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Approach to the Management of Refractory Epilepsy

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ABSTRACT

Epilepsy is a global public health problem. It affects 1-2% of the population. Between 70-80% of all patients with epilepsy are controlled with medical treatment and 20-30% are chronic refractory, which is considered refractory / drug-resistant epilepsy. 5-10% of these are candidates for surgery. Drug resistance is a major problem for the patient, with devastating consequences, which include persistence of seizures and morbidity derived from epilepsy, medication, social isolation, unemployment, decreased quality of life, and can include sudden death. The historical antecedents related to epilepsy surgery, the concepts of refractory epilepsy and ILAE considerations, the causes of pharmacologically intractable seizures, as well as the groups of surgically remediable syndromes are reviewed. The management of patient with refractory epilepsy is detailed, including the optimization of the initial pharmacological treatment, as well as the non-pharmacological treatment, which includes surgery and other alternative methods, and psychological and psychiatric management. To this end, the descriptors refractory / drug-resistant epilepsy, surgery in epilepsy, surgically remediable syndromes, pharmacological and non-pharmacological treatment were included in the Academic Google. The Medline, Scielo, Scopus and Medscape databases were used.

INTRODUCTION

Epilepsy is a global public health problem that requires an adequate response. It is a clinical condition with self-remission in up to 50% of cases [1]. According to reports from the World Health Organization (WHO), an estimated 50 to 69 million people suffer from this disease, the majority living in developing countries [2]. It can be stated that epilepsy affects 1-2% of the population [3,4]. Two million new cases occur in the world each year. The annual incidence of unprovoked epileptic seizures is 33-198 per 100,000 inhab / year, and the incidence of epilepsy is 23-190 per 100,000 inhab / year [5]. The global prevalence of active epilepsy varies from 2.7 to 41 per 1000 inhabitants, although in most reports the rate of active epilepsy ranges from 4-8 per 1000 inhabitants [5]. This disease, in turn, can lead to death, a danger that is not

taken into account and could be preventable [6]. International statistics show annual mortality rates of 2.1 per 100,000 inhabitants per year, varying from 1 to 8 in the different countries. The causes of death in epilepsy, therefore, must be identified and actions must be taken, including treatment and education, to avoid preventable deaths [7]. Special mention should be made of drug resistance in these patients. Between 70-80% of all patients with epilepsy are controlled with medical treatment and 20-30% are chronic refractory, which is considered drug-resistant epilepsy [8]. 5-10% of these are candidates for surgery [9-11]. Drug resistance is a major problem for the patient, with devastating consequences, including persistence of seizures and morbidity derived from epilepsy, medication, social isolation, unemployment, and decreased quality of life [9,12]. In turn, this condition carries a poor prognosis, with an increased risk of sudden death and a mortality rate of 1/200 inhabitants / year as a direct consequence of the crisis [13]. Some authors point out that mortality rates in cases refractory to medical treatment for all causes are lower in children aged 1-14 years (4.1 deaths / 1000 inhabitants / year) and increase with age (32.1 deaths per 1000 inhabitants / years between 55-72 years). In patients who are refractory to treatment, a significant health cost is also described, derived from the use of new and multiple drugs and a greater need for health care [3,14]. For all these reasons, the integral management of the patient with this disease is essential and the need to take into account the appropriate use of antiepileptic medication and surgery in patients with criteria, as part of non-pharmacological treatment [9]. To elaborate it, the Google Academic search engine and the descriptors refractory/drug resistant epilepsy, epilepsy surgery, surgically remediable syndromes, pharmacological and non pharmacological treatment were used. The Medline, Scielo, Scopus and Medscape databases were used.

