Antonenko S. A. Main mechanisms and features of epileptogenesis of post-traumatic epilepsy. Journal of Education, Health and Sport. 2019;9(10):346-357. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3594665
http://ojs.ukw.edu.pl/index.php/johs/article/view/7663
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/7663

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 03.10.2019. Revised: 08.10.2019. Accepted: 30.10.2019.

UDC: 616.853–085.213: 616.12

MAIN MECHANISMS AND FEATURES OF EPILEPTOGENESIS OF POST-TRAUMATIC EPILEPSY

S. A. Antonenko

City Hospital № 5, Odessa

Abstract

One of the most frequent and formidable consequences of traumatic brain injury (TBI) is post-traumatic epilepsy (PTE), which is the main identified cause of symptomatic epilepsy at a young age.

The work highlights the "trigger" mechanisms of brain damage, including oxidative stress, leading to the disintegration of all levels of the central nervous system, contributing to the development of neuropathological syndromes, and especially PTE.

The questions of differentiation of PTE from other epileptic paroxysms, the dependence of the development of PTE on the severity of TBI, the main risk factors for this type of epileptogenesis, its phasing, as well as disorganization and damage to the antiepileptic system are considered. The place of a nonspecific response to damage in the form of immediate and early seizures, their metamorphosis as the formation of PTE was determined.

The existing spectrum of convulsive seizures is described, including partial, taking into account the localization characteristic of TBI with a predominance of lezional forms.

Key words: **post-traumatic epilepsy; epileptogenesis; risk factors**

УДК: 616.853–085.213:616.12

ОСНОВНЫЕ МЕХАНИЗМЫ И ОСОБЕННОСТИ ЭПИЛЕПТОГЕНЕЗА ПОСТТРАВМАТИЧЕСКОЙ ЭПИЛЕПСИИ

С. А. Антоненко

Городская больница № 5, г. Одесса

Одним из наиболее частых и грозных последствий черепно-мозговой травмы (ЧМТ) является посттравматическая эпилепсия (ПТЭ), которая является основной идентифицированной причиной симптоматической эпилепсии в молодом возрасте.

В работе освещаются "триггерные" механизмы повреждения мозга, в т.ч. окислительный стресс, приводящие к дезинтеграции всех уровней ЦНС, способствующих развитию нейропатологических синдромов и в первую очередь ПТЭ.

Рассматриваются вопросы дифференциации ПТЭ от других эпилептических пароксизмов, зависимость развития ПТЭ от тяжести ЧМТ, основные факторы риска такого рода эпилептогенеза, его этапности, а также дезорганизации и повреждения антиэпилептической системы. Определено место неспецифического ответа на повреждение в виде немедленных и ранних припадков, их метаморфоз по мере формирования ПТЭ.

Описан существующий спектр судорожных припадков, в т.ч. парциальных с учетом характерной для ЧМТ локализации с преобладанием лезиональных форм.

Ключевые слова: посттравматическая эпилепсия; эпилептогенез; факторы риска

Currently, various medical aspects of the consequences of traumatic brain injury (TBI), their study, diagnosis, and treatment approaches remain relevant for a large contingent of doctors and scientists from various fields of health.

High socio-economic significance is associated with the fact that head injury occurs mainly in young people at the most working age. The mechanisms of development of traumatic brain injuries in modern medical science continue to be studied and refined.

Naturally, the formation of the long-term consequences of head injury begins with pathological processes in the acute period.

