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Epilepsy surgery in pediatric population: a perspective from low-income countries

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Abstract

The paper is a compendium of the talks delivered at the Spanish symposium on 'Epilepsy: Pediatric Epilepsy. When Drugs Do not Work' in the 'Joint 16th International Child Neurology Society and 49th Child Neurology Society meeting' held in October 2020, this paper addresses the challenges and barriers of epilepsy surgery in the pediatric population with drug-resistant epilepsy from different perspectives, including epidemiology, multifactorial limitations, potential benefits, therapeutic approaches and novel techniques that have incremented the utilization of epilepsy surgery. The main objective of this symposium and subsequent paper is to let de readers know about other alternatives that can be used in their patients to improve their quality of life and outcomes, taking into account the devastating consequences in all aspects of life (risk of prolonged seizures, status epilepticus, physical injuries, shortened life span and risk of "Sudden Unexpected Death in Epilepsy Patients" (SUDEP). Despite evidence of the beneficial effects of surgery in children (reduction in seizure severity/frequency, improvement in cognitive and neurodevelopmental functions, reduced mortality, improvement in quality of life), class I evidence for the superiority of epilepsy surgery over continued medical treatment in pediatric surgical candidates and reduced cost in the long term, it continues to be an underutilized resource. It is essential to concentrate the effort of all possible stakeholders, including governmental and non-governmental agencies, to recognize the importance and create epilepsy surgery programs.

Keywords: Refractory epilepsy, children, epilepsy surgery, drug-resistant epilepsy, pediatric, low-income countries.

Introduction

The "International League against Epilepsy" (ILAE) defined "drug-resistant epilepsy (DRE)" as the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [1].

A prospective study found that 47% of patients became seizure-free with the first antiseizure medications (ASM). Among patients with no response to the first medication, 14% became seizure-free when changed to a second or third drug. This indicates that early response to therapy is a good prognostic factor. In this study, 36% of patients did not achieve sustained seizure freedom, and a higher proportion of patients with "symptomatic o" or "cryptogenic" epilepsy continue to have seizures despite therapy [2], emphasizing the fact that patients with structural lesions should have an early referral, for consideration of epilepsy surgery after failing 2 ASMs. A more recent study from the same authors corroborated previous observations that the probability of achieving seizure freedom declined for each unsuccessful ASM regimen tried [3].

Nevertheless, there are multiple variables that influence response to treatment. A longitudinal observational study showed that patients with generalized epilepsy are more likely to achieve seizure freedom than patients with generalized encephalopathy or focal epilepsy [4]. Another multicenter prospective observational study demonstrated that 11.8 - 17.4 % of patients achieved seizure freedom with the third ASM. The number of patients becoming seizure-free decreased with an increasing number of drug trials [5, 6].

A recent study of patients with DRE showed that brain surgery is associated with a reduction in mortality in selected cases, especially when patients are rendered seizure-free or experience significant palliation of generalized tonic-clonic seizures [7]. These findings provide further evidence of early consideration for epilepsy surgery.

Establishing epilepsy surgical programs in Low-income Countries

The consensus definition created by the ILAE task force provides clinicians with a practical tool to identify patients that can benefit from alternative therapies, including surgery [8].

Epilepsy surgery has been associated with reduced seizure burden and improved cognitive outcomes and quality of life. Despite the high-level evidence available for epilepsy surgery as an effective and safe procedure, it is one of the most underutilized evidence-based therapies. There are about 100,000 to 2000,000 surgical candidates in the USA, but only 3,000 – 4,000 surgeries are performed [9, 10, 11, 12, 13, 14].

If access to surgical evaluation is a problem in high-income countries, low-income countries face a more complex situation. The prevalence of epilepsy in these regions is higher, and there are barriers and limitations to epilepsy surgery, which have been the subject of ample research. These multifactorial barriers include financial aspects (high infrastructural cost) and scarcity of adequately trained personnel and resources. The availability of EEG correlates with per capita income, and there is a positive trend for the availability of CT and MRI by income group [15, 16].

An extensive review of the availability of epilepsy surgery centers in low-middle income countries showed that some countries in Latin America and Asia are performing epilepsy surgery, and their seizure-free and quality of life outcomes are similar to the ones in high-income countries. Nevertheless, these centers are located in large cities and are probably driven by highly motivated neurosurgeons; therefore, this is not a general and well-established practice [17].

There are other issues to take into consideration. There is insufficient education about the effectiveness of epilepsy surgery and possible intrinsic misconceptions from neurologists or primary care providers caring for patients with DRE.

Surveys on attitudes toward epilepsy surgery in Europe and North America [18, 19] reveal ambiguous attitudes from neurologists and hesitation about surgical options from epilepsy patients. The mere publication of guidelines had little impact on the provision of services and behavioral changes from providers. Underestimation of the biopsychosocial burden of the disease, overestimation of the expected success rate of new clinical trials, and equivocal conceptions of the benefit-risk ratio of surgery are significant contributors to the paucity of surgical centers.

The socioeconomic situation in low-income countries is an essential factor in the current treatment gap, including access to surgery. Much of the health care financing in these regions is covered by out-of-pocket payments [20], and patients may lack the economic resources to access appropriate care, which may be centralized in urban areas.

