Surgical treatment of epilepsy

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Abstract

Antiepileptic drugs continue to be the mainstay of treatment of patients with epilepsy. However, we must have surgical therapy as an option for those patients who are not completely free of seizures, and for those who are free of seizures but suffer toxic side effects. Advances in diagnostic testing and surgical techniques have greatly improved the safety and efficacy of surgical treatment, particularly for clearly defined, surgically remediable syndromes, such as mesial temporal lobe epilepsy and certain pediatric disorders. Epilepsy surgery has become an option to be considered alongside various other medical treatment options.

Key words: epilepsy, epilepsy surgery, temporal lobe epilepsy.

Introduction

The history of surgical treatment of epilepsy goes back to the nineteenth century, in 1886, when Victor Horsley performed the first documented cases of excision of an epileptic focus, at the National Hospital for the Paralyzed and Epileptic in London[1]. His ability to identify these foci was based essentially on the work of John Hughlings Jackson, and his new concepts of seizure semiology, works that were later confirmed by David Ferrier through electrical stimulation of the cortex of monkeys. However, it was the work of Penfield and Jasper[2] in the first half of this century, that were pioneering in the use of supplementary neurophysiological information for presurgical evaluation and surgery itself. Thus, a basic triad of factors involved in the performance of these surgeries (neurologist, neurophysiologist and neurosurgeon) was defined from the beginning, and the neuroradiologist was added later.

In recent years, surgical treatment of epilepsy has increase considerably[3], both in terms of the number of places where it is practiced, and above all, in the technical advances that have been achieved in this area.

This therapy assumes great significance, firstly, due to the prevalence and incidence of new cases of epilepsy in the general population, and secondly, because of the significant percentage of patients with poor control, although in recent years, several more effective antiepileptic drugs (AEDs), with fewer side effects, have appeared. In the U.S., the estimated prevalence of epilepsy is 4 per 1000 inhabitants, giving a global population of more than 800,000 people epilepsy carriers. Approximately 30-45% of patients are in poorly controlled conditions, indicating some 350,000 potential candidates for other treatment types. Given that only 12.5% to 25% of these patients qualify for surgical treatment, the number of patients requiring surgery in the U.S. will be approximately 75,000 - 100.000.[3-5]

Epidemiological data obtained by groups in Oporto, Portugal, indicate that the prevalence of epilepsy in the general population is 4.1 per 1000 inhabitants, with an annual incidence of approximately 40/100,000. Extrapolating the same calculations for the Portuguese population, it is roughly estimated that there are at least 30,000 patients with focal seizures and 2,700 eligible for surgery. 250 new surgical candidates will be added to this number each year.[6]

Selection of candidates

The first problem that arises is the selection of candidates for surgery. In addition to patients with epileptogenic intracerebral lesion, which is itself a reason for surgical intervention (tumor, MAV), the criterion more uniformly followed is the selection of patients with epilepsy that is refractory to treatment. However, today, some authors[4,7] point to the existence of certain epileptic syndromes that a priori, always have a better prognosis with surgical treatment (as in the case of mesial temporal sclerosis) and therefore

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constitute a uniform indication for surgery.

Refractory epilepsy to treatment is when the patient presents an unacceptable frequency of epileptic seizures, even though they are taking adequate doses of AED, or when there are unbearable side effects. An unacceptable frequency must be defined in terms of seizures, and by the patient himself, because apparently similar conditions can have completely different impacts on the lives of different patients (social repercussions, employment, family, inability to drive, etc.). In the final analysis, of the various actors involved in this problem (doctor, patient, family), the patient himself is the one who can define, with greater accuracy, whether or not he has refractory epilepsy.

