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Update on epilepsy: literature review

Atualização em epilepsia: revisão de literatura

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ABSTRACT: *Objectives:* Epilepsy is one of the most frequent neurological diseases. Due to the high incidence and damages caused by the lack of control of seizures, it is necessary to have knowledge about the peculiarities of epilepsy in order to provide an adequate intervention for each patient. The present study aimed to describe the updates on definitions, types of epilepsy, etiological classifications, diagnosis, main pharmacological and alternative treatments. *Methods:* This is an integrative literature review, with a descriptive approach. A survey was conducted in the databases SciELO, LILACS and MEDLINE, with a complementary survey in books on epilepsy and antiepileptic drugs. *Results:* A total of 48 articles and 6 books that were related to the objective proposed and described the updates on epilepsy were selected. The articles analyzed were published from 2001 to 2017. *Conclusions:* By defining the type of seizures and identifying the cause, it is possible to determine the appropriate treatment, conducted according to the singularity and the response of each patient. This promotes a satisfactory treatment choice and improvement in quality of life, minimizing or even avoiding harm.

Keywords: Epilepsy; Anticonvulsants; Seizures.

RESUMO: *Objetivos:* A epilepsia é uma das doenças neurológicas que ocorre com maior frequência. Devido à alta incidência e prejuízos advindos da falta de controle das crises faz-se necessário o conhecimento das peculiaridades da epilepsia a fim de promover ao paciente a intervenção adequada. O presente estudo visou descrever a atualização sobre definições, tipos de epilepsia, classificações etiológicas, diagnóstico, principais tratamentos farmacológicos e alternativos. *Métodos***:** Trata-se de uma revisão integrativa da literatura com caráter descritivo. Realizou-se uma busca nas bases de dados como SciELO, LILACS, MEDLINE e pesquisa complementar em livros sobre epilepsia e drogas antiepiléticas. *Resultados:* Foram selecionados 48 artigos e 6 livros na pesquisa que correspondiam ao objetivo proposto. Os artigos analisados equivalem aos anos de 2001 a 2017. *Conclusão:* Por meio da definição do tipo de crise epilética e a identificação da causa é possível delinear o tratamento apropriado, conduzido de acordo com a singularidade e a resposta de cada paciente, promovendo dessa forma, uma escolha terapêutica satisfatória e melhoria da qualidade de vida, minimizando ou mesmo excluindo danos.

Descritores: Epilepsia; Anticonvulsivantes; Crises epiléticas.

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INTRODUCTION

Since the beginning of mankind, there have been reports of epilepsy. The term was attributed the meaning of "taken, struck, possessed" and first appeared in Greece. Due to lack of knowledge about the disease, the Greeks and several different populations have associated epilepsy with spiritual possessions, fostering a false belief and mysticism that, unfortunately, persists until today[1], even though Hippocrates had already described the disease in one of the books of the Hippocratic school, called On The Sacred Disease, dissociating it from a divine, sacred or demoniac origin, stating that the brain was responsible for this affection[2].

In the 19th century, with the advances in neurophysiology, epilepsy began to be seen by the scientific community as a disease of the brain. One of the pioneers, John Hughlings Jackson, a British neurologist, proposed an organized anatomical and physiological basis for the hierarchy and location of brain functions, contributing significantly to the search for treatment and to the understanding that it was a disease and not a spiritual attribution, which is an aspect that still leads to discrimination and stigmatization[1].

Epilepsy is characterized by neuronal hyperactivity and brain circuits that lead to excessive and synchronous electrical discharges. It appears in different ways: interictal electroencephalographic discharges, which can extend and cause seizures and, in more severe cases, prolonged or repeated seizures with shorter intervals, characterizing a seizure disorder[3]. If a seizure occurs as a result of acute events such as traumatic brain injury, water-electrolyte imbalance or concomitant diseases it is not classified as epilepsy, but as a provoked seizure[4].

The following factors are involved in the occurrence of a seizure: imbalance between excitation and inhibition of the brain, related to neuronal firing and excessive action potential discharge; uncontrolled neuronal membrane potential and synchronization of nerve cells[5].

A seizure can start in a point in one or both hemispheres of the brain (focal seizures), or in a part that encompasses the two hemispheres of the brain (generalized seizures). Focal seizures start in a focus with excessive neuronal discharges and can go to both hemispheres, evolving into generalized seizures[1,3].

According to the classification established by the International League Against Epilepsy (ILAE) in 2017, there are six etiological groups for epilepsy: genetic, structural, infectious, metabolic, immune and unknown. Genetic epilepsy is a direct result from a known or presumed genetic mutation; structural etiology refers to abnormalities visible on neuroimaging studies; infectious etiology is when an infectious process leads to epilepsy, and not just seizures occurring in the setting of acute infection such as meningitis or encephalitis; metabolic epilepsy is a direct result from a known or presumed metabolic disorder. Metabolic causes refer to manifestations or biochemical changes as inborn errors of metabolism. Immune etiology is when there is evidence of immune-mediated central nervous system inflammation, and an unknown cause is when the etiology of the epilepsy has not been defined[6].

