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ЛИТЕРАТУРНЫЕ
ОБЗОРЫ

LITERATURE
REVIEW

FEATURES OF TREATMENT OF FOCAL EPILEPSIA IN ADULTS

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Now it is quite difficult to determine the true cause of the development of epilepsy. This is especially true of idiopathic and cryptogenic forms, which develop for no apparent reason. In such a process, there are no changes in the brain, or other conditions that can trigger the development of pathology. If there is an idiopathic form of epilepsy, the patient is supposed to get a disability. This is due to the fact that this disease leads to a significant limitation of a person in his work activity. We will not expand on how epilepsy is treated in the complex, because with each individual focal diagnosis the doctor prescribes his own set of drugs. But we will only talk about general principles. So, in most cases, the disease can be cured without surgery, only medicamentously. This does not mean, however, the rejection of social and therapeutic assistance, without which it will be difficult for a person to adapt in the society.

Keywords: focal epilepsy, seizures, antiepileptic drugs, therapeutic drug monitoring.

Epilepsy is a chronic disease of the brain, the main manifestation of which are epileptic seizures. Advances in the treatment of epilepsy are achieved by improving the diagnosis of various forms of the disease and individualization of therapy. Focal epilepsy, the clinical core of which is focal seizures, including those with impaired consciousness and secondary generalization, is the most common form of the disease in adults - up to 60-70% of cases, about half of which have temporal epilepsy [1]. There is a symptomatic focal epilepsy caused by brain damage of a known organic nature, and presumably symptomatic (cryptogenic). Diagnosis of focal epilepsy includes the following stages, allowing to verify the diagnosis and assess the patient's health [2]:

- 1) the study of the seizure seizures;
- 2) anamnesis collection;
- 3) study of neurological and somatic status;
- 4) neuropsychological testing (assessment of the cognitive and emotional-emotional sphere);
- 5) electroencephalographic studies, including video electroencephalography;
- 6) neuroimaging (magnetic resonance imaging of the brain, including with the use of regimes that allow to optimize the diagnosis of hippocampal lesions and heterotopia of gray matter);
- 7) laboratory studies (clinical and biochemical analysis of blood, ultrasound examination of internal organs).

Only after confirming the epileptic nature of

seizures and diagnosing epilepsy does the doctor determine the tactics of the patient's management. The goal of epilepsy treatment is to save the patient from attacks and improve the quality of life. In patients with rare seizures (less than 1 per year), one can refrain from prescribing antiepileptic drugs (PAD) [3], explaining to the patient the importance of compliance with sleep and rest, refusal of alcohol. In some cases, when an epileptogenic focal brain lesion is detected (according to the methods of neuroimaging), treatment begins after the first attack. According to international and Russian recommendations, treatment for the first time diagnosed epilepsy begins in the monotherapy regime. In Uzbekistan, as the monotherapy of the first line in focal epilepsy, the following PADs were recorded: basic (carbamazepine, valproate), a new generation of PAD (lamotrigine, oxcarbazepine, topiramate, levetiracetam, gabapentin). Pregabalin, lacosamide is registered in our country as an additional therapy. "The old" PAD (barbiturates, diphenine) are not drugs of the first order of choice. Antiepileptic drugs of the new generation differ from the basic and "old" drugs with better tolerability [2,4,5]. The choice of PET should be based on data on efficacy, tolerability, side effects, pharmacokinetics, pharmacodynamics, mechanisms of action, inter-drug interactions, the rate of titration (the speed of reaching the required doses) of the PET, as well as patient data (age, sex, comorbid pathology). As a rule, PAD is prescribed in minimal

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doses with subsequent increase. Observance of the recommended regimens of titration of doses of drugs is extremely important for achieving good tolerability and, as a consequence, compliance – patient compliance with medical recommendations. In some patients with frequent seizures, especially in hospital settings, it is possible to force the titration of the PAD [6]. With insufficient effectiveness or poor tolerance of monotherapy, the first line of the patient is transferred to a second line monotherapy. Only in the absence of effect or poor tolerance of 2-3 drugs in the monotherapy regimen, duotherapy is recommended, and later on in certain cases simultaneous administration of three PADs is also acceptable [7].