According to current convention[5,8-10], however, it is appropriate that each patient undergoes at least two 1st line AEDs (phenytoin, carbamazepine, sodium valproate, phenobarbital) in monotherapy, up to the maximum doses, then in association and, subsequently, the patient should be introduced to 2nd line drugs (in particular, one of the new AEDs: lamotrigine, vigabatrin, etc.). This process should take place over a period of one year, preferably two, until the epilepsy is considered refractory. According to some authors, if the response is negative with the two 1st line AEDs in appropriate monotherapy, the chances of controlling the seizures with associations of drugs is around 15% to 20%.[11]

The type of epileptic crisis is also important when selecting patients. Stereotypical focal seizures, always with similar characteristics, will probably correspond to a single epileptic focus, thereby comprising a group with major indication for epileptic surgery. This is especially true of patients with temporal lobe epilepsy. Focal epilepsy originated in other areas of the brain, particularly the frontal lobe, present specific issues to resolve.

Other crises, however, due to the risk they represent for some patients (in terms of morbidity and mortality), even if their frequency is not exceptionally high, may have indication for surgery. These include atonic seizures (drop attacks) and some other types of generalized seizures, namely tonic and tonic-clonic. In this case, the appropriate surgical intervention (callosotomy) is not intended to treat the epilepsy itself, but primarily, to stop the spread of electrical stimulation and, consequently, its generalization.

In the clinical evaluation of a patient, it is possible to consider some biological indexes that, taken together, may give us an indication of the persistence of seizures, even with therapy that is considered adequate:[9]

1 - Frequency: daily or weekly focal seizures will probably be difficult to treat; if they develop into outbreaks (cluster) this trend will be even greater;

2 – Early onset: early onset of seizures, particularly in childhood, means an increased risk that they will persist; children with very frequent febrile convulsions or status epilepticus with fever are more likely to develop temporal lobe epilepsy as adults;

3 - Secondary generalization: motor generalization of non-motor partial seizures and spreading to the motor cortex of extra limbic focus also constitute additional risk factors;

4 - Structural damage: this is, obviously, a risk factor;

5 - Concomitant neurological changes: patients with underlying neurological dysfunction have a higher likelihood of the epileptic crises persisting.

Alongside all these indicators, some authors[12,13] also indicate that in the specific case of children, certain epileptic syndromes, including West syndrome and Sturge-Weber syndrome, should be viewed as possibly requiring early surgical therapy for their control. There are several case series[14] that are already showing a better prognosis, both in terms of seizure frequency, and in particular, regarding motor and cognitive development of children among those who undergo surgery, compared with other patients treated medically.

Some exclusion criteria should be weighed[5]:

a) Relative contraindications

- Progressive neurological or medical disease;
- Behavioral changes that affect post-surgical rehabilitation;
- Concomitant medical illnesses that significantly increase the risks of surgery;
- IQ <70 (for focal resections);
- Changes in memory function in the contralateral hemisphere;
- Behavioral or intellectual changes that prejudice the pre-operative evaluation;
- Active psychotic illness not related to the periictal periods.

b) Absolute contraindications

- Generalized primary epilepsy;
- Minor epileptic seizures that do not interfere with quality of life.

Neurobiological considerations in epilepsy

Once the patient is considered refractory to medical therapy (e.g., after 2 years of treatment with AED), the possibility of surgery should be considered immediately, and if there are no important contraindications present, the process of pre-surgical evaluation should be initiated. This approach is even more important in children, especially younger children.[15,16]

This urgency is linked to the fact that brain maturation continues throughout childhood, and includes changes in neuronal cytoarchitecture and the glia, processing of neural networks, and the development of neurochemical pathways and receptors. This maturation process is important on two fronts: on the one hand, it influences the epileptic patterns in the child, giving them specific characteristics of evolution and clinical expression; on the other hand, it may suffer changes induced by the epileptic syndromes, which are sometimes very severe. Thus, several age--dependent epileptic encephalopathies, cases of West, Lennox-Gastaut and Landau-Kleffner syndromes, are usually associated with a suspension or even a regression of the processes of maturation of the Central Nervous System (CNS).