According to Shorvon[7], there has been a greater focus on the classification of the seizure type rather than on the etiology, even with the etiological classification established by the ILAE. There has been no specific distinction between the different classifications of etiology, which are essential for effective treatment, assessment of prognosis and clinical course.

Even with the definition of the cause, about 30% of epilepsy patients do not achieve adequate seizure control with the available drug therapy, presenting refractory epilepsy. The lack of seizure control is associated with cognitive, motor, psychological and social impairments[8,9,10]. These factors directly affect the health and disease process of these individuals, leading to consequences that end up being the cause of new disorders. Therefore, it is necessary to know the particularities of epilepsy for an adequate intervention. This study aims to describe the updates on epilepsy and the main pharmacological and alternative treatments.

METHOD

This is an integrative review of the updates on epilepsy, addressing the definitions, types, etiological classifications and pharmacological and alternative treatments published in previously selected electronic databases and books on epilepsy. The databases Scientific Electronic Library Online (SCIELO), Latin American and Caribbean Health Sciences Literature (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE) were consulted as data source, using the descriptors: Epilepsy; Anticonvulsants; Seizures.

The articles selected after reading the abstracts followed the inclusion criteria, namely: studies addressing epilepsy, new definitions, classifications and treatments of epilepsy, published from 2001 to 2017. After obtaining the search results, the titles of the studies found were read and those not related to the theme, not published in the pre-established period of time or not available in full text were excluded.

RESULTS AND DISCUSSION

The search returned 152 articles, of which 48 were used in the present study. The articles selected were those that were directly related to the inclusion criteria and met the established objective. To complement the research, 6 books addressing epilepsy and antiepileptic drugs were selected.

Incidence and prevalence of epilepsy

Epilepsy is one of the most frequent neurological diseases. It affects approximately 1% of the world population and its incidence varies according to age, gender, race, type of epilepsy syndrome and socioeconomic conditions. There is a higher prevalence of epilepsy in developing countries compared to developed countries, with 1.5 to 2.0% more cases in the former[11].

Regarding the predominance of epilepsy in developed countries, idiopathic and developmental epilepsy are the most common among children, and degenerative and vascular processes predominate among older adults. In developing countries, on the other hand, most cases are related to infections, parasites and traumatic brain injuries, which demonstrates etiological differences[3].

It is estimated that, in Brazil, 340 thousand new cases of epilepsy are diagnosed per year, with 1.8 million patients with active epilepsy and at least 9 million people who have had a seizure at some point in their lives[4].

The child and adolescent age group is highlighted, as epilepsy usually has a higher incidence and prevalence at these ages. Children under one year old are at special risk, as the incidence of seizures can reach 5/1,000 live births in the neonatal period[12].

Classification of seizures, epilepsies and epilepsy syndromes

Epilepsy is considered as a disease and not as a disorder of the brain, as it was previously called. Epilepsy is now characterized by one of the following conditions: at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; one unprovoked (or reflex) seizure and probability of further seizures estimated at least 60% of recurrence, after two unprovoked seizures occurring over the next 10 years; diagnosis of an epilepsy syndrome[13].

For the classification of epilepsy, the physician must start by classifying the type of seizure, then the type of epilepsy and, in many cases, it is possible to identify a specific epilepsy syndrome. Complementing the diagnosis, the physician should attempt to identify the etiology of epilepsy to determine adequate treatment and prognosis[14].

Seizure types

The 2017 ILAE established a revised basic and an expanded classification of seizures types, dividing them into those of focal, general or unknown onset, with specific categories of motor and non-motor seizures that can be added. The difference between the expanded and the basic classification is that the former presents specific subcategories for seizures with motor and nonmotor symptoms. Use of one versus the other depends on the desired degree of detail[6].

Focal seizures can be subdivided into aware or impaired awareness seizures, which replace the former classifications of simple partial and complex partial seizures, respectively. Compared to the 1981 classification, expanded in 2010, the new ILAE 2017 eliminated the terms simple partial, complex partial, dyscognitive, psychic and secondarily generalized. The latter was replaced by the seizure type "focal to bilateral tonic-clonic". New types of focal seizures were included (automatisms, behavior arrest, hyperkinetic, autonomic, cognitive and emotional). It was decided that atonic, clonic, epileptic spasms, myoclonic and tonic seizures can be either focal or generalized[6].

In the expanded classification, focal seizures were divided into motor and non-motor onset. Motor-onset seizures are: Automatisms, Atonic, Clonic, Epileptic spasms, Hyperkinetic, Myoclonic and Tonic. Nonmotor onset seizures are: Autonomic, Behavior arrest, Cognitive, Emotional and Sensory. Focal aware or impaired awareness seizures may optionally be further characterized by one of the motor - onset or nonmotor - onset symptoms, considering the first prominent sign or symptom, except for focal behavior arrest seizures, which have this characteristic as the dominant aspect throughout the seizure. In focal seizures, the state of awareness can be omitted when it is not known or not applicable, classifying the seizure by its motor or nonmotor-onset characteristics. As a rule, atonic seizures and epileptic spasms do not have specified awareness[6].

