DRUG-RESISTANT EPILEPSY: CURRENT CONCEPTS, PATHOGENESIS, RISK FACTORS, OUTCOMES OF SURGICAL TREATMENT

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ABSTRACT

Despite the wide choice of antiepileptic drugs (AEDs), a third of patients remain resistant to the effects of modern AEDs. Drug-resistant epilepsy (DRE) is characterized by the inability to control seizures in a patient when using at least two adequate AED regimens at an effective daily dose as monotherapy or in combination. In this case, the mechanisms responsible for drug resistance are mainly either increased excretion of AEDs by transporters from epileptogenic tissue (the multidrug transporter hypothesis) or a decrease in the sensitivity of drug receptors in epileptogenic brain tissue. It is assumed that there are other mechanisms, but they remain understudied. A number of factors are associated with the risk of DRE developing in patients with diagnosed epilepsy, including genetic, iatrogenic, brain malformations, and others. Patients with DRE have a higher probability of developing psychopathological disorders (depression, anxiety, psychosis), the proportion of which is significantly higher than in the general population. They have a 10-fold increased risk of death due to injury, cognitive decline, and sudden unexpected death in epilepsy (SUDEP). The priority treatment method for DRE is surgery. Early identification of DRE is critical for identifying potential treatment alternatives and determining whether a patient is a surgical candidate. Analysis of data from clinical and instrumental research of operated patients with DRE in the early and late postoperative period will allow us to identify factors of unfavorable outcome and to increase the effectiveness of treatment for this category of patients.
The aim *was to study and to summarize literature data on the pathogenesis and risk factors of drug resistance to antiepileptic drugs in patients with epilepsy, justifying the need for timely identification of drug resistance and referral of patients with drug-resistant epilepsy to specialized centers for possible surgical treatment.*

Key words: *drug-resistant epilepsy, pathogenesis, surgical treatment of drug-resistant epilepsy, outcomes of surgical treatment, risk factors*

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СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О ФАРМАКОРЕЗИСТЕНТНОЙ ЭПИЛЕПСИИ, ПАТОГЕНЕЗЕ, ФАКТОРАХ РИСКА И ИСХОДАХ ЕЁ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ

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РЕЗЮМЕ

Несмотря на большой выбор противоэпилептических препаратов (ПЭП), треть пациентов остаются устойчивыми к действию современных ПЭП. Фармакорезистентная эпилепсия (ФРЭ) характеризуется невозможностью контроля над приступами у больного при применении по крайней мере двух адекватных схем ПЭП в эффективной суточной дозе в качестве монотерапии или в комбинации. При этом механизмами, ответственными за резистентность к фармакопрепаратам, в основном являются либо повышенное выведение ПЭП переносчиками из эпилептогенной ткани (гипотеза мультилекарственных транспортеров), либо снижение чувствительности рецепторов к лекарству в эпилептогенной ткани головного мозга. Предполагается наличие и других, но недостаточно изученных механизмов. С риском развития ФРЭ у пациентов с диагностированной эпилепсией связан ряд факторов, включая генетические, ятрогенные, пороки развития головного мозга и другие. Больные с ФРЭ имеют более высокую вероятность развития психопатологических расстройств (депрессия, тревога, психозы), доля которых значительно выше, чем в общей популяции. У них в 10 раз повышается риск летального исхода вследствие травм, снижения когнитивных функций и внезапной смерти (SUDEP, sudden unexpected death in epilepsy). Приоритетным методом лечения ФРЭ является хирургическое. Раннее выявление ФРЭ имеет решающее значение для установления потенциальных альтернатив лечения и определения того, является ли пациент кандидатом на хирургическое вмешательство. Анализ данных клинических, инструментальных методов исследования оперированных больных ФРЭ в раннем и отдалённом послеоперационном периоде позволит выявить факторы неблагоприятного исхода и повысить эффективность лечения данной категории больных.

