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Management and Assessment of the Patient with Refractory Epilepsy: Some Considerations

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ABSTRACT

Introduction: Pharmacological resistance in patients with epilepsy is a major problem, with devastating consequences, implying a poor prognosis, including mortality. In this article we will specify the conceptual aspects of refractoriness in epilepsy and the necessary considerations in the pre-surgical clinical evaluation of patients who may be candidates for surgery.

Methods: For its elaboration, the Google Academic search engine was used and the descriptors refractory epilepsy, candidates for surgery in epilepsy, medical intractability, causes of intractable seizures, consequences of uncontrolled epilepsy, surgically remediable epilepsy syndromes, pre-surgical evaluation. The Medline, Scielo, Scopus and Medscape databases were used.

Results: Aspects related to non-pharmacological management and the role of surgery in epilepsy, the concepts of medical intractability, the consequences of uncontrolled epilepsy, the causes of intractable epileptic seizures and the elements to be taken into account in epilepsy were reviewed. pre-surgical evaluation, specifying surgically remediable syndromes and the corresponding investigations.

Conclusions: Epilepsy surgery has been increasingly recognized as a viable non-pharmacological treatment for patients with medically refractory epileptic seizures, which must be performed in a timely manner. An adequate pre-surgical evaluation must be carried out, in order to specify the surgically remediable syndromes and, therefore, an adequate selection of the candidates and a consequent post-surgical evolution.

INTRODUCTION

Epilepsy is a public health problem that requires an adequate response [1,2]. It affects 1-2% of the world population [3] and 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 [4]. About 70-80% of all patients with epilepsy are controlled with medical treatment and 20-30% may be chronic refractory [1,5,6], although some authors consider that up to 40% of patients may be of difficult pharmacological control [7,8]. It is generally agreed that about a third of patients with epilepsy are refractory/resistant to medical treatment [9,10]. Of these, 5-10% are candidates for epilepsy surgery [11,12]. Pharmacological resistance is a major problem for the patient, with devastating consequences, including seizure

persistence and morbidity derived from epilepsy, medication, social isolation, unemployment and decreased quality of life [1,13,14]. It also implies a poor prognosis, with a mortality rate of 1/200 inhabitants/year as a direct consequence of the seizures [11]. Some authors point out that mortality rates in cases refractory to medical treatment for all causes increase with age (32.1 deaths per 1000 inhabitants/year between 55-72 years) [15-17]. An increased risk of sudden unexplained death is also described [7,18], as well as a significant health cost derived from the use of new and multiple medications and a greater need for health care [19,20]. Taking this into consideration, a comprehensive management of patients with difficult-to-control epilepsy is necessary and, therefore, non-pharmacological treatment is justified, including surgery and other alternative methods [1].

METHODS

In this article we will specify the conceptual aspects of refractoriness in epilepsy, surgically remediable syndromes and the necessary considerations in the pre-surgical clinical evaluation of patients with refractory epilepsy who may be candidates for surgery, with the aim of make an adequate selection and therefore the post-surgical results are satisfactory. For its elaboration, the Google Academic search engine was used and the descriptors refractory epilepsy, candidates for surgery in epilepsy, medical intractability, causes of intractable seizures, consequences of uncontrolled epilepsy, surgically remediable epilepsy syndromes, pre-surgical evaluation. The Medline, Scielo, Scopus and Medscape databases were used.

RESULTS

Non-pharmacological management: surgery in epilepsy

Comprehensive care for patients with epilepsy can be divided for educational purposes into prophylactic/preventive, pharmacological, non-pharmacological, and psychological/psychiatric [21]. In refractory epilepsy (or difficult to control/drug resistant) there is a risk of progressive increase in cognitive impairment, behavioral changes, psychosocial dysfunction, psychiatric disorders and even mortality. For these reasons, the use of alternative methods, including surgery, is justified [2]. In the last years, epilepsy surgery has been increasingly recognized as a viable non-pharmacological treatment for patients with medically refractory seizures. Unfortunately, it is often 20 years before patients are referred for evaluation for epilepsy surgery [22]. This delay is probably due to the perception of some health professionals regarding epilepsy surgery as a "last resort" procedure. Most epilepsy centers define intractability as the failure of at least 2 or 3 first-line Anti-Seizure Medications (ASM) [23].