Since surgical success primarily depends on correct localization and delimitation of the epileptogenic zone and its complete removal (without added deficits), it is important to assemble an adequately trained interdisciplinary team. This team should include a neurologist/epileptologist, neurophysiologist, neuroradiologist, neuropsychologist, and neurosurgeon, ideally with formal epilepsy surgery training. There is also a need to define specific presurgical evaluation protocols, depending on resource availability. Establishing such teams can initially be facilitated by collaborative work with experts working in well-established epilepsy centers [11]. The goal is to create long-term, self-sustainable programs which can become a source of local training. In Latin America, there is an ongoing effort to support the establishment of epilepsy centers, distinguishing between "basic" and "advanced" centers [21]. The "basic" centers have the capacity to perform temporal /lesional epilepsy, but they do not offer the evaluations needed for children with diverse and complex etiologies, such as migrational disorders, tuberous sclerosis complex, or extratemporal epilepsy.

In conclusion, collaborative projects directed to support infrastructure, educate primary care providers, and provide advanced training in epilepsy surgery are necessary and important to improve the accessibility of epilepsy surgery in low-income countries [21, 22].

Epidemiology of drug-resistant epilepsy

Epilepsy is one of the most common chronic neurologic conditions in children affecting 0.5% to 1%. Prevalence and incidence of epilepsy worldwide vary considerably. It is mainly higher in low- and middle-income countries (LMIC). Unfortunately, high-quality data are scarce, and there is variation in the local socioeconomic and cultural environment, affecting different LMICs. Therefore, it becomes difficult to validate similarities and differences affecting these regions.

In general, about 7% to 20% of children meet the diagnosis of DRE [7, 8, 9]. This diagnosis is associated with poorer quality of life (QOL) and significant comorbidities, such as psychiatric-social impairments, resulting in poor psychosocial outlook, stigmatization, cognitive decline, increased risk of injury, and shortened life span.

Epilepsy surgery offers a palliative or curative solution for this group of children. It is well known that early surgery results in better neurocognitive and motor outcomes, especially during the first years of life [23]. The data available about the status of epilepsy surgery in LMIC is extremely scarce and heterogeneous to provide any reasonable conclusion. A recent scoping review done by Watila et al. [17] concluded that the extent of epilepsy surgery utilization, the procedural costs, and postoperative outcomes in LMICs are not well studied. Of 1365 publications, only 148 publications from 31 LMICs met the eligibility: representing

21.7% of the 143 LMICs. Most of the publications consisted of longitudinal studies, case series, and case-control studies which are not representative of the general situation of each country.

The cost of epilepsy surgery in LMICs is about 6% of the total cost of surgical procedures performed in western countries [32], but not necessarily affordable for most people living in these regions, and epilepsy surgery continues to be an underutilized resource in poor resource regions.

Stereo EEG (SEEG) in children

The adoption of SEEG in the USA coincided with an increment in the utilization of epilepsy surgery in the pediatric population [21] and a rapid discovery of genes associated with epilepsy (especially in the early onset cases) [22]. With more centers performing SEEG, there has been an increment in peer-review publications dedicated to SEEG in the pediatric population, with more than 232 publications at the time of writing this article (source PubMed.gov National Library of Medicine).

The increased interest in using SEEG arises from the three-dimensional capability that this presurgical technique offers. SEEG has some advantages over intracranial subdural grid exploration. SEEG allows the exploration of challenging to access brain regions, such as the inter-hemispheric regions, the insulo-opercular area, the limbic system, mesial temporal structures, and deeply located lesions, including depth of the sulcus dysplasia, periventricular heterotopias, and hypothalamic hamartomas. SEEG also helps with surgical planning and re-evaluating patients who had previously failed epilepsy surgery. Indications for SEEG are:

1. Anatomo-electroclinical discordance between the different modalities
2. Early involvement of eloquent cortex in the seizure onset or propagation
3. Negative MRI and electro-clinical hypothesis indicate focal epilepsy
4. Need to confirm or refute the electro-clinical hypothesis in lesional versus non-lesional epilepsy cases or temporal versus extratemporal epilepsy [33, 34, 35].
5. Need for simultaneous recording between deep structures and cortical surface.

The SEEG has some limitations [36], the sampling bias being the main one. This is not different from other intracranial exploration modalities, such as intracranial subdural grid evaluations and strips recording. To avoid sampling bias, it is very important that the SEEG planning is based on a good individualized hypothesis developed by a group of physicians or a team with high skills in seizure semiology, neuroanatomy, neuroimaging, neurosurgery, and invasive neurophysiological recording. Another important limitation of the SEEG is the language evaluation, which can be missed or misinterpreted if electrodes are placed based on traditional anatomical locations and not considering the patient's particular characteristics who can have language migrated or displaced, particularly in cases with early lesions and atypical anatomy. Finally, SEEG is a technique that is highly dependent on modern neuroimaging and skilled personnel, generating an additional barrier to bringing it to developing countries.

SEEG can identify the epileptogenic zone in 89-95% of pediatric cases [37, 38]. The goal of SEEG is the surgical resection of the epileptogenic zone with subsequent seizure freedom, but other outcomes are possible, including no resection, decision for thermocoagulation, or neurostimulation. Resection has been reported in 70-74% of the children evaluated with SEEG [37, 38]. In a study published from the Cleveland Clinic, the leading causes for not resecting the epileptogenic zone were high risk for functional deficit, bilateral independent ictal onset, and diffuse hemispheric ictal onset [38].

Long term outcome of pediatric SEEG is lacking in the medical literature. The outcome for cases undergoing resection was Engel I in 33-55