***Целью исследования** явилось изучение и обобщение данных литературы по патогенезу, факторам риска фармакоустойчивости к ПЭП больных эпилепсией с обоснованием необходимости своевременного выявления фармакорезистентности и направления пациентов с ФРЭ в специализированные центры для возможного оперативного лечения.*

***Ключевые слова:** фармакорезистентная эпилепсия, патогенез, хирургическое лечение фармакорезистентной эпилепсии, исходы хирургического лечения, факторы риска*

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MODERN CONCEPTS OF PHARMACORESISTANT EPILEPSY

Epilepsy is one of the most common chronic disabling neurological diseases, 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 diseases [3]. Despite the availability of more than 20 modern antiepileptic drugs (AEDs) for the symptomatic treatment of epilepsy, about 30–40 % of patients with epilepsy remain resistant to pharmacotherapy [1, 2, 4].

Drug-resistant epilepsy (DRE) is characterized by the inability to achieve seizure cessation with two "adequate" AED regimens as monotherapy or in combination [5]. It is considered a multifactorial phenomenon based on numerous genetic and acquired mechanisms.

Among the DRE genetic causes are the increased rate of metabolism of AEDs in individuals homozygous or heterozygous for the fast allele of genes that are biotransformed in the liver) [6]; decreased or absent sensitivity of cortical neuron receptors to AEDs. One of the acquired mechanisms can be considered the epileptogenesis initiation by seizures with changes in nervous tissue through neuroplasticity [7].

In recent years, the development of neuroscience, neuroimaging and the use 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, disturbances in the structural and functional connectomes, i.e. the set of structural and functional networks in the nervous system, have been identified. The networks are divided into nodes and connections between nodes (edges), in which changes are noted.

The nodes typically correspond to different areas of the temporal lobe and extratemporal structures [9].

The medical and social DRE consequences are significant for the patient's physical and mental health. Socioeconomic and psychological limitations that reduce their quality of life increase the risk of mortality [10]. According to numerous studies, they have higher levels of cognitive deficits, emotional disorders, mental illnesses, and difficulties or inability to perform certain social roles [11].

The quality of life (QoL) of patients with epilepsy is quite low. This is influenced by the presence of comorbid mental and behavioral disorders, cognitive impairment, the inability to receive timely consultation from a specialist, and the high cost of modern AEDs. The presence of epileptic seizures and the personal characteristics of patients cause a wary attitude towards them from others and stigmatization of such patients in society.

In patients with focal onset seizures, taking two or more anticonvulsants for at least 2 years, or in patients with significant side effects from anticonvulsants and in case the seizures affect or limit daily life and its quality, surgical treatment is indicated [1, 12]. The epileptogenic focus removal in patients with DRE allows achieving complete seizure control in an average of 59–80 % of patients [13–15], as well as significantly improving their QoL [16, 17].

Patients with epilepsy who are indicated for surgical treatment need to assess the risks of remote surgical outcomes, as well as to evaluate their neuropsychological status and QoL. However, there are currently insufficient prospective long-term studies on the efficacy and safety of various surgical treatment methods for patients with DRE. To assess the surgical treatment efficacy, it is important to determine the prognostic factors for a favorable outcome. Surgical treatment of patients with DRE generally yields good results, but the scope and methods of surgical intervention, the risks of adverse outcomes, the state of the psychoemotional and cognitive sphere, especially in the remote postoperative period, remain insufficiently studied.

PATHOGENESIS OF DRUG-RESISTANT EPILEPSY

In recent years, several putative mechanisms underlying drug resistance in epilepsy have been identified. Based on experimental and clinical studies, two main neurobiological theories have been proposed: 1) decreased sensitivity to the target drug in epileptogenic brain tissue (target hypothesis); 2) removal of AEDs from epileptogenic tissue due to overexpression of multidrug transporters (multidrug transporter hypothesis). However, none of them fully explains the neurobiological basis of pharmacoresistance [2, 18].