However, many doctors define medical intractability differently. They will often attempt numerous ASM changes and readjustments, before referral for pre-surgical evaluation is considered, although the chance of being seizure-free is only 5%. The introduction of newer ASMs with better tolerability and fewer drug interactions has had a significant impact on the treatment of epilepsy, as efficacy can be optimized with fewer dose-limiting adverse effects and the possibility of monotherapy use. However, a significant proportion of patients still suffer from intractable epilepsy. In addition, the epileptogenic process itself produces interictal dysfunction with adverse consequences on cognition and mood, which may be irreversible, especially in children. After failure of 2 first-line ASMs, the probability of seizure freedom with additional therapeutic regimens may be as low as 5-10% [24].

Some studies support the idea that early surgical intervention can be beneficial in the quality of life of patients and the improvement of cognitive functions and their social incorporation [25]. Bernhardt and Cascino, in a combined cross-sectional and longitudinal analysis in patients with drug-resistant temporal lobe epilepsy, demonstrated progressive neocortical atrophy (atrophy of temporomesial structures, including the hippocampus and endorhinal cortex) over a mean interval of 2.5 years that is distinct from aging. normal, probably representing damage induced by epileptic seizures. The cumulative nature of the atrophy underlies the importance of early surgical treatment in this group of patients. The analysis confirmed that progressive atrophy in TLE is related to the duration of epilepsy and not to age [26,27].

A study by Engel et al also showed that early surgical treatment may be beneficial. For patients who had mesial temporal lobe epilepsy and disabling seizures for no more than 2 consecutive years after adequate trials of 2 ASMs,

resection surgery plus drug treatment resulted in a decreased likelihood of seizures for at least 2 years after treatment, as well as improvement in health-related quality of life, than continuation of ASM treatment alone [28].

Medical intractability

The identification of patients with refractory epilepsy is essential to optimize pharmacological treatment, initiate the evaluation process to determine if they are surgical candidates and, depending on each case, promote surgery or other non-pharmacological alternatives [29].

Refractory or medically intractable epilepsy is considered to be epilepsy without satisfactory control of epileptic seizures, despite appropriate medical treatment with the maximum tolerated doses [30]. The individualized maximum tolerated dose is equal to the highest dose that a patient can take without experiencing recurrent undesirable adverse effects, not necessarily related to the plasma concentration of the drug. This dose is reached by increasing the amount of Antiseizure Medication (ASM) to be taken until the recurrent or dose-dependent adverse effect is experienced and then decreasing it until it disappears, this last amount would be the maximum tolerated dose.

It should be noted that after the failure of two first-line ASM (Phenytoin, Carbamazepine, Valproate, Phenobarbital, Primidone) the possibility of new ASM producing good results is low and surgery should be considered [30,31]. It is considered that, if there has been no response to the use of two ASM, control with the association of a third may be less than 5% [32]. Specifying that a patient is a carrier of epilepsy that is difficult to control pharmacologically is necessary to define the course of action to follow. However, the definition of intractability has been widely debated and several conceptions have been handled in this regard. The different experiences and criteria of the researchers were summarized by Berg, who considered that in order to reach a consensus, practical guidelines for researchers in this field could be considered [23] as there is no agreement on this.

The Executive Committee of the International League Against Epilepsy (ILAE) during the 28th International Congress of Epilepsy in Budapest, Hungary (2009), considered as medically resistant Epilepsy the failure of two treatment programs with ASM tolerated and appropriate (in mono or polytherapy) in order to ensure that the patient is free of seizures in a sustained manner. According to this concept, seizures persist and seizure-free status is not achieved with the management of Antiseizure Medications (ASM) [33,34].

It is our opinion that in the concept of refractoriness, treatment time should be included and, like Gillian, we consider that the most conventional definition includes the failure of at least three first-line antiepileptic drugs, in a period of at least 2 years [35]. In a shorter period, it is difficult to determine the refractoriness of a patient, according to our experience. Determining intractability also requires an understanding of how seizures affect patients' quality of life in terms of their psychological, interpersonal, and occupational functions. For example, even as few as 2 or 3 crises a year can disable a person whose occupation requires transportation by motor vehicle. A monthly crisis can be absolutely insignificant for one subject and overwhelming for another depending on aspirations, employment, expectations, etc. of each one [36]. With the approval of several newer ASMs and vagus nerve stimulation in recent years, more treatment options are available. However, long-term ASM trials in patients with well-defined and surgically remediable epilepsy (eg, hippocampal sclerosis or a well-defined structural lesion) offer a diminishing chance of seizure freedom (5-10%). and delay surgical treatment that can substantially reduce or perhaps eliminate seizures [37]. Therefore, it is of utmost importance to recognize that patients with location-related epilepsy with hippocampal sclerosis or a well-defined lesion have a universally poor prognosis with medical treatment, but a good prognosis with surgical treatment. These patients must be identified early in life before the psychosocial consequences of prolonged disability preclude useful rehabilitation.

