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Pharmacoresistance in epilepsy and ways for overcoming it (literature review)

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Epilepsy is the most taking place disease of the human nervous system. Despite the fact that we are continuously introducing new medicines into therapy of this illness we still are failing to take control over seizures in 1/3 cases. Persisting seizures gain considerable influence on patients' living standard and within children audience cause delays in person maturity. Given article shows deep analysis of the last years researches which gave background to discover main mechanisms of pharmacoresistance. The issues of pathophysiological features of medicine resistance and reasons of false diagnostics are as well discussed. Authors highlighted few pathologic conditions where applied differential diagnostics allowed to avoid diagnostical mistakes. True definition of the certain seizures features according to the up to date classification makes it possible for clinical staff to prescribe correct anticonvulsant therapy, so far diminishing the risk of pseudo resistance outcome of disease. The article introduces criteria of natural resistance which if being recognized allows to perform dew time surgical treatment and therefore cuts seizures in most of the cases.

Keywords: epilepsy, pharmacoresistance, classification, comorbidity, differential diagnosis, treatment.

Introduction

According to the International League Against Epilepsy (ILAE) 65 million people worldwide suffer from epilepsy, of which 400–450 thousand live in the Russian Federation [1]. Epilepsy is a curable disease and with a right treatment 70 % of patients remission occurs or seizures frequency decreases more than 50 % [2]. Unfortunately, despite on emer-

gence of many "new" antiepileptic drugs (AEDs), a proportion of drug-resistant epilepsy in a population of people suffering from this disease has not changed and it is about 30 % [3–5].

According to the definition of ILAE, pharmacoresistance is ascertained in case of epileptic seizures persistence, despite full-fledged attempts to use two or more tolerable and correctly chosen AED intake regimens. There is no specific list of such schemes. A selected scheme with taking into account data of evidence-based medicine and the current clinical situation can be considered correct [6]. Analyzing in each case the patient's pharmacoresistance of epilepsy, it is necessary to answer the following questions:

1) whether the diagnosis of epilepsy was given correctly and the paroxysmal conditions are "pseudo-epileptic" seizures;
2) whether the patient is taking adequate antiepileptic therapy with his existing epileptic syndrome;
3) whether the patient is compliant with the prescribed treatment;
4) how curable is a severe progressive disease of brain including genetically determined canalopathies which is a basis of epilepsy;
5) whether the epilepsy in the patient is combined with drug or alcohol addiction, etc.

Thus, in order to talk about pharmacoresistance and to overcome the issue of further patient management with possibility of using surgical methods of epilepsy treatment, it is necessary to analyze existing situation and make an adequate decision in each concrete case.

Pathophysiological aspects of epilepsy

Epilepsy is a chronic disease characterized by repeated, predominantly unprovoked seizures with impaired motor, vegetative, cognitive or mental functions due to excessive neuronal discharges in the gray matter of the cerebral cortex [7].

The clinical manifestations of epilepsy depend from the site of origin, duration and distribution of discharge. An epileptic focus is a group of neurons that generate excessive focal neuronal discharges. Epileptic neurons (pacemakers) involve all new neural populations to a pathological process. They are prone to spontaneous paroxysmal depolarization shift and generation of a neuronal discharge [8]. A pathophysiological basis for the emergence of epileptic pathology is considered a paroxysmal depolarization shift of a neuron membrane potential and an increased tendency to the depolarization. In order to develop epilepsy as a disease the organization of an epileptic system is necessary [2]. The epileptic system is the formation of stable pathological interneuronal connections between the epileptic focus and the subcortical-stem structures [8].

It is known that tonic-clonic seizure develops only with involvement of a critical mass of neurons and with condition of excitation spread to contralateral cerebral hemisphere relatively to the focus [9–11].