According to **the target hypothesis**, drug resistance is considered to be the result of the absence or loss of sensitivity of ion channel receptors and neurotransmitter receptors to AEDs [2, 19]. It is assumed that in order to provide an antiepileptic effect, a drug must affect target molecules in the brain. These are primarily voltage-dependent ion channels, neurotransmitter receptors, and transporters or metabolic enzymes involved in the release, absorption, and metabolism of neurotransmitters [20].

In the work of T.A. Sazhina et al. (2019), the presence of local changes in the structure in the epileptic focus area and a decrease in the activity of receptors to gamma-aminobutyric acid (GABA) were noted. It was shown that pathological processes affecting the glutamatergic and GABAergic systems in patients with DRE are accompanied by a change in the content of apoptotic proteins. This could 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 action mechanisms simultaneously does not exclude other mechanisms of resistance.

Multidrug transporter hypothesis. It is known that lipophilic substances, which include AEDs, are transported across the blood-brain barrier (BBB) with the help of proteins, in particular P-glycoprotein (PGP) and the family

of multidrug resistance-associated proteins (MRP) – proteins located in the capillary endothelium membrane [2, 18, 22]. They are able to transport excess lipophilic substances, including AEDs, back into the bloodstream, which have penetrated beyond the BBB by diffusion. It has also been shown that multidrug transporters can control the movement of AEDs from the extracellular spaces of the brain to endothelial cells with their subsequent release into the blood [2, 23]. A special genetically determined system controls the process of movement of substances across the BBB. This system limits the passage of ionized hydrophilic substances and large molecules through the BBB.

PGP and MRP in the BBB are thought to act as an active defense mechanism limiting the penetration of lipophilic substances into the brain [24]. A wide variety of compounds, including many lipophilic drugs, are substrates for either PGP or MRP, or both. P-glycoprotein is secreted by tissues with secretory activity (small intestine, liver, kidneys) and at the blood-tissue level (BBB, placenta, blood-testis barrier), which determines the concentration of the drug in the body, its excretion, and concentration 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 possible explanation for pharmacoresistance.

Recent advances in neuroscience, particularly in the field of connectomics (**neural network hypothesis**); allow detailed assessment of network organization, dynamics, and functions at the individual level. Data can be assessed 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 areas of the brain in epileptogenesis, forming an epileptic system. The connectomics approach allows for the assessment of network organization personalized measures and the variability elucidation in clinical outcomes [26]. The neural network hypothesis requires further research to determine their structural and functional organization in DRE, as well as changes during the course of the disease and against the background of treatment (medication and surgery).

It is necessary to emphasize the importance of acquired drug resistance mechanisms, in particular, epileptic seizures themselves can trigger the kindling mechanism. Kindling is a phenomenon when repeated subconvulsive stimulation of certain brain areas leads to progressive development of seizure activity [27]. Based on this and insufficient information on drug resistance from the point of view of cellular and molecular factors, a hypothesis of **the drug resistance intrinsic severity to AEDs** was formulated. According to it, drug resistance is an integral property of epilepsy associated with the severity of the disease [2, 28]. According to this hypothesis, drug resistance is the result of the impact of neurobiological factors that determine a particular level of disease severity as a whole, that is, the phenotypic variability of this form of epilepsy [8, 29]. Therefore, drug resistance in this situation may be a consequence of the factors underlying epilepsy and its severe course.

In addition, there are undoubtedly other mechanisms of drug resistance that need to be identified and studied in detail.

RISK FACTORS FOR THE DEVELOPMENT OF PHARMACORESISTIENCE IN PATIENTS WITH EPILEPSY

Identification of patients with DRE and their timely referral for specialized treatment is often delayed. Such patients are more susceptible to high risk of morbidity and mortality. Identifying risk factors for DRE and changing the approach to treating a specific patient allows avoiding the use of ineffective AEDs, side effects from drug therapy, and worsening of the disease.

