IJIMM, Volume 3, Issue 2, 2025 ISSN: 2995-5319
http://medicaljournals.eu/index.php/IJIMM/issue/view/3

INTERNATIONAL JOURNAL OF INTEGRATIVE AND MODERN MEDICINE

Generalized Epilepsies: Modern Concepts and Therapeutic Approaches

Khudoyorova Dilnoza Rizoevna
Department of Internal Medicine and Endocrinology Bukhara State Medical Institute named after Abu Ali ibn Sina

Rajabov Hikmat Toshevich
Department of Psychiatry, Medical Psychology and Narcology of the Samarkand State Medical University

Annotation: In recent years, the concepts of generalized epilepsy have undergone significant changes: focal features have been identified in generalized epilepsies and typical features of idiopathic generalized epilepsies in focal epilepsies. The closeness of these forms is also confirmed by genetic studies, when a variety of focal and generalized phenotypes are observed in different members of the same family with one genetic disorder. In this regard, the Terminology and Classification Commission of the International League Against Epilepsy (ILAE) proposes to abandon the distinction between epilepsy forms based on the focal-generalized principle, replacing it with the concept of a neural network involving various local and general mechanisms of the brain in each individual case. These neuropathophysiological concepts explain the reasons for the ineffectiveness and sometimes even aggravation of the severity of the disease of pharmacotherapy based on the focal-generalized seizures model. The modern approach makes it preferable to choose a drug with a broad spectrum of action (helping with any types of seizures and forms of epilepsy) taking into account its effectiveness, dose titration rate, dosage form, side effects and cost. Among the drugs with a broad spectrum of action (valproate - VPA, levetiracetam, lamotrigine, topiramate) as the first choice for the initial treatment of generalized epilepsies, the original forms of VPA with controlled release of the active substance - Depakine Chrono and Depakine Chronosphere are priority. The main pharmacokinetic and pharmacodynamic properties of drugs for the treatment of epilepsy and algorithms for the treatment of individual forms of generalized epilepsy are considered.

Keywords: SGeneralized epilepsies, valproate, carbamazepine, levetiracetam, topiramate, lamotrigine, generalized epilepsies, valproate, carbamazepine, levetiracetam, topiramate, lamotrigine.

The first decade of the 21st century was characterized by a significant enrichment of the clinical semiotics of epileptic syndromes and seizures, improvement of ideas about the mechanisms of development and specific clinical manifestations of epilepsy, development of a large number of new antiepileptic drugs (AEDs) and identification of new aspects of the action of already known ones. The ideas about the relationship between structural, neurodynamic and genetic factors in this disease were also enriched. All this forced us to reconsider the terminology, classification of epilepsies and syndromes, approaches to their pharmacotherapy, since the previously used paradigm of drug selection based on the dichotomy of "focal - generalized seizures" without taking into account the form of epilepsy, neurophysiological, genetic and other aspects is often not only ineffective, but also leads to aggravation of the disease. Systematization of new knowledge directly affects the effectiveness of clinical practice. The purpose of this publication is to systematize modern concepts of generalized epilepsies and, on this basis, formulate the principles and algorithms of their pharmacotherapy. Delayed speech and general development, attention deficit and hyperactivity, impaired emotions and behavior. In successive fragments of the recording over 40 s, an increase in the amplitude of centrotemporal spikes with the addition of bifrontal sharp waves is visible, then - the appearance of generalized bilaterally synchronous spike-wave complexes, serial bilaterally synchronous spike-wave complexes and, finally, patterns of typical absences, manifested by impaired consciousness

Evolution of the concept of generalized epilepsies.