Consequences of uncontrolled epilepsy

Patients with uncontrolled epilepsy often have low self-esteem, impaired social relationships, and reduced occupational functions [38]. The evidence in the literature supports the idea that patients with more frequent epileptic seizures have a worse quality of life than those with fewer seizure events. Quality of life decreases as seizure frequency increases to 10-12 per year. Mood disorders also occur more frequently in

patients with epilepsy than in patients with other medical conditions with a similar degree of disability. Approximately 20-30% of patients with epilepsy have a comorbid mood disorder. In patients with Temporal Lobe Epilepsy (TLE), approximately 50% have concomitant mood disorders consisting of depression and anxiety [38]. Patients with intractable epilepsy also have loss of autonomy, as they cannot drive and are often shielded from responsibility by family members for fear of getting hurt. Indeed, Gilliam et al reported that patients with intractable epilepsy report driving, independence, and employment as their most common concerns [39].

Occupational status is also affected in patients with intractable epilepsy [40]. Jacoby and his colleagues also found that reduced levels of employment were associated with worsening seizure control [41]. Intractable epilepsy is also associated with reproductive endocrine disorders, such as polycystic ovary syndrome, hypogonadotropic hypogonadism, and anovulatory cycles. Some of this increased risk is associated with certain ASMs, such as valproic acid. Epilepsy patients may also have reduced libido and reduced sexual arousal; this may be related in part to the older enzyme-inducing ASMs [42]. Recent evidence indicated that these enzyme-inducing ASMs can cause sexual dysfunction in men by increasing testosterone metabolism and increasing sex hormone-binding globulin production, thereby reducing free testosterone levels [43].

The risk of injury and mortality in patients with intractable epilepsy is higher than in the general population. The increased risk of mortality is related to the aetiology of epilepsy, the degree of seizure control, and the extent of neurological disability. The most common causes of mortality are sudden unexplained death and accidents [18]. The risk of injury is related to a higher frequency, severity and type of epileptic seizures. Recurrent seizures themselves, the epileptogenic process, or reactive inhibitory mechanisms may contribute to the progressive nature of epilepsy. However, patients with refractory epilepsy clearly have impaired psychosocial and occupational functions that are less likely to improve the longer they remain seizure-free with surgery. Patients with epilepsy also have interictal dysfunction, including material-specific memory deficits, mood disorders, neuropsychological dysfunction, and metabolic abnormalities in brain regions outside the epileptogenic region [44]. Epilepsy usually affects people before or during the most productive years of their lives. For these reasons, it is imperative that patients with intractable epilepsy be referred for evaluation for epilepsy surgery with the goal of eliminating or reducing seizures, eliminating ASM side effects, and restoring psychosocial function and quality of life.

Causes of intractable epileptic seizures. surgically remediable syndromes

There are factors that allow early identification of patients at risk of drug resistance [45]:

1. Failure of the first antiseizure medication.
2. High initial frequency of epileptic seizures.
3. Presence of early risk factors for epilepsy, for example, onset of epileptic seizures before the age of 5 years, head trauma with loss of consciousness >30 min, meningoencephalitis, neonatal seizures or febrile seizures (underlying etiology)
4. Abnormalities in the temporal lobe, demonstrated by magnetic resonance imaging.

In general, the most important predictor of drug resistance in children and adults is difficulty in controlling seizures early in the course of the disease. In children, additional predictive factors have been reported, such as high initial frequency of seizures, epilepsies of infectious/structural etiology, intellectual disability, intelligence quotient CI<70 [46].

Among the causes of intractable seizures, the following have been described [47]:

- misdiagnosis of epilepsy
- misclassification of seizures or epilepsy
- inappropriate choice of antiseizure medication for the type of epileptic seizure
- insufficient dose or wrong combinations of antiseizure medications
- defects in intestinal absorption or patients who do not metabolize the medication normally
- the presence of sustained stress, home unhappiness, emotional or personality changes
- structural brain injury as a cause of epilepsy
- Progressive diseases of the Central Nervous System.

The detailed questioning, which allows a timely Differential Diagnosis of cerebral crises, is one of the most important points in the approach to Refractory Epilepsy. There are 4 large groups of recurrent cerebral seizures, which must be differentiated from epileptic seizures: hypoxic seizures, psychogenic seizures, toxic seizures and sleep disorders [15].