In clinical practice, some therapeutic errors are made that result in failure to control seizures or even worsening of the disease. Therefore, with a high probability, these errors incorrectly indicate the presence of DRE in patients. Such errors most often include incorrect assessment of the type of seizures; the presence in the patient of a condition that imitates epilepsy (psychogenic non-epileptic seizures, fainting, transient ischemic attacks, metabolic disorders, various motor disorders, especially of the extrapyramidal system, sleep disorders) and/or their combination with epilepsy [5].

In the treatment of patients with epilepsy, as in the treatment of other diseases, iatrogenic or nosogenic factors may occur that reduce or neutralize the effect of the therapy. Iatrogenic factors are associated with medical activity (inadequate dose and/or incorrectly selected drug (or drugs), irregular treatment of the patient, drug withdrawal for diagnostic purposes, etc.). Nosogenic factors are associated with the patient's behavior [30]. These may include the patient's failure to comply with the rules for taking the medication (frequency, dosage) or stopping taking it, etc.

There are factors that provoke attacks and, accordingly, increase the risk of developing DRE. In this regard, the patient should be informed about the adverse effects on health of stressful situations, sleep deprivation, alcohol, hyperthermia, etc. Attacks can be provoked by surgical interventions, metabolic and hormonal disorders, menstruation, pregnancy, childbirth, etc. [31]. Such provoking factors can be determined during the initial collection of the patient's anamnesis.

According to foreign researchers, risk factors for the DRE development may include early onset of the disease and its long course, frequent seizures (especially focal type). The anamnesis of these patients often includes indications of febrile seizures, possibly

epileptic status. It is also necessary to take into account the polymorphism of epileptic seizures, neurological deficit or mental retardation at the time of diagnosis. With regard to drug resistance, the lack of response to the first AED (if chosen correctly), abnormal electroencephalogram (EEG) and the presence of interictal epileptiform activity should be alarming [1, 32, 33].

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

Epilepsy is a common manifestation of brain tumors. The type of brain tumor and its location will certainly be determining factors in the risk of developing epilepsy. Brain tumors that are most at risk of seizures are slow-growing primary tumors (low-grade gliomas), tumors with hemorrhage, and multiple metastases. Seizures, which are symptoms of a brain tumor, are difficult to treat. According to S. Dupont (2008), tumor evolution, modifications of tumor and peritumor tissue, and related treatments are usually associated with drug resistance when prescribing AEDs [35].

Cerebral cortex malformations (CCM) are considered to be one of the significant causes of epilepsy and developmental disorders in children. CCM are macroscopic or microscopic abnormalities of the cerebral cortex that occur as a result of disruption of the cortical plate formation stages. In most cases, they are genetically determined (there are abnormalities in genes that participate in neuronal proliferation, migration, and cortex stratification during embryogenesis) [36]. CCM may be caused by intrauterine factors associated with infection, hypoxia, and intoxication [5].

A number of diseases (tuberous sclerosis, focal cortical dysplasia, hemimegalencephaly, lissencephaly, subcortical laminar heterotopia, etc.) are accompanied by the DRE development [5, 37].

As practice shows, in temporal lobe epilepsy, the most frequent histopathological finding during surgical interventions, in cases of drug resistance, is mesial temporal sclerosis with the death of neurons in the hippocampus and adjacent structures. Similar changes are often found in the amygdala, entorhinal cortex, temporopolar areas of the cortex and temporal lobe. In patients with DRE requiring surgical intervention, the most frequent histological diagnosis in adults is hippocampal sclerosis [38]. It has been revealed that cortical dysplasia, atypical febrile seizures, brain tumors, traumatic brain injury, cerebral malformations have a fairly high risk of damage to the hippocampal region [39]. All these factors lead to a decrease in the number of neurons and hyperexcitability of unaffected nervous tissue.

PSYCHOEMOTIONAL STATUS IN PATIENTS WITH PHARMACORESISTANT EPILEPSY

The underlying cause of cognitive, emotional and behavioral disorders that commonly occur in patients with DRE is seizure activity [40].