According to the 1989 classification of epilepsies and epileptic syndromes, generalized epilepsy is defined as epilepsy in which all types of seizures are primarily generalized. In turn, seizures are considered primarily generalized if "the first clinical manifestations indicate initial involvement of both hemispheres; the initial electroencephalographic pattern associated with the seizure is also initially bilateral" [1, 2]. In this classification, generalized epilepsies are divided into idiopathic (i.e., having no cause other than genetic predisposition), symptomatic (associated with another brain lesion), and cryptogenic (i.e., "presumably symptomatic"). During 1999-2010, these positions were consistently revised by the working group of the Commission on Terminology and Classification of the International League Against Epilepsy (ILAE). The clinical-electroneurophysiological definition of a generalized seizure was clarified: “A generalized epileptic seizure is conceptualized as occurring at a specific point and rapidly involving bilaterally distributed neural networks. Such bilateral networks may include cortical and subcortical structures, but do not necessarily affect the entire cortex. Although the onset of individual seizures may appear localized, the localization and lateralization do not coincide from one seizure to another. Generalized seizures may be asymmetric” [3]. As for the etiology of “symptomatic generalized” syndromes, internal contradictions were found: 1) the definitions of some of them (West, Lennox-Gastaut syndromes, etc.) contained features and characteristics of focal forms; 2) for some other forms, data on their genetic nature were subsequently obtained. As a result, some of the "symptomatic generalized" epilepsies in further proposals of the MPEL commission were transferred to the idiopathic section (epilepsy with myoclonic-atonic seizures, epilepsy with myoclonic absences), and West and Lennox-Gastaut syndromes, along with a number of other forms, were transferred to a new heading: "epileptic encephalopathies". Thus, in reality, all primary generalized forms of epilepsy turned out to be idiopathic [4]. This subgroup currently includes: benign myoclonic epilepsy of infancy; epilepsy with myoclonic-atonic seizures; epilepsy with myoclonic absences; childhood and juvenile epilepsies with absences; juvenile myoclonic epilepsy; epilepsy manifested only by primary generalized tonic-clonic seizures; generalized epilepsy with febrile seizures+ and idiopathic generalized epilepsy with variable phenotypes. The latter variant is distinguished because in a significant number of cases of epilepsy initially classified as one of the generalized forms listed above, seizures characteristic of other variants may be observed as the disease progresses [4, 5].Along with this, facts of the closeness of focal and generalized idiopathic epilepsies were accumulating. One of the first to point out the possible origin of absences from the prefrontal cortex was V.V. Karlov, who later substantiated this position using the method of computer localization of sources on the electroencephalogram (EEG) [6]. Focal manifestations on the EEG in epilepsies with absences were also found in the medial temporal, occipital and premotor cortex [7, 8]. At the same time, cases and groups of patients with focal idiopathic epilepsies of childhood (occipital-lobar, rolandic) have been described, in which, in addition to typical focal seizures, clinical and electroencephalographic absences were observed [1, 9-14] (Fig. 1). It is important to note that in a significant number of cases such evolution (aggravation) of focal epilepsies occurs under the influence of treatment with some AEDs (carbamazepine, phenytoin, lamotrigine, vigabatrin, tiagabine, phenobarbital) [11, 12, 14-18]. It has been shown that these drugs lead not only to secondary generalization of focal idiopathic epilepsies and aggravation of idiopathic generalized epilepsies, but also to the addition of new types of seizures, epileptic status, cognitive disorders. Delayed speech and general development, attention deficit and hyperactivity, emotional and behavioral disorders. In successive fragments of the recording over 40 s, an increase in the amplitude of centrotemporal spikes with the addition of bifrontal sharp waves is visible, followed by the appearance of generalized bilaterally synchronous spike-wave complexes, serial bilaterally synchronous spike-wave complexes, and, finally, patterns of typical absences, manifested by impaired consciousness.disturbance of emotions and behavior. In successive fragments of the recording over 40 s, an increase in the amplitude of centrotemporal spikes with the addition of bifrontal sharp waves is visible, then the appearance of generalized bilaterally synchronous spike-wave complexes, serial bilaterally synchronous spike-wave complexes and, finally, patterns of typical absences, manifested by a disturbance of consciousnessdisturbance of emotions and behavior. In successive fragments of the