Nevertheless, such factor as a structural condition of the epileptic focus plays an important role from the many factors that potentially affect the rate of epileptic activity generalization [12]. The organization of the focus of epileptic activity is accompanied by certain of the anatomical structure disorders of neurons, their membrane excitability, and a number of neurochemical changes. However, with neuroimaging is not always possible

to determine structural changes of the brain tissue which are triggers of epileptic seizures, and also clinically to identify onset of an epileptic seizure in the presence of a structural focus in a brain matter. Disruption of neurophysiological processes in epilepsy is associated with a disorder of ionic, transmitter, and energy processes [13].

According to the "GABA-theory" of epileptogenesis the insufficiency of GABA-ergic effects on neurons and glial cells of the brain contributes to their over excitation, the formation of the epileptic focus, and epileptic systems.

Last years a development of neuroimaging research methods and using of mathematical models based on graph theory in clinical and fundamental epileptology allowed to consider epilepsy as a disease of neuronal networks. The set of structural and functional networks in the nervous system is accepted to call a connectome. In patients with epilepsy disorders of the structural and functional connectomes are found. Changes are noted both in the nodes correspond to the different areas of the temporal lobe and extra temporal structures, and in the quantitative and qualitative characteristics of the ribs (connections between the nodes) [14]. Thus, a single pathological focus involves other distant parts of the brain in epileptogenesis, forming the epileptic system. Modern studies of the pathophysiological mechanisms of the epileptic seizures development show that epilepsy is a disease of neuronal networks and not a symptom of a local brain damage. From this point of a view, seizure can begin both in the neural network of the neocortex and in the thalamocortical or limbic neural network.

A number of zones are distinguished in the pathological epileptic system. Among them the "irritative zone" is a section of the cortex that generates interictal discharges on EEG. However, the "irritative zone" does not accurately reflect the epileptogenic zone. "Seizure onset zone" or "seizure zone" is a zone defined by EEG, MEG or functional MRI (fMRI). As the irritative zone it can be determined by using scalp or intracranial EEG.

The boundaries of the seizure onset zone in a certain extent depend from a methodology used by the scalp and intracranial EEG. In fact, the "seizure onset zone" is a reflection of a complex system activity interacting with the specific topographic regions. An "epileptogenic focus" is a histologically abnormal area of the cortex suspected of causing an epileptic seizure; it is identified by using MRI [15]. With a same localization of epileptogenic focus can form the different epileptic systems, which in turn, causes the emergence of various forms of epilepsy and types of epileptic seizures [2].

"Zone of a functional deficiency" is a zone of the cortex. A function of which is impaired in the interictal period. It is determined by a deficit detected on neurological examination, a cognitive testing, by changes in tissue metabolism or perfusion and functional connectivity abnormalities on fMRI and also by the non-epileptiform changes on EEG.

"Symptom-producing zone" presents an area of the cortex that "produces" aura and other ictal phenomena that can help to define a localization of focus.

Significant role in a development of epilepsy is belonged to an antiepileptic system of the brain. It includes cerebellum, reticular nucleus of pons, caudate nucleus et al. The following are involved in providing protective antiepileptic mechanisms:

1. humoral factors (hypercapnia in tonic phase of generalized tonic-clonic seizure (GTCS));
2. neurophysiological factors (transfer of recruiting sharp wave rhythm of tonic phase of GTCS to spike-wave rhythm and ensure the transformation of the life threatening tonic phase into more favorable clonic phase);

3. adaptation processes with participation 17-hydroxycorticosteroids and catecholamines.

Thus, it is necessary to form a system that provides a "flow" of epileptic activity outside the epileptic focus with involvement of subcortical structures and insufficiency of the antiepileptic protection system for the realization of epileptic seizures [2]. Cases of "breakthrough" of epileptic activity from focus with development of clinical manifestations of the disease indicate the insufficiency of antiepileptic mechanisms and the formation of the epileptic system [15].

By the course of disease the epileptic system becomes more complex, new pathways and new structures are involved, which are the basis of seizure polymorphism that occurs over time in the most cases [15].

