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BIOMARKERS OF EPILEPSY

More than 50 million people worldwide suffer from epilepsy. Almost in 30% of cases it is not possible to achieve control over attacks, despite the use of a wide range of antiepileptic drugs, and surgical treatment. To date, there are no methods of treatment and prevention of the development of epilepsy in people at risk. All this indicates the need for a search for biomarkers of epileptogenesis, diagnosis, disease progression, drug response and treatment safety.

As biomarkers of epilepsy, the following are considered: electrophysiological changes, the presence of a clinical attack, genetic changes, micro ribonucleic acid (microRNA) of plasma / serum / cerebrospinal fluid; protein biomarkers, plasma exosome biomarkers, cerebral cortex microRNAs; biomarkers, strain gauge images / diffusion-weighted images of magnetic resonance imaging (MRI).

The authors review the literature on modern studies of various biomarkers of epilepsy, which allow a personalized approach to assessing the diagnosis, treatment and response to epilepsy therapy.

Keywords: epilepsy, epileptic seizures, biomarkers, microRNA.

Introduction. According to epidemiological studies, today there are more than 50 million people diagnosed with epilepsy in the world, of which control over epileptic seizures is achieved only in 70% of cases, despite the use of various combinations of antiepileptic drugs (AED). The remaining group consists of patients with uncontrolled epileptic seizures, the search for control over which is an important and urgent problem that requires the development of new approaches, both in the diagnosis and treatment of epilepsy [15].

The relevance of the search for new non-invasive biomarkers for the diagnosis of epilepsy is high due to the fact that there are no diagnostic approaches and therapeutic methods to timely identify, suspend or weaken the process of epileptogenesis in individuals at risk for the formation of epilepsy [25]. Further research on the search for new biomarkers of epilepsy will allow the formation of informative and accessible test systems that will help in the diagnosis of the disease [12].

A biomarker is an indicator used to evaluate normal or pathogenic biological processes, as well as responses to various effects on the body, including therapeutic interventions [7].

Currently, active research is underway to search for biomarkers in cancer [26], some neurodegenerative diseases, such as Alzheimer's disease [17], the developed strategies can be applied to the search for biomarkers of epilepsy.

In this practice, the biomarker must meet the following criteria: specificity, sensitivity, predictive value, reliability and availability. Biomarkers have different characteristics: molecular, histological, radiological and physiological.

In 2015, the US National Institutes of Health, in conjunction with the Food and Drug Administration, the National Institutes of Health and the Food and Drug Administration (FDA-NIH) developed the classification of biomarkers "The BEST biomarker categories", which includes: biomarkers of risk of disease; diagnostic biomarkers; biomarkers monitoring; biomarkers prognosis (prognostic); predictive biomarkers; pharmacodynamic biomarkers (biomarkers of drug response (PM)); biomarkers of therapy safety [11].

The boundaries between different categories of biomarkers are not strict. A single biomarker can be divided into subtypes and included in several categories depending on when and how often it is measured. Development of new biomarkers takes place in the process of analytical and clinical validation with demonstration of clinical significance [17].

About 30 publications in the last 4 years are devoted to the study of different types of biomarkers in the field of epilepsy: plasma / serum / liquor microRNA; protein biomarkers, plasma exosome biomarkers, cerebral cortex microRNA; biomarkers, strain / diffusion-weighted MRI images; electrophysiological biomarkers: diagnosis of epilepsy [18, 24], temporal epilepsy [27], idiopathic generalized epilepsy [8] pharmacoresistant epilepsy [12]. None of the found biomarkers is currently used in wide practice for the diagnosis of epilepsy, and the need to search for such remains relevant [7].

Let us consider the main biomarkers of epilepsy.

Diagnostic biomarkers. Diagnostic biomarkers are used to identify or confirm the presence of a disease for which treatment can be indicated. Diagnostic biomarkers of epilepsy include markers of epileptogenesis, drug resistance, and high risk of epileptic status. Some of the biomarkers of epileptogenesis can be considered as prognostic for individuals who have suffered acute cerebrovascular accident. Also, prognostic indicators include the outcome of surgical treatment of epilepsy and prognosis of conservative treatment. The «gold» standard for diagnosing epilepsy is epileptic seizures. Epilepsy is a disease with heterogeneous etiology and, as a consequence, with different outcomes/prognoses and responses to therapy [20].