Generalized seizures are divided into motor and nonmotor seizures. In the expanded version, motor seizures are: Tonic-clonic, Clonic, Tonic, Myoclonic, Myoclonic-tonic-clonic, Atonic and Epileptic spasms. Non-motor seizures are: (Absence) Typical, Atypical, Myoclonic and Eyelid Myoclonia. The latter are classified as nonmotor because they are most significant as characteristics of absence seizures[6]. Seizures with eyelid myoclonia may rarely have a focal onset[15]. The other divisions are similar to those of the 1981 classification, with the addition of myoclonic-atonic seizures that occurred in Doose syndrome[16], common in epilepsy with myoclonic–atonic seizures, myoclonic–tonic–clonic seizures common in juvenile myoclonic epilepsy[17], myoclonic and absence seizures with eyelid myoclonia, described by Jeavons[18].

Seizures of unknown onset can be referred to as unclassified or with additional features included in the expanded version, such as motor (tonic-clonic and epileptic spasms) and nonmotor (behavior arrest). They are referred to as not classifiable in situations where the onset of the crisis cannot be determined, for exemple, cases in which the patient was asleep and it was not possible to define whether the onset of the tonic-clonic crisis that was in progress was focal. A seizure of unknown onset can later be classified as focal or generalized[6].

Characterization of focal seizures

Cognitive crises imply impaired language or other functions of the cognitive domain or the presence of positive features such as déjà vu, hallucinations, illusions or perceptual distortions. Emotional seizures involve anxiety, fear, joy and other emotions, or appearance of affect without associated subjective emotions[6].

Autonomic crises are characterized by autonomic phenomena, which can involve cardiovascular, gastrointestinal, vasomotor and thermoregulatory functions. Examples include palpitations, nausea, hunger, chest pain, urge to urinate or defecate, goosebumps, sexual arousal, a sense of heat or cold, piloerection, pallor, tachycardia or bradycardia/asystole, flushing, pupillary changes and weeping[19].

Hyperkinetic seizures include violent, sudden and pedaling movements. And behavior arrest seizures have cessation of activity as the dominant aspect throughout the seizure[6].

Automatisms tend to be coordinated and repetitive movements resembling voluntary movements. Most of the time, they are associated with impaired awareness and subsequent amnesia. Examples are: oral automatisms such as chewing, tooth grinding, lip pursing; manual or pedal, with bilateral or unilateral distal components such as fumbling, tapping, manipulating movements; gestural, with fumbling or exploratory movements with the hand, directed towards self or environment; mimetic, with facial expressions like fear; vocal, with screams; verbal, with short words or phrases; gelastic, with bursts of laughter; hyperkinetic, with pedaling movements and hypokinetic, with arrest/decrease of ongoing motor activity[20].

It should be noted that atonic, clonic, epileptic spasms, myoclonic and tonic seizures can be either focal or generalized[6]. The latter are described below.

Characterization of generalized seizures

Tonic-clonic (grand mal) seizures are characterized by sudden loss of consciousness, with tonic and subsequent clonic contraction of the four limbs, with apnea, sphincter relaxation and sialorrhea[21].

In typical absences (petit mal), the patient presents brief episodes of impaired awareness with minor motor events, oral and manual automatisms, eye-blinking, increased or decreased muscle tone and autonomic events with abrupt onset and termination[3].

Atypical absences show less impaired awareness, slower onset and termination and altered muscle tone[22].

Eyelid myoclonia are rapid jerks of the eyelids when closing the eyes, which causes rapid eye-blinking and upward deviation of the eyes. This phenomenon may appear in isolation or manifest along with very brief absence seizures lasting only a few seconds[21].

In myoclonic seizures there are sudden and brief shock-like muscle contractions that can affect facial muscles, trunk, extremities, individual muscles or groups of muscles and that can be isolated or repetitive[22].

A tonic-myoclonic seizure is followed by a tonic seizure. Sometimes, a series of myoclonic spasms occur before the increase in tone[6].

Myoclonic-atonic seizures are found mainly in childhood epilepsies. These seizures are characterized by myoclonic jerks in the upper limbs, usually flexed, followed by loss of muscle tone, head-drop and knee flexion[21].

In clonic, tonic and atonic seizures, there may be loss of consciousness with a clonic (myoclonia), tonic (muscle contraction) and atonic component, characterized by a sudden fall to the ground[3].

In epileptic spasms there may be sudden flexion, extension or mixed flexion-extension of proximal and truncal muscles, lasting 1-2 seconds, but not more than 2 seconds. Spasms typically occur in a series, usually on wakening. Subtle forms may occur with only chin movement, grimacing, or head nodding. Spasms may be bilaterally symmetric, asymmetric, or unilateral[19].