According to Fang M. et al. [16], the stable pathological neural networks are formed as a result of impaired plasticity of the brain neurons, which are not suppressed at the molecular level by the endogenous antiepileptic system. Various hypotheses of a pathogenesis of the drug-resistant epilepsy are spoken. For example about a relation with pharmacodynamics of a drug (hypothesis of "transporters" and "target") and with the features of the disease (hypothesis of "intrinsic severity") [6]. Special attention should be paid to a group of people with connective tissue dysplasia because they may have disruption in the pharmacokinetics and pharmacodynamics of the drugs [17].

There are also evidences of increasing of the autoantibodies level to GABA receptors in the brain in patients with epilepsy and blockade of an interaction of GABA receptors with antiepileptic drugs (benzodiazepines and phenobarbital) [18].

About some changes in the classification of epilepsy

The definition of epilepsy was supplemented by ILAE in 2014 and is still relevant today. In conformity with this definition epilepsy is considered a brain disease that meets to any of the following conditions: 1) at least two unprovoked (or reflex) seizures occurring with interval more than 24 h; 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60 %) after two unprovoked seizures, occurring over the next 10 years; 3) the established diagnosis of epileptic syndrome [19].

The new classification of epilepsy ILAE 2017 has three levels and it is intended for use in clinical practice [19; 20].

The first level in a structure of the classification ILAE 2017of epilepsy defines the type of seizure and marks onset of seizure — focal, generalized, unknown. From the classification of seizure types, it follows that tonic, clonic, myoclonic and other seizures can be both focal and generalized. Instead of "focal seizure with secondary generalization" it is suggested to use the term "focal onset seizures with transition to bilateral tonic-clonic seizure". In some cases, the first level is the only possible one (for example the absence of routine EEG or video-EEG-monitoring and imaging exams — MRI, PET, etc.). There may not be enough information to establish diagnosis of the next level when the patient has only one seizure. Focal seizure originates from networks of neurons limited to one hemisphere. These networks can be localized or spread more widely. Focal seizure may have origin from subcortical structures. With more widely spread seizure becomes bilateral tonic-clonic. The previously used term "secondarily generalized seizure" is outdated and not recommended for use.

The second level involves determining the type of epilepsy — focal, generalized, combined (generalized and focal), and unknown. The type of epilepsy diagnosed at the second level can become the final diagnosis in absence of opportunity to move to the next level — identification of epileptic syndrome.

Focal seizures are more common than generalized seizures [21]. According to O'Brien T. J. et al. [22], the proportion of focal forms of epilepsy reaches up to 60 %. Symptomatic and presumably symptomatic focal epilepsies constitute the largest group of focal epilepsies. Symptomatic focal epilepsies are based on local brain damage of various etiologies. A latent period between injury and development of seizure varies considerably — from several months (for example after traumatic brain injury) to several years and even up to 10–20 years, as for example in the case of cortical malformations [23]. According to experimental and clinical studies a transformation of normal pattern activity of brain neurons into paroxysmal is accompanied by a change in expression of cytokines and neurotrophins in the hippocampus and temporal cortex. IL-1b changes the blood-brain barrier permeability and neuronal excitability by increasing glutamatergic transmission and has pro-convulsive effect [24].

The third level is the diagnosis of epilepsy syndrome which is an aggregate of characteristics, including the type of seizure, EEG data, and neuroimaging. It often has an age-dependent character, provoking factors, chrono-dependence and, in some cases a prognosis. Definition of the syndrome is important to clarify etiology, treatment, and prognosis of the disease [19; 20].

It also should be considered *comorbidity* of epilepsy (conditionally — the fourth level), which means intellectual and mental disorders. Particular attention is paid to assessment of cognitive and behavioral disorders in epileptic encephalopathies and encephalopathies of development.

Structural, genetic, infectious, metabolic, and immune epilepsy, and as well as epilepsy of unknown etiology are distinguished by etiology in the classification ILAE 2017of epilepsy. In this case, the patient's epilepsy can be attributed to more than one etiological category. For example epilepsy in a patient with tuberous sclerosis can have both structural and genetic etiology. Knowing of structural etiology has crucial meaning for choice of surgery, and genetic etiology for genetic consultation of the family members and for choice of innovative methods of target drug therapy.