In addition to direct brain damage, neuronal ischemia is an essential component in brain injury. In this case, the “trigger” mechanisms are hyperactivation of glutamate (mainly ionotropic, for example, NMDA) receptors, an increase up to toxic levels of intracellular concentration of free calcium, nitrogen-containing components (including highly reactive nitric oxide), activation of the cytokine response system, and a sharp increase the formation of active alternating radicals with a simultaneous decrease in the severity of the enzymatic and non-enzymatic units of antioxidant protection [1]. The latter mechanism is known as “oxidative stress”, initiating the propagating death of neurons [2, 3]. A vicious pathological circle is formed in which a cascade of interrelated pathological reactions can be clearly traced: traumatic injury neurons helps to increase the production of exciting neurotransmitters, deficiency of macroergic substances, the accumulation of free calcium, nitric oxide, pro-inflammatory cytokines, endogenous cannabioids and other substances, which together “triggers” enhanced lipoperoxidation processes. At the same time, active radicals destabilize the functioning of cell membranes and, thereby further accelerating lipid degradation, contribute to the excess intake of glutamate, calcium ions, and other altering components through microdefects into the cell [4].

The disintegration of the functioning of various organs and systems is developing, which, according to academician G.N. Kryzhanovsky, is the leading mechanism for the development of the main neuropathophysiological syndromes [5].

According to the WHO, the number of head injuries increases annually by 2% and amounts to 35-40% of all injuries [6].

One of the most formidable and fairly frequent complications of TBI is PTE. According to the definition [7-9], PTE is a chronic disease that developed after a brain injury and is characterized by repeated unprovoked attacks of impaired motor, sensory, autonomic and mental functions resulting from excessive neural discharges.

However, there is an opinion [10] that the term PTE does not disclose the entire complexity and diversity of paroxysmal conditions that may accompany a head injury. It is necessary to take into account the mechanisms, conditions of damage, the diversity of interested structures and systems, the locality or diffusion of the lesion, as well as their combination; static and dynamic effects of the type of impact or impulse with contact or inertial phenomena, deformations, changes in the volume of the skull, variants of linear, angular rotational acceleration, the effect of compressive and tensile forces and other

mechanical effects; disturbances of cerebral circulation, cerebrospinal fluid dynamics, neurodynamic processes with the release of excitatory amino acids, hyperactivation of glutamate receptors, an increase in the concentration of free calcium, nitrogen-containing components, active alternating radicals to toxic levels, as well as a decrease in antioxidant protection, the initiation of neuron death, etc. [11, 12]; Neuroendocrine and immune systems are necessarily involved in the pathological process [13].

The difficulty in interpreting the terminology lies in the fact that, according to the latter, under “PTE” any episindrome occurring after a head injury has been considered [10]. The diagnosis is based only on the existing fact of the development of epiparoxism after head injury [10] without taking into account its occurrence in the parallel development or existence of various factors, as well as their combination affecting epileptogenesis.

PTE refers to symptomatic epilepsy (E), which is mainly associated with a certain localization of the pathological process.

Nevertheless, various mechanisms of the development of PTE imply and are accompanied by a variety of clinical and paraclinical manifestations, including the frequency, delayed occurrence and coverage of the entire known spectrum of epileptic paroxysms [14]. Various combinations of epidemic seizures with other pathological manifestations of the consequences of TBI are possible [6, 16].

In continuation of the foregoing, E of the early TBI period should be distinguished, when changes in the metabolism and functioning of the brain under extreme conditions come to the fore with the development of damage to blood vessels, axons, changes in intracranial pressure, vasoparesis, vasospasm, changes in blood supply, electrolyte balance, acid-base balance, and liquorodynamics, edematous and dislocation syndromes [6].

V.N. Grimailo and T.A. Litovchenko (2015) [17] indicate a direct relationship between the severity of TBI and the risk of developing PTE, especially during the first 5 years after brain damage.

In the general structure of E, post-traumatic forms account for 5-7%, and of all newly registered forms, 10% [18] with a maximum value in young people. PTE is the most common cause of E in the age group in the range of 15-30 years, in these cases it accounts for 20% of all symptomatic forms of E [8, 9]. There is similar evidence that PTE is most common in people 15-24 years old, and, depending on the severity of TBI, these indicators range from 1.9 to 37% [14]. According to Kin Ding [13] in the USA, the prevalence of PTE, depending on the severity of TBI, is from 2 to 50%.