recording over 40 s, an increase in the amplitude of centrotemporal spikes with the addition of bifrontal sharp waves is visible, then the appearance of generalized bilaterally synchronous spike-wave complexes, serial bilaterally synchronous spike-wave complexes and, finally, patterns of typical absences, manifested by a disturbance of consciousnessdisorders [10]. Understanding the relationship between idiopathic focal and generalized epilepsies has been facilitated by genetic and neurophysiological studies in animals and humans. In rats with genetic absence epilepsy, a population of neurons with increased readiness for paroxysmal depolarization shifts and local epileptic discharges has been found in the orofacial cortex. The development of absence in them is preceded by the activation of these orofacial neurons with the appearance of spike-wave activity, spreading along the corticofugal pathways to the nonspecific nuclei of the thalamus and along the callosal fibers to the mirror area of the opposite hemisphere, resulting in the formation of a cortical-subcortical-cortical bilateral system that implements absence. Pharmacological blockade of hyperactive orofacial neurons makes absences impossible, which proves the primary cortical genesis of absence seizures [33, 34]. This model explains the occurrence of absences in childhood rolandic epilepsy in the best possible way. “Centrotemporal spikes” (orofacial cortex), which are included in the official name of this epilepsy (see Fig. 1) and manifested by orofacial seizures, can develop into typical absences according to the mechanism described above (Fig. 4). Additional data on the significant similarity of generalized and focal epilepsies were obtained as a result of genetic studies of families in which one mutant gene causes various phenotypic manifestations of focal and generalized epilepsy. The most impressive is the description of a family whose members suffered from autosomal dominant epilepsy, manifested by 11 phenotypes: idiopathic occipital early-onset; idiopathic occipital late-onset; idiopathic rolandic; temporal lobe; focal motor; multifocal; four forms of generalized epilepsy (juvenile myoclonic; childhood with myoclonic absences; childhood with absences; generalized with tonic-clonic seizures febrile seizures+) and an unclassified form of epilepsy [7]. Neuroimaging studies of idiopathic generalized epilepsies have revealed a significant number of anomalies in the microstructural development of the cortex [8]. All this forced us to reconsider the question of the relationship between "focal-generalized" and "idiopathic-symptomatic" epilepsies. Thus, the above data develop and enrich the well-known position that epilepsy is a manifestation of structural and functional reorganizations in the brain, affecting numerous centers and subsystems with short-range and long-range connections, and the occurrence of seizures and non-seizure psychoneurological manifestations is caused by complex neural networks implementing individual variants of the course of the disease. At the same time, on the same grounds, the MPEL working group postulated a number of rather unexpected provisions in the final document,which, as applied to the topic of this report, are as follows. The terms "localization-related (focal, partial)" and "generalized" are discarded, since many syndromes include both types of attacks. The term "idiopathic" is proposed to be excluded or replaced by the definition "genetic", but only in cases where EEG of a 22-year-old patient with juvenile myoclonic epilepsy. Seizures begin with twitching of the left arm and end with a generalized tonic-clonic seizure with loss of consciousness. Previously, treatment with finlepsin aggravated myoclonic seizures. Treatment with benzonal reduced myoclonic seizures, but did not affect generalized tonic-clonic seizures. The focus of epileptiform activity is in the premotor and frontopolar areas on the right (leads Ep2, E4, E8), corresponding to the onset of seizures in the left arm. On the right is a three-dimensional computer localization of epileptiform activity sources. During treatment with benzonal, discharges migrated, sometimes becoming bifrontal, sometimes moving to the left frontal area with seizures in the form of bilateral or right-sided myoclonus in the arms. Treatment with Depakine chrono resulted in remission of seizures and normalization of EEG. Application of the experimental model of the cortico-thalamocortical mechanism of generation of a generalized pattern of spike-wave activity to epilepsy with centrotemporal spikes with absences. Paroxysmal high-frequency discharges of epileptic neurons (similar to the population of epileptic neurons in the orofacial cortex of experimental animals), which are manifested by "centrotemporal spikes", spread along the corticofugal pathways to the nonspecific nuclei of the thalamus and along the callosal fibers to the mirror area of the opposite hemisphere, resulting in the formation of a cortical-subcortical-cortical bilateral system that implements absence

discharges confirmed by special genetic analysis. further for the sake of convenience and comfort is impossible."