The «gold» standard for the diagnosis of epilepsy is the occurrence of a clinical

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or electrographic epileptic attack, which is used as a reference diagnosis at the stage of determining the epileptic or non-epileptic nature of the attack. However, there are many situations where an epileptic seizure occurs as a natural, acute, symptomatic or provoked event in response to a transient pathological condition [5] that does not guarantee a diagnosis of epilepsy. Many people who experience provoked or reactive epileptic seizures do not have epilepsy.

According to the WHO, up to 10% of people worldwide suffer a single epileptic attack, which does not indicate the presence of epilepsy, since the following criteria must be met for diagnosis: 1) at least two unprovoked (or reflex) epileptic attacks with an interval of more than 24 hours; 2) one unprovoked (or reflex) attack and the probability of recurrence of attacks close to the overall risk of relapse (≥60%) after two spontaneous attacks in the next 10 years; 3) diagnosis of epileptic syndrome [4,20].

A type of clinical or electrographic attack serves as a predictive biomarker for the response to antiepileptic therapy. Different genetic markers (for example, genes for epileptic encephalopathy) associated with a particular type of epileptic seizure can predict the course of the disease, that is, they are also predictive biomarkers. Thus, a diagnostic biomarker (in this case, a clinical or electrographic attack) can not only identify the disease, but also be used for diagnostic classification, and therefore serve as both a prognostic and predictive biomarker of epilepsy [7].

Prognostic biomarkers. Prognostic biomarkers are used to determine the prognosis of a disease, its relapse or progression, for example, biomarkers for assessing the development of cognitive impairment in patients with epilepsy. Prognostic biomarkers differ from disease risk biomarkers because they apply to groups of people with epilepsy who receive or do not receive therapy [7]. It is important to note that the type of AED can affect the sensitivity and specificity of prognostic biomarkers in the differential assessment of results. The response to the treatment methods used may vary. Most often and more expectedly, this is a decrease in the symptoms of the disease, with an improvement in the survival rates of patients, however, in some cases it is necessary to face the development of adverse effects [15].

Prognostic biomarkers can be used in studies to stratify patients with epilepsy into biomarker-positive and biomarker-negative treatment groups, with the main endpoint being the effect in the biomarker-positive group of patients. Studies of prognostic biomarker-positive subjects are important to demonstrate the potential for the development of research methods of treatment, for example, antiepileptic drugs. It is important to note that prognostic biomarkers for assessing the effectiveness of the treatment of epilepsy may be characteristics of a person's biological constitution or the disease process itself. For example, the type of epileptogenic brain damage (structural changes) or the patient's genetic characteristics (genetic epilepsy variants) can predict the response to a particular probe, emphasizing the relevance of a personalized approach and further research to find new prognostic biomarkers. Gallek et al. (2016) found that the carriage of a combination of genes: ZNF852, CDCP2, PRRT1, FLJ41170 with downregulation of expression in the lateral temporal cortex of the brain is a predictive biomarker of a positive outcome for the surgical treatment of epilepsy [13].

Pharmacodynamic biomarkers. Pharmacodynamic biomarker or response biomarker – used to prove the occurrence of a biological reaction in response to exposure to a medical product or environmental factor. Changes in pharmacodynamic biomarker levels in response to treatment it may provide information that it is biologically active and / or has an impact on the clinical end point, in addition, it becomes possible to determine the range of doses of the drug for further therapy, its duration, as well as to predict the risk of adverse reactions. Pharmacodynamic biomarkers require serial evaluation, as a result of which they often fall under the category of monitoring.

To date, only one of the published studies searching for markers of epilepsy has evaluated pharmacodynamic biomarkers / response biomarkers. Walker L.E. et al. (2017) on an animal model of epilepsy showed that treatment with anakinra / BoxA / ifenprodil prevents the increase in the level of amphoterin protein (high-mobility group protein B1 - HMGB1) in blood plasma in rats with epileptic status. HMGB1 is a key activator of inflammation after the development of an epileptic seizure [24]. However, the assessment of HMGB1 level was carried out only during treatment without studying the effect after treatment and the dose-dependent effect [15, 24].