Drug Interactions. Ineffectiveness of drug therapy is the reason for the patient's additional examination, revision of the diagnosis. The general algorithm for assigning a PET is shown in different sources [8]. Rational duotherapy helps to increase the effectiveness of treatment and minimize dose-related side effects. Choosing duotherapy, the doctor should remember the mechanisms of action of the PAD, the summation of side effects, the possibility of interaction of the PAD with each other and with other medicines. Inter-drug interactions are most often realized through the induction and inhibition of hepatic enzymes involved in drug metabolism. For example, carbamazepine, phenobarbital, phenytoin are powerful inducers of hepatic enzymes, reduce plasma levels in many drugs. Levetiracetam, gabapentin, pregabalin, lacosamide are not metabolized in the liver, do not affect hepatic enzymes and therefore have an almost perfect pharmacokinetic profile [1,3,9]. Consider the problem of inter-drug interactions on the example of lamotrigine. Lamotrigine is metabolized in the liver by glucuronization with the enzyme glucuronosyltransferase (UGT1A4). The concentration of lamotrigine in the blood plasma increases with the simultaneous administration with valproate - a glucuronidation inhibitor [4,10], but decreases under the influence of phenytoin, carbamazepine, phenobarbital, primidon - inducers of glucuronidation. Thus, the combination of valproate with lamotrigine allows to reach the effect by using smaller doses than in monotherapy.

Therapeutic drug monitoring. At present, the

method for determining the concentration of PAD in biological fluids, in particular in blood plasma and saliva, called therapeutic drug monitoring (TDM), is becoming more accessible. Therapeutic drug monitoring is a reliable method of assessing compliance and individual pharmacokinetic parameters in patients with epilepsy [11]. The use of TDM allows studying intra-individual changes in different clinical situations, comparing the obtained data with the recommended allowable concentrations (formerly used the term "therapeutic concentrations") for all PADs. The recommended allowable concentrations have been established on the basis of numerous studies. It is shown that when finding the concentration values within the indicated corridor, the majority of patients note a combination of efficacy with good tolerability [12]. Indications for carrying out TDM in the application of various PADs are as follows [7]:

- establishing an individual therapeutic concentration when a satisfactory clinical effect is achieved. Knowledge of this parameter will allow further in the event of the possible appearance of endogenous (body mass fluctuations, development of somatic pathology, etc.) and exogenous (the need for taking other medications, etc.) factors to correct treatment;
- confirmation of the toxic effects of drugs, which is expected on the basis of identifying the characteristic clinical symptoms;
- checking compliance (adherence to treatment), especially with resistant seizures or disruption of drug remission;
- control of the concentration of the drug in the blood in clinical cases associated with potential pharmacokinetic variability (in children, the elderly, patients with concomitant diseases, with a change in the dosage form of the drug - for example, the use of generics);
- monitoring the concentration of the drug in the blood in situations where it is expected to be an obligate change, for example, during pregnancy, with polytherapy;
- control of the concentration of drugs with non-linear pharmacokinetics (phenytoin). On the basis of a comparison of the characteristics of the pharmacokinetics of PAD, the following groups of drugs are distinguished, depending on the degree of

necessity of TDM on the background of their administration:

- TDM is necessary - carbamazepine, phenobarbital, phenytoin;
- TDM is recommended - ethosuximide, lamotrigine, oxcarbazepine, valproate;
- TDM is useful, especially if there is a further increase in the dose of the drug, - topiramate;
- TDM is probably useful - levetiracetam, gabapentin.

