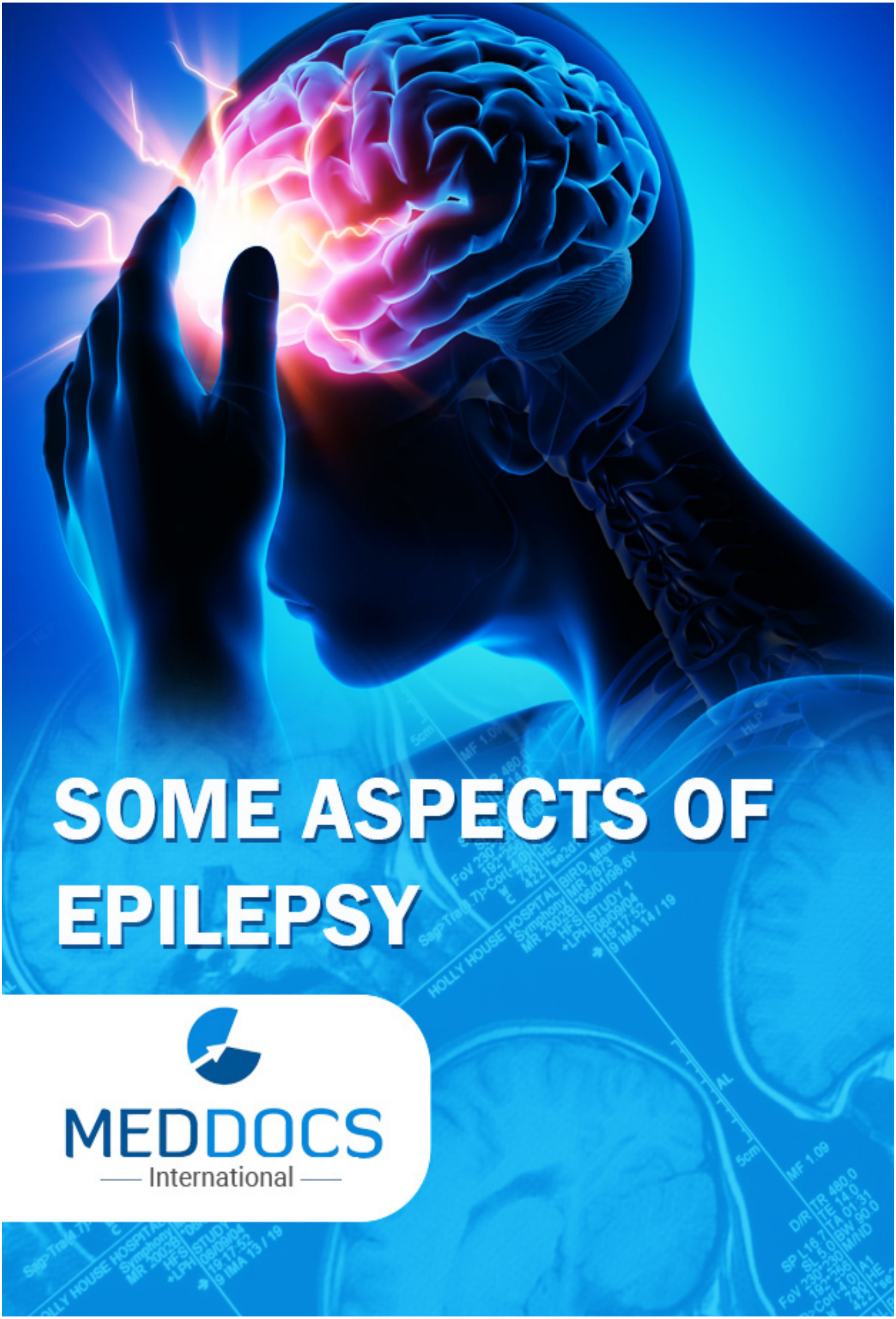

SOME ASPECTS OF EPILEPSY

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General Considerations in the Treatment of the Patient with Epilepsy

Juan E Bender del Busto[1*]; Liuba Hernandez Toledo[2]

[1]Department of Neurology. International Center of Neurological Restoration (CIREN), Cuba

[2]Department of nursing, International Center of Neurological Restoration (CIREN), Cuba

Corresponding Author: Juan E Bender del Busto,

Philosopher doctor. Second degree specialist in Neurology. Full Professor and Researcher. International Center of Neurological Restoration (CIREN). Havana, Cuba

Email: jebender@infomed.sld.cu

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Introduction

It is considered that epilepsy can occur in any person without distinction of age, sex, race, social origin or geographical characteristics. It is a global public health problem that requires an adequate response, which according to reports from the World Health Organization (WHO), an estimated 50 to 69 million people suffer from this disease, most of them living in developing countries [1-3].