Monitoring biomarkers. A biomarker of monitoring is an indicator measured sequentially to assess the state of a disease in order to prove the effect of a medical product or environmental factor. The sequential nature of the measurements allows us to record changes in the values of the biomarker as an indicator of the current state of the person. Thus, the category of monitoring biomarkers may include other groups of biomarkers represented in the classification when they are measured sequentially. As an example, the registration on the electroencephalogram of epileptic spikes, complexes «acute-slow wave» in the cortical region, corresponding to the site of brain damage (for example, with craniocerebral trauma).

Safety biomarkers. Safety biomarkers are indicators measured before or after exposure to a medical product or environmental factor to determine the likelihood, presence, and toxicity of an adverse effect. One of the tasks, in this case, is to identify the risk group among patients with epilepsy, for which should not be prescribing some AED because of the significant risk of adverse reactions [1]. Genetically determined changes in liver cytochrome P450 enzyme activity and glucuronidation are examples of safety markers for patients taking AED. Markers of drug response safety include pharmacogenetic features of pharmacokinetics, pharmacodynamics and safety of AED. For example, single-nucleotide variants (SNV) of cytochrome P450 genes, uridine-5' - diphospho-glucuronosyltransferase determine the peculiarities of metabolism of many anticonvulsants, one of which is valproic acid (VA). To date, algorithms have been developed for personalized dose selection of VA in patients with epilepsy, taking into account the carrier of the SNV gene CYP2C9*2 and CYP2C9*3, which minimizes the risks of adverse reactions [2, 3, 6].

Biomarkers susceptibility / risk biomarkers. Susceptibility/risk biomarkers indicate an increased or lower risk of epilepsy in a healthy person.

For example, an animal model showed that CD1 mice carrying the APP/PS1 gene mutation had a higher risk of epilepsy after traumatic brain injury (TBI) [29]. Thus, biomarkers of susceptibility / risk allow identifying individuals at risk of epilepsy in need of dynamic monitoring, as well as actualize the use of preventive measures.

Currently, much attention is paid to neurophysiological and neuroimaging biomarkers of epilepsy diagnosis. However, there are no screening diagnostic biomarkers of epileptogenesis [14]. The development of new methods

of treatment of epilepsy remains a priority international direction of modern research [22]. The search for new biomarkers of epileptogenesis is laborious, including because, this requires long-term EEG monitoring. The only known serum biomarker confirmed on an animal model of epilepsy is the level of amphoterin (B1 – HMGB1). The study of its concentration makes it possible to differentiate epileptogenic and non-epileptogenic zones of the rat brain after epileptic status [24]. Therefore, for the diagnosis of epilepsy, the search for non-invasive or minimally invasive, informative and cost-effective biomarkers continues.

Recently, microRNA research has been proposed as new biomarkers that meet the requirements [18].

MicroRNAs are candidates for use as biomarkers in cardiovascular, oncological diseases, acute conditions: ischemic strokes, traumatic brain injuries [10, 23].

Several microRNAs have been shown to be involved in regulating cholesterol in the brain, disorders in the metabolism of which can trigger neurodegenerative diseases such as Alzheimer's disease, Nieman-pick type C disease, Smith-Lemley-Opitz disease, Huntington's disease and Parkinson's disease [28].

In psychiatric practice, miRNAs are considered for the diagnosis of depressive disorders, schizophrenia, autism spectrum diseases [19].

A prerequisite for the use of microRNA as a possible biomarker of epilepsy is stability in serum. In addition, it is a good study of the levels of expression in brain tissues and peripheral blood circulation in animal models of epilepsy [12, 18], as well as the availability of separate data on changes in microRNA levels in both peripheral blood and brain tissues of epilepsy patients [12, 15].

Over the past 5 years, several targeted and wide-genomic studies of miRNA expression in epilepsy have been carried out. According to the obtained these changes were found in more than 100 different microRNAs in the animal model and in patients with epilepsy, which proves the relationship of microRNA expression levels with epilepsy [12, 30].