Types of epilepsy

After diagnosis of the seizure type, the next step is the diagnosis of the epilepsy type, which includes focal epilepsy, generalized epilepsy, combined generalized and focal epilepsy and also an unknown epilepsy group. The main objective of this classification is to identify the types of seizures that are most likely to occur in a given patient, the triggers for their seizures, the prognosis, including learning difficulties, cognitive impairment, psychiatric disorders, and mortality risk, and then select the treatment[14].

Focal epilepsies were defined as seizures that originate in only one hemisphere of the brain. They may be more localized or widely distributed in that hemisphere and may originate in subcortical structures. Each type of seizure would have a consistent ictal onset, with a preferential spread pattern, involving or not the contralateral hemisphere[23]. They can evolve into generalized seizures, which occur in bilaterally distributed neural networks and quickly spread[24]. In the new 2017 ILAE classification, the terminology for this type of seizure was replaced by focal to bilateral tonic-clonic seizures[6].

Different types of seizures may occur, including focal aware seizures, focal impaired awareness seizures, focal motor seizures, focal non-motor seizures and focal to bilateral tonic-clonic seizures[14].

For a diagnosis of Generalized Epilepsy, the electroencephalogram (EEG) must show generalized spike-wave epileptiform activity. The diagnosis is clinical, supported by the finding of typical discharges on the EEG. However, there are cases of patients with generalized tonic-clonic seizures and normal EEG. In this situation,

there must be evidence to support the clinical diagnosis, for example, myoclonic jerks and positive family history. Individuals with generalized epilepsies can have several types of seizures, including absence, myoclonic, atonic, tonic and tonic-clonic seizures[14].

In relation to combined generalized and focal epilepsies, the diagnosis of both types of seizures is made on clinical grounds, supported by discharges in the EEG. Ictal recordings are helpful, but not essential. Interictal EEG can show both generalized spike-wave and focal epileptiform discharges, but epileptiform activity is not required for diagnosis. Common examples in which both types of seizures occur are Dravet Syndrome and Lennox-Gastaut Syndrome. The unknown category is when there is not enough evidence to characterize epilepsy as focal, generalized or both, such as a patient with several symmetrical tonic-clonic seizures without focal features and normal EEG recordings. These are seizures that cannot be clearly classified until information allows a precise diagnosis[14].

Epilepsy syndrome

According to the guidelines in the 2017 ILAE Classification, after defining the type of epileptic seizure and the type of epilepsy, there is a possibility of diagnosing an epilepsy syndrome[6]. An epilepsy syndrome is characterized by a set of signs and symptoms that commonly occur together, which can be clinical (intellectual or psychiatric impairment, for example) or alterations detected in complementary exams (EEG, imaging). Electroclinical syndromes are grouped by age of onset and remission (where applicable), seizure triggers, diurnal variation or even the prognosis. An epileptic syndrome will not always have a specific correlation with an etiological diagnosis, but it may have implications for the therapeutic approach[14].

In the previous ILAE classification, all electroclinic epilepsy syndromes were described and grouped by age of onset[24]. In the current 2017 classification, syndromes were divided into two groups: idiopathic generalized epilepsies and self-limited focal epilepsies. However, only the main syndromes were cited in the new classification[14].

The electroclinical syndromes, arranged by age at onset, as classified by the 2010 ILAE, are described below:

• Neonatal period: Benign neonatal seizures; Benign familial neonatal epilepsy; Early myoclonic encephalopathy and Ohtahara syndrome. Infancy: Febrile seizures; Febrile seizures plus; Benign infantile epilepsy; Benign familial infantile epilepsy; West syndrome; Dravet syndrome; Myoclonic epilepsy in infancy; Myoclonic encephalopathy in nonprogressive disorders and Epilepsy of infancy with migrating focal seizures.

• Childhood: Febrile seizures; Febrile seizure plus; Early-onset childhood occipital epilepsy (Panayiotopoulos syndrome); Epilepsy with myoclonic atonic (previously astatic) seizures; Childhood absence epilepsy; Benign epilepsy with centrotemporal spikes; Autosomal - dominant nocturnal frontal lobe epilepsy; Late onset childhood occipital epilepsy (Gastaut type); Epilepsy with myoclonic absences; Lennox - Gastaut syndrome; Epileptic encephalopathy with continuous spike - and - wave during sleep and Landau-Kleffner syndrome.

• Adolescence – Adult: Juvenile absence epilepsy; Juvenile myoclonic epilepsy; Epilepsy with generalized tonic–clonic seizures alone; Progressive myoclonus epilepsies; EAutosomal dominant epilepsy with auditory features; Other familial temporal lobe epilepsies.

• Variable age of onset: Familial focal epilepsy with variable foci (childhood to adult) and Reflex epilepsies.

• Distinctive constellations/surgical syndromes: Mesial temporal lobe epilepsy with hippocampal sclerosis; Rasmussen syndrome; Gelastic seizures with hypothalamic hamartoma and Hemiconvulsion-hemiplegia-epilepsy.

