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ALTERNATIVE AND ADJUNCTIVE THERAPIES FOR PHARMACORESISTANT EPILEPSY IN CHILDREN AND ADULTS: CURRENT STATE OF THE PROBLEM

Abstract. This article presents an analytical review of alternative and adjunctive treatment strategies for epilepsy in children and adults resistant to standard antiepileptic drug therapy. Dietary approaches (including classical and modified ketogenic diets), vagus nerve stimulation, neurosurgical interventions, hormonal therapy, intravenous immunoglobulins, antiviral agents, and non-pharmacological methods such as psychotherapy, biofeedback, acupuncture, phytotherapy, homeopathy, and aromatherapy are discussed. Indications, contraindications, efficacy, and limitations of each approach are analyzed from the perspective of evidence-based medicine. The review demonstrates that an individualized multimodal strategy incorporating alternative therapies may significantly improve seizure control and quality of life in patients with pharmacoresistant epilepsy.

Key words: epilepsy; pharmacoresistance; alternative therapy; ketogenic diet; vagus nerve stimulation; neurosurgery; immunoglobulins; children

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АЛЬТЕРНАТИВНЫЕ И АДЪЮВАНТНЫЕ МЕТОДЫ ЛЕЧЕНИЯ ФАРМАКОРЕЗИСТЕНТНОЙ ЭПИЛЕПСИИ У ДЕТЕЙ И ВЗРОСЛЫХ: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ

Аннотация. В статье представлен аналитический обзор альтернативных и адъювантных методов лечения эпилепсии у детей и взрослых, резистентных к стандартной противоэпилептической фармакотерапии. Рассмотрены диетотерапия (включая классическую и модифицированную кетогенные диеты), стимуляция блуждающего нерва, нейрохирургические вмешательства, гормональная терапия, внутривенное введение иммуноглобулинов, противовирусные препараты, а также немедикаментозные подходы — психотерапия, биологическая обратная связь, акупунктура, фитотерапия, гомеопатия и ароматерапия. Проанализированы показания, противопоказания, эффективность и ограничения каждого метода с позиций доказательной медицины. Показано, что комплексный индивидуализированный подход с использованием альтернативных методов способен улучшить контроль приступов и качество жизни пациентов с фармакорезистентной эпилепсией.

Ключевые слова: эпилепсия; фармакорезистентность; альтернативная терапия; кетогенная диета; стимуляция блуждающего нерва; нейрохирургия; иммуноглобулины; дети

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BOLALAR VA KATTALARDA FARMAKOREZISTENT EPILEPSIYANI DAVOLASHDA MUQOBIL VA QO'SHIMCHA USULLAR: MUAMMONING HOZIRGI HOLATI

Annotatsiya. Maqolada bolalar va kattalarda standart antiepileptik dori vositalariga chidamli epilepsiyani davolashda muqobil va qo'shimcha terapevtik yondashuvlarning tahliliy sharhi keltirilgan. Parhez terapiyasi (klassik va modifikatsiyalangan ketogen dietalar), adashgan nervni stimulyatsiya qilish, neyroxirurgik usullar, gormonal davolash, vena ichiga immunoglobulin yuborish, antivirus preparatlari hamda dori-darmonlarsiz yondashuvlar — psixoterapiya, biofeedback, akupunktura, fitoterapiya, gomeopatiya va aromaterapiya muhokama qilinadi. Har bir usulning ko'rsatmalari, cheklovlari va samaradorligi dalillarga asoslangan tibbiyot nuqtai nazaridan baholanadi. Individual va kompleks yondashuv farmakorezistent epilepsiyada tutqanoq nazoratini va hayot sifatini yaxshilashi mumkinligi ko'rsatilgan.