Symptomatic (structural) focal epilepsy

By "symptomatic" is assumed to the forms of epilepsy with a known etiological factor and verified structural changes in the brain that are cause of epilepsy. Most symptomatic focal epilepsies are structural in their etiology. As the name suggests, symptomatic epilepsy is manifestation of another disease of the nervous system: tumors, brain dysgenesis, metabolic encephalopathy, consequences of hypoxic-ischemic and hemorrhagic brain damage, etc. Often neurological, cognitive impairments, and also resistance to antiepileptic therapy occur by these forms of epilepsy [7]. "Probably symptomatic" or "cryptogenic" forms of epilepsy are called syndromes with undetermined and unclear etiology.

It should be taken into account also the fact that in 20–30 % of people with paroxysmal conditions the seizures are not epileptic in their nature and the antiepileptic drug

treatment turns out to be ineffective in the case of misdiagnose and forces to think about the pharmacoresistance of the assumed alleged epilepsy.

Differential diagnosis of paroxysmal conditions

Differential diagnosis of paroxysmal conditions is difficult and sometimes not well known to a wide range of family doctors and even neurologists and psychiatrists. It is necessary to remember that psychogenic non-epileptic seizures (PNES); paroxysmal conditions caused by brain circulatory disorders and dysmetabolic disorders; paroxysmal conditions with various intoxications; hypnotic nature paroxysms; and parasomnias may be among the diseases and conditions with which it is necessary to carry out the differential diagnosis of epilepsy [25; 26].

Psychogenic non-epileptic seizures include motor components, alter of response reactions to external stimuli, and loss of consciousness level. Features of PNES clinical manifestation include: behavior change before the seizure, vegetative symptoms in the form of increase and difficulty in breath rate, heart palpitation, faintness; often expressed emotional reactions (fear, aggression, crying, etc.); complaints of headache and "special state of consciousness". The following attrack attention: seizure's onset gradual, its duration course (over 2–3 minutes), and seizure's gradual completion, which usually occurs while a patient is awake. Seizures are non-stereotyped but may resemble with any type of epileptic seizures. During the seizure, there may be breaks in its course, tight closing of the eyelids, and resistance when trying to open them. Sometimes patients answer to simple questions and at this time the motor equivalent of the seizure stops. Vocalization is possible during the seizure, not at its beginning, rocking movements of the head from side to side, lack of rigidity of limbs and trunk muscles. For PNES the following signs are atypical: seizures at night; rolling over on the stomach during the seizure; short duration of seizure; tongue biting, trunk and limb injuries; motor stereotype of seizure; inhibition of pupillary reactions; seizures in very young children; identification of organic pathology when using neuroimaging research methods. Patients with PNES are usually in conscious, remember about their seizure, especially a motor seizures in the post seizure period [25]. Thoroughly collected anamnesis and complaints, assessment of somatic, neurological, neuropsychological status, as well as 24-hour video and EEG monitoring data, allows to exclude true epilepsy in patient. There are also indications of increase in prolactin content in blood serum by 2–2.5 times after an epileptic seizure compared with control, which can also be one of the distinguishing criteria of epileptic seizures from non-epileptic seizures [25]. It is necessary to take into account that manifestations of non-epileptic seizures are observed in about 10–20 % of patients with epilepsy. During the seizure, they will have EEG also corresponding to this pathology.

When carrying out differential diagnostics, one must also keep in mind patients with epilepsy with non-convulsive paroxysms. This type of generalized seizures characterized by sudden onset, short-term loss of consciousness without convulsions, stereotype, sudden cessation, partial or complete amnesia, presence of paroxysmal changes on the EEG.

Cerebral circulation disorders can also be the cause of paroxysmal conditions requiring differential diagnosis with epileptic seizures. This includes faintings (or syncopes), drop-attacks, transient ischemic attacks (TIA).