It can be asserted that epilepsy affects 1-2% of the population [4-7].

It is one of the most frequent disorders of the Central Nervous System (CNS), for some the second neurological disease, which is seen more frequently (72.5%) in primary health care worldwide, after headache (73.5%). It constitutes, in turn, the fourth cause of neurological disability (7.9%), after Migraine (8.3%), Dementia (12.0%) and Cerebrovascular Disease (55%) [8].

It is currently considered by the International League Against Epilepsy (ILAE) and the International Office for Epilepsy (IBE), as a disease and not a disorder [9,10].

The knowledge of humanity of this disease dates back more than 3000 years. Its history can be traced to the same history of man, since it has left its mark engraved in each of the different civilizations.

It was known by the name ¨Morbo Sacro¨ or ¨Sacred Disease¨ and ¨attacks¨ or epileptic crises with the term ¨epilambaneim¨ which means ¨attack¨, ¨surprise¨, ¨to take possession¨, or ¨to fall over itself¨ (for which its manifestations caused fear), of where it derives the term through which is known this illness at the moment: Epilepsy. Hippocrates described him for the first time in his book "The Sacred Disease" [11].

The most frequent age of onset is childhood and adolescence due to obstetric trauma before or during childbirth, cranial trauma, encephalitis or meningoencephalitis and in some countries of Latin America cerebral parasitism, for example cysticercosis. However, as the longevity of the planet increases, the incidence and prevalence of epilepsy have also increased due to cerebrovascular diseases, brain tumors or demential diseases, which are more frequent in the elderly [12].

The first treatments included from the exorcism to the practice of bloodletting and trepanation [11].

However, scientific therapy dates back to the 19th century

with the accidental discovery of bromide salts [11]. From then on a variety of drugs were incorporated into the therapeutic arsenal of this disease.

They have also been included more recently in the management of this, different techniques and alternative methods.

It is to signify that this disease, because it is fully associated with alterations in the psychological and social sphere of the patients who suffer from it, as well as presenting frequent psychiatric manifestations, the management of these is essential [13,14].

It is for it that, in our consideration for the complexity of this pathology, for the social implication that presents and its psychobiological and even economic consequences, the patient with epilepsy must be managed with a multidisciplinary character.

The goal in this article is to expose and reflect on the use of antiepileptic drugs described so far, those under investigation and future development trends, in order to guide the patient therapeutically in an appropriate manner and minimize the complications of this disease.

Management of a patient with suspected epilepsy.

In the management of a patient with suspected epilepsy, there are concerns or questions that the doctor should consider: *We are in front of an epileptic event?, That crisis/epilepsy type does the patient suffer?*, *What is the cause of crisis/epilepsy?*, What therapeutic behavior should we follow? [15].

After making the correct diagnosis of a patient, but before prescribing a specific antiepileptic, the doctor must take into account a number of additional issues. A complete understanding of these issues should allow for the best outcome for the patient, regardless of the drug or other therapy chosen [16,17].

However, before entering into the complexities of treatment strategies, we need to make a brief reminder about the accuracy of the patient's diagnosis. The correct diagnosis is, after all, the foundation on which the therapy is based. An inadequate diagnosis is likely to lead to insufficient and potentially harmful treatment.

This is a complex issue, given that epilepsy is a heterogeneous set of syndromes with innumerable causes and a wide variety of clinical expressions.

So, how are we going to make a correct diagnosis of the patient with the disease? We can only do this by recognizing that multiple levels of diagnosis are present, and these must be identified in each patient, which can be summarized as follows: Etiological diagnosis, Diagnosis of seizures and Diagnosis of epileptic syndrome (if possible), [18] those that are based, in turn, on the chronopathogram of the comicial events, the physical examination and the necessary complementary investigations.

Once the patient's diagnosis is safe, what are the treatment issues that should be considered to optimize the outcome for the individual?

To do this we must consider that the treatment of epilepsies can be summarized in three major groups: Prophylactic/preventive, pharmacological, non pharmacological: surgery and alternative treatment, not to mention, the psychological/psychiatric management.

We will approach the pharmacological treatment and the general aspects of its management and we will ignore the other topics, for the specific purposes of this review.