The criteria for assessing the degree of brain damage can be the duration of loss of consciousness, post-traumatic amnesia, and brain neuroimaging data. In this regard, a mild TBI includes loss of consciousness up to 30 minutes with amnesia for less than an hour and normal neuroimaging; with moderate TBI - loss of consciousness from 30 minutes to a day, amnesia 1-7 days, pathological changes in CT, MRI are possible; severe head injury is characterized by prolonged coma (more than a day), amnesia for more than a week, and pathological neuroimaging, including with bruising, bruising, etc. [14].

According to general population studies, a severe head injury increases the risk of developing PTE by 29 times compared to mild, in which this indicator increases by only 1.5 times [9, 19]. In children under 14 years of age, the specific gravity of PTE can be up to 14% [14], while at the same time in people over 65 this indicator is 8%.

Car accident is the main cause of PTE (47% of cases in the population) [14], especially in childhood - reaching 64.3% [18]. In cases of head injury due to a drop, PTE develops in 30%, during rest and sports in 14%, and in attacks in 7% of victims.

The neurophysiological polymorphism of PTE is that traumatic brain injury is characterized by a predominantly focal nature of the development of the pathological process, however, a lot of clinical and experimental evidence of the presence of diffuse brain damage has accumulated lately. These morphofunctional changes coexist and interact with each other with varying degrees of predominance [14]. Given the mechanisms of brain injury and the mild excitability of its neurons, it can be argued that TBI directly or indirectly affects all epileptogenic, including and deep subcortical zones of the central nervous system [14].

The epileptogenesis of PTE, the possibilities and conditions for the generation of spontaneous activity of neurons are not fully understood. However, it is known that a cascade of transformations, such as adhesive-inflammatory process, gliosis, neurogenesis, synaptogenesis, neuronal proliferation, collateral sprouting, as a kind of morphofunctional "remounting" stimulate the formation of an epileptic focus [20-22]. This occurrence of a pathological determinant explains the possible long latent period of PTE manifestation [14].

According to KB Magnitskaya (2007) [23], it is necessary to take into account the staged formation of a pathologically enhanced excitation generator (violation of the plasticity of interneuronal processes, failure of the ensemble activity of neurons; genetic predisposition and existing anomalies of brain development; trophic disorders; kindling; impaired production of inhibitory mediators; electrolyte metabolism; changes in the composition of glia). An imbalance in the concentration of endogenous bioactive substances and the presence of epilepticized neurons induce intact cells, combining and synchronizing their activity, but in

the early stages it is not enough to realize paroxysm. In the later stages, the inhibitory mechanisms are weakened, and the power of the pathological excitation generator increases, which makes it possible to activate it with weak stimuli. Activity is maintained and increased, facilitating the occurrence of subsequent paroxysm. An important point in epileptogenesis is the possibility of the emergence of secondary generators, which over time can dominate, thereby determining the diversity and transformation of paroxysms in the structure of PTE, as well as under the influence of antiepileptic drugs. The number of secondary generators can increase, and the foci of epiactivity can "migrate" and change roles.

The hyperexcitation generator forms a pathological determinant that implements relationships with other central nervous system subsystems and “epilepticizes” the brain.

During the formation of PTE, disorganization of work and damage to the antiepileptic system are possible, which is manifested in anatomical and functional changes in the caudate nucleus, thalamus, hypothalamic sclerosis, cystic formations in the cerebellar space, cerebellum, unusual position of the tonsils, etc. [23-24].

In turn, immediate (during the first day after a head injury) and early (during the first week from the moment of brain damage) seizures can be interpreted as an immediate nonspecific (presumably stem) response to rather intense damage [10]. Such a CNS reaction cannot be attributed to E, which is a long-term developing chronic disease. Early convulsive seizures occur in 6–10% of victims [8], in severe TBI in 10–15%, especially in people over 30 [14], and in the presence of risk factors, in 30%.

