition of short-term and long-term memory, stability of attention (P <0,05) improved. The maximum was reached at the time of the third presentation (7.4 ± 1.3 words), which was significantly higher (P <0.05) than at the beginning of the study (6.8 ± 1.0 words). Similarly, the indicators of long-term memory, which on average exceeded the original by 8% - respectively.

In the process of the claimed therapy of 2 groups of patients with PIE registered control of seizures for more than 24 weeks in 42.1% (P <0.05). Significant reduction in the frequency of attacks (more than 50%) - 47.3%. Positive dynamics is registered in relation to complaints and subjective experiences. Changes in bioelectrogenesis (more than 40.0%, P <0,05).

After therapy, psychoemotional disorders were normalized: the severity of anxiety or their disappearance decreased (by 63.2%, p <0.05), as well as depressive symptoms - by 52.6% (p <0.05). A decrease in concentration time and switching of attention was registered, however, they did not reach the normative values. The examined patients had an increase in the ability to memorize the presented words, the volume of direct and delayed reproduction. Also, after therapy, the process of memorizing words was significantly higher than before therapy in three presentations by 10%; 11%; 15%; in the deferred period - by 12%.

Thus, in both groups of symptomatic epilepsy received a positive effect of treatment as seizures and comorbid pathology.

The anticonvulsant effect of ethylmethylhydroxypyridine succinate with the prevention of the tonic component and potentiation of PEP is due to the fact that it is a derivative of 3-hydroxy-2-methylpyridines, which are involved in the regulation of excitation and inhibition of neurons, interrupts the main pathological mechanisms of CNS damage. its neuron - and membrane-protective properties.

An important feature is that ethylmethylhydroxypyridine succinate is able to reduce the increased sympathetic (arousing) effects of Semax and is necessary to obtain a pronounced anticonvulsant effect; enhancing the vasodilating capacity of ethylmethylhydroxypyridine succinate to influence the synthesis of nitric oxide, as well as through the intervention of regulatory neuropeptides on the hypothalamus.
Semax inhibits the processes of primary and delayed neuronal death, is effective in the rehabilitation of TIBI, PIE, PTE, in cognitive dysfunction in conditions of maladaptation and stress.

Mg - a substance of systemic action involved in the mechanisms of excitability of neurons, neuromuscular transmission, activates and controls ionic balance, homeostasis of minerals by blocking ion channels and preventing the trigger mechanism of Ca entry into the neuron, regulates synthesis and efficiency (including energy) neurotransmitters, neuropeptides, hormones. Protects the body from hyperactivation of neurons, including due to the stress response and stimulates the processes of adequate adaptation. Reduces the activity of cholinesterase, which is associated with the processes of depolarization of membranes, stimulates the production of dopamine and serotonin, regulates the state of pain and antinociceptive systems, inflammatory, allergic and immune reactions; associated with a state of positive stress.

**Conclusion.** Thus, the proposed approach in treatment has a beneficial effect on the main pathogenetic links in the development of TIBI, PTE, PIE. The alternating effect of the proposed drugs on the background of PEP leads to a significant reduction in the number and duration of epileptic seizures in symptomatic focal epilepsy and other types of seizures. At the same time, there is a significant decrease in complaints and subjective experiences, as well as neurological indicators, including cognitive deficit, psycho-emotional layers, comorbid conditions, large number of somatic pathology. A possible effect may be to reduce the dosage of PEP and their side effects with the normalization of bioelectrogenesis.

**References**

1. Antonenko S. A., Stoyanov A. N., Gryshchenko G. V., Skorobrekh V. Z., Kaptalan A. O. Post-Traumatic Mechanisms of Epileptogenesis // УЖМБС 2020, 5(6): 9–16

2. Stoyanov O.M. Uchast’ vegetativnoyi sistemi shhodo paroksizmal’nosti ta formuvannya posttravmaticchnoi epі’lepsi’yi / O.M. Stoyanov, S.S. Mashhenko, S.O. Antonenko, A.O. Kaptalan // Journal of Education, Health and Sport. – 2016. – Vol. 6, N 11. – P. 889-904 (in Russian)

3. El’skij V. N. Nejrogormonal’ny’e regulyatorny’e mekhanizmy’ pri cherepno-mozgovoye travme / V. N. El’skij, S. V. Zyabliczev. – Doneczk: Izd-vo «Novy’jmir», 2008. – 240 s. (in Russian)

4. Glutatione elevation and its protective role in acrolein-induced protein damage in synaptosomalmembranes: relevance to brain lipid peroxidation in neurodegenerative disease /
5. Novikov V.E., Maslov N.N. Vliyanie meksidola na techenie posttravmaticheskoj e`pilepsii // E`ksperimental`naya i klinicheskaya farmakologiya. - 2003. - T. 66. - #4. - S. 9-11. (in Russian)

6. Kolesnik E.A. Kliniko-patogeneticheskie osobennosti i korrekciya giperkineticeshkikh rasstrojstv pri vegetativny`kh disfunkcziyakh // E.A.Kolesnik / Ukrayins`kij vi`snik psikhonevrologi`yi - t. 28. - #1 (102). - S. 6-10. (in Russian)

7. Stoyanov O.M. E`ksperimental`noeobosnovanie i dozozavisimy`ee`ffekty` terapii meksikorom ishemicheskogo porazheniya mozga u kry`s / A.N.Stoyanov, R.S.Vast`yanov, E.A.Kolesnik, S.S.Mashhenko, S.A.Antonenko // Ukrayins`kij vi`snik psikhonevrologi`yi - Tom 27, vipusk 4 (101), 2019. - S. 25-31. (in Russian)

8. Serdyuk N.B. Osobennosti kognitivnyh rasstrojstv pri parcial`noj epilepsii i ih medikamentoznoy`a korrekciya (rol` nejropeptida AKTG 4-10 kak modulyatora regressii kognitivnogo deficita). - Diss. ... kand.med.nauk. - M., 2006. – S. 156. (in Russian)