Pharmacoterapy

It should be kept in mind in this topic, that the therapy in this disease is still suppressive, symptomatic and not curative [19].

From 1909, the year of the founding of the International League Against Epilepsy (ILAE), modern approaches to the medicinal therapy of epilepsy were formulated and many novel drugs were introduced [19].

It was the studies of Tracy Putnam (1894-1975) and H. Houston Merritt (1902-1978) that marked the end of the empirical use of substances, in search of new antiepileptic drugs [20-22].

The introduction of different drugs/procedures in clinical practice is detailed in each period.

1850 Bromides/chloral hydrate/Borax, 1910 Phenobarbitone, 1930 Ketogenic diet, 1938 Phenytoin, 1941 Acetazolamide, 1944 Trimethadione, 1950 Adrenocorticotropic Hormone (ACTH), 1954 Primidone, 1957 Methosuximide, 1958 Ethosuximide, 1962 Sulthiame, 1963 Diazepam, 1965 Carbamazepine, 1967 Valproic Acid, 1968 Clonazepam, 1975 Clobazam [23,24].

Drugs introduced between 1989 and 1994

Vigabatrin (1989), Lamotrigine (1990), Oxcarbazepine (1990), Felbamate (1993) y Gabapentin (1994) [25].

Drugs introduced between 1995 and 2008

Topiramate (1995), Tiagabine (1996), Levetiracetam (1999) Zonisamide (2000), Pregabaline (2004), Stiripentol (2007), Rufinamide (2007), Lacosamide (2008) [26].

Other antiepileptic drugs that are currently in active development

Retigabine, eslicarbazepine acetate, fluorofelbamate, remacemide, valprocemide and propylsopropyl acetamida, Brivaracetam, seletracetam, carisbamato, Ezogabine, Ganaloxone, Perampanel, T-2000, 2-Deoxy-D-glucose, Huperzine A, JZP-4, ICSC 700-008, NAX-5055, NS1209, Tonabersat and YKP3089 [27-32].

In experimental phase they are [33-35]:

-CPP-115 (Vigabatrin derivatives) (1*S*,3*S*)-3-amino-4 difluoromethylenecyclopentanecarboxylic acid

- Antinflamatory agents:

HE3286 (Triolex) androstene-3β,7β,17β-triol (βAET)

VX-765 (S)-1-(S)-2-3,3-dimethyl-butanoyl)-pyrrolidine-2-carboxylic acid

-Other new components:

2-Deoxy-D-Glucose, Cannabinoids, Everolimus, NAX 810-2, Propofol Hemi-Succinate, Isovaleramide, Losigamone, Safinamide and Talampanel.

There is interest and recent public debate about the potential use of marijuana and one of its active substances, cannabidiol (CBD) (non-psychotropic compound) in the treatment of various neurological conditions such as chronic pain, multiple sclerosis and especially certain for patients with refractory seizures and catastrophic epilepsies such as Dravet's syndrome [36-38].

Mention is also made of intravenous immunoglobulin (IVIG), composed of products purified from human blood. The products generally contain more than 95% unmodified IgG and traces of IgA or IgM [39,40].

The mechanism of action of IVIG in epilepsy appears to be primarily immunological, but the therapeutic effects of IVIG can also have an impact on immune system pathways, including modulation of plasma levels of interferon, interleukin-6 (IL-6). And IL-828 [39,40].

Obviously, taking into account the didactic purposes of this review, aspects related to pharmacokinetics, indications, doses, interactions and adverse reactions of antiepileptic drugs.

It is our criterion that we should not be satisfied with the advances of today's epileptology and we should continue in the search for an effective therapeutic.

There is a clear need to insist on the study of conventional animal models and to explore other fields that include molecular research, in which neuronal hyperexcitability can be reduced and, in addition, components with antiepileptogenic and neuroprotective properties are identified [41].

Recent research shows that genetic differences in patients could influence the response to treatment [42].

Several novel approaches to the treatment of epilepsy are also studied, including the transfer of different genes and stem cell transplantation. On the other hand, multiple therapeutic targets are described, including neuropeptides, neurotrophic factors and inhibitory neurotransmitters [43].

For this, it is important to take advantage of the results that are continually being made available to the scientific community thanks to the synergy of basic and clinical multidisciplinary research.

This means that the clinical applicability of the neurobiological results must be evaluated, so that the new information can be translated into diagnostic and therapeutic terms, and consequently the guidelines and recommendations will be produced.