In 5% of patients hospitalized due to head injury, and in severe trauma with neurological complications and penetrating wound of the meninges, in half the cases.

Most often, such clinical phenomena manifest themselves in children (2-17%), with severe trauma they reach 30-35% and usually have a favorable prognosis, which is confirmed by EEG data. More likely to cause paroxysms in children in cases of impressed fractures of the skull, penetrating head injury, intracranial, especially subdural hematomas. A close correlation with the severity of TBI was noted [14]. Half of the early paroxysms are recorded in the first week, and most of them manifest on the first day after a head injury (72-84%) in the form of generalized tonic-clonic seizures. In the future, they become focal (more than 50% - simple partial, often motor manifestations of clonic seizures on the side opposite to the focus) or secondary-generalized. Yu.V. Alekseenko [10] does not exclude the occurrence of one type of paroxysm in one patient. In children, quite often (10%) an epistatus develops [8].

There are options for the occurrence of early paroxysms against the background of a reduced threshold for convulsive readiness and the presence of premorbid burden. It is known

that chronic alcohol intoxication, withdrawal symptoms, the onset of delirium will contribute to the appearance of a developed and other convulsive attacks provoked by a head injury. Convulsions of withdrawal symptoms take the second place in frequency (15%) of all seizures. Perhaps this is due to the occurrence of total brain damage against the background of a neurotransmitter balance altered by ethanol and its metabolic products, intracellular transport of minerals, etc.

There is an abstinence hypothesis of the stimulation of epileptogenesis due to the periodic abolition of ethanol resembling a kidding model E. The role of the total effect is assumed when the stress factor of alcohol withdrawal is superimposed on traumatic brain damage.

One of the possible options is the occurrence of paroxysm in patients with E provoked head injury.

There is evidence that epileptogenesis depends on the nature of the brain injury with some differences. In cases of open TBI, cicatricial changes in the area of the convexital parts of the brain, and especially the cortex, prevail and interfere with the formation of E. [8].

With a closed head injury, multiple bruises occur, including in the hippocampus. As a result, regardless of the foci in the neocortex, epiactivity in the damaged hippocampus begins to gradually dominate. [8].

In the distant period, delayed secondary brain damage occurs, including with the accumulation of glutamate and the appearance of excitotoxicity, the damaging effect of free radicals, etc. An important role is played by disorders in the immune system, as well as disorganization of the CNS [10, 25, 26]. The correlation of the occurrence of E. and the degree of development of hydrocephalus, hypoperfusion of the temporal lobe are described. PTE may occur if the glial barrier is insufficiently formed at the site of brain damage [27]. The above will undoubtedly contribute to the gradual formation of convulsive activity of the CNS with the manifestation of paroxysms after several years, i.e. a long latent period is possible. This position is confirmed by statistics on the development of a second seizure over two years in 18-86% of people who have had a head injury, which provides all the reasons for diagnosing PTE.

In terms of the manifestation of paroxysms, PTE is distributed as follows: 40% in the first 6 months; 50-60% - during the year and 80% - during two years from the time of the head injury. The connection of paroxysms with the transferred brain injury is completely lost and reaches the background value with a significant time interval - up to 10-15 years [14].

The structural features of the skull, the causes and mechanisms of traumatic injury determine the most frequent localization of the focus of altered neuroactivity in the frontal and temporal regions of the brain, which in turn are highly epileptogenic zones [14]. According to the video of EEG monitoring [8], it was found that foci of epileptic activity are localized in: temporal (56%), frontal (36%), parietal (5%) and occipital (3%) lobes.

Based on the presence of anatomical and physiological correlations of brain injury and epileptiform activity, the lezional form of PTE is distinguished when pathological activity occurs perifocally in the area of damage.The non- lezional form of symptomatic E refers to damage to the hippocampal departments and predominates in the structure of acquired E.

As mentioned above, PTE covers the entire spectrum of existing convulsive seizures: without a change in consciousness, partial - with confusion, as well as symptomatic and secondary-generalized. Nevertheless, primary-generalized convulsions as well as absences are much less common and, possibly, TBI is not their cause [14].