Refractory epilepsy; historical background

In refractory epilepsy (or difficult to control / drug resistant), there is a risk of progressive increase of: cognitive impairment, behavioral changes, psychosocial dysfunction and psychiatric disorders. It is a serious medical problem [15,16], associated with decreased quality of life, adverse reactions to combination therapy, and higher mortality compared to the general population [17]. For this reason, the use of alternative treatments, including surgery, is justified [1]. We will relate some historical aspects of epilepsy surgery, which has been performed since time immemorial. There is evidence that this procedure was already carried out during the Neolithic period and probably, during the Mesolithic, in 8000 BC. For curative purposes. It is known that the ancient Egyptians made trepanations to treat the "evil of the gods" [18,19]. In Antiquity and the Middle Ages, cranial surgery was used to create an outlet for pathogenic humors and vapors, a method that was used for centuries in patients with epilepsy [1]. In the 19th century, trepanation was carried out with rational bases and William Gowers used it in those cases whose cause was attributed to a cranial injury with bone depression or that the onset of seizures suggested the etiology located on the surface of the brain, the motor region and areas adjacent to the Rolando fissure [20,21]. Bouchet and Cazauvieilh first described the association between epilepsy and hippocampal sclerosis in 1825, based on the anatomopathological study available at the time of the brains of patients with “mental alienation crisis”. They considered that the lesions were a consequence and not a cause of epilepsy, a term that was used exclusively for generalized seizures, locating the origin of the epilepsy in the medulla oblongata [22,23].

Benjamin Dudley of the University of Transylvania, Kentucky, reported in 1828 five patients with focal post-traumatic epilepsy treated with trepanation. In 1879, William Mac Ewen resected a frontal meningioma in a patient presenting with epileptic seizures [21]. In the late 19th century, Hughlings Jackson (1880) recognized partial seizures as epileptic and associated limbic seizures (which he termed "intellectual seizures" or "dream states") with lesions in the mesial temporal structures. His contemporaries, the neuropathologists Sommer (1880) and Bratz (1899), suggested the possible epileptogenic role of hippocampal sclerosis [24,25]. In the modern era Victor Horsley is recognized as the first to publish in 1886 his experience in the surgical treatment of epilepsy. Some consider that the history of epilepsy surgery began with his first surgery on a Hughlings Jackson patient, with focal motor seizures related to a depressed skull fracture. This intervention was successfully performed in a 22-year-old patient with focal post-traumatic epilepsy on May 25, 1886 [18]. The authors who had preceded him pointed out numerous postoperative

complications, mainly septic, but good results in controlling the disease. The Horsley et al. Patients had mainly neocortical lesions whose location was based on ictal semiology. This author reported three cases of post-traumatic epilepsy, operated by him by using cortical electrical stimulation to identify the areas of the motor cortex [1]. It is considered that Horsley and Mac Ewen were the first to locate and remove epileptogenic lesions, identifying symptomatogenic areas according to the pioneering works of Jackson [26, 27]. The introduction of the electroencephalogram in 1929, by Hans Berger, was a great step forward in the field of epileptology, revolutionizing the diagnosis of the disease [1]. In the 1930s, the works of Penfield and Jasper in Montreal [28] took up this field by introducing electrocorticography, after the introduction of the Electoencephalogram (EEG) at the end of that decade, which allowed a better localization of the area to be resected. Bancaud and Talairach in Paris developed stereoencephalography or recording with deep electrodes in the 1960s, with a resurgence of interest in surgical therapy, and in the 1970s video-EEG was introduced, which is of crucial importance in pre-surgical evaluation. The first telemetric recording with deep electrodes was carried out by Paul H. Crandall, being a fundamental element in this evaluation in the last 30 years [27]. Later, a stage of decline occurred, as the expected results were not observed in surgery, more because of the inadequate selection of the patient than because of the technique itself [28]. With the advent of microneurosurgery, the new concepts associated with epileptogenesis, modern Computed Tomography (CT) images, Positron Emission Tomography (PET) and especially Nuclear Magnetic Resonance (MRI), increased significantly from the 90's the interest in epilepsy surgery [29]. These studies are useful and essential in the presurgical evaluation stage.

It is the opinion of the authors dedicated to this topic, that the surgical treatment of epilepsy has offered relief for countless patients, as confirmed by many neurosurgery centers around the world. As a therapy to consider, it may be appropriate in selected cases. However, if the diagnosis of epilepsy is established and there is no surgical criterion, treatment with Antiepileptic Drugs (AEDs) should be optimized [30].