Kalit so'zlar: epilepsiya; farmakorezistentlik; muqobil davolash; ketogen dieta; adashgan nerv stimulyatsiyasi; neyroxirurgiya; immunoglobulinlar; bolalar

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Introduction. The problem of epilepsy treatment has been one of the most pressing issues in neurology for many decades. Various aspects of drug treatment of this disease have been extremely widely presented in the periodical press since the 1970s [1-3]. At the same time, the most important task for domestic and foreign researchers is the search and development of new and/or alternative methods of therapy. This is explained by the significant number of patients suffering from epileptic syndromes resistant to conventional drug treatments. In the USA alone, by the beginning of the 21st century, there were from 500 to 800 thousand patients with refractory epilepsy [4]. Apparently, in the Russian Federation the number of patients with these conditions is quite comparable with the epidemiological data of American researchers. In modern pharmacology, it is difficult to find any drug that has not been tried in the past in the treatment of epilepsy. Currently, the list of antiepileptic drugs (AEDs) officially approved and used in the treatment of epilepsy is significantly limited [5-8].

The situation is similar with alternative therapies for epileptic seizures. Many of them, despite their past use, are now of merely historical interest. An example is electroconvulsive therapy (ECT) for epilepsy, used in the first half of the 20th century but long since consigned to history and no longer in clinical use. Having summarized all the alternative therapy options for epilepsy presented in modern literature, we should list 9 main approaches, of which at least 6 are non-drug: 1) diet therapy (use of ketogenic and other diets), 2) stimulation of the vagus nerve ("vagal stimulation"), 3) neurosurgical methods, 4) administration of steroid hormones, 5) use of intravenous human immunoglobulins, 6) antiviral agents, 7) acupuncture, 8) psychotherapy, 9) homeopathic preparations, phytotherapy and aromatherapy [2-4, 9].

It should be noted that alternative methods of treating epilepsy have clearly defined indications and, accordingly, contraindications for their use.

Ketogenic diets (KD)are the main (and practically the only) dietary method of treating epilepsy in children [10]. The classical ketogenic diet, proposed by RM Wilder et al. over 80 years ago, is based on inducing a state of ketoacidosis in the body by providing the caloric content of the diet almost exclusively due to the fat component [11]. The so-called "liberalized" version of the ketogenic diet was developed in the 1970s by PR Huttenlocher et al. (1971). It differs from the Wilder diet by using medium-chain triglycerides (MCT) as the main source of fat, as well as by an almost physiological content of proteins and carbohydrates in the diet [12]. The specific mechanisms by which the antiepileptic properties of ketogenic diets are realized remain unclear, although it is assumed that a certain role (in addition to the actual state of ketosis and acidosis) belongs to dehydration, as well as a number of metabolic and endocrine factors [13]. The pronounced positive effect of the ketogenic diet in epilepsy in children resistant to other treatments has been confirmed by numerous studies in various countries [14, 15]. However, the advantages and disadvantages of both types of ketogenic diets remain a subject of debate. In any case, if these diets are successfully used, the therapeutic diet should be followed for at least 1-2 years (during which time AEDs can be completely discontinued) [9]. In the Russian Federation, the first experience with the use of KD in the treatment of resistant epilepsy in children has been obtained, the results of which are quite satisfactory [16]. Contraindications to the use of ketogenic diets include the simultaneous administration of valproic acid, which significantly limits the possibility of using this method of dietary therapy [10]. The economic feasibility of using ketogenic diets is confirmed by a number of relevant publications [17].

Prescribing the so-called "oligoantigenic" (intensely hypoallergenic) diet to children with both epilepsy and migraine may result in improved control of epileptic and migraine attacks [9]. It remains unclear how this diet reduces the frequency of these attacks. It is suggested that the therapeutic effect may be related to neurotransmitter-like substances present in foods and/or resulting from the gastrointestinal tract's reaction to certain foods. It is interesting to note that attempts to detect elevated IgE antibody levels in patients with epilepsy/migraine and skin testing usually do not yield positive results. The oligoantigenic diet (like the ketogenic diet) is quite expensive, and careful monitoring by a neurologist and nutritionist is required when following it.