According to V.O. Generalov [28, 29], lezional form is the main type of seizure, which includes partial seizures, secondary-generalized ones with slow clinical and encephalographic generation. The author indicates a frequent combination of such attacks with simple and complex partial paroxysms, while any of them can be generalized a second time. Partial or focal seizures are very diverse in their clinical picture - from deviations in behavior to tonic-clonic seizures. They are easy to miss because of possible subclinical manifestations when only subjective experiences and the presence of behavioral correlates are noted.

An important feature of temporal convulsions is that in 2/3 of observations there are vegetative, psychotic, somatosensory, olfactory, taste and other types of aura. Manifestations of simple seizures are diverse and associated with contralateral discharges in the corresponding fields of the temporal cortex of the brain and associated with the aura. Complexes are accompanied by impaired consciousness and can begin with simple. Localization of the focus in the frontal lobe rarely provokes the development of an aura, motor components predominate [30].

It is worth noting that not every patient who has had a head injury even with the presence of risk factors develops PTE. Apparently, genetic determination should be considered. It is known that a family history increases the risk of developing PTE by 6-17% compared with 3-4% without it. However, a congenital and / or genetic predisposition is a relatively weak provocative factor for PTE, compared with the severity of the injury [14]. The most significant of them for early convulsions are: young age, especially children under 5

years old; acute intracerebral hematoma; diffuse cerebral edema; intracranial foreign body; focal neurological deficit; skull fracture; loss of consciousness at the time of injury for more than 30 minutes [8].

The main risk factors for the development of PTE include: the duration of coma after head injury for more than 7 days; lack of response to the light of one of the pupils in the acute period of the injury; the presence of early seizures in history (in adults); penetrating head injury; dented fracture of the skull; brain contusion; focal neurological deficit; displacement of the median structures of the brain more than 5 mm; premorbid chronic alcoholism; multiple neurosurgical interventions; subdural hematoma; age over 65 years; brain tissue loss [30, 31].

According to the formula for "weighted categories of injuries" [31], a significant incidence of PTE is associated with centro-parietal localization of head injury; early attacks the presence of intracerebral hematoma.

As mentioned above, in severe TBI with the presence of neurological complications, late seizures can be recorded in 50% of patients. The highest risk of PTE is associated with gunshot wounds of the brain, penetration of the membranes by a bone or a metal object, while the risk of PTE formation increases to 60% [8].

There is also evidence that the likelihood of PTE increases with extensive lesions, involving the frontal and temporal lobes [17], multiple bilateral concussions (up to 66%) [8], and non-linear gunshot damage to two lobes of the brain. Also, the risk of PTE is increased in patients after hemorrhagic heart attacks [32], spontaneous intracerebral hematoma [33], which may be confirmed by Willmore L.J. (1978) [34] the hypothesis that bleeding in contact with nerve tissue is an important factor in the development of PTE [35].

In the first year after a head injury, the likelihood of developing an epileptic seizureis 12 times higher than in the population [34]. During this period, convulsive paroxysms debut in 57% of patients suffering from PTE. Perhaps the mechanism of long-term compensation is triggered (even with a mild CNS injury) or an attempt to regenerate, which leads to the formation of pathological neural connections, while the critical time for the occurrence of PTE is up to 2 years [15]. After 5 years from TBI, the correlation between the occurrence of epileptic seizures weakens and no longer has a linear relationship [17].

References

1. Isaeva R.KH. Immunologicheskie izmeneniya pri cherepno-mozgovoj travme / R.KH.Isaeva, I.A.Avtonyuk, A.V.Gridyakina, A.E.Evstaf'eva // Mezhdunarodnyj zhurnal prikladnykh i fundamental'nykh issledovanij. – 2014. – № 8 (chast' 2) – S. 41-47

2. Seo W. Comparisons of acute physiological parameters influencing outcome in patients with traumatic brain injury and hemorrhagic stroke / W. Seo, H. Oh // Worldviews Evid. Based Nurs. - 2009. - Vol. 6. N 1. - P. 36-43.

