DRUG-RESISTANT EPILEPSY: CURRENT CONCEPTS, PATHOGENESIS, RISK FACTORS

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Abstract: Drug-resistant epilepsy (DRE) remains one of the most significant challenges in modern neurology, affecting up to 30–40% of patients despite the availability of more than 20 modern antiepileptic drugs (AEDs). PRE is a multifactorial phenomenon with genetic, molecular, cellular, and acquired mechanisms. Key pathogenetic theories include the target hypothesis, the multidrug transporter hypothesis, and the neural network hypothesis. Acquired mechanisms such as seizure-induced kindling contributes to disease progression and resistance. Risk factors for PRE include early onset of epilepsy, high seizure frequency, febrile seizures, neurological deficits, cognitive impairment, and genetic variability in ion channel and metabolic genes. Structural causes such as cortical malformations, mesial temporal sclerosis, and brain tumors play an essential role in the development of drug resistance. Although surgical treatment achieves seizure freedom in up to 59–80% of patients and significantly improves quality of life, the variability of outcomes and long-term risks remain insufficiently studied. Further research is needed to identify prognostic factors and optimize personalized treatment strategies for PRE.

Keywords: Drug-resistant epilepsy; antiepileptic drugs; drug resistance; kindling; multidrug transporters; cortical malformations; hippocampal sclerosis; epilepsy surgery; quality of life.

ФАРМАКОРЕЗИСТЕНТНАЯ ЭПИЛЕПСИЯ: СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ, ПАТОГЕНЕЗ, ФАКТОРЫ РИСКА

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Аннотация: Фармакорезистентная эпилепсия (ФРЭ) остаётся одной из наиболее значимых проблем современной неврологии, встречаясь у 30–40% пациентов, несмотря на наличие более 20 современных противоэпилептических препаратов (ПЭП). ФРЭ является мультифакториальным явлением, включающим генетические, молекулярные, клеточные и приобретённые механизмы. Ключевыми патогенетическими теориями считаются гипотеза мишени, гипотеза мультилекарственных транспортёров и гипотеза нейронных сетей. Приобретённые механизмы, такие как киндлинг (раскачка), индуцируемый приступами, способствуют прогрессированию заболевания и развитию резистентности. К факторам риска ФРЭ относятся ранний дебют эпилепсии, высокая частота приступов, фебрильные судороги, неврологический дефицит, когнитивные нарушения, а также генетическая вариабельность генов ионных каналов и метаболизма. Существенную роль в развитии лекарственной устойчивости играют структурные причины, такие как пороки развития коры головного мозга, мезиальный височный склероз и опухоли мозга. Хотя хирургическое лечение позволяет достичь свободы от приступов у 59–80% пациентов и значительно улучшает качество жизни, вариабельность исходов и отдалённые риски остаются недостаточно изученными. Необходимы дальнейшие исследования для определения прогностических факторов и оптимизации персонализированных стратегий лечения ФРЭ.

Ключевые слова: фармакорезистентная эпилепсия; противоэпилептические препараты; лекарственная устойчивость; киндлинг; мультилекарственные транспортёры; пороки развития коры; склероз гиппокампа; хирургия эпилепсии; качество жизни.

FARMAKOREZISTENT EPILEPSIYA: ZAMONAVIY TUSHUNCHALAR, PATOGENEZ VA XAVF OMILLARI

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Annotatsiya: Farmakorezistent epilepsiya (FRE) zamonaviy nevrologiyaning eng muhim muammolaridan biri bo‘lib qolmoqda. U 30–40% bemorlarda uchraydi, garchi 20 dan ortiq zamonaviy antiepileptik dori vositalari (AED) mavjud bo‘lsa ham. FRE ko‘p omilli hodisa bo‘lib, genetik, molekulyar, hujayraviy va orttirilgan mexanizmlarni o‘z ichiga oladi. Asosiy patogenetik nazariyalar — nishon gipotezasi, ko‘p dori tashuvchilar gipotezasi va neyron tarmoqlar gipotezasi. Tutqanoqlar bilan qo‘zg‘atilgan “kindling” mexanizmi kasallik rivojlanishiga va rezistentlikka hissa qo‘shadi. FRE uchun xavf omillari qatoriga erta boshlanishi, tutqanoqlarning yuqori chastotasi, febril tutqanoqlar, nevrologik yetishmovchilik, kognitiv buzilishlar, shuningdek ion kanallari va metabolizm genlarining genetik o‘zgaruvchanligi kiradi. Struktural sabablar, masalan, miya qobig‘i rivojlanishidagi nuqsonlar, mezial temporal skleroz va miya o‘smalari, dori-moddalarga qarshilik rivojlanishida muhim rol o‘ynaydi. Garchi jarrohlik davolash 59–80% bemorlarda tutqanoqlardan xalos bo‘lishni va hayot sifatini sezilarli darajada yaxshilashni ta’minlasa-da, natijalarning o‘zgaruvchanligi va uzoq muddatli xatarlar yetarlicha o‘rganilmagan. FRE bo‘yicha prognoz omillarini aniqlash va shaxsiylashtirilgan davolash strategiyalarini optimallashtirish uchun qo‘shimcha tadqiqotlar zarur.