Clinical aspects to consider in refractory epilepsy

It is a basic problem to define the refractory criterion, with a view to the use of non-pharmacological treatments, including surgery, with the aim of improving the quality of life of patients, by trying to free them from seizures. The challenges that arise are, therefore: Defining a medically intractable epilepsy and the epileptogenic zone, its relationship with adjacent functional areas and the possible impact on quality of life after a possible successful surgical intervention [31]. Various authors have widely debated the criterion of intractability and various conceptions have been handled in this regard. One of the concepts issued was: Refractory or medically intractable epilepsy is that which lacks satisfactory control of epileptic seizures, despite adequate medical treatment with the maximum tolerated doses [32]. Lack of satisfactory control is equal to Individual quality of life, since undesirable adverse effects are individual. A monthly crisis can be absolutely insignificant for one subject and overwhelming for another depending on aspirations, employment, expectations, etc. of each, that is, of their concept of quality of life [3]. Individualized maximum tolerated dose is equal to the highest dose a patient can take without experiencing recurring undesirable side effects. Not necessarily related to the plasma concentration of the drug. This dose is reached by increasing the amount of Antiepileptic Drug (AED) to take until it experiences the recurrent adverse effect or dose dependent and then decreasing it until it disappears, the latter amount would be the maximum tolerated dose [3]. It should be noted that after the failure of 2 first-line AEDs (Phenytoin, Carbamazepine, Valproate, Phenobarbital, Primidone) the possibility that new or additional AEDs will have good results is low and the possibility of surgery should be evaluated [32,33]. It is considered that, if there has been no response to the use of two Antiepileptic Drugs (AEDs), the control with the association of a third may be less than 5% [34,35]. The Executive Committee of the International League Against Epilepsy (ILAE), during the 28th International Congress of Epilepsy in Budapest, Hungary (2009), defined drug-resistant epilepsy as the failure of two treatment programs with Antiepileptic Drugs (AEDs), properly selected, and tolerated and used in monotherapy or combination regimens (mono or combination therapy) in order to guarantee the maintained condition of freedom from crisis

[16,30,36]. The terms refractory, drug-resistant, drug-resistant epilepsy, and drug-intractable epilepsy have been used interchangeably to denote the absence of seizure control despite AED medication [3]. Drug-resistant epilepsy implies a significant impact on quality of life (due to seizures, adverse effects to AEDs or both), alters psychosocial functions, decreases academic functioning, and limits the social opportunities of patients. It is associated with increased mortality, including deaths from accidents, and suicides. The risk of fatal accidents in people with epilepsy is 2.5 times higher than in the general population [37].

There are factors that allow early identification of patients at risk of drug resistance [15,38]:

1) Failure of the first AED.

2) Presence of early risk factors for epilepsy, eg occurrence before 5 years of age, head trauma with loss of consciousness> 30 min, meningoencephalitis, neonatal seizures or febrile seizures.

3) Anomalies in the temporal lobe demonstrated by Magnetic Resonance.

In general, the most important predictor of drug resistance in children and adults is difficulty in controlling attacks early in the course of the disease. Additional predictive factors have been reported in children such as high initial seizure frequency, symptomatic epilepsies, intellectual disability with intelligence quotient (IQ) <70 [38].

Among the causes of intractable seizures are the following, which are very important when making a differential diagnosis of surgically treatable epilepsies: [39]

1 - Incorrect diagnosis of Epilepsy.

2 - Inadequate classification of seizures or epilepsy.

3 - Inappropriate choice of drug for the type of seizure, insufficient dose and / or wrong combinations.

4 - Defects in intestinal absorption or patients who unusually metabolize the drug.

5 - Maintained stress, home unhappiness, emotional or personality changes.

6 - Structural brain injury as a cause of Epilepsy (active or scarring).

7 - Progressive diseases of the Central Nervous System (metabolic or otherwise).

Most authors agree that a clinical - electroencephalographic diagnosis can be established of at least 2 forms of Temporal Lobe Epilepsy (TLE): Mesial Temporal Lobe Epilepsy, whose anatomical substrate is almost always hippocampal sclerosis and lateral epilepsym, or neocortical less well defined and with findings that overlap those of the previous form, which is much more frequent [40]. Within the group of drug-resistant focal epilepsies, the most studied has been Temporal Lobe Epilepsy (TLE), followed by Frontal Lobe Epilepsy (FLE), the latter within Extratemporal Epilepsy (EE) [41,42]. Temporal Lobe Epilepsy (TLE) is the most common type of focal epilepsy, with the mesial temporal structures being the ones that are mainly involved in the genesis and spread of interictal epileptic discharges and epileptic seizures. This disease, caused mainly by hippocampal mesial sclerosis [43,44], has been conceptualized as a neural network disease that, in addition, can involve brain regions far beyond the temporal-mesial lobe [45,46]. Frontal lobe epilepsy (FLE) is the second most common form of focal epilepsy [43,44,47].