Pregnancy, lactation and labour period with epilepsy. Among patients with epilepsy, special categories are identified that require a special approach - women of childbearing age and elderly patients [2,8]. When choosing a PAD for women of childbearing age, the following aspects should be taken into account: the interaction of PAD and oral contraceptives, teratogenicity of PAD, changes in plasma PAD concentrations during pregnancy, and the ability of PAD to cause postnatal cognitive deficits in children. Since most of the estrogen component of oral contraceptives is hydroxylated by the enzyme CYP3A4, the received PAD inducers of this enzyme reduce the effectiveness of hormonal contraception. If translation into PAD without enzyme-inducing properties is not possible, reception of contraceptives containing at least 50 µg of the estrogen component or the rejection of hormonal contraception is recommended [6,7,11]. The 18% decrease in the concentration of synthetic progesterone under the influence of lamotrigine has no clinical significance. Activation of glucuronidation of lamotrigine under the influence of the progesterone component of oral contraceptives leads to a decrease in its level in blood plasma on the days of taking contraceptives as compared to the level on days without hormones, and such fluctuations can trigger an attack [12]. Teratogenicity of PAD is assessed as data on pregnancy registries of women with epilepsy are accumulated, since controlled studies are impossible for ethical reasons. To date, there are data on the increase in the frequency of large abnormalities of development in 2-3 times against the background of valproate (dose-dependent effect). The frequency of developmental abnormalities rises to 10% on the background of polytherapy. The dose-dependent effect of lamotrigine on the frequency of developmental abnormalities

and, probably, the teratogenic effect of topiramate is determined. Disruption of drug remission during pregnancy can be associated with increased clearance of PAD, vomiting, weight gain [1,2].

Therefore, the increase in the clearance of lamotrigine, phenytoin, oxcarbazepine, levetiracetam during pregnancy is described, which requires correction of the doses of the drugs. Measurement of the level of intelligence in children aged 2 years and older, born of mothers who took PAD during pregnancy, made it possible to evaluate PAD for the ability to cause a postnatal cognitive defect [5,9]. It has been shown that valproate is probably associated with a cognitive deficiency, phenytoin and phenobarbital may be associated with cognitive deficits, and carbamazepine probably does not cause cognitive deficits in children [4,10]. Undoubtedly, the received data require specification, but the doctor should do everything possible to minimize the risk of negative impact of the PAD. The allocation of elderly epilepsy patients to a special group is due to the following pharmacokinetic features [8,12]:

- Decreased bioavailability of drugs (mainly due to impairment of absorption);
- increasing in the content of the free fraction of the PAD due to the reduction of the fraction associated with the protein;
- increasing in the plasma levels of metabolized drugs due to a decrease in enzyme activity;
- increasing in the level of plasma in the blood of the kidneys, due to a decrease in clearance.

Initial doses of PAD in epilepsy patients, as a rule, are therapeutic. The rarity of the development of resistant to therapy seizures in the elderly allows you to lead patients on monotherapy [5]. Naturally, the optimal PAD for the elderly should not have a negative effect on the work of the heart and other internal organs, on the cognitive and other functions of the brain, and interact with other drugs. According to the recommendations of the International Antiepileptic League (based on data from randomized clinical trials), gabapentin and lamotrigine are the drugs of choice for the therapy of newly diagnosed epilepsy in the elderly. Unfortunately, up to 30% of patients with epilepsy are resistant to PAD [6].

Autonomous nerve system and seizures.