Drop-attacks are caused by transient ischemia of brainstem. Typical drop-attacks are not accompanied by loss of consciousness and are characterized by a sudden fall without precursors associated with abruptly reduced muscle tone of limbs and trunk. Their occurrence can be triggered by throwing a head back or turning it to the side in case of stenotic lesion of vertebral arteries and cervical osteochondrosis. As a rule, these are accompanied by other symptoms of vertebrobasilar insufficiency [25].

In differential diagnosis with *TIA* it should be taken into account the younger age of epilepsy onset, consciousness changes during the seizure, post-seizure confusion, and the short duration of episodes (less than 3 minutes), and typical EEG for epilepsy. TIA is not characterized by the limitation of paroxysm with only one of the signs. In particular, transient consciousness loss, isolated dizziness, pelvic organs dysfunction, transient blackout, and falling. Identification of focal symptoms of affected pool, noise or pulsation weakening of the carotid arteries, often cervical spine pathology is typical characteristic. Usually the age of patients is over 50 years old. In addition, the EEG in the interictal period is normal. The screening instrumental method TIA of detecting is Doppler ultrasound exam of the neck and head great vessels. Methods such as Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) in vascular and tissue modes and wide range of laboratory studies, including immunological methods are used to clarify the cause of vascular insufficiency.

The most common causes of seizures in case of *metabolic disorders* are hypoglycemia and eclampsia. Paroxysmal disorders with convulsive syndrome in diseases of the liver and thyroid gland were described [26]. Hypoglycemia can be caused by endocrine diseases, drugs, tumors, gastrointestinal diseases, infections, and other pathologies. Hypoglycemia convulsions are asymmetric in contrast to epileptic ones. In rare cases, hypoglycemia can result in status epilepticus. Sometimes taking anaprilin (obzidan) by patients with diabetics can cause hypoglycemia. Blood glucose test is recommended for all patients who have seizure without an epileptic anamnesis. Patients with hypoglycemic seizures, both in the interictal period and during the seizure do not have epileptic phenomena on EEG. *Eclampsia* is currently considered to be a variant of acute hypertensive encephalopathy. There are focal and secondarily generalized convulsions. They can occur before, during and after childbirth, and are accompanied by a diffuse slowdown of bioelectric activity on EEG with the foci of epileptiform activity. It is assumed that causes of seizures are the foci of microhemorrhages and microinfarctions in the brain.

Seizures can also occur in *acute renal and hepatic insufficiency, porphyria, acute adrenal and thyroid insufficiency, alcohol abstinence and intoxications.* Most often, paroxysmal states are provoked by drugs that cause excitement and stimulation of the central nervous system (amphetamines, cocaine, phencyclidine, etc.). Convulsions can occur both at the first drug intake and in chronic drug addicts with an overdose, independently from the way of taking drugs. Opiates overdose, which usually causes depression of central nervous system or sudden drug abolition, can also be reason of convulsion syndrome.

Chronic alcoholics often have convulsions during the first 48 hours after stopping binge drinking of. Generalized tremor and myoclonic flinching are determined in the neurological status. Convulsions are generalized clonic-tonic in nature. Repeated convulsive episodes are possible. In severe cases, if treatment has not been started, alcoholic delirium and even status epilepticus may develop. EEG is usually normal in the interictal period and only during the convulsions there can be epileptic patterns. A specific

treatment for alcohol-dependent convulsions is taking lorazepam from 2 to 5 mg intramuscularly.

Psychomotor epileptic seizures also should be distinguished from *narcoleptic paroxysms*. When carrying out differential diagnostics, one should pay attention to the following signs: narcolepsy seizures begin with irresistible sleepiness but they are not stereotyped; the pupils are narrow during the seizure and not wide as in epilepsy; the patient easily reacts to shout and push, fully awakening.