Important actions have been carried out by the International League Against Epilepsy (ILAE) through its various committees (in genetics, neurobiology, psychobiology, epidemiology, therapeutic strategies, diagnostic methods and care policy of health) to help developing countries in establishing research and projects geared to their specific problems [44].

General Aspects of Treatment [45].

Having epilepsy commonly introduces several consequences that are relatively unique, including:

- Restrictions on driving and unsafe acitivites, persistent stigma, and the small but real possibility of sudden death.
- Undesired chronic effects of AEDs on cognitive ability, mood, weight (both gain and loss), childbearing, and sexual function.
- Cultural and financial stress, and some AED regimens can be inconvenient and threaten compliance.

Such issues are just as important, and can be as complex, in patients with mild epilepsy (or even a first seizure) as they are in those with intractable seizures.

The doctor should never forget [18]:

-The diagnosis of Epilepsy is eminently clinical. , por lo cual el manejo farmacológico debe iniciarse al realizarse el diagnóstico de epilepsia, aún cuando la etiología sea indeterminada.

-Successful treatment requires therapeutic management plans that are individualized for each patient.

-The goal is to provide each patient with maximal control of seizures without significant adverse effects from AEDs and psychiatric comorbidity, especially depression, profoundly affect quality of life.

-For a patient with epilepsy, independence, driving, employment, safety, and social stigma are very real and serious concerns.

-Although "no seizures, no side effects" should be the primary goal in management.

-The pharmacokinetic principles of antiepileptic treatment must be taken into account (absorption, apparent volume of distribution, binding to proteins, elimination, control of serum levels) [46].

The older AEDs all produce alteration of hepatic metabolism via alteration of the cytochrome P450 system.

Strong hepatic enzyme inducers: Phenytoin, Carbamazepine, Phenobarbital, and Primidone.

The newer antiepileptic drugs either have no hepatic-inducing properties or are only minimally inducing.

Recommendations to the patient [10,18] :

-Not ingestion of alcoholic beverage.

-Do not drive vehicles (except 3 years or more free crisis).

- Sleep at night no less than 8 hours.

-Avoid stressful situations and additional responsibilities.

-Do not work unprotected in heights, or in places that offer danger in case of crisis.

-Avoid great physical efforts.

-Do systematic study, not exhausting.

-Avoid spearfishing and swimming (unless watched).

-The patient must know that the effectiveness of the treatment is the suppression of the crises and not the disappearance of the inter-critical electroencephalographic anomalies.

-Orient registration with number, duration, time and severity of epileptic seizures.

Errors in the antiepileptic treatment [18]:

-Inappropriate positive diagnosis.

-Do not start when the diagnosis is made (wait for the EEG or imaging studies to impose it).

-Instart medication at full entry dose and not progressive.

-Initial use of polytherapy.

-No choice of the drug according to type of attack, syndrome or special group.

- Treatment of a unique crisis without individualized analysis.

-Interrupt him: during puberty, without crisis-free period or suddenly (sudden replacement) [47].

-Do not take into account the half-life of antiepileptics and their plasma levels.

-Do not take into account the interaction of drugs, or the combination of drugs with similar effects.

-Use of drugs that lower the epileptogenic threshold.

-Do not take into account the side effects of antiepileptic drugs.

-Consider the effectiveness of the treatment: disappearance of the inter-critical electroencephalographic anomalies and not the suppression of the crises (with normal functionality).

We must treat all epileptic patients?

-A single seizure in adults or children usually does not require treatment unless:

- there is evidence of a brain lesion or major abnormalities on the EEG
- particularly generalized spike-and-wave discharges.

-A first nonfebrile seizure between 2 and 5 years may be the first manifestation of epilepsy (myoclonic-astatic type) that will require vigorous treatment to prevent the development of epileptic status or epileptic encephalopathy.

-Rolandic spikes in children do not indicate the need for drug treatment unless seizures are frequent and upsetting to the family.

-If a second seizure would be hazardous to an adult, for reasons related to employment or driving, treatment may be warranted after a first isolated seizure, provided that excellent compliance can be anticipated and the seizure is not related to precipitating factors such as sleep deprivation [48].

The risk of recurrence followed by a first unprovoked crisis in children and adults varies from 27 to 71%. Most recurrences occur early, with approximately 50% of recurrences 6 months after the initial crisis and more than 80% in the first 2 years of the initial crisis. Late recurrences are unusual, but they can occur 10 years after the initial event [49].

A relatively small number of factors are associated with the risk of recurrence of the crises. The most important are the etiology of the crises, the electroencephalogram and whether the first crisis occurred in wakefulness or during sleep. Factors not associated with a significant change in the risk of recurrence include the age of debut, the number of crises in the first 24 hours and the duration of the initial crisis.