Among the comorbid disorders accompanying epilepsy, depression occupies a special place, accounting for 4–12 % during remission and 20–55 % or more in DRE. Depression most often develops in patients with structural focal epilepsy with frequent (more than once a month) seizures and taking 2–3 AEDs [41, 42].

Considering the interhemispheric functional brain asymmetry, one can assume the importance of focus lateralization in the development of depressive disorders. In the studies conducted to study the dependence of the risk of developing depression on the epileptogenic focus lateralization, ambiguous results were obtained. However, most scientists believe that depression is more typical for patients with left-hemispheric focal epilepsy [43]. This can be explained by the fact that patients with a left-sided focus are more critical of their condition, and patients with right-sided hemispheric damage are characterized by understatement or denial of the negative aspects of their behavior. A. Grabowska-Grzyb et al. (2006) found that depression was observed in 49.5 % of 203 patients with DRE. It was also shown that depression and epilepsy can be caused by the same reasons [44].

A two-way relationship between epilepsy and depression, as well as epilepsy and suicidality, has been confirmed [45]. Depression may act as an independent risk factor for the development of the first unprovoked epileptic seizure [46]. It should be noted that depressive disorders in epilepsy have their own characteristics, differing from depression in other neurological diseases and from primary depression [47]. Depressive disorders are usually classified by the temporal relationship with epileptic seizures as: 1) preictal depression; 2) ictal depression; 3) postictal depression. Preictal depression occurs several hours, less often – days, before the onset of the seizure and is characterized by dysphoria, irritability and anxiety. Ictal depression is usually observed against the background of simple focal seizures. They are short-lived, stereotypical, associated with the emergence of guilt, anhedonia and suicidal thoughts. Postictal depression lasts for several hours or days after the attack and is characterized by increased sensitivity to frustrating factors, anhedonia, feelings of helplessness, guilt, irritability, and a sense of failure. Crying attacks, sometimes suicidal thoughts and suicidal tendencies are possible. These patients may have a medical history of major depression or bipolar disorder [47].

Anxiety disorders in patients with epilepsy are detected in 10–25 % of cases, according to other authors – in 50 % or more [48, 49].

There may be cause-and-effect and temporal relationships between clinical manifestations of anxiety disorder and epileptic seizures. Thus, anxiety and the emergence

of fears may precede the onset of a seizure, and these symptoms are often part of the structure of simple focal (most often temporal) and complex focal seizures with automatisms [50].

Behavioral disorders in patients with epilepsy are also more common than in the general population. In DRE, they can be diagnosed as independent disorders or associated with affective disorders (recurrent and bipolar depressions, dysthymia), such as hyperkinetic disorder [50].

Cause-and-effect relationships have not been sufficiently studied, since it can be difficult to obtain objective information about the presence and typology of behavioral disorders throughout the life of a patient with epilepsy.

Thus, the study of psychoemotional status disorders in DRE remains a pressing issue in modern neurology and psychiatry. The occurrence of psychoemotional disorders is an integral part of the DRE course and is reflected in the general condition of the patient and his QoL at different stages of the disease.

Cognitive impairments are quite common in patients with epilepsy, among which memory and attention impairments and bradyphrenia in the interictal period predominate. Organic damage to brain structures, neuronal dysfunction, interictal epileptic activity, repeated seizures, and the use of certain AEDs play an important role in the pathogenesis of cognitive impairments [51].

Seizures cause progressive cellular and metabolic changes that correlate with hippocampal neuronal loss, neoneurogenesis, and synaptic reorganization, as well as increased susceptibility to induced and spontaneous seizures. Behavioral and cognitive impairments occur and worsen with the cumulative number of seizures [52]. Memory problems are more pronounced in focal epilepsies than in generalized forms of epilepsy, with short-term memory being particularly affected. Memory impairments correlate with the long-term course of uncontrolled epilepsy [53].