Vagal stimulation. The introduction of this therapeutic method provided a new non-pharmacological approach to the treatment of epilepsy [18]. Electrical stimulation of the left vagus nerve using a special implantable device is a new method for the treatment of drug-resistant epilepsies. By 2001, the Neuro Cybernetic Prosthesis system had been implanted in more than 7,500 patients worldwide, with the total treatment duration exceeding 8,000 so-called "patient-years." The use of vagus nerve stimulators is approved in the USA, Canada, and 16 countries of the European Community. In German-speaking countries, more than 300 stimulators had been implanted by 2001 [19]. The use of vagal stimulation (VNS - short for "vagal nerve stimulation") is recommended for adult patients and children over 12 years of age with partial epileptic seizures resistant to AEDs [18]. In some cases, this method is effective against generalized seizures. Like pacemakers used in cardiology, vagus nerve stimulators are implanted in the chest below the clavicle. The vagus nerve can be stimulated at a frequency of approximately once every 5 minutes for 30 seconds [4]. In some epileptology centers in Europe, the anticonvulsant effect of stimulators has been confirmed, which turned out to be comparable in effectiveness to new AEDs (lamotrigine, topiramate, gabapentin,

tiagabine). In 30% of patients, a decrease in the frequency of epileptic seizures by more than 50% was noted [19]. Recent publications have emphasized the undoubted effectiveness of vagus nerve stimulation in children [20, 21]. Vagal stimulation is considered safe and well-tolerated. Despite the high initial cost of the equipment, it is believed that this treatment method fully pays for itself within 2-3 years [19].

Neurosurgical methods. Surgical correction plays an increasingly important role in the treatment of epilepsy. Currently, there are four main types of neurosurgical interventions for epilepsy: 1) removal of one lobe, usually temporal (temporal lobectomy); 2) removal of the cortex (topectomy); 3) removal of a cerebral hemisphere (hemispherectomy); 4) separation of the hemispheres by transection of the corpus callosum [4]. The most common neurosurgical operation is temporal lobectomy, which is resorted to when the patient has confirmed mesial temporal sclerosis. As a result, approximately 75% of patients achieve control over epileptic seizures. Hemispherectomy is performed in patients with severe damage to one of the cerebral hemispheres (with comparative preservation of the contralateral hemisphere). Corpuscallosotomy is clinically effective in cases where patients have multifocal brain damage with rapid spread of epileptic activity from one hemisphere to the other [4, 22].

In chronic focal encephalitis (Rasmussen syndrome), hemispherectomy is effective [2]. Various literature sources indicate the feasibility and proven effectiveness of the following neurosurgical intervention options for certain types of epilepsy: 1) anterior temporal lobectomy, 2) limited temporal resection, 3) extratemporal neocortical resection [22-24].

MJ Brodie and SC Schachter (2001) list four types of neurosurgical treatments for different types of epilepsy: 1) focal resection (indications: partial-onset epileptic seizures originating in the resected area of the cerebral cortex); 2) corpuscallosotomy (indications: tonic, clonic, or tonic-clonic seizures with falls and physical injuries, large lesions that cannot be resected, and secondary bilateral synchrony); 3) hemispherectomy (indications: Rasmussen syndrome or other types of unilateral pathology of the cerebral hemispheres associated with functional impairment in the contralateral upper limb); 4) subpial transections (indications: partial-onset epileptic seizures originating in the area of the cerebral cortex that cannot be resected) [18]. Until the 1990s, neurosurgical treatment of epilepsy remained limited, but recently it has become increasingly used in treatment-resistant epilepsies in patients of any age [4].

Steroid hormones. Despite the lack of a clearly established autoimmune basis in the development of epilepsy, steroid hormones have found use in the treatment of certain types of epilepsy resistant to traditional treatment, including West and Lennox-Gastaut syndromes, severe infantile myoclonus epilepsy, and Landau-Kleffner syndrome [2, 3, 9]. Prednisolone (at a dose of 2-6 mg/kg/day) or adrenocorticotropic hormone (ACTH) at a dose of 10-120 IU/day intramuscularly can be administered in various regimens (at intervals from several weeks to several months). In this case, ACTH (or Synacthen-depot, its synthetic analogue) is considered preferable to prednisolone, since its molecule itself can function as a specific antiepileptic neuropeptide and also stimulate the production of endogenous corticosteroids in the body [5, 9]. Steroid hormones are known to suppress infantile spasms in 50-60% of children, but their effectiveness in other types of epilepsy is much less impressive [9, 25, 26]. The disadvantage of ACTH therapy is that at least daily intramuscular injections are