However, a group of surgically remediable syndromes are recognized, due to their excellent evolution after surgery and repeated poor response to AEDs. These are entities with defined clinical and laboratory characteristics, which have been shown to "cure" or improve after surgery in a significant percentage of cases [3].

- Temporal Lobe Epilepsy (TLE): Includes mesial temporal lobe epilepsy associated with hippocampal sclerosis (the most common cause of drug-resistant seizures), and lateral or neocortical temporal lobe epilepsy [48,49].
- Extratemporal epilepsies: Includes frontal lobe epilepsies (second cause of drug-resistant focal seizures), parietal lobe epilepsy, occipital lobe epilepsy [50-52].
- Epilepsies of multilobar regions (sensorimotor cortex, frontoparietotemporal opercular region, and the temporoparietooccipital junction) [50].
- Diffuse hemispheric syndromes: hemimegalencephaly, Sturge Weber syndrome, Rassmussen encephalitis [53,54].

Management of the patient with refractory epilepsy

The differential diagnosis of epileptic seizures is one of the most important points in the approach to drug-resistant epilepsy, since patients with non-epileptic cerebral seizures must obviously be excluded [55,56]. After defining the criterion

for an epileptic-type cerebral seizure, the concept of refractoriness should be considered and the possibilities of pharmacological treatment must be emphasized [36]. The identification of patients with refractory epilepsy is essential to optimize pharmacological treatment, initiate the evaluation process to determine whether they are good surgical candidates and, depending on each case, promote surgery or other non-pharmacological alternatives [30]. There are currently more than two dozen Antiepileptic Drugs (AEDs) available for the treatment of seizures. However, according to Reddy [57], the number of patients with drug-resistant epilepsy has been on the rise in recent years, approximately estimating that, of the total number of epileptic patients worldwide, 40% show resistance to AEDs. In addition, these drugs are used for symptomatic treatment, so they are only capable of controlling the occurrence of epileptic seizures (ES), showing little or no impact on the underlying disease [57,58]. A rational combination therapy is recommended in patients with refractory epilepsy, seeking combinations of AEDs that increase efficacy (supraditive effect) and minimize adverse effects (infraditive effect) [59,60]. It is also recommended to combine AEDs with different mechanisms of action and with a complementary spectrum of action to try to cover all types of ES in the patient [61], avoid AEDs with an overlapping toxicity profile and adjust doses according to the characteristics of the patient (age, gender, physical condition and comorbidity), consider that using more than 2 AEDs usually associates more adverse effects than a real improvement in the control of ES (especially in the elderly or in polymedicated patients) and individualize the treatment to the type of ES , epilepsy and even epileptic syndrome depending on the etiology or even the gene [30]. It is considered that, in all patients with drug resistance criteria, the surgically remediable syndrome should be defined and promptly sent to an epilepsy surgery center to undergo presurgical evaluation, since surgery has been the only curative therapeutic alternative that has favorably impacted the evolution of the disease in terms of freedom from crisis, considerably improving the quality of life of the patient [62].

Non-pharmacological treatment

There are today multiple alternatives and treatment options for people with drug-resistant epilepsy, leading to epilepsy surgery. The recognition that people with drug-resistant epilepsies can benefit from surgical treatment has increased substantially in recent years, taking into consideration that careful patient selection is essential for safe and effective surgery. Epilepsy surgery is defined as any neurosurgical intervention, regardless of whether it is resection, disconnection or stimulation surgery, and whether or not there is a base lesion substrate, in patients who meet drug resistance criteria [63]. The basic problem of epilepsy surgery is the selection of patients and its objective is to improve their quality of life, by suppressing or significantly reducing seizures. The challenges that arise in relation to this treatment are: determining the location and extension of the Epileptogenic Zone (EZ) and its relationship with adjacent functional areas, anticipating the impact of the quality of life, the cognitive and emotional state of the patient after performed the intervention, as well as the possible impact of the operation on the social situation of the patient [64]. The main problem in determining the Epileptogenic Zone (EZ) is that there is no diagnostic method or combination of these that allows to accurately determine the location and extent of the cortical area that must be resected to ensure that patients eliminate seizures. High-resolution Magnetic Resonance (MR) the problem could be described as the demonstration that a focal lesion defined by MR is actually epileptogenic, which is guaranteed with the use of prolonged video-EEG monitoring [65].