• Epilepsies attributed to and organized by structural - metabolic causes: Malformations of cortical development (hemimegalencephaly, heterotopias, etc.); Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.); Tumor; Infection; Trauma; Angioma; Perinatal or prenatal insults; Cerebrovascular accident.

• Epilepsies of unknown cause[24].

The epilepsy syndromes currently classified by the ILAE 2017 are:

• Idiopathic generalized epilepsies: encompass 4 epilepsy syndromes, which are childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and generalized tonic-clonic seizures alone (formerly known as generalized tonic-clonic seizures on awakening, but the term "awakening" was removed because these seizures can occur at any time of day). The "idiopathic" terminology is maintained for the 4 epileptic syndromes mentioned above; however, one should be attentive, because, in most cases, these syndromes have genetic etiology, as supported by the increasing recognition and discovery of the genes involved in many epilepsies. In individual cases, the term Genetic Generalized Epilepsy may be used where the clinician is comfortable with invoking a genetic etiology.

• Self-limited focal epilepsies: There are several self-limited focal epilepsies, typically beginning in childhood. The most common is self-limited epilepsy with centrotemporal spikes, previously called "benign epilepsy with centrotemporal spikes". Also included in this group are the self-limited occipital epilepsies of childhood. Other self-limited frontal lobe, temporal, and parietal lobes epilepsies have also been described, with some beginning in adolescence and even in adulthood[14].

Epilepsy syndromes that presented the term "benign", such as benign epilepsy with centrotemporal spikes, may be associated with transient or long-lasting cognitive effect[14]. The term "benign" was replaced by "self-limited" and "pharmacoresponsive", as it is understood that

the term "benign" underestimates the consequences of the disease[24] "Self-limited" refers to the likely spontaneous resolution of a syndrome. "Pharmacoresponsive" means that the epilepsy syndrome is expected to be controlled with drug therapy[14].

After using elements to classify the type of seizure, epilepsy and/or epilepsy syndrome, the next step is to define the etiology of epilepsy, given its relevance for establishing targeted therapy and prognosis. Resource poor countries will not always have the means to support an accurate classification. This should be taken into account, even though classification is an appropriate method[6].

Positive family history and laboratory tests such as the detection of antineuronal antibodies or genetic mutations may support the definition of etiology, when conditions are available. According to the new 2017 ILAE classification, there are 6 etiological groups: structural, genetic, infectious, metabolic, immune and unknown etiology. Epilepsy can be classified into more than one etiological category, as the same patient may have both structural and genetic etiology, such as patients with tuberous sclerosis. Structural etiology is a possible indication for epilepsy surgery, while genetic etiology is key for genetic counseling and consideration of new therapies such as mTOR (mammalian target of rapamycin*)* inhibitors[14].

Etiologies of epilepsies

Structural etiology

The structural etiology refers to abnormalities visible on neuroimaging, which along with clinical and electrographic findings lead to the understanding that the abnormality is the likely cause of the patient's seizures[14]. Structural etiologies can be acquired, such as stroke, trauma, infection, hypoxic-ischemic encephalopathy; or genetic, such as many malformations of cortical development. A polymicrogyria may be secondary to mutations in genes such as GPR56[25].

Despite there being a genetic basis for these malformations, the structural abnormality determines the existence of epilepsy. Whenever a structural etiology has a well-defined genetic basis, such as tuberous sclerosis complex, both etiological terms, structural and genetic, can be used[14].

Genetic etiology

Genetic epilepsies result from a known genetic mutation or from one that can be inferred from genetic etiology, in which seizures are the main symptom of the disease. In the majority of cases, the underlying genes are not yet known, and the genetic etiology may be based solely on a family history suggestive of autosomal dominant heredity. For example, in the syndrome of benign familial neonatal epilepsy most families have mutations of one of the genes of the potassium channels. In the syndrome of autosomal dominant nocturnal frontal lobe epilepsy, the underlying mutation is only known in a small proportion of individuals[26].

A large number of genes have been identified by molecular genetics. Gene mutation is responsible for the most frequently arising *de novo* epilepsies in 30-50% of children with severe epileptic and developmental encephalopathies, the most common example being Dravet syndrome. Understanding the phenotypic spectrum associated with mutations of a specific gene is critical information, since the identification of a mutation in a gene, on its own, may not enable prediction of the outcome. Therefore, the electroclinical presentation must be considered to interpret the case[14].

If the individual has a *de novo* mutation, their offspring will have a 50% risk of inheriting the mutation. However, this does not mean that their children will have epilepsy, as its expression will still depend on the penetrance of that mutation. A genetic etiology does not exclude an environmental contribution. For example, several patients with epilepsy are more likely to have seizures under the influence of sleep deprivation, stress and other factors[14].