required. In addition, ACTH and corticosteroids (prednisolone, betamethasone, hydrocortisone) often cause numerous and potentially serious side effects [27]. Currently, a whole group of neuroactive steroids with an antiepileptic focus is being developed [9]. One of them is ganaxolone (epalon is short for epiallopregnanolone), which is expected to be useful in the treatment of partial seizures and infantile spasms, without having any of the side effects inherent in ACTH or prednisolone [9, 27]. Since the age category of patients with epilepsy observed by pediatricians extends up to 18 years, progesterone, which can be used in girls who have reached puberty, deserves some attention among other (non-steroidal) hormones. As K. Yu. Mukhin (1996) points out, the pronounced positive effect of oxyprogesterone capronate on the course of epileptic seizures allows us to recommend this drug as an adjunct to anticonvulsant therapy in the treatment of resistant forms of menstrual (catamenial) epilepsy [28]. Oxyprogesterone capronate (12.5% solution) is recommended to be administered 1-2 ml intramuscularly on the 20th-22nd day of the menstrual cycle [29]. The advisability of this approach is confirmed by observations of other researchers [30].

Immunoglobulins for intravenous administration. Experimental data indicate that epileptic seizures can be induced by neuronal antibodies [9]. Therefore, immune status disturbances in epilepsy, as well as the possible autoimmune nature of the disease, are no longer a revelation for neurologists and epileptologists [31]. Donor immunoglobulins contain antibodies directed against various autoantibodies (AAB), which (theoretically) can “switch off” the expected production of neuronal AAB. In addition, like steroid hormones, immunoglobulins are capable of exerting a non-specific immune effect that reduces the frequency of seizures [25]. The rapid response observed in some patients to high doses of intravenous immunoglobulins suggests that the described therapy has a direct antiepileptic effect, independent of any influence on the immune system [31]. The effectiveness of high-dose immunoglobulin administration can be expressed in achieving 30% clinical remission, as well as in a 30% reduction in the number of epileptic seizures. Infusions of intravenous immunoglobulins are successfully used in Lennox-Gastaut syndrome and a number of other refractory epilepsies [31]. Single doses, ranging from 100 to 1000 mg/kg/day, are usually repeated at intervals of 1-3 weeks. The total duration of therapy is determined empirically. It is assumed that if a clinical effect is not recorded after 3 single infusions, then it is unlikely to be achieved in the future [9]. Children with confirmed deficiency of the 2nd subclass of IgG and IgA receive obvious benefit, although most "responder" patients (those responding to therapy) do not have any obvious signs of immune dysfunction [9, 31]. When using immunoglobulins, one should keep in mind their relatively high cost and the potential (albeit rare) risk of developing anaphylactic reactions or transmitting specific infections with these blood products [9]. The development and industrial production of domestic immunoglobulins for intravenous administration makes it possible to reduce the cost of treatment [32, 33]. Antiviral drugs (acyclovir, etc.) are significantly effective in treating certain types of epilepsy that develop as a result of viral infection (primarily, herpes viruses of various types). In the works of I.I. Protas et al. (1993, 2000), it is indicated that although the incidence of chronic herpes encephalitis of the Rasmussen type among adults is quite low, it is much more common in the child population [34, 35]. Although there is currently no consensus regarding the etiology of Rasmussen's syndrome, data on attempts to include antiviral drugs in the complex therapy of this condition, accompanied by the achievement of a clear clinical effect, have been published repeatedly [36]. In particular,