It is necessary to remember also about *parasomnias,* which include a large group of various pathological phenomena that paroxysmally arise during sleep or incomplete awakening. For example sleepwalking (somnambulism, lunatism) is characterized by periodically recurring episodes of physical activity combined with partial or complete impaired consciousness in awakening from slow wave sleep. This phenomenon is usually observed in patients with emotionalism, hypersensitivity and is considered as manifestation of neurosis or psychopathy. To confirm the sleepwalking diagnosis presence of following symptoms and manifestations is necessary: walking during the sleep; impairment of consciousness or ability to think coherently; additionally at least one of the following symptoms — difficulties when trying to wake up a child, confused thoughts during awaking, complete or partial amnesia of the episode, presence of habitual activity at an unusual time, dangerous or potentially dangerous behavior. At the same time, delta sleep persistence is recorded on EEG during the paroxysm. The possibility of nocturnal seizures of temporal lobe epilepsy with symptoms of ambulatory automatism should be taken into account. According to V. A. Karlov (1990), epileptic seizures account for up to 3 % of sleepwalking cases. Sleepwalking clinical manifestations that allow one to suspect epilepsy are: child's age up to 3 years old and after 12 years old; occurrence of the seizure in the second half of the night; stereotypical character of motor activity; inability to wake up the child; presence of epileptiform activity on EEG during when awake. Epilepsy psychomotor seizures are usually shorter, accompanied by an aura and oroalimentary automatisms (with frontal focus localization), and there are daytime paroxysms. The presence of typical epileptic activity during a sleepwalking episode is the confirmation of the epileptic genesis of the seizure. Additional research methods (CT, MRI, PET) can reveal brain structural changes in case of focal epilepsy.

Comorbidity in patients with epilepsy

More than 50 % of people with epilepsy have one or more comorbidities. Psychopathological disorders (depression, anxiety, autistic disorder, etc.) and somatic diseases (type 1 diabetes, arthritis, chronic obstructive pulmonary disease, etc.) are associated with epilepsy [27].

In this case, mainly anxiety and depressive disorders are considered [28; 29], rarely concomitant somatic pathology [28]. The phenomenon of sexual function normalization after temporal lobe resection performed on pharmacoresistant epilepsy was described [28]. ECG abnormalities (bundle branch block, ST segment changes, and first-degree AV block) were identified in patients with drug-resistant epilepsy. These ECG abnormalities are revealed in about 35 % of patients without diagnosed heart disease [30]. There are indications of tension headache in interictal period mainly in patients with epilepsy, that aggravate the course of disease and require adequate correction, in-

cluding the use of cognitive-behavioral therapy technologies, psychotherapy and relaxation techniques [31].

It is believed that migraine and epilepsy have common pathophysiological changes leading to hypersynchronization of CNS neurons [32]. Migraine has been described as a trigger of an epileptic seizure.

In recent times, much attention is paid to study of gut microbiota state and drug-resistant epilepsy. It was revealed that in patients with drug-resistant epilepsy the intestinal flora contains Clostridium XVIII, Atopobium, Holdemania, Dorea, Saccharibacteria, Delftia, Coprobacillus, Paraprevotella, Ruminococcus, Gemmiger, Akkermansia, Neisseria, Coprococcus, Fusobacterium, Methanobrevibacter, Phascolarctobacterium, and Roseburia. Bacteroides and Barnesiell prevail in intestinal flora of patients sensitive to pharmacotherapy [33]. In addition, seizures decrease of symptomatic epilepsy in more than 50 % of cases was observed with probiotic treatment [34].

Treatment questions of drug-resistant epilepsy

One of the priority areas of epileptology is a diagnostics and treatment problem of drug-resistant epilepsy form.

When establishing diagnosis of epilepsy early prescribing AED is done — monotherapy is preferable. AED is selected according to the type of epileptic seizures. If to achieve an effect with one drug is impossible, rational AEDs combinations are used taking into account the pharmacokinetics and pharmacodynamics features of the prescribed AED and its level control in a blood.

For patients to assess the therapy effectiveness except keeping seizure diary, it is necessary to do dynamic video-EEG monitoring with the periodicity of 1 time in 4-6 months after a therapy start or correction. In order to assess the antiepileptic therapy safety, it is necessary to control the abdominal organs condition (ultrasound exam 1 time in a year), to do an electrocardiographic study (1 time in every 6 months), do complete blood count and urinalysis (1 time in every 3 months), biochemical blood test (1 time in every 6 months).