OUTCOMES OF SURGICAL TREATMENT OF PHARMACORESISTANT EPILEPSY

The priority method of DRE treating is surgical treatment. Currently, data on the long-term results of surgical treatment of patients with DRE after various types of surgical interventions are accumulating [54]. However, there is no single point of view on the effectiveness of different treatment methods, risk factors for favorable and unfavorable outcomes of surgical treatment. Surgical treatment of epilepsy is usually performed on young people who need an assessment of the risks and long-term results of the operation. Prognostic factors for a good outcome of epilepsy surgical treatment include the presence of structural changes in the brain according to neuroimaging data (mesial temporal sclerosis, space-occupying process), the absence of focal cortical dysplasia and other cortical congenital malformations. In addition, it is necessary to consider the "consistency" of the results of neuroimaging and electroencephalographic monitoring, and there should be a sufficient volume of epileptogenic focus surgical resection [12, 13, 55].

The traditional surgical approach is considered to be anterior temporal lobectomy. Anterior temporal lobectomy with amygdalohippocamectomy (AGHP) includes resection of the medial complex, which consists of the amygdala, hippocampus, and parahippocampal gyrus. Additionally, the neocortex, which is not involved in the pathological process, is resected. Many studies have shown that AGHP is superior to long-term drug therapy in terms of seizure control in patients with DRE [56, 57]. Other surgical techniques are also currently used. Such techniques include stereotactic radiosurgery, MRI-guided laser interstitial thermal therapy (MgLiTT), and stereoelectroencephalography-guided radiofrequency thermocoagulation (SEEG-guided RFTC) [58]. In some cases, DRE surgical treatment is impossible. Limitations are associated with the presence of multiple epileptogenic foci, the impossibility of localizing the foci, or the location of the pathological substrate that is dangerous for any surgical intervention (proximity to functionally significant zones). For such patients, neurostimulation techniques are used, including vagus nerve stimulation, deep brain stimulation, and responsive neurostimularion [58, 59].

The central epileptogenic role of mesial temporal structures in temporal lobe epilepsy has been demonstrated in animal models of temporal lobe epilepsy as well as in structural cerebral pathology under the control of electrophysiological and neuroimaging studies. Thus, more targeted mesial temporal resections that spare the temporal neocortex, selective amygdalohippocampectomy (SAH), have been considered as a possible means of providing equivalent seizure control with fewer neuropsychological consequences [60, 61].

According to a large study (prospective and retrospective), including 745 and 766 people, respectively, who underwent SAH and AGHP, the proportion of the IA outcome according to J. Engel in the overall group was 68 %. For SAH this figure was 66 %, for AGHP – 71 %. A meta-analysis demonstrated a statistically significant decrease in the chances of being seizure-free in patients who underwent SAH compared to patients who underwent AGHP [62]. According to another study, seizure control in SAH was achieved in 78.2 %, and in 85.7 % of cases with AGHP [63]. Another study indicates good results of seizure control and IA outcome according to J. Engel in patients with DRE: 72 % with AGHP, 71 % with SAH [64]. Another meta-analysis found no statistically significant differences in outcomes between AGHP and SAH [65].

Our study showed that patients who underwent AGHP had a favorable outcome in terms of seizure control. The outcomes of surgical treatment were studied in 31 patients 6 months after surgery, in 21 patients – 1 year after surgery, and in 2 patients – 2 years after surgery. The proportion of patients with significant improvement (I and II

outcome classes according to J. Engel) was 87.1 %, 76.2 %, and 50 %, respectively, during the observation period [66]. As a rule, after surgery, patients remain on a reduced dose of AED, which reduces the expected effect of the surgery and requires further monitoring of the patient's somatic and mental functions with correction or discontinuation of pharmacotherapy [59].