The surgical treatment modalities that exist for these patients are [66-68]:

- Resective surgeries:
- Non-lesional focal resection: corticotomies, frontal lobectomy, occipital lobectomy, resections of the temporal lobe in its modalities of selective resection (amiadal hypocampectomy) and non-selective.
- Lesional focal resection: Lesionectomy with corticotomy
- Multilobar resection: Hemiferectomy and its variants (functional hemispherectomy, hemidecortication, perinsular hemispherotomy, and others)

Disconnection surgery: Callosotomy, Multiple subpial transection.

Neuromodulation (includes invasive and non-invasive therapies)

- Neurostimulation (Central Nervous System and Peripheral Nervous System)

- Responsive Neurostimulation (NeuroPace®)
- Non-Invasive Brain Stimulation: Transcranial Magnetic Stimulation, Direct Current Stimulation
- Gene Therapy

Radiosurgery: Stereotactic Gamma Knife.

Lasser ablation: Minimally invasive procedure performed with laser, under the guidance of Magnetic Resonance (MR).

Undoubtedly, surgical therapy is more efficient than pharmacotherapy and remains the only curative treatment modality with a level of evidence A. Surgery produces global and specific improvement. This improvement starts early (in the first 3 months), is sustained in the long term and is clinically significant [67]. Numerous case studies and observational studies about the efficacy of epilepsy surgery have been conducted. Because of the difficulty of study design and ethical implications in delaying surgical therapy, randomized controlled trials comparing medical versus surgical treatment for refractory epilepsy were lacking until 2001. Currently, three randomized controlled trials have shown the superiority of surgery compared to continued medical treatment in patients with drug-resistant epilepsy, not only for seizure control but also for quality of life [67].

Prognosis of surgery

The postsurgical evolution varies according to the underlying pathology. The percentage of success of surgical treatment in extratemporal surgery (30-40%) is lower than that of patients with temporal epilepsy (> 70%). This distinction between TLE and extratemporal is important to optimize the selection of patients for surgery, those with TLE are excellent surgical candidates, while extratemporal epilepsy more often requires invasive records to identify the epileptogenic area and delineate the eloquent cortex [69]. The benefits of TLE surgery have been proven by randomized controlled trials that provide class 1 evidence of its efficacy, and by a large number of multicenter trials around the world that provide consistency of efficacy. In General, the prognosis of epilepsy surgery is variable, and depends basically on: a) possibility of complete resection b) disconnection of the "epileptogenic zone" c) interruption of the "epileptogenic network"[69].

General complications of epilepsy surgery

In epileptic patients who are candidates for surgical treatment, the rapid discontinuation of AEDs is required during the presurgical evaluation of Video-Electroencephalogram (v-EEG) monitoring [70-73]. However, this procedure can trigger the so-called “rebound effect”, which is characterized by transient seizure generalization or even prolonged increase in frequency of partial seizures [70]. Other adverse events observed during the presurgical evaluation of v-EEG monitoring could be the status epilepticus or sudden unexpected death in epilepsy [74,75]. These are dramatic events, but also uncontrolled seizures during the rebound effect could be damaging, because they were associated with development of brain hypoxia and neurodegeneration. The risk of adverse events and rebound phenomena can be different in relation to administered AEDs, but we still lack an easily quantifiable seizure prediction indicator to control the occurrence of Spontaneous Recurrent Seizures (SRSs) during the presurgical evaluation of patients with refractory epilepsy [76]. A variety of complications may occur after epilepsy surgery. However, the majority of these complications result in only temporary impairment, as the effects tend to com-pletely resolve over time. Permanent neurologic complications associated with the most common epilepsy surgical procedure, temporal lobe resection, are low [77]. The complications of the intervention can be those of any surgical procedure that involves brain structures, such as neurological deficits, vascular sequelae (deep vein thrombosis, hemorrhage and subdural hematoma) and infectious (meningitis, brain abscess) [77]. A total of 6735 patients with epilepsy who had undergone the epilepsy surgery were studied by three independent researchers to find the relevant studies published from January 1, 2009, until the end of January 6, 2019 [78]. The prevalence of major and minor complications was 5.4% and 3.2% respectively. The prevalence of complications related to the temporal epilepsy surgery and the extra-temporal epilepsy surgery based on 3 studies was 7.9% and 8.2 % respectively. The frequency of neurological and surgical complications after epilepsy surgery was 4.4% and 4.1% respectively. The overall rate of complications caused by epilepsy surgery was reasonably low (5%), implying that epilepsy surgery especially temporal lobe resection can be safe preferably when performed by an experienced surgeon. The risks associated with surgical resection are relatively low, with low morbidity, and mortality of less than 1% in most of the series reported, in general.