The antiepileptic therapy selection should not be carried out empirically. The modern approach assumes a strict accord of the drug to the epilepsy form and the seizures semiology.

For the first drug selection, attending physician should rely on the ILAE recommendations for the AEDs initial monotherapy for various types of epileptic seizures and epileptic syndromes [35], as well as on expert opinions, for example on recommendations of new and old AEDs use in epileptic seizures and major epileptic syndromes treatment [36].

Currently, the following generations of AEDs are distinguished (listed drugs are registered in the Russian Federation): the I AEDs generation — phenobarbital, phenytoin, ethosuximide, clonazepam, carbamazepine, valproic acid; II AEDs generation — lamotrigine, gabapentin, topiramate, pregabalin, oxcarbazepine, levetiracetam, zonisamide, vigabatrin; III AED generation — lacosamide, eslicarbazepine, rufinamide, perampanel, brivaracetam [37; 38].

It is necessary to consider an action mechanism of the AEDs. There are drugs with a narrow spectrum of action: sodium channels blockers — carbamazepine, oxcarbazepine, lacosamide, eslicarbazepine, phenytoin; AEDs with GABA-ergic activity — phenobarbi-

tal, gabapentin, benzonal; calcium channels blockers — ethosuximide [36; 39]. Broad-spectrum drugs (multicomponent action mechanism) — valproic acid, levetiracetam, topiramate, lamotrigine, zonisamide, perampanel, brivaracetam.

To this day, carbamazepine is the "gold standard" for the *focal* epilepsies treatment. In this connection the latest AEDs for these diseases treatment are compared with it in effectiveness and tolerability terms. However, this drug has a number of negative properties which create problems in clinical practice. In this connection a pharmaceutical industry strives to save a main action mechanism and an "application point" in the latest AED generations but to neutralize side phenomena and cross-effects. So, hepatic enzymes induction and as a consequence self-induction and metabolism effect of drugs used simultaneously with it; high neuro-, cardio- and hematotoxicity; mortality from cardiogenic causes are noted in carbamazepine [40]. Currently, there is a sufficient arsenal of alternative AEDs with the similar action mechanism. Treatment of *focal seizures* in adult patients with structural and metabolic epilepsies is traditionally carried out by prescribing of the following AEDs (listed in priority order): carbamazepine, levetiracetam, phenytoin, zonisamide, valproic acid, gabapentin, lamotrigine, oxcarbazepine, eslicarbazepine, lacosamide, phenobarbital, topiramate, clonazepam are used in start monotherapy [36]. Carbamazepine, levetiracetam, zonisamide, topiramate, valproic acid, lamotrigine, oxcarbazepine, eslicarbazepine, lacosamide, brivaracetam, perampanel, gabapentin, pregabalin, phenobarbital, clonazepam, phenytoin are used in polytherapy. In this case, polytherapy significantly expands the spectrum of used AEDs because of that some of the newest drugs are registered in the Russian Federation for use only as a polytherapy part.

In treatment of isolated *generalized seizures* valproic acid, phenobarbital, phenytoin, levetiracetam, lamotrigine, topiramate are used in a start monotherapy [37]. Lamotrigine, oxcarbazepine, topiramate, valproic acid, levetiracetam, perampanel, phenobarbital, clonazepam, phenytoin are recommended for polytherapy

In *myoclonic seizures* treatment: valproate, topiramate, zonisamide, levetiracetam are used in monotherapy. In polytherapy: valproate, topiramate, levetiracetam, zonisamide, clonazepam, phenobarbital, ethosuximide [40]. Not recommended for use: carbamazepine, oxcarbazepine, eslicarbazepine, gabapentin, phenytoin, pregabalin. Limitations are often associated with a high aggravation risk, sometimes with potential inefficiency.

In *absences* treatment (this form is considered in the juvenile absence epilepsy context) only valproic acid is used as monotherapy; it is possible to use levetiracetam, zonisamide, topiramate, ethosuximide or lamotrigine together with valproic acid in polytherapy [41]. Not recommended for use: carbamazepine, oxcarbazepine, eslicarbazepine, gabapentin, phenytoin, pregabalin.