The direct implication of seizures on cerebral suffering, whether in the adult brain or in the developing brain, is not linear, except in cases of prolonged status epilepticus. However, if a single seizure does not seem to constitute a very important noxa, the cumulative effect of this stimulation in the developing cerebrum seems to raise other considerations.[16] In the limbic system in particular, this repetitive stimulation appears to induce changes in synaptic reorganization and create alterations in the expression of certain genes, thereby enhancing neuronal excitability.

In parallel with these factors, the motor, sensory, cognitive and psychosocial impairment that are evident in patients with chronic epilepsy, and can limit normal development, also need to be considered.

Presurgical evaluation

The presurgical evaluation differs between the various centers that perform epilepsy surgery and depends, on the one hand, on the experience of each center, and on the other, on the underlying material limitations.

In general, it can be assumed that a pre-surgical evaluation should be performed in stages[4,5,8,9,12,13] dividing the procedures into three major groups:

- Noninvasive;
- Invasive;
- Intraoperative.

Noninvasive

Background: a correct assessment of the anamnestic data collected from the patient or family is usually essential in the initial characterization of epilepsy; this stage also includes an adequate review of therapy to which the patient has previously been submitted, particularly AEDs.

Medical and Neurological observation: evidence of asymmetry may be important in the diagnosis of a focal lesion of the CNS;

Neuropsychological assessment: allows better characterization of the cognitive functions and sometimes leads to a correlation between the defect and an underlying focal lesion;

Psychosocial and psychiatric assessment: this is important, first to characterize the patient himself, and secondly, to assess his motivation for epilepsy surgery and his understanding of what is proposed and what is asked of him, in terms of pre-and post--surgical collaboration;

Inter-ictal electroencephalogram (EEG): electroencephalography continues to be the cornerstone of the process of localizing an epileptic focus. Some years ago, this assessment was relied heavily on information provided by the inter-ictal EEG, in particular, the existence of a focal paroxysmal activity with consistent characteristics. This examination should, however, be complemented with some more specific analyses, such as sleep deprivation, sleep, outpatient EEG, brain mapping and special electrodes: anterior temporal, sphenoidal, nasopharyngeal, etc.);

Video-EEG: enables the seizure to be recorded, both in terms of image or EEG, resulting in a correct characterization of the clinical seizure, the ictal paroxysmal activity, including origin, and a correlation between the two. Here the use of special electrodes can also be of great importance;

Imaging study: cranioencephalic nuclear magnetic resonance (CE-MRI) with coronal T2 images. This is an essential step in this evaluation process, allowing the identification of lesions that might not be evident on the computerized tomography (CT). Coronal slices are essential, including the study of the temporal lobes, with weightings in T1 (for anatomical and volumetric evaluation) and T2 (for identification of the mesial sclerosis). This test may be complemented

with volumetric studies (these are more sensitive than visual analysis in cases of mesial temporal sclerosis) and MRI spectroscopy, which allows the determination of pH, levels of phosphocreatine, adenosine triphosphate, lactate, N- acetylaspartate, choline and other amino acids in the selected regions. With this technique it may be possible, for example, to determine a decrease in N-acetylaspartate levels in the region of the epileptic focus, probably due to cell loss and glucose, and also phosphorus, otherwise there is an increase in lactate levels.

PET and SPECT: positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been increasingly used in the process of pre-surgical evaluation. Inter-ictal PET reveals areas of decreased glucose metabolism, which often correspond to the epileptic focus identified in the EEG. During the crisis, the focus shows a marked increase in this metabolism. The Inter-ictal PET can be positive in 70% of patients with temporal lobe epilepsy and in 60% of those with frontal lobe epilepsy. SPECT is less specific than PET, although it is less time-consuming to perform, and generally more accessible. Ictal and post ictal SPECT (in which the product is injected up to 20 minutes after the seizure and the examination carried out up to 6 hours afterwards) have a high probability of localization of the epileptic focus (97% and 71% in some studies) when performed in the inter-ictal phase, and its sensitivity is less than 50%. The information provided by these tests is complementary to the results of the EEG and MRI studies.