According to current concepts, the diagnosis of epilepsy after a single unprovoked crisis, associated with a high risk of recurrence, may give rise to the decision to initiate treatment or not.

It must be borne in mind that a therapeutic decision is not the same as a diagnosis and must be customized according to the wishes of the patient, the risk-benefit ratio in each specific case and the available options.

The physician should weigh the possibility of avoiding a second crisis and the risks that it entails, against the risk of adverse drug effects and costs for the patient.

When to start treatment with antiepileptic drug after a simple crisis [10,18]:

Definitely:

-With structural damage: Brain tumors, arteriovenous malformation and infection, such as abscess, herpetic encephalitis.

-Without structural injury: History of epilepsy in siblings (but not parents), Electroencephalogram with defined epilepsy pattern, History of previous symptomatic convulsion (convulsion in the context of an illness or childhood), Febrile crisis, which is a very controversial topic, History of an anterior brain injury, cerebral hemorrhage, infection of the Central Nervous System (CNS), head trauma and initial epileptic Status.

-Possible.

• Unprovoked seizure with any of the risk factors mentioned above-

-Probably not (although short-term therapy can be used)

• Alcohol abstinence

• Drugs abuse

• Epileptic crisis in the context of an acute illness (ie, high fever that can trigger simple febrile seizures, dehydration, hypoglycemia)

• A crisis immediately after an acute trauma to the head

• Specific benign epilepsy syndromes, such as benign epilepsy with centrotemporal tips.

• Crisis caused by excessive sleep deprivation (eg, college student at exam time)

Aspects to be considered after a single crisis (which creates a real uncertainty in the attending physician) [18]:

• Was it really an epileptic seizure?

• Was the first crisis safe?

• Are there risk factors for a second attack?

• Is the neurological examination abnormal?

• Is the EEG pathological?

• Is the structural study abnormal?

• Is the story of the brothers and parents known? Do you have epileptic seizures too?

• Can you be allowed to drive this person?

• Should there be limitations in your work?

• What are the risks of not treating the patient?

• What are the risks of treating the patient?

Indication of studies after a crisis:

The indication for a brain imaging study should be considered, depending on the clinical context (history and physical examination).

The Electroencephalogram (EEG) in general, should be obtained as soon as possible after the crisis.

Pseudoseizures can sometimes be difficult to diagnose and require prolonged video-EEG monitoring.

Initiation of the treatment [10,50]:

• Having established the diagnosis that it was an epileptic seizure and not a pseudoseizure, such as a syncopal episode.

• Correctly identify the type of epilepsy.

• Be certain that the risk of recurrence for that patient is high.

• The selection of DAE therapy should be carefully performed in relation to the type of seizure, severity, type of epilepsy or epileptic syndrome, the etiology and the triggering factor.

• Therapy should be initiated (preferably in monotherapy) at a low dose and gradually increased to an effective level to avoid side effects ("start low, go slow") [47.51].

• If there is toxicity with low doses that may be ineffective, gradually replace the first AED with a second drug.

• Some antiepileptic drugs usually require prolonged titration.

• If the attacks continue (without toxicity), increase the dose according to tolerance.

• If epileptic seizures still persist, the transition to another first-line drug (in a second monotherapy) can be assessed.

• If anticonvulsant monotherapy is not successful, adjuvant treatment with a second-line drug should be considered (biterapia).

• Rational polytherapy (selecting the association that best suits the characteristics of the patient and their epilepsy, taking into account the pharmacokinetic and pharmacodynamic characteristics of each DAE) has been defended, but remains speculative in relation to the best efficacy based on the use of AED with different modes of action.

• For the association of AED to imply increasing efficacy without increasing toxicity, the theoretical basis of rational combination therapy proposes to consider the mechanism of action of each drug, its spectrum, tolerability, and pharmacodynamic and pharmacokinetic interactions.

• In the event of continuous epileptic seizures, a reassessment of the differential diagnosis should be made and surgery considered.

Detention of treatment [52]:

There are no rules defined as to the best time or even the best way to proceed when deciding to suspend treatment.

• At 12 months, 60% -70% of treated patients will be crisis-free.

According to the recent considerations of a group of ILAE experts, it is estimated that epilepsy is resolved in subjects with an age-related epileptic syndrome who have reached the corresponding age or in those who have remained without seizures during the last 10 years. years and who have not taken antiepileptic medication for at least the past 5 years [49].