Kalit so‘zlar: farmakorezistent epilepsiya; antiepileptik dorilar; dori-moddalarga qarshilik; kindling; ko‘p dori tashuvchilar; miya qobig‘i nuqsonlari; gipokamp sklerozi; epilepsiya jarrohligi; hayot sifati.

INTRODUCTION

Modern concepts of drug-resistant epilepsy. Epilepsy is one of the most common chronic disabling neurological disorders, affecting more than 70 million people worldwide [1, 2]. Patients with epilepsy have 3.1 times more physical, mental, or social limitations compared to patients without epilepsy due to cognitive, psychopathological, and other comorbid conditions [3]. Despite the availability of more than 20 modern antiepileptic drugs (AEDs) for symptomatic treatment of epilepsy, about 30–40% of patients remain resistant to pharmacotherapy [1, 2, 4].

Drug-resistant epilepsy (PRE) is characterized by the inability to achieve seizure freedom when using two “adequate” AED regimens, either as monotherapy or in combination [5]. It is considered a multifactorial phenomenon, based on numerous genetic and acquired mechanisms. Among the genetic causes of PRE are the accelerated metabolism of AEDs in individuals who are homozygous or heterozygous for the rapid allele of genes biotransformed in the liver [6], and reduced or absent sensitivity of cortical neuronal receptors to AEDs. One of the acquired mechanisms is the initiation of epileptogenesis by seizures, leading to neural tissue changes through neuroplasticity [7].

In recent years, advances in neuroscience, neuroimaging, and the application of mathematical models based on graph theory in clinical and fundamental neurology have made it

possible to consider epilepsy as a disease of neural networks [8]. In patients with epilepsy, structural and functional connectome abnormalities have been identified, i.e., alterations in the collection of structural and functional networks in the nervous system. In networks, nodes and connections between nodes (edges) are distinguished, in which changes are noted. Nodes usually correspond to various regions of the temporal lobe and extratemporal structures [9].

The medical and social consequences of PRE are significant for both the physical and mental health of the patient. Socio-economic and psychological limitations reduce their quality of life and increase the risk of mortality [10]. According to numerous studies, they have higher levels of cognitive deficits, emotional disturbances, psychiatric disorders, and experience difficulties or inability to fulfill certain social roles [11]. The quality of life (QoL) of patients with epilepsy is at a rather low level. This is influenced by the presence of comorbid psychiatric and behavioral disorders, cognitive impairments, inability to receive timely consultation from a specialist, and the high cost of modern AEDs.

The presence of epileptic seizures and the personality traits of patients cause a wary attitude from others and lead to stigmatization of such patients in society. Patients with focal onset seizures who take two or more antiepileptic drugs for at least 2 years, or patients who experience significant side effects from antiepileptic drugs, and in cases where seizures affect or limit daily life and its quality, are indicated for surgical treatment [1, 12].

Removal of the epileptogenic focus in patients with PRE allows achieving complete seizure control in an average of 59–80% of cases [13–15], as well as significantly improving their QoL [16, 17]. Patients with epilepsy who are candidates for surgical treatment require assessment of the risks of long-term postoperative outcomes, as well as evaluation of their neuropsychological status and QoL. However, at present, there are insufficient prospective long-term studies on the efficacy and safety of various surgical treatment methods in patients with PRE.

To evaluate the effectiveness of surgical treatment, it is important to determine prognostic factors of favorable outcomes. Surgical treatment of patients with PRE generally yields good results, but the extent and methods of surgical intervention, risks of adverse outcomes, and the state of psycho-emotional and cognitive functions, especially in the long-term postoperative period, remain insufficiently studied.

MAIN PART

Pathogenesis of pharmacoresistant epilepsy. In recent years, several proposed mechanisms underlying drug resistance in epilepsy have been identified. Based on experimental and clinical studies, two main neurobiological theories have been put forward: (1) decreased sensitivity of drug targets in the epileptogenic brain tissue (the target hypothesis); (2) removal of AEDs from epileptogenic tissue due to excessive expression of multidrug transporters (the multidrug transporter hypothesis). However, neither of them fully explains the neurobiological basis of drug-resistance [2, 18].