Invasive

Wada test and cerebral angiography: The Wada test is and angiographic examination that consists of injecting sodium amytal (amobarbitol) in the carotid arteries (Wada classic) or the posterior cerebral arteries (superselective Wada). This test will provide information about the dominant hemisphere for language and the memory adaptation in each hemisphere, and may even reveal any hemispheric dysfunction. It is an essential test when planning surgery of the temporal lobe. However, it is of lesser importance when evaluating children, as the plasticity of the brain during the first decade of life may allow the transfer of verbal dominance between hemispheres. Angiography, performed in parallel, can demonstrate the changes in vascularization in the affected hemisphere, or even identify vascular malformations. The features of the vascular paths in these patients may also be important when planning stereotactic insertion of deep electrodes;

Monitoring of EEG activity with subdural and epidural deep electrodes: monitoring of intracranial EEG activity may be indicated when it is necessary to accurately locate the epileptogenic zone, in cases where this cannot be located by noninvasive methods. Intracerebral deep electrodes, tape or network subdural electrodes, or epidural electrodes may be used. The first need to be inserted by stereotaxis, the second by craniotomy, and the last through a burr hole. These electrodes also allow cortical stimulation, to assist the identification and mapping of epileptogenic zones and in particular, the functional mapping of sensory cortical areas prior to surgical intervention. These monitors can be kept in place for periods of up to two weeks or more. The Ictal EEG characteristics are variable, and may consist of polyspikes or tips of variable frequency, attenuation of electrical activity, activity with high frequency and low amplitude, etc. This technique, in which several combinations of electrodes can be used, enables precise localization of the focus in 60-80% of cases.

Intra-operative

Electrocorticography: enables identification of the epileptic focus during surgery;

Functional mapping: it also is possible to map different functions in this phase. This is done in two steps:

1) While awake: language, motor, sensory areas;

2) During sleep: direct motor stimulation and somatosensory stimulation (evoked potentials).

Surgical therapy

The surgical procedure most frequently performed is focal resection, particularly temporal lobotomy. The temporal lobes are usually slightly wider in the nondominant hemisphere (in classical terms, 4-5 cm in the dominant hemisphere and 5-6 cm in the nondominant hemisphere), and its degree of success is also higher in this case[5,8]. In the dominant hemisphere, resection may still be constrained by functional mapping of language function and electrocorticographic localization of the epileptic focus. Besides classic temporal lobotomy, other techniques in which exeresis is limited to the mid-line structures are also used in this region (tonsillectomy, hippocampectomy,

amygdalo-hippocampectomy).[8]

The success rates of this surgery vary:[17] 50 to 70% of patients remain free of seizures that alter consciousness or trigger abnormal movements, but maintain auras with some frequency; 20-25% show a very marked improvement; and 10-15% show no significant change. Approximately 10-20% of patients who are seizure-free may, in the future, suspend their medical treatment altogether. The most common risks of surgery may include permanent aphasia, hemiparesis or hemianopsia, but overall, these changes occur in no more than 2% of patients treated.[18]

Frontal lobotomy is another type of frequently performed surgery. Resection in the pre-frontal areas may be extensive, while surgery focused on the supplementary motor area should be restricted and defined by the localization of the epileptic focus, and functional mapping of the primary motor area. The results are inferior to those obtained with temporal lobotomy: 30-50% of patients remain free of seizures that alter consciousness or cause abnormal movements, and the failure rate can range from 25% to 35% of patients.[19]

Parietal and occipital lobotomy may also be performed, but usually only when an underlying structural lesion is identified. In these cases, the success rate is comparable to that of temporal lobotomy.

Two other types of surgery are also performed: hemispherectomy and callosotomy.