However, certain easily definable and surgically remediable syndromes are readily identified, have an excellent prognosis for seizure control, and minimal surgical morbidity. In children with catastrophic epilepsy due to diffuse hemispheric syndromes, early surgical intervention stops seizures and reverses cognitive decline so that these patients can develop normally and eventually lead relatively normal lives.

Due to its excellent evolution after surgery and repeated poor response to antiepileptic seizures medication [47], the so-called surgically remediable syndromes are described.

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.

Below we mention these pictures, in the order of frequency with which they occur in epilepsy surgery services.

Temporal lobe epilepsy (TLE): Most authors agree that a clinical - electroencephalographic diagnosis of at least two forms of TLE can be established: mesial epilepsy and less well-defined lateral or neocortical epilepsy and with findings that are overlap those of the previous form, which is much more frequent [30,48,49]. Temporal Lobe Epilepsy (TLE) is considered to be associated in 80% of cases with hippocampal sclerosis [50]. Approximately 40-67% of these patients have a history of a complicated febrile seizure (a febrile seizure lasting > 30 min). These patients usually present epileptic seizures in late childhood, at which time the seizures are well controlled with ASM. As the child enters adolescence and early adulthood, seizures recur and become refractory to multiple trials of medication [51].

Seizure episodes originating in the temporal lobe make up the most frequent epileptic syndrome in adults. Due to its focal nature and its resistance to medical treatment, which reaches approximately 50% of patients, TLE is a well-known syndrome caused by hippocampal sclerosis [25,52]. In these patients, surgery is a widely accepted therapeutic option [53,54], constituting a procedure that the American Academy of Neurology has recommended as the shock treatment in medically refractory temporal lobe epilepsy since 2003 [55]. There is level 1 evidence to suggest that for patients who are candidates for temporal lobectomy, epilepsy surgery is superior to medical treatment [56]. However, there is currently a consensus that in order to obtain a significant improvement in quality of life after temporal lobectomy, patients should be operated on after two years of adequate therapeutic attempts, without obtaining control of the crises, since that the risk-benefit ratio of surgery favors the latter [57,58].

Extratemporal epilepsy: Frontal lobe (second cause of focal seizures refractory to medical treatment), parietal lobe epilepsy and occipital lobe epilepsy. Focal extratemporal epilepsies can also be treated effectively with surgical techniques, particularly when a clearly defined lesion is present on high-resolution MRI. In fact, surgical outcome improves from 20% seizure-free in uninjured patients to 70% seizure-free in injured patients [59]. The pathological substrate of seizures of extratemporal origin include low-grade gliomas: developmental tumors such as gangliogliomas and dysembryoplastic neuroepithelial tumors, Arteriovenous Malformations (AVMs), cavernous malformations, encephalomalacia, and cortical developmental malformations.

Multilobar regions: (sensorimotor cortex, frontoparietotemporal opercular region, and temporoparietooccipital junction)

Diffuse hemispheric syndromes: Hemigalencephaly, Sturge Weber Syndrome, Hemiplegia/congenital infantile paresis, Epilepsy/Hemiconvulsion/Hemiplegia Syndrome, Rassmussen Encephalitis [47]. These pathological processes are managed with focal resections or hemispherectomies that are considered curative procedures within the topic of Epilepsy Surgery. However, there is a group of patients whose pre-surgical approach does not allow the identification of a resectable area or hemisphere, but whose epilepsy is so damaging to their quality of life, due to the intensity and frequency of the crises, that only surgery is capable of offering some relief and improvement in it. The procedure in these cases is callosotomy. In their potential candidates, as in any other patient who is a candidate for surgery, all lines of ASM should be tested in

mono or polytherapy, bearing in mind that it is a palliative procedure, not a curative one.

LENNOX-GASTAUT syndrome is the quintessential example of a patient who can improve her quality of life with this treatment [60].

Other diffuse hemispheric abnormalities amenable to focal cortical resection

Schizencephaly: defined as a cleft lined with gray matter. This cleft extends from the pial surface to the ventricle, is usually centrally located, and is often associated with contralateral hemiparesis. It comes in 2 forms: closed lip (type 1) and open lip (type 2). Porencephaly: is defined as a cyst that is contiguous with the lateral ventricle and is most commonly associated with a perinatal ischemic insult. Ho et al reported that patients with unilateral porencephaly, such as those with schizencephaly, might also be excellent surgical candidates when they have seizures with temporal lobe semiology and noninvasive data localizing seizures to a single temporal lobe [61,62].