MicroRNAs are an important class of small non-coding RNAS that play a critical role in brain development and function. New studies show that the levels of several microRNAs vary as a result of convulsive activity in animal models, and also differ in those areas of the brain from which seizures occur in patients with epilepsy (for example, the hippocampus) [16].

However, most of these studies were performed using small samples and / or without a control group. The vast majority of studies do not report any limit values of biomarkers, allowing differentiating epilepsy with the control group [15]. The specificity of epilepsy biomarkers in comparison with other brain diseases important for differential diagnosis is insufficiently studied. Problem related to investigation of epilepsy biomarkers associated with the use of anticonvulsants [21] regulate microRNA expression. On the other hand, the use of other drugs may also affect the analysis of biomarkers [9].

In the future, the search for biomarkers will form test systems and improve the diagnosis of epilepsy and epileptogenesis.

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КЛИНИЧЕСКАЯ ХАРАКТЕРИСТИКА СПОСОБОВ БЛОКАДЫ НИЖНЕГО ЛУНОЧКОВОГО НЕРВА

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Nowadays the improvement of health care system in long-term state policy is of great importance which is based on the development and adaptation of innovative technologies. At the same time dental help to the population is the most massive that is connected with the prevalence of pathological processes of organs and tissues of the oral cavity where methods of inferior alveolar nerve block are widely applied.

There is a set of anesthesia methods that have various technological and methodological features for inferior alveolar nerve block. At the same time, the general point for all types of anesthesia is anesthetic injection into the mandibular foramen area and the upper back quadrant of the branch of the lower jaw where a set of anatomical-topographical markers, which the dentist when performing local anesthesia, has to present accurately for himself, is used. Anatomical-topographical features of the inferior alveolar nerve allow carrying out this block by extra- and intraoral access. The extra access is submalar method through the lower jaw incisure, a submaxillary method – from bottom edge of the lower jaw and from the edge of the lower jaw branch.

Palpation, portiligature methods of mandibular anesthesia and also torus anesthesia are often used in clinical dentistry among intraoral methods of anesthesia. Vazirani-Akinosi, Laguardia and Egorov-Lapis' methods are applied for inferior alveolar nerve block in clinical situations connected with restriction opening of the mouth. Besides, the stem anesthesia at oval foramen by S.N.Waisblat's method is used for the mandibular nerve block. This technique is used when carrying out the traumatic operations demanding anesthesia in the field of tissues of the whole lower jaw. Gow-Gates's method has its peculiarity which characterizes its efficiency of anesthesia in the conditions of tissues inflammation of the lower jaw. The submalar method is used by Bershe (1922) and P.M. Egorov (1985) methods, where there is a relaxation of chewing group of muscles due to deactivating of motion branches of the mandibular nerve. It should be noted that the modified intraoral mental anesthesia, recommended by S. Malamed, is applied.

In general, methods of inferior alveolar nerve block are widely used in clinical dentistry for treatment-and-prevention. A set of anatomical-topographic points is used that demand certain experience and skills of the doctor causing some difficulties. This situation needs the improvement of mandibular anesthesia methods for maximum anesthesia technology simplification with complex clinical, laboratory and functional researches that will promote further safety and analgesic effect.

Keywords: lower jaw, anatomy and topography, inferior alveolar nerve, mandibular anesthesia, extra - and intra oral methods, maxillary artery, efficiency and safety of anesthesia.

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Nowadays the priority tasks of health care development are quality improvement of the provided medical care by introducing of the innovation technologies, having positive impact on strengthening and maintaining health of the population [2, 15, 26, 32]. In clinical dentistry, one of the key factors is adequate anesthesia which is constantly improving and searching of effective methods [1, 25].

It should be mentioned that there is a set of anesthesia methods which have various technology and methodological features for inferior alveolar nerve block [3, 4, 6, 18, 28, 29]. The general reference point for all types of anesthesia is anesthetic administration to the area of mandibular foramen and upper back quadrant of the mandible branch [3, 4]. At the same time the dentist uses a set of anatomical-topographical reference points when performing a local anesthesia. So, 11 approximate points of a needle, 6 directions of needle advance in horizontal position and 5 – in vertical position, 9 "targets-points" directly in the field of mandibular foramen and 12 – on mandible branches where the needle contacts with an internal surface of a mandible branch are applied for orientation. Such situation