Callosotomy is a functional surgery in which disconnection of the two hemispheres is carried out, slowing or halting the spread of an inter-hemispheric epileptic seizure. This procedure is used in patients with seizures that are refractory to medical therapy, whether of focal origin, but unresectable, or of multifocal, bilateral and independent origin, or not localized.[4,5,12] This technique is sometimes performed in two surgical stages, the first to disconnect the anterior 2/3 and then, if necessary, disconnecting the remainder in a second stage. If the first procedure is successful, this generally avoids one of the major side effects; disconnection syndrome. This technique is most effective in cases of tonic, tonic-clonic or atonic seizures. The frequency of these crises is reduced, on average, by 70% to 80% after partial callosotomy and 80% to 90% after total resection.[20-22] Partial seizures usually do not benefit from this intervention.

Hemispherectomy, which consists of disconnection of the hemisphere, which is then left in place (functional hemispherectomy), is only used in selected cases, usually in patients with severe epilepsy who already present major neurological deficits in the affected hemisphere (particularly motor, sensory and language functions).[4,5,12] When carried out very early in childhood, there seems to be a compensation of the contralateral hemisphere, with recovery of some of these functions (e.g. walking, talking, etc.) The results are generally good, with marked control of seizures in more than 75% of patients.[5]

Other types of surgery,[4,5] still under investigation, include multiple subpial transection (consisting of resection of the tangential intracortical fibers with preservation of the ascending and descending vertical fibers, for control of seizures originating in essential primary cortical areas, without inducing deficit), focal resections for West syndrome (usually in parietal--temporal-occipital areas), thalamic stimulation for generalized secondary seizures, stereotactic tonsillectomy, and stimulation of the vagus nerve.

Particular situations in childhood

There are many situations that are unique to, or more common, among children due to growth abnormalities or abnormalities in the neuronal migration, glia, or other support elements, or other, less understood pathological conditions. These situations may justify early surgery, due to their severity, especially in terms of prognosis.

Neurocutaneous diseases

Tuberous sclerosis and Sturge-Weber Syndrome are conditions that are usually accompanied by seizures early in life. AED control is effective in a significant proportion of patients, but a significant number may have refractory epilepsy, making them candidates for surgical treatment. In Sturge-Weber syndrome, the most common type of surgery is focal resection or hemispherectomy. The results are generally good, both in terms of seizure control and in the subsequent psychomotor evolution, and there are case series that document the improved evolution of these patients in relation to non-operated groups.

Cortical dysplasia

These are situations that are histopathologically characterized by changes in neuronal migration, in combination with the appearance of abnormal cellular elements. These may consist of lissencephaly (agyria),

an extreme variant in which the formation of the tertiary sulcus is absent, and macrogyria (pachygyria), in which focal or regional dysplastic alterations are found in the cerebral hemispheres. These conditions are generally associated with complex partial seizures, with secondary generalization or generalized seizures, often refractory to therapy. Focal resection or hemispherectomy may be indicated.

Hemimegalencephaly

This is a rare condition characterized by a large, dysmorphic brain hemisphere. The neuropathological examination can identify elements in the cortical layer that are suggestive of cortical dysplasia, focal pachygyria and even tuberous sclerosis. This asymmetry has a tendency to worsen in the postnatal period, followed by mental deterioration and contralateral focal epilepsy. Early hemispherectomy is one of the recognized solutions for this condition.

Rasmussen's encephalitis

A condition characterized by chronic focal inflammatory changes in the brain tissue, accompanied by focal epilepsy, with progressive worsening. The viral etiology of the condition is not yet confirmed. Hemispherectomy is also the procedure of choice, since focal resections do not halt the progression of the disease. When performed early, it can enable control of seizures and reverse mental deterioration.[3]

West Syndrome

Although considered a generalized form of epilepsy, some authors report the possibility of an early focus[24,25] for at least some of the seizures. Focal resection, particularly of parietal-temporal-occipital areas, appears to give good results in some patients. An alternative therapy is hemispherectomy.

Landau-Kleffner Syndrome

This is characterized by partial seizures, with or without secondary generalization, focal EEG changes and acquired aphasia. Although it usually responds well to medical treatment, some cases are refractory, therefore surgical therapy - in this case multiple subpial transection - may be recommended. ■

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