According to the target hypothesis, drug-resistance is considered the result of absence or loss of sensitivity of ion channel receptors and neurotransmitter receptors to AEDs [2, 19]. It is assumed that, to ensure an antiepileptic effect, the drug must act on molecular targets in the brain. These are primarily voltage-gated ion channels, neurotransmitter receptors, and transporters or metabolic enzymes involved in the release, uptake, and metabolism of neurotransmitters [20]. In the work of T.A. Sazhina et al. (2019), local structural changes in the area of the epileptic focus and reduced activity of gamma-aminobutyric acid (GABA) receptors were noted. It was shown that pathological processes affecting glutamatergic and GABAergic systems in patients with PRE

are accompanied by altered levels of apoptotic proteins, which may be one of the causes of neuronal death [21]. However, the presence of a significant number of patients with resistance to several AEDs with different mechanisms of action does not exclude other resistance mechanisms.

The multidrug transporter hypothesis. It is known that lipophilic substances, including AEDs, are transported across the blood–brain barrier (BBB) by proteins, particularly P-glycoprotein (PGP) and the family of multidrug resistance-associated proteins (MRP), located in the endothelial cell membranes of capillaries [2, 18, 22]. They are capable of transporting back into the bloodstream an excess of lipophilic substances, including AEDs, that have diffused across the BBB. It has also been shown that multidrug transporters can control the movement of AEDs from the extracellular spaces of the brain into endothelial cells, with subsequent efflux into the blood [2, 23].

The movement of substances across the BBB is regulated by a genetically determined system. This system restricts the passage of ionized hydrophilic substances and large molecules. PGP and MRP in the BBB are thought to act as an active protective mechanism limiting the penetration of lipophilic substances into the brain [24]. A wide variety of compounds, including many lipophilic drugs, are substrates for PGP, MRP, or both. P-glycoprotein is secreted by tissues with secretory activity (small intestine, liver, kidneys) and at blood–tissue interfaces (BBB, placenta, blood–testis barrier), which determines the drug concentration in the body, its elimination, and its levels in susceptible tissues such as the brain [25]. Most AEDs (phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, etc.) are substrates for P-glycoprotein [19]. Thus, increased expression of such transporters in epileptogenic tissue likely reduces the amount of drug reaching epileptic neurons, which may be a plausible explanation for drug-resistance.

Recent advances in neurobiology, especially in connectomics (the neural network hypothesis), allow detailed assessment of the organization, dynamics, and functions of networks at the individual level. Data can be evaluated using fundamental forms of network analysis based on graph theory, which can reveal patterns of organization prone to abnormal dynamics and epileptogenesis [26]. A single pathological focus involves other distant brain regions in epileptogenesis, forming an epileptic system. The connectomics approach makes it possible to assess personalized measures of network organization and to determine the variability of clinical outcomes [26]. The neural network hypothesis requires further research to determine the structural and functional organization in PRE, as well as changes during the course of the disease and under treatment (pharmacological and surgical).

It is necessary to emphasize the importance of acquired mechanisms of drug-resistance, in particular that epileptic seizures themselves may trigger the kindling mechanism. Kindling represents a phenomenon in which repeated subconvulsive stimulation of certain brain regions leads to the progressive development of seizure activity [27].

Based on this and the insufficiently complete information about drug-resistance from the perspective of cellular and molecular factors, the hypothesis of the intrinsic severity of drug-resistance to AEDs was formulated. According to this hypothesis, drug-resistance is an inherent property of epilepsy, associated with the severity of the disease [2, 28].

In line with this concept, drug-resistance is considered the result of the influence of neurobiological factors that determine the overall severity of the disease, i.e., the phenotypic variability of this form of epilepsy [8, 29]. Thus, in this situation, drug resistance may be a consequence of factors underlying epilepsy and its severe course. In addition, it is undeniable that other mechanisms of drug-resistance exist, which must be identified and studied in detail.

Risk factors for the development of drug-resistance in epilepsy patients. The identification of patients with PRE and their timely referral for specialized treatment is often delayed. Such patients are at higher risk of morbidity and mortality. Determining the risk factors for PRE and adjusting the treatment approach for a specific patient makes it possible to avoid the use of ineffective AEDs, adverse effects of drug therapy, and worsening of the disease course.