3. Niizuma K. Oxidative stress and mitochondrial dysfunction as determinants of ischemic neuronal death and survival / K. Niizuma, H. Endo, P.H. Chan // J. Neurochem. - 2009. - Vol. 109, Suppl. 1. - S. 133-138.

4. Boldyirev A.A. Svobodnyie radikalyi v normalnom i ishemicheskom mozge / A.A. Boldyirev, M.L. Kukley // Neyrohimiya. - 1996. - T.13. - S. 25-29.

5. Dizregulyatsionnaya patologiya nervnoy sistemyi / pod red. E.I.Guseva, G.N. Kryizhanovskogo. – M. : OOO «Meditsinskoe informatsionnoe agentstvo», 2009. - 512 s.

6. Kurbanova S.A. Kliniko-neyrofiziologicheskie osobennosti simptomaticheskoy posttravmaticheskoy epilepsii Avtoref.diss... k.med.n. - M., 2007. - 18 s.

7. Haltiner A.M., Temkin N.R., Dikmen S.S. Risk of seizure recurrence after the first late posttraumatic seizure. Arch Phys Med Rehabil 1997;(78):835—40.

8. Zaytsev O.S. Rannie sudorozhnyie pristupyi i posttravmaticheskaya epilepsiya / O.S.Zaytsev, O.A.Grinenko, G.G.Shaginyan // Neyrohirurgiya i nevrologiya Kazahstana . - # 4 (21), 2010. - S.20-24

9. Savitskiy I.V. Endotelialnaya disfunktsiya pri posttravmaticheskoy epilepsii / I.V.Savitskiy, A.A.Mironov, I.V.Myastkovskaya / Jornal of Education, Health and Sport. 2016; 6 (6) ; 245-252.

10. Alekseenko Yu.V. Posttravmaticheskaya epilepsiya: problemyi diagnostiki, lecheniya i profilaktiki / Yu.V.Alekseenko // Meditsinskie novosti. - # 11, 2006. - S 25-28.

11. Bramlett H.M. Патофизиология ишемического и травматического поражения мозга: сходство и различия / H.M.Bramlett, W.D.Dirtrich // Медицина неотложных состояний. - 2006. - № 5. - С. 36-43.

12. Volohova G.A. Intensifikatsiya protsessov lipoperoksidatsii i ugneteniya aktivnosti antiradikalnyih mehanizmov kak odnonapravlennyie mehanizmyi povrezhdeniya mozga / G.A.Volohova, A.N.Stoyanov, R.S.Vastyanov // LIki UkraYini. - # 5 (131) / 2009. - S. 92-97.

13. Hertsev V. N., Stoyanov A. N., Bocherova T. I. Applied clinical and pathogenetic aspects of interdisciplinary cooperation in the diagnosis and treatment of concussion of brain. Journal of Education, Health and Sport. 2017;7 (5):913-927.

14. Ding K, Gupta PK, Diaz-Arrastia R. Laskowitz D, Grant G, editors. Translational Research in Traumatic Brain Injury. Boca Raton (FL): CRC Press/Taylor and Francis Group; 2016. Chapter 14.

16. Pesochina E.A. Znachenie nasledstvenno-konstitutsionalnyih faktorov v formirovanii otdalennyih posledstviy cherepno-mozgovoy travmyi Avtoref. diss... k.med.n. - Harkov - 1989 - 23s.

17. Grimaylo V.N. Osobennosti sindroma vegetativnoy distonii u patsientov s posttravmaticheskoy epilepsiey / V.N.Grimaylo, T.A.Litovchenko, Yu.V.Yakubenko, T.V.Markova // Mezhdunarodnyiy meditsinskiy zhurnal. - #3, 2015. - S 32-35.