Infectious etiology

The most common etiology worldwide is epilepsy caused by an infection[28]. An epilepsy of infectious etiology results from a known infection, in which seizures are a core symptom of the disease. An infectious etiology is not related to a patient who has acute symptomatic seizures in the acute phase of infections such as meningitis or encephalitis. Common examples in specific regions of the world include cysticercus infection such as neurocysticercosis, tuberculosis, HIV (Human Immunodeficiency Virus), cerebral malaria, subacute sclerosing panencephalitis, cerebral toxoplasmosis and congenital infections such as Zika virus and cytomegalovirus, which may have a structural correlate. The infectious etiology can also refer to epilepsy that appears after an infection, as is the case of viral encephalitis leading to seizures after the acute phase of the infection[14].

Metabolic etiology

Epilepsy of metabolic etiology directly results from a known or presumed metabolic disorder, in which seizures are the main symptom. Metabolic causes refer to metabolic defects with clinical manifestations or biochemical changes throughout the body, such as porphyria, uremia, amino-acidopathies or pyridoxine-dependent seizures. Most metabolic epilepsies are likely to have a genetic basis, but some can be acquired, such as cerebral folate deficiency. The identification of specific metabolic causes of epilepsy is extremely important due to the implications for treatment and potential prevention of intellectual impairment[14].

Immune etiology

Immune epilepsy results directly from an immune disorder in which seizures are the main symptom, when there is evidence of autoimmune-mediated central nervous system inflammation. The frequency of diagnosis is increasing because there is greater access to antibody testing. Examples include anti-NMDA (N-Methyl-D-aspartate) receptor encephalitis and anti LGI1 (Anti leucine-rich glioma inactivated 1) limbic encephalitis[29]. This etiological subgroup deserves a specific category, mainly because of its implications for treatment with targeted immunotherapies[14].

Unknown etiology

Unknown etiology means that the cause of the epilepsy is not yet known. As the classification itself indicates, the nature of the causes is undetermined, and there may be a probable genetic basis or structural/metabolic disorder not yet identified[21].

Many patients with epilepsy remain with an unknown cause. The determination of a specific diagnosis requires an extended evaluation; however, in many cases, this is not possible, as several countries have a shortage of resources.

New terminologies and applications

As a result of frequent epileptic activity, epileptic encephalopathy may occur. This condition contributes to severe cognitive and behavioral impairment and can be applied to all epilepsies at any age, as deemed appropriate, and not only to severe epilepsies beginning in infancy and in childhood, as previously defined [6].

The ILAE definition proposes the term "resolved epilepsy", previously defined as "cured", to classify the remission of the disease. A period of at least ten years without seizures and five years off antiseizure medication was established for the application of the term resolved epilepsy[14].

Antiepileptic drug therapy

The appropriate choice of antiepileptic drugs (AEDs) is based on information collected about the type of seizure and/or epilepsy syndrome, age, tolerability, safety and efficacy of the AED[30]. Complete seizure control is the main objective of the drug therapy; however, 20% to 30% of patients do not achieve complete control. These patients can even present partial seizure control, but do not achieve complete remission. In these cases, when the possibility is evaluated, surgery might be indicated[23].

Refractory epilepsy can not be easily defined. In order to ascertain this diagnosis, it is necessary to use all types of antiepileptic drugs in monotherapy and in combination, which is not possible in less than ten years of therapy. Therefore, it is a relative concept and it can be based on lack of seizure control after the use of several AEDs[31].

The definition of refractory epilepsy varies from study to study and there is no single classification. Some studies consider it to be the occurrence of one seizure per month for a specified period of time, while others include the ineffective drugs into the definition[32].

More accepted definitions classify epilepsy as refractory when there is no appropriate control of seizures with the use of at least two or three antiepileptic drugs, at the maximum tolerated dose, for a period of 18 to 24 months, or, if seizures are controlled but with an unacceptable side effect[33].

The first indication of treatment for epilepsy in general is the use of monotherapy. If there is no satisfactory response, two more attempts at monotherapy should be made, followed by combination. If seizures still persist and new combinations fail, surgical intervention should be evaluated[34]. In cases where polytherapy is necessary and monotherapy has failed, the chance of effectiveness is approximately 10%[31].

In order to verify the response to treatment in relation to the time of drug therapy, it is necessary to identify the frequency of the seizures. If the person has monthly seizures, it takes longer to verify the effectiveness of the drug, usually several months. In cases of more frequent seizures, such as weekly seizures, one or two months of are already enough to assess the therapeutic response and, if there is an improvement, a longer treatment time is indicated[31].

According to Benbadis and Tatum[35], the emergence of new antiepileptic drugs has resulted in a 50% seizure reduction and some of them have been used as adjunct treatment for the control of refractory partial seizures. These new drugs are: felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam and zonisamide. However, a study conducted by Yacubian[36] demonstrated that traditional drugs should be considered as the first choice for the treatment of epilepsy in general.

Regarding the new antiepileptic drugs, there is Felbamate, which is indicated for focal and generalized seizures. Gabapentin is another AED used as adjunct therapy for focal seizures in patients with intolerance to multiple drugs with potential interactions. Lamotrigine has a broad spectrum of activity in various types of seizures, both as an adjunct treatment or as monotherapy; however, one important side effect of this drug is rash, which can progress to Stevens-Johnson syndrome[37].