Predictive factors of relapse [18,49]:

• Epileptic syndrome, for example, Juvenile Myoclonic Epilepsy (JME)

• Underlying structural pathology

• Continuous epileptiform abnormality on the EEG

• Severe prolonged epilepsy before remission

• Increase in age

In children, it is possible to try to stop the medication after having been free of seizures for 2 years, while for adults the interval of absence of seizures before reducing and suspending an AED is 3 to 5 years.

The risk of recurrence of crises after having suffered unprovoked crises diminishes with time, although it never reaches the level of people who have never suffered a crisis. Most recurrences are early. Late recurrences are rare after 5 years. After 10 years without antiepileptic medication it is likely that the annual risk of crisis is very low.

Common precipitating factors of epileptic crisis [18]:

• Stress, sleep deprivation, fatigue and exercise, stroboscopic lighting (photosensitive epilepsy), alcohol consumption, omitting antiepileptic medication, medications that can reduce the seizure threshold, metabolic factors, menstruation (catamenial epilepsy), fever (infection) and hyperventilation.

Serum dosage of antiepileptic drugs [53]:

Although there are no randomized studies, a positive impact of pharmacological analysis on the clinical outcome in epilepsy has been demonstrated, the evidence from non-randomized studies and above all clinical experience does indicate that the measurement of serum concentrations of Antiepileptic Drugs (AED) of old and new generation, may have an important role to guide the management of the patient, provided that the concentrations are measured with a clear indication and interpreted in a critical manner, taking into account the entire clinical context, which in our opinion It's essential.

Situations in which measurements of AED are more likely to be beneficial, should include [47]:

1. when a person has reached the desired clinical result, with a view to establishing an individual therapeutic concentration, which can be used later to evaluate possible causes for a change in the response to drugs;

2. as an aid in the diagnosis of clinical toxicity;

3. to assess compliance, especially in patients with uncontrolled seizures;

4. to guide dose adjustment in situations associated with pharmacokinetic variability (eg, children, the elderly, patients with associated diseases, formulation of drug changes);

5. when the pharmacological change is foreseen (for example, in pregnancy, or when in other clinical circumstances a drug is added or eliminated);

6. to guide dose adjustments of antiepileptics with dose-dependent pharmacokinetics, especially phenytoin.

Some general indications for the measurement of serum concentrations of antiepileptic drugs [53]:

1. After the start of treatment or after adjusting the dose, when the doctor decides to aim for a pre-selected concentration for that patient.

2. Once the desired clinical response has been achieved, to establish the "individual therapeutic range."

3. to assist the physician in determining the magnitude of an increase in dose, especially with AED that show a dose-dependent pharmacokinetics (most notably, phenytoin).

4. When there are uncertainties in the differential diagnosis of signs or symptoms suggestive of AED toxicity related to concentration, or when toxicity is difficult to assess clinically (for example, in young children or in patients with mental disabilities).

5. When epileptic seizures persist despite an apparently adequate dosage.

6. When a pharmacokinetic alteration is suspected, due to factors related to age, pregnancy, associated diseases or drug-drug interactions.

7. To evaluate possible changes in the concentration of DAE in stable state, when a change is made in the formulation of drugs, including switches that have generic formulations.

8. Whenever there is an unexpected change in the clinical response.

9. When a bad compliance is suspected.

The therapeutic monitoring of the antiepileptic drug has been used as a tool to optimize the treatment of epilepsy for almost 50 years. Although solid evidence for its usefulness in improving clinical outcomes is scarce, it continues to play a role in the treatment of this disease [54].

However, the physician must take into account that, due to individual variation, many patients may require concentrations outside the reference ranges.

In many situations, patient management is best guided by the determination of "individual therapeutic concentration" defined as the concentration with which an individual is free from epileptic seizures, with good tolerability, or the best compromise between improvement in control of the crises and the adverse effects related to the concentration.

With this concept, serum monitoring of DAEs can provide important information for decisions about dose adjustments of most antiepileptic drugs in patients with unexpected treatment outcomes or in situations associated with pharmacokinetic disorders eg during pregnancy, in different disease states, in conjunction with drug interactions, and in certain age groups (children and the elderly), where the clinical evaluation of the effects of treatment can be particularly difficult.

Conclusion

There are general principles that the modern physician must take into account in the proper use of antiepileptic drugs to achieve a scientific management of the disease, with judgment and individuality. There are different drugs in active development, but even without effective therapy, the necessary investigations should continue in this regard.

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