18. Barhatov M.V. Primenenie preparata Meksidol v kompleksnom lechenii detey s posttravmaticheskoy epilepsiey / M.V. Barhatov, A.V. Nosyirev, A.V. Dehtyar, M.Yu. Galaktionova // Byulleten eksperimentalnoy biologii i meditsinyi, 2006, prilozhenie 1 - S. 9-13.

19. Hervan S.T. Epilepsy after brain insult: targeting rpileptogenesis. Neurology, 2002; 59 (Suppl. 10).

20. Antonawich F.J., Azmitia E.C., Kramer H.K., Strand F.L. Specificity versus redundancy of melanocortins in nerve regeneration // Ann. NY Acad. Sci., 1994, v. 739, P. 60-73.

21. Nevrologiya. Natsionalnoe rukovodstvo - Gusev E. I., Konovalov A. N., Skvortsova V. I., Geht A. B. - M.: GOETAR-Media- 2013 god - 1040 s.

22. Gardner Govard Struktura razuma: teoriya mnozhestvennogo intellekta : Per. s angl. - M.: OOO "I.D.Vilyams", 2007. - 512 s.

23. Magnitskaya K.B. Epileptogenez i patogeneticheskaya terapiya / Epilepsiya u detey: problemyi i resheniya. - Materialyi mezhd. konf. - Volgograd, 2007. - S.6-13.

24. Patofiziologiya: rukovodstvo k prakt. zanyatiyam: Uchebnoe posobie / pod red. V.V.Novitskogo, O.I.Urazovoy. - M., 2011. - 336 s.

25. Vastyanov R.S. FunktsIonalna perebudova ta zmIna lokalIzatsIYi korkovih motornih neyronIv v umovah hronIchnoYi epIleptichnoYi aktivnostI / R.S.Vastyanov, O.A.Shandra // Tavricheskiy mediko-biologicheskiy vestnik. - 2012. - t. 15. - # 3. - S. 51-53.

26. Avakyan G.N., Generalov V.O., Oleynikova O.M. i dr. Simptomaticheskaya posttravmaticheskaya epilepsiya. Klinika, diagnostika i lechenie. // Metodicheskie rekomendatsii. M. 2004. - 40 s.

27. Guzeva V.I. Epilepsiya i neepilepticheskie paroksizmalnyie sostoyaniya u detey. — M.: OOO «Meditsinskoe informatsionnoe agentstvo», 2007. — 568 s.

28. Generalov V.O. Epilepsiya i strukturnyie povrezhdeniya mozga Avtoref.diss... d.med.n. - M., 2010. - 35 s.

29. Generalov V.O., Mishnyakova L.P., Fedin A.I. Vliyanie lokalizatsii ochaga epilepticheskoy aktivnosti na sroki razvitiya posttravmaticheskoy epilepsii.// Materialyi X Vserossiyskogo s'ezda nevrologov. Yaroslavl. 2006 - S. 535.

30. Fazel S. et al. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study //The Lancet. – 2013. – T. 382. – №. 9905. – C. 1646-1654.

31. Feeney DM, Walker AE. The prediction of posttraumatic epilepsy. A mathematical approach. Arch Neurol 1979;36:8–12.

32. De Carolis P, D'Alessandro R, Ferrara R, et al. Late seizures in patients with internal carotid and middle cerebral artery occlusive disease following ischaemic events. J Neurol Neurosurg Psychiatry 1984;47:1345–1347.

33. Faught E, Peters D, Bartolucci A, et al. Seizures after primary intracerebral hemorrhage. Neurology 1989;39:1089–1093.

34. Willmore LJ, Sypert GW, Munson JB. Recurrent seizures induced by cortical iron injection: a model of post-traumatic epilepsy. Ann Neurol 1978;4:329–336.

35. Aisen P. Some Physicochemical Aspects of Iron Metabolism. In Ciba Foundation Symposium (51st ed). New York: Elsevier, 1977:1–14.