Mortality as a result of epilepsy surgery in the modern era is rare [78].

NEUROMODULATION

Invasive brain stimulation technologies are allowing the improvement of multiple neurological diseases that were non-manageable in the past. Epilepsy is one of the conditions that can benefit from these emerging technologies [79]. Neuromodulation allows the possibility to treat different pathologies as reversible and non-lesional alternatives. The term "neuromodulation" is essentially electrical stimulation of the nervous system in order to modulate or modify a specific function (as in movement disorders, pain, epilepsy), and can be delivered in different ways: through stimulation over skin surface, peripheral nerve stimulation, cortical stimulation, or deep brain stimulation [79]. The choice of neuromodulation techniques has greatly increased over the past two decades. While Vagal Nerve Stimulation (VNS) has become established, newer variations of VNS have been introduced. Deep Brain Stimulation (DBS) is now approved for clinical use. In addition, Responsive Neurostimulation (RNS) has provided exciting new opportunities for treatment of drug-resistant epilepsy. While neuromodulation mostly offers only a 'palliative' measure, it still provides a significant reduction of frequency and intensity of epilepsy [80].

VAGUS NERVE STIMULATION (VNS)

This was the first neuromodulator device approved for use by the Food and Drug Administration (FDA) of USA in 1997. It was initially approved for use in patients older than 12 years, but recently in 2017, approval has also been given for use in children more than 4 years of age with partial seizure with RE. It's an invasive, open-loop device. A generator implanted in the chest wall intermittently stimulates the vagus nerve with pre-programmed current and timing. It is one of the most widely available techniques worldwide [80]. It consists of effective stimulation mediated primarily by afferent fibers A and B of the vagus nerve. VNS appears to have an anti-crisis (increases the threshold), abortifacient (culminates the crisis) and potentially anti-epileptogenic (chronic modulatory process) effect. It is the only neuromodulation modality approved by the Food Drug Administration (FDA) [81]. It is an effective and safe adjunctive therapy. It is well tolerated in children and adults (> 50,000 patients).

- Seizure frequency decreases (50% reduction in 50% of patients), but seizure freedom is rarely achieved (4-5%), many patients do not benefit
- There are no criteria to differentiate responders and non-responders

The effectiveness of vagus nerve stimulation improves over time. Reduction of seizures to a considerable degree usually occurs within a few months after gradually increasing the intensity or rate of the stimulation pulse. Long-term analysis has shown VNS to be efficacious in focal, generalized as well as syndromic epilepsy [82]. VNS device ushered in the modern age of neurostimulation. It is the only neuromodulation device approved for use in children. Epileptologists have extensive experience with the device and implantation is relatively simpler. It can be used to treat both focal and generalized epilepsy. Additional unique benefits include mood elevation and is the device of choice for patients with co-existent depression. Some disadvantages include poorer efficacy as compared to other modalities, MRI incompatibility and difficulty in device removal due to adhesion formation [80].

Deep brain stimulation (DBS)

In DBS the electrodes are directly implanted into the deeper epileptogenic targets in the brain to abort the episode. It is an invasive, open-loop neuromodulator device. Although many targets were studied for use by DBS, efficacy in Anterior Nucleus (AN) of thalamus was the first to be established. Direct targeting of the anteroventral AN near the mammillothalamic tract has been shown to be most efficacious [83,84]. DBS seems to be effective for both focal and generalized seizures, although maximum benefit seems to be in temporal lobe epilepsy. Although the efficacy seems to be slightly higher than VNS, DBS requires more frequent battery changes due to higher stimulation parameters and its more expensive. Other disadvantages are the risk of target mismatch and a more elaborate surgical procedure as compared to VNS.