Topiramate has a broad spectrum of activity in focal and generalized seizures. Nephrolithiasis is a rare side effect, and paresthesias and carbonic anhydrase inhibition reflexes are common side effects. Tiagabine has no significant side effects, and a limited spectrum of activity

in focal crises. Levitiracetam is indicated for focal seizures and has good tolerability[35].

Zonisamide is indicated as an adjunct therapy in focal seizures; nephrolithiasis and weight loss are possible side effects. Oxcarbamazepine is used as adjunct therapy and as monotherapy for focal crises, with hyponatremia as its side effect[37].

The traditional drugs used to treat epilepsy are: phenobarbital, phenytoin, carbamazepine, valproate and benzodiazepines, which bind to plasma proteins and are metabolized by the liver[23].

Phenobarbital is used in focal and generalized seizures and status epilepticus. Side effects are sedation, ataxia and hyperactivity. Phenytoin is used in focal and generalized seizures. Side effects are sedation and ataxia. Gingival hyperplasia and hirsustism may occur due to the proliferation of fibroblasts and lymphadenopathy[36]. There may be a deficiency in insulin secretion, particularly in diabetic and pre-diabetic patients[38]. A skin rash might be an idiosyncratic reaction of both phenobarbital and phenytoin[36].

Carbamazepine is effective in treating focal and generalized seizures. There are reports that it can trigger or exacerbate absence seizures. Side effects are food intolerance, sedation and ataxia. Idiosyncratic reactions include leukopenia, aplastic anemia, rash and Stevens-Johnson syndrome. Oxcarbamazepine has the same principle as carbamazepine, but the difference is in positions 10 and 11 of the molecule, where oxcarbamazepine has a ketone group, which reduces side effects. Its half-life is longer, so it is administered two times a day[36].

Valproic acid provides good seizure control in generalized tonic-clonic, absence, myoclonic and primary seizures, with a lesser effect on focal seizures. Side effects are tremor, weight gain, dyspepsia, nausea, vomiting, anorexia, alopecia, peripheral edema, encephalopathy, teratogenesis, agranulocytosis, aplastic anemia, allergic dermatitis, Stevens-Johnson syndrome, hepatotoxicity and platelet changes[39].

Benzodiazepines act at the receptor sites in the central nervous system, specifically at the receptor sites of the most common inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). They also affect channel opening frequency. Clonazepam and diazepam are used in emergency situations and clobazam and nitrazepam are used for chronic treatment of epilepsy[23].

The Brazilian Ministry of Health has a Clinical Protocol and Therapeutic Guideline (PCDT) with guidelines on diagnosis, treatment and monitoring of epilepsy. The PCDT recommends the following drugs for the treatment of epilepsy: carbamazepine, clobazam, ethosuximide, phenytoin, phenobarbital, primidone, gabapentin, topiramate, lamotrigine and vigabatrin. These medications are on the list of drugs available in the Unified Health System (SUS) and in the 2020 National List of Essential Medications (RENAME), along with other drugs such as valproic acid and levetiracetam[40].

Alternative treatments: ketogenic diet, vagus nerve stimulation and cannabidiol

The ketogenic diet is a lipid-rich low-calorie diet, with reduction of glucose and restriction of fluid. Its objective is to achieve a state of ketosis and it has an antiepileptic effect, whose mechanism of action is not completely understood. It is more effective in children and adolescents because it enables the brain to revert to the most primitive form of metabolism[41].

This diet is indicated when drug therapy does not provide adequate seizure control in children with multiple refractory seizures. It shows positive results in myoclonic, atonic, generalized tonic clonic, focal and absence seizures[42].

The main complications of this diet are hypoglycemia, excess ketosis, diarrhea, reduced appetite, thirst, drowsiness, dehydration, metabolic acidosis, hyperuricemia and hyperlipidemia. Exams should be monitored, and any alteration should be observed[31].

Vagus nerve stimulation is a minimally invasive method that is another alternative treatment for refractory epilepsy. It is a pulse generator that is implanted under the skin, below the clavicle, in the same position as a pacemaker[43].

Its mechanism of action is still not known. However, it is believed that it activates projections in the nucleus of the solitary tract to the limbic forebrain[23], through the release of noradrenaline by the locus coeruleus in the limbic cortex and of serotonin by the dorsal raphe nuclei in the telencephalon and diencephalon[44].

The pulse generator is programmed through the computer and stimulation usually begins two weeks after the surgical implant. Most patients experience reduced seizure frequency, improved cognition, better quality of life and reduced depression, but there is no report of complete seizure control. The most common side effects are hoarseness, coughing and paresthesia of the pharynx due to the intensity of the stimuli[43].

Another treatment used for epilepsy in selected cases is cannabidiol. *Cannabis sativa* is a plant that contains approximately 100 pharmacologically active components. One of these components, the cannabidiol (CBD), was identified in 1963[45]. It has no psychoactive effect, a low toxicity and high tolerability in humans and animals[46].