For undifferentiated forms of epilepsy, it is preferable to start with broad-spectrum AEDs.

Currently, it is necessary to follow generally accepted concept of AED prescription: start with monotherapy; in case of remission is absence- alternative monotherapy; when it is ineffective — rational polytherapy. It should be noted that if one AED is ineffective, it is not necessary to switch to polytherapy immediately without using all the possibilities of monotherapy [7].

The action of antiepileptic drugs is aimed on suppressing the brain epileptic activity, i.e. to suppress the excitation generator work (epileptic focus). At the same time, decrease of antiepileptic system activity is one of the important mechanisms of reducing effective-

ness anticonvulsants up to tolerance development. Therefore, directed search of drugs that increase endogenous antiepileptic system activity of brain is important task of future research.

Epileptogenic zone verification is one of the most important issues for a clinician when prescribing "adequate" (targeted) antiepileptic therapy. Determination the most accurate localization and length of the epileptogenic zone is necessary to resolve the surgical treatment issue. However, despite technical advances routine visual examination and MRI do not allow to diagnose with a sufficient degree of reliability or to reveal structural abnormalities in 30–50 % of cases. Although a brain tissue damage is confirmed by histological methods [42]. Currently, this diagnostic feature is one of the main barriers to introduce effective epilepsy surgery into. Also, situations when the epileptic activity focus may not coincide with the morphological focus identified by MRI examination are not uncommon, which are found in 22–38 % of cases [43; 44].

Diagnostic algorithm expansion with using neurophysiological complex (video-EEG, intraoperative electrocorticography, EEG with implantable intracerebral electrodes), neuroradiological (PET, MEG) allow to determine morpho-functional changes in the brain. Currently, clinic-electrophysiological and radiological parallels are actively studied which are presenting great interest both for clinical medicine and fundamental science.

It should be considered also the fact of existence somatic diseases and psychopathological syndromes can affect the disease course and the failure of compensation. One of the priority directions in epileptology is a study of factors that influence formation of remission in epilepsy or failure of it which is connected in significant extent with the presence of comorbid somatic disorders, and primarily the cardiovascular system diseases [30; 45]. However, comorbidity is generally assessed without epilepsy forms differentiation in patients.

In addition to pharmacotherapy the international standards include non-drug treatments for refractory epilepsy such as chronic n. vagus stimulation (VNS therapy) and the ketogenic diet but certainly, the most radical is surgical treatment. Epileptic seizures and lifelong dependence from anticonvulsant therapy can stop in case of complete removal of the epileptogenic zone. (Weibe S. et al., 2001) emphasizes that depending from a lesion location up to 80 % of patients with drug-resistant forms of epilepsy achieve seizures control as a result of surgical treatment if the operation was performed within two years from the onset of the disease [46]. However, after surgery patients often remain on reduced dose of antiepileptic drugs, which reduces the expected effect of the surgery. This causes of necessity their further observation and control over the state of somatic and mental functions with correction or cancellation of pharmacotherapy.

Conclusion

The most discussed problem in epileptology is pharmacoresistance of epilepsy and ways for overcoming it. The correct definition of the seizures type and epileptic syndrome is necessary condition for the prescribing of adequate therapy. It is very important to exclude "pseudo-epileptic" seizures at the earliest level. In prescribing anticonvulsant therapy it is necessary to achieve patient compliance to prescribed treatment. It is essential to diagnose and correct comorbid disorders in patients of this profile. It is possible to choose non-drug, surgical or combined treatment options in pharmacoresistance only after thor-

ough analysis of carried out treatment, complex examination of the patient using modern high-tech research methods. Surgical intervention presents the final stage in the long and laborious process of preoperative examination and treatment conducted by neurologists, neurophysiologists, neuropsychologists, neuroimaging specialists, the purpose of which is reliable identification of the epileptogenic zone, removal of it, disintegration of the pathological epileptic system, and activation mechanisms of the antiepileptic protection of the brain.

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