This cardinal position naturally caused a negative reaction among some leading epileptologists, which was reflected in the discussion at the 29th International Congress on Epilepsy in Rome (2011), which was held under the appropriate title: "Challenges in the Development of a New Approach to the Classification of Epilepsy [2]". First of all, it should be noted that the principles of the 1989 classification organically correspond to the paradigm of clinical neurological thinking, reflecting two axes of diagnosis: localization and etiology. Considering that at least 100 forms of epilepsy and epileptic syndromes have been described to date, quite organically structured in the 1989 classification, which logically provides an overview of this set, the rejection of the general concept of this classification only because of the adoption of new terminology seems unjustified. The division into focal and generalized epilepsies has a clear therapeutic meaning, and the division by etiology, in addition, has an independent clinical practical value. One of the purposes of classification is to facilitate communication. The proportion of patients in the population receiving valproate and the proportion of patients with disease remission in the same population

References

1. Panayiotopoulous C.P. A clinical guide to epileptic syndromes and their treatment. Revised second edition based on the ILAE classification and practice parameter guidelines. Springer, 2010;620 p.
2. 29th International Epilepsy Congress. 28th August – 1st September 2011. Rome. Italy. Plenary Session. Challenges in developing a new approach for classification in epilepsy. Chairs: A. Berg & Capivola.
3. Berg A.T., Berkovic S.F., Brodie M.J. et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2011;52(6):1058–62.
4. Engel J.Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001;42:796–803. 5. Воронкова К.В., Холин А.А., Пылаева О.А. и др. Идиопатические генерализованные эпилепсии: современный взгляд. Фокальные черты идиопатических генерализо ванных эпилепсий. Medi.ru. Эпилепсия 2010;1:3–8.
5. Карлов В.А., Гнездицкий В.В. Абсансная эпилепсия у детей и взрослых. М.: Прессервис, 2005;63 с.
6. Зенков Л.Р. Клиническая эпилептология. Рук-во для врачей. Изд. 2-е, испр. и доп. М.: МИА, 2010;408 с.
7. Caraballo R.H., Fontana E., Darra F. et al. Childhood absence epilepsy and electroencephalographic focal abnormalities with or without clinical manifestations. Seizure 2008;17(7):617—24.
8. Cerminara C., Montanaro M.L., Curatolo P. et al. Lamotrigine-induced seizure aggravation and negative myoclonus in idiopathic rolandic epilepsy. Neurology 2004;63:373—5.
9. Gelisse P., Genton P., Bureau M. et al. Are there generalised spike waves and typical absences in benign rolandic epilepsy? Brain Dev 1999;21(6):390—6. 11. Hamano S., Mochizuki M., Morikawa T. Phenobarbital-induced atypical absence seizure in benign childhood epilepsy with centrotemporal.
10. Khudoyorova Dilnoza Rizoevna. (2023). Syndrome of Thyrotoxicosis, Approaches to Diagnosis and Treatment. American Journal of Pediatric Medicine and Health Sciences (2993-2149), 1(6), 81–86. Retrieved from
11. СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ ДР Худоёрова, ВКЭР ОЖИРЕНИЕAnalytical Journal of Education and Development 2 (10), 403-407 14 2022

12. САХАРНЫЙ ДИАБЕТ В УСЛОВИЯХ ВИРУСНОЙ ПАНДЕМИИ COVID-19ДР ХудоероваTA'LIM VA RIVOJLANISH TAHLILI ONLAYN ILMIY JURNALI 2 (10), 417-422
13. ИПОТИРЕОЗ И СЕРДЕЧНО-СОСУДИСТЫЕ ЗАБОЛЕВАНИЯ СОВРЕМЕННЫЙ ВЗГЛЯД НВ ПРОБЛЕМУ
14. ДР ХудойороваBARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI 2 (11), 160-165
15. Ризоевна, Х. Д. (2022). Ведение Лечения Диффузного Токсического Зоба У Пациентов С Эндокринной Офтальмопатией. Central Asian Journal of Medical and Natural Science, 3(6), 339-342.
16. Miller, N. & Kathryn, M. M. (Eds.) (1999) The Cost-Effectiveness of Psychotherapy: a Guide for Practitioners, Researchers, and Policymakers. Oxford, University Press. Minkoff, K. (2001)
17. Developing Standards of Care for Individuals with Co-occurring Psychiatric and Substance Use Disorders. Psychiatric Services52, 597-599.