Non-invasive brain stimulation

It basically comprises Transcranial Magnetic Stimulation (TMS), Direct Current Stimulation (DCS). Repetitive TMS (rTMS) should be considered in the future as a relatively safe and inexpensive non-invasive therapeutic method in patients with drug-resistant epilepsies. It has been shown in recent years that low frequency rTMS ≤ 1Hz can reduce the frequency of

seizures, and the epileptiform discharges, mainly in those patients with epileptogenic areas located in the cortex such as malformations of cortical development [85]. The antiepileptic efficacy of rTMS should be determined in randomized and controlled clinical trials that make it possible to evaluate the placebo effect, clarify methodological aspects of the technique, inclusion criteria for patients, effects of AED, and determine the evolution measures [85]. There are other options to consider when the patient is not a candidate for any type of surgical modality, namely:

Ketogenic diet

The Ketogenic Diet (KD) is a modality of treatment used since the 1920s as a treatment for intractable epilepsy. It has been proposed as a dietary treatment that would produce similar benefits to fasting, which is already recorded in the Hippocratic collection. The KD has a high fat content (90%) and low protein and carbohydrate. Evidence shows that KD and its variants are a good alternative for non-surgical pharmacoresistant patients with epilepsy of any age, taking into account that the type of diet should be designed individually and that less-restrictive and more-palatable diets are usually better options for adults and adolescents [86]. The ketogenic diet (and Atkins most used in adults) increases the amount of fat intake, increases the production of ketone bodies and the control of seizures and has been used more in children. Its objective is to maintain the state of ketosis, reduce seizures, improve quality of life and cognitive function (attention, learning, memory, etc.). Approximately 50% of patients have a 50% decrease in seizures after 6 months of treatment [87]. The evidence suggests that KDs could demonstrate effectiveness in children with drug-resistant epilepsy, however, the evidence for the use of KDs in adults remains uncertain. Authors identified a limited number of studies which all had small sample sizes. Due to the associated risk of bias and imprecision caused by small study populations, the evidence for the use of KDs was of low to very low certainty [88].

Cannabidiol

There is recent and interest in the potential use of marijuana and one of its active substances, Cannabidiol (CBD) (non-psychotropic compound) in the treatment of refractory epileptic seizures and catastrophic epilepsies, however, the data in humans they are limited and do not allow conclusions to be drawn [89-92]. Several studies showed promising results for treating special epileptic encephalopathies, but the efficacy for treating epilepsy in general is still under investigation [93]. The Therapeutic Potential of Cannabidiol (CBD) in seizure disorders has been known for many years, but it is only in the last decade that major progress has been made in characterizing its preclinical and clinical properties as an antiseizure medication. The mechanisms responsible for protection against seizures are not fully understood. CBD has a low and highly variable oral bioavailability, and can be a victim and perpetrator of many drug-drug interactions [94]. A pharmaceutical-grade formulation of purified CBD derived from Cannabis sativa has been evaluated in several randomized placebo-controlled adjunctive-therapy trials, which resulted in its regulatory approval for the treatment of seizures associated with Dravet syndrome, Lennox-Gastaut syndrome and tuberous sclerosis complex [95]. Despite impressive advances, significant gaps in knowledge still remain. Areas that require further investigation include the mechanisms underlying the antiseizure activity of CBD in different syndromes, its pharmacokinetic profile in infants and children, potential relationships between plasma drug concentration and clinical response, interactions with other co-administered medications, potential efficacy in other epilepsy syndromes, and magnitude of antiseizure effects independent from interactions with clobazam [94].

Psychological and psychiatric care

This is an aspect in the comprehensive management of the patient with refractory epilepsy, which must be taken into account, whether the patient is a candidate for surgery or not, since people suffering from this disease experience discriminatory behavior in many areas of life, with a Associated psychiatric comorbidity, all of which implies that it is considered a complex pathology, with social, psychobiological and economic consequences [96]. Indeed, there is a general consensus that the incidence of neurobehavioral disorders is higher in patients with epilepsy than in the general population, even more in patients refractory to treatment [97,98]. The presentation of psychotic disorders, bipolar affective disorders, depression, mania, suicidal behaviors, and anxiety and personality disorders have been described in patients with refractory epilepsy. All this is feasible to occur in patients with

refractory epilepsy with surgical criteria or not [99,100]. The incidence of psychiatric pathology in these patients implies the need to take this aspect into account.

CONCLUSIONS

• Refractory epilepsy involves a major health problem, with devastating consequences, including decreased quality of life and even the risk of sudden death.

• The refractoriness criterion must be defined after the establishment of effective and timely pharmacological management.

• Non-pharmacological management of patients, including surgery and other alternative methods, is used with satisfactory results.

• The psychological or psychiatric management of patients refractory to treatment should not be ignored.

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