Resistance can be observed from the onset of the disease or form during the course of the illness [13]. When establishing resistance, the question arises of choosing non-drug therapies: vagal stimulation or surgical intervention on the brain. Stimulation of the vagus nerve consists of subcutaneous implantation of the device that generates pulses and the connection of the electrodes to the left vagus nerve [1,8,12]. The mechanism of action of vagus nerve stimulation is not completely clear, presumably, it is associated with activation of the reticular formation of the brain stem. In 1/3 patients with resistant seizures, their frequency decreases by more than 50%. Patients during an aura can change parameters of stimulation, preventing further development of an attack. Recently, the methods of surgical treatment of epilepsy have been improved [2,13]. In patients with mesial temporal epilepsy and hippocampal sclerosis, anterotemporal resection with

hippocampectomy is successfully performed. As is known, in 50% of patients with this form of epilepsy there are attacks resistant to drug treatment. After the operation, 60% of patients have no seizures, even in the face of cancellation of PAD, in 20% of patients the frequency of seizures is significantly reduced, 10% of patients have no positive effect, and 10% have worsened. No less successful is focal cortical resection, including extra-temporal resection, leading to the absence of seizures in 40-60% of patients [6,7,10]. Multiple subpial transections are more palliative, but in combination with focal cortical resection, good results have also been obtained. Methods are being developed to stimulate the anterior thalamus nuclei, radiosurgery technology using a gamma knife. Thus, managing patients with epilepsy is a complex and painstaking work over many years, requiring the interaction of the doctor and the patient [5].

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XÜLASƏ

BÖYÜKLƏRDƏ FOKAL EPİLEPSİYANIN MÜALİCƏSİNİN XÜSUSİYYƏTLƏRİ

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Günümüzdə epilepsiyanın inkişafının həqiqi səbəbini təyin etmək kifayət qədər çətinidir. Bu xüsusilə epilepsiyanın hər hansı bilinməyən səbəbdən yaranan idiopatik və kriptogen formalarına münasibətdə özünü doğruldur. Belə vəziyyətlərdə beyində və ya digər orqanlarda bu patologiyanın inkişafına səbəb olan dəyişikliklər olmur. Əgər epilepsiyanın idiopatik forması varsa, pasiyent əlillik qrupu almalıdır. Bu onunla əlaqədardır ki, bu xəstəlik insanın

əmək fəaliyyətini əhəmiyyətli dərəcədə azaldır. Biz epilepsiyanın kompleks müalicəsi haqda danışmayacağıq, çünki hər individual fokal diaqnozla həkim özünün seçdiyi preparatlardan istifadə edir. Amma biz ümumi prinsiplərdən söhbət açacağıq. Beləliklə, əksər hallarda xəstəliyi cərrahi müdaxilə olmadan, medikamentoz yolla müalicə etmək olar. Amma sosial və terapeutik yardımsız xəstələrin cəmiyyətdə adaptasiyası mürəkkəb olduğundan, bu metodları da kompleks müalicəyə daxil etmək lazımdır.

Açar sözlər: fokal epilepsiya, qıcolmalar, epilepsiyaəleyhi preparatlar, terapeutik dərman vasitəsinin monitorinqi..

РЕЗЮМЕ

ОСОБЕННОСТИ ЛЕЧЕНИЯ ФОКАЛЬНОЙ ЭПИЛЕПСИИ У ВЗРОСЛЫХ

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Сейчас довольно сложно определить истинную причину развития эпилепсии. Это особенно верно в отношении идиопатических и криптогенных форм, которые развиваются без видимой причины. В таком процессе нет изменений в мозге или других состояний, которые могут спровоцировать развитие патологии. Если существует идиопатическая форма эпилепсии, пациент должен получить инвалидность. Это связано с тем, что это заболевание приводит к значительному ограничению человека в его трудовой деятельности. Мы не будем раскрывать, как эпилепсия лечится в комплексе, потому что с каждым индивидуальным фокальным диагнозом врач предписывает свой собственный набор лекарств. Но мы будем говорить только об общих принципах. Таким образом, в большинстве случаев болезнь можно вылечить без хирургического вмешательства, только медикаментозно. Это не означает, однако, отказ от социальной и терапевтической помощи, без которой человеку будет сложно адаптироваться в обществе.

Ключевые слова: фокальная эпилепсия, судороги, противоэпилептические препараты, мониторинг терапевтического лекарственного средства.

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