RSMacLachlan et al. (1996) reported the successful use of ganciclovir in the treatment of this epileptic syndrome [37].We have our own experience of successful use of acyclovir in Rasmussen syndrome, which resulted in the achievement of stable and long-term remission [38]. Antiviral treatment should be carried out while continuing the selected background therapy (using traditional and/or new AEDs). Acupuncture. Despite the general concept of abandoning most of the available physiotherapy methods for paroxysmal conditions (including epilepsy), acupuncture continues to be used for this disease. The presence in the available literature of only isolated reports on the use of acupuncture in the treatment of epilepsy does not allow us to draw any conclusions regarding the effectiveness of this therapy or the indications for its use [9]. Suppression of epileptic activity in laboratory animals during electroacupuncture can be explained by increased recurrent inhibition of the cerebral cortex, as well as the hippocampus, with the release of various neurotransmitters, including GABA (gamma-aminobutyric acid) and serotonin [39]. Psychotherapy (behavioral therapy). Behavioral therapy, which is the most widespread of all known psychotherapeutic methods, deserves special attention in neuropediatrics [9]. As M. Ya. Vayntrub (2000) points out, an important role in the psychotherapy of epilepsy is played by the patient's characterological features, their changes in the patient, as well as strong psychological contact with the physician (and the physician with the patient and his relatives) [40]. The main methods of behavioral therapy are usually divided and considered as part of 3 main categories: 1) reward/punishment; 2) self-control; 3) biological feedback (BFB) [9, 41]. The first category of psychotherapeutic methods can be used in patients of any age (with any level of intellectual development) and is indicated for: 1) self-induced seizures and 2) the so-called "reflex" epilepsies (seizures provoked by sensory stimuli) [40, 41]. The self-control method (including relaxation and independent termination of the seizure) is feasible only in patients over 5-6 years of age, is difficult to apply to individuals with significant learning disabilities and is indicated for: 1) self-induced seizures; 2) reflex epilepsies; 3) epileptic seizures that intensify under the influence of emotional factors (e.g., anxiety, etc.) [41]. Biofeedback (based on the principle of self-modification of one's own EEG data) is used in the same intellectually intact categories of patients as the self-control method, namely: 1) reflex epilepsies; 2) epileptic seizures that intensify against the background of changes in emotional status [9]. In the Department of Psychoneurology of the Research Institute of Pediatrics of the Scientific Center for Children's Health of the Russian Academy of Medical Sciences, the computer biofeedback device has found clinical application since 2002. Phytotherapy (the so-called "herbalism"), homeopathy and aromatherapy. These very controversial and ambiguous methods of treating epilepsy are considered in one group of therapeutic strategies by R. Appleton and J. Gibbs (1998) [9]. This group of therapeutic methods provides, respectively: oral administration of herbal preparations; the use of extremely small doses of those drugs that, when taken in large quantities, can cause epileptic seizures; the use of odors to reduce the frequency of epileptic seizures. It is indicated that none of the above methods can be recommended for the treatment of epilepsy, since to date no controlled clinical studies have been conducted to determine their potential effectiveness [9]. Aromatherapy may be useful (for achieving a state of relaxation) as a component of behavioral therapy. Nevertheless, the aromas of camphor, hyssop (pharmacy), sage, and rosemary should be strictly avoided, since it is known that these substances can lead to a deterioration in the condition of patients and an increase in the frequency of seizures [9]. Such treatments should be approached with caution, as the

epileptological training and experience of some physicians practicing them are often inadequate, potentially leading to a worsening of epilepsy. It should be noted that in some cases, the combined or isolated use of homeotherapy, herbal medicine, and aromatherapy can usually achieve positive results, but the so-called "placebo effect" cannot be ruled out.that in a number of cases, the combined or isolated use of homeotherapy, phytotherapy and aromatherapy methods usually allows for a positive result to be achieved, but the so-called “placebo effect” cannot be ruled out.that in a number of cases, the combined or isolated use of homeotherapy, phytotherapy and aromatherapy methods usually allows for a positive result to be achieved, but the so-called “placebo effect” cannot be ruled out.

Conclusion. As can be seen from the presented data from the domestic and international literature, many issues related to the treatment of epilepsy in children and adults using alternative therapeutic approaches remain unresolved. Some of these approaches are not widely used due to their high cost, while the effectiveness of others has not been confirmed by evidence-based medicine [42-44]. It is hoped that in the near future, adequate alternative therapeutic methods will be able to take their rightful place in the arsenal of treatment strategies for epilepsy, the most common paroxysmal disorder of brain function. Ignoring alternative treatments for refractory epilepsy in children is tantamount to abandoning therapeutic measures. Such tactics inevitably lead to a decrease in the quality of life and a deterioration in the health of patients, which is extremely difficult to justify.

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