In the middle of the last century, the effectiveness of epilepsy surgical treatment was assessed mainly by such indicators as complete or partial remission, reduction in seizure frequency, and the degree of changes in instrumental research methods. In recent years, the results of epilepsy surgical treatment have been assessed not only by reducing the frequency and/or cessation of epileptic seizures, but also by improving the quality of life, neuropsychological status, and cognitive sphere of operated patients.

Neuropsychological assessment of the functions of specific brain regions subject to resection and the patient's mental reserve capabilities allows predicting postoperative cognitive impairment. Successful surgery can halt the decline in mental abilities due to resistant epilepsy and reverse this negative trend by "releasing" functions that were secondarily affected before surgery [67]. However, surgery carries a risk of additional impairments that, together with comorbid disorders, can accelerate the decline in cognitive functions, especially in old age. From a neuropsychological point of view, early detection of drug resistance is of great importance, along with early and complete seizure control with maximum preservation of functional tissues during surgical treatment [67]. Many studies demonstrate the superiority of SAH in preserving neurocognitive functions [68, 69].

The study by W. Chengxiong et al. (2018) reported equal results in J. Engel's outcomes for SAH and AGHP, but worse results in neurocognitive impairment were observed with AGHP [70]. A large study by H. Clusmann reported better results after SAH in terms of attention, verbal memory, and overall neuropsychological performance [71]. U. Gleissner et al. (2002) reported the first results after 3 months and then after a year in 140 patients who underwent SAH. They noted that a more selective procedure may have important cognitive consequences. After 3 months, almost half of the patients with left-sided SAH had significant verbal memory loss; functional impairment was less pronounced in right-sided surgeries. Of 115 individuals who were followed for one year, no significant recovery in verbal memory was observed compared to an earlier time period [72].

The problem of QoL of patients with DRE is associated not only with the clinical manifestations of the disease, but also with the need for constant medication, with a personal reaction to it, with difficulties in integrating into society and their stigmatization. In the medical literature, there are more than 80 questionnaires for assessing QoL in epilepsy. At the same time, many of them assess the impact of epilepsy in general or its individual symptoms on the patient's life. An example of the most common special questionnaire for patients with epilepsy is the Quality Of Life In Epilepsy Patients (QOLIE) questionnaire, presented in different length versions for adults (QOLIE-89, QOLIE-31 and QOLIE-10) [73–75].

According to the results of a systematic review by A. Saadi et al. (2016), including data from more than 7,000 patients with epilepsy, the average QoL score on the QOLIE-31 questionnaire was 59.8 points with a maximum score of 100 points. Moreover, in high-income countries, this indicator was significantly higher [75]. Other studies using various QoL questionnaires in patients with epilepsy have shown a positive effect of surgical treatment of epilepsy on this indicator [76, 77]. According to the study by V. Ives-Deliperi, J.T. Butler (2017), there is also a significant improvement in QoL scores on the QOLIE-31 scale in patients with DRE after surgical treatment at 6 and 12 months compared to patients on drug therapy [77].

CONCLUSIONS

Understanding the mechanisms underlying resistance to AEDs may help develop more effective therapeutic options for patients with DRE. Development of a P-glycoprotein inhibitor is an important goal in the pharmacotherapy of resistant epilepsies. Identification of genes that influence the risk of developing DRE is of great importance for both research and clinical purposes. The discovery of new genes and their effects may expand our knowledge of the processes underlying susceptibility to DRE, potentially leading to the discovery of new treatments.

Identification of patients with DRE and timely provision of specialized care to them is often delayed. These patients are more susceptible to a high risk of comorbid diseases and mortality. However, identifying risk factors for DRE and changing the approach to treating a specific patient allows avoiding the use of ineffective AEDs and their side effects, worsening the course of the disease, etc.

Surgical treatment of this category of patients shows good results, however, the volume and methods of surgical intervention, the risks of adverse outcomes, the state of the psychoemotional and cognitive sphere, especially in the late postoperative period, remain insufficiently studied.

Evaluation of QoL in DRE is necessary, like other indicators, to determine the effectiveness of the treatment and rehabilitation of patients.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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