Cannabidiol (CBD) and Tetrahydrocannabinol (THC) are the most common components in *cannabis sativa*. They have opposing effects: while THC is the main psychoactive component, due to its role as a partial agonist of cannabinoid receptors (CB_1), CBD acts by reducing the effects of the activation of this receptor[47].

Cannabinoids act by binding to receptors; one of

them, the CB1, is located in the central nervous system[45] and is present in both inhibitory gabaergic neurons and excitatory glutamatergic neurons[47]. Cannabidiol acts on this receptor by inhibiting synaptic transmission by blocking voltage-dependent calcium-activated (Ca^{2+}) potassium (K^{+}) channels. The mechanism of action of cannabidiol has not been fully elucidated; however, it is believed that this is how cannabidiol can reduce seizures[45].

Its antiepileptic effect has been proven, as clinical studies show the beneficial effects of CBD against seizures, such as a significant improvement of seizures in refractory epilepsis, total or partial remission in most of the patients analyzed, and even increased alertness in many children[48].

A double-blind, placebo-controlled trial conducted by Devinsk et al. in 2017, evaluated 120 children and young adults with the Dravet syndrome and drug-resistant seizures. One group received CBD 20 mg per kg per day and the other group received placebo, in addition to standard treatment. The use of CBD resulted in a significant reduction in seizure frequency and a higher rate of adverse events compared to placebo[49].

Although cannabidiol shows excellent results, there is still no clarification on safety of long-term administration, pharmacokinetic properties, mechanism of action and pharmacological interaction with other cannabinoids[50]. Therefore, it should be used with caution in patients in the stage of cognitive development, particularly children and adolescents[51].

The Federal Council of Medicine (CFM) regulated the use of cannabidiol in Brazil in resolution No. 2,113/14. It is indicated in cases of drug-resistant epileptic syndromes. The medications used by the patient are kept, in association with cannabidiol[52]. In Brazil, the medical use of drugs based on CBD and THC was authorized by the National Health Surveillance Agency - ANVISA[53].

Cannabidiol has a demonstrated anticonvulsant effect, so it is being used therapeutically. However, it requires further research to elucidate its properties and safety.

Diagnostic exams

According to Smith[54], the electroencephalogram has a fundamental role in the identification of seizures and patterns of syndromes; it also contributes to the selection of appropriate drug therapy and assists in the prognosis.

Ambulatory and video electroencephalogram are indicated for patients who do not have a clearly defined diagnosis and for differentiation between nocturnal epilepsy and parasomnias, diagnosis of psychogenic non-epileptic seizures, characterization of seizure type, quantification of seizure frequency and evaluation of candidates for surgery[54].

Computed tomography is also used for diagnosis; however, for a better investigation, magnetic resonance imaging has a better resolution, which helps to visualize structural changes. New techniques, such as multiplanar reconstruction, can help identifying lesions when conventional methods cannot. This method has a 94% sensitivity for detecting injuries[55].

For many patients with epilepsy, the electroencephalogram or the resonance cannot identify epileptogenic focus and some have to undergo interictal and ictal scalp EEG, an invasive method to evaluate surgical intervention. There are less invasive methods such as PET (positron emission tomography) and SPECT (single photon emission computed tomography), which are functional neuroimaging exams that identify alterations of blood flow with the use of radiopharmaceuticals and which have been proven to be useful in the identification of the epileptic area[55].

Care for people with epilepsy

Knowledge about epilepsy and recognition of crises are essential for professionals who care for epileptic patients. In addition, it is necessary to have skill and determination in situations in order to avoid neurological problems and take action to avoid greater risks such as falls, aspiration of pulmonary secretions and injuries. Actions such as administration of anticonvulsants, maintenance of an open airway, lateral positioning of the head, administration of oxygen if necessary are management and damage prevention measures[56].

Patient and family members must be informed about the disease, the importance of adhering to treatment and complying with regular medication schedules, the adverse drug effects and the risks of untreated epilepsy. Professionals should verify if the treatment is being properly carried out and provide guidance regarding care during and after seizures[57].

The seizure diary is an important instrument to assist medical treatment. It contains information on duration, frequency, time and characterization of the seizures, body parts involved, triggering factors, state of consciousness, pharmacological actions and side effects. Family members who live with the patient should be instructed to make these notes, as the seizure diary allows a qualified and unique treatment that may lead to improvement in the patient's quality of life[57].

CONCLUSION

Epilepsy has peculiarities that must be well defined and understood, especially when it is difficult to control. The knowledge about the type of crisis, the etiology, the predisposing factors and the pharmacological actions for each type of crisis is essential for an adequate management of epilepsy.

The constant observation of the patient's evolution,

recording details of all aspects of the epilepsy and checking the particularities of each case, enables appropriate interventions that, in many situations, result in satisfactory results, in a holistic view of the patient's health.

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