Diffuse hemispheric syndromes in children

Children with intractable infantile spasms and diffuse hemispheric abnormalities, such as hemimegalencephaly, Sturge-Weber syndrome, porencephalic cyst, Rasmussen encephalitis, or perinatal unilateral cerebral infarction, may be candidates for functional hemispherectomy or multilobar resection if the patient has a useless hand. These patients need to be identified early, particularly those with the affected dominant hemisphere, as language may switch to the opposite hemisphere if surgery is performed when the patient is younger than 6 years [63,64].

Presurgical evaluation

The basic problem in epilepsy surgery [2] 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, therefore:

• Timely define when to consider epilepsy refractory to treatment with ASM.

• Determine the epileptogenic zone and its relationship with adjacent functional areas and

• anticipate the impact on quality of life after the intervention.

In the light of Epilepsy Surgery, the concept of "Epileptic Focus" - becomes the Epileptogenic Zone (EZ) which theoretically means: area of the brain that is necessary and sufficient to initiate seizures and whose resection or disconnection is required to that they cease [37].

Other specific brain areas have also been defined in refractory epileptic patients that are closely related to the EZ: irritative zone and electrical seizure onset zone, epileptogenic lesion, ictal symptomatogenic zone and functional deficit zone [37].

Candidates for epilepsy surgery are carefully chosen and undergo a pre-surgical evaluation program, with the rigorous objective of trying to identify surgically remediable syndromes, and define the epileptogenic zone. The overall objective of epilepsy surgery is to reduce or eliminate the presence of epileptic seizures without causing added neurological damage and improving the quality of life of patients [47].

Surgery is intended to reduce [2]:

1- the impact of refractory critical disorder on individual educational and social development;

2- the risks of bodily injury or death secondary to the crises;

3- the possibility of secondary epileptogenesis;

4-the possibility of progressive cognitive deterioration secondary to frequent ictal activity, brain injury and chronic drug ingestion.

From the first consultation, patients (and their relatives) will be extensively informed that the criteria for entering the evaluation program are considered [2]:

-The goal of surgery.

-The need for invasive evaluation that can leave neurological sequelae.

-The need to withdraw drugs totally or partially to evaluate crises.

-The probability that despite all the evaluations, including the invasive ones, the patient will not be a candidate for surgery and must continue their medical treatment.

-The results of the surgery [65,66]:

a - Absence of crises with medical treatment at well-tolerated doses lower than the previous ones, fewer drugs than the previous ones if they were in pre-surgical polytherapy, and in a percentage of the cases without drugs.

b - Considerable decrease in crises (up to +90%) with the same previous requirements.

c - No significant effects on seizures or, more rarely, worsening of seizures.

d - Any of the above, plus neurological sequelae ranging from a worsening of memory, to more or less intense motor or visual focalization signs.

Research in the presurgical evaluation

The patients evaluated if they meet the criteria for refractoriness, will begin their pre-surgical evaluation stage, from then on the case will be discussed collectively to move from one stage to the other and/or to define their exclusion from the program. The first stage will be performed on an outpatient basis. Anamnesis, comprehensive general and neurological examinations are essential [2]. Among the non-invasive investigations, interictal EEG will be performed with additional extracranial electrodes, Axial Tomography of the Skull (TA), Magnetic Resonance Imaging (MRI) of the skull and SPECT (Single Positron Emission Computerized Tomographic) interictal, dosage of plasmatic drug levels antiepileptic drugs, as well as Neuropsychological, Psychiatric and Ophthalmological evaluation (in patients with temporal lobe epilepsy) [67,68]. Once the passage to the second stage has been defined, functional MRI, ictal SPECT and video-EEG recording will be performed, the latter in the Telemetry Unit.

The subsequent decision of the surgical procedure and the respective technique rests with the epilepsy surgery group [2].

CONCLUSIONS

Epilepsy surgery has been increasingly recognized as a viable non-pharmacological treatment for patients with medically refractory epileptic seizures, which must be performed in a timely manner, considering that intractability has an enormous impact on various components of an individual's life. It also increases the risk of injury and mortality and may be associated with progressive cognitive and structural/functional brain changes that may be reversible if identified and treated early. Surgically remediable syndromes and adequate pre-surgical evaluation must be taken into account, with the aim of an adequate selection of candidates and a good post-surgical evolution.

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