In clinical practice, certain therapeutic errors are tolerated, resulting in a lack of seizure control or even deterioration of the condition. Consequently, these errors often mistakenly suggest the presence of PRE in patients. Such errors are more often related to an incorrect assessment of seizure type; the presence of conditions mimicking epilepsy (psychogenic non-epileptic seizures, syncope, transient ischemic attacks, metabolic disorders, various motor disorders, especially extrapyramidal syndromes, sleep disorders), and/or their combination with epilepsy [5].

In the treatment of epilepsy, as with other diseases, iatrogenic or nosogenic factors may occur, which reduce or nullify the effect of therapy. Iatrogenic factors are related to medical practice (inadequate dose and/or inappropriate drug choice, irregular treatment, discontinuation of medication for diagnostic purposes, etc.). Nosogenic factors are related to patient behavior [30]. These include non-compliance with medication rules (dosage, frequency), discontinuation of treatment, and others.

There are also factors that provoke seizures and, accordingly, increase the risk of developing PRE. For this reason, patients should be informed about the harmful effects of stressful situations, sleep deprivation, alcohol, hyperthermia, etc. Seizures can also be triggered by surgical interventions, metabolic disorders and hormonal disturbances, menstruation, pregnancy, childbirth, and others [31]. Such provoking factors can be identified during the initial history-taking of the patient.

According to foreign researchers, risk factors for the development of PRE may include early disease onset and long duration, frequent seizures (especially focal type). These patients often have a history of febrile seizures or even status epilepticus. Polymorphism of epileptic seizures, neurological deficits, or intellectual disability at the time of diagnosis should also be considered. With regard to drug-resistance, the absence of a response to the first AED (when correctly chosen), an abnormal electroencephalogram (EEG), and the presence of interictal epileptiform activity should be alarming [1, 32, 33].

Genetic factors likely play an important role in the development of many epileptic conditions—from classical idiopathic (genetic) generalized epilepsies to epileptic encephalopathies, focal epilepsy, and PRE. In recent years, numerous studies have shown that genetic variability is associated with drug resistance in epilepsy, including genes of voltage-gated sodium and potassium channels, as well as genes of endogenous and xenobiotic metabolism [34].

Epilepsy is also a common manifestation of brain tumors. The type and localization of the tumor are, of course, decisive risk factors for the development of epilepsy. Brain tumors most at risk of seizures are slow-growing primary tumors (low-grade gliomas), tumors with hemorrhage, and multiple metastases. Seizures as symptoms of brain tumors are difficult to treat. According to S. Dupont (2008), tumor evolution, modifications of tumor and peritumoral tissue, and associated treatment methods are usually linked with drug resistance when prescribing AEDs [35].

Cortical malformations as a cause of drug-resistant epilepsy. Cortical malformations (CM) are considered one of the significant causes of epilepsy and developmental disorders in children. CM represent macroscopic or microscopic anomalies of the cerebral cortex that arise due to disturbances in the stages of cortical plate formation. In most cases, they are genetically

determined (with anomalies in genes involved in neuronal proliferation, migration, and cortical layering during embryogenesis) [36]. The causes of CM may also include intrauterine factors such as infection, hypoxia, and intoxication [5].

A number of conditions (tuberous sclerosis, focal cortical dysplasia, hemimegalencephaly, lissencephaly, subcortical laminar heterotopia, etc.) are associated with the development of PRE [5, 37]. Clinical practice shows that in temporal lobe epilepsy, the most common histopathological finding during surgical interventions in cases of drug-resistance is mesial temporal sclerosis, characterized by neuronal loss in the hippocampus and adjacent structures. Such changes are often observed in the amygdala, entorhinal cortex, temporopolar regions, and temporal lobe.

In patients with PRE requiring surgical intervention, the most frequent histological diagnosis in adults is hippocampal sclerosis [38]. It has been established that cortical dysplasias, atypical febrile seizures, brain tumors, traumatic brain injuries, and cerebral malformations carry a sufficiently high risk of damaging the hippocampal region [39]. All these factors lead to a reduction in the number of neurons and hyperexcitability of the unaffected neural tissue.

CONCLUSION

Drug-resistant epilepsy is a complex and multifactorial condition that continues to pose a major clinical and social problem. Its pathogenesis involves genetic predisposition, altered drug targets, overexpression of multidrug transporters, neural network dysfunction, and acquired mechanisms such as kindling. A broad spectrum of risk factors—from early disease onset and febrile seizures to cortical malformations and brain tumors—contributes to poor response to pharmacotherapy. While surgical treatment offers favorable seizure control and improved quality of life for many patients, the variability in cognitive and psychosocial outcomes highlights the need for individualized approaches. A deeper understanding of molecular, genetic, and network-level mechanisms, as well as long-term outcome studies, is essential for improving therapeutic strategies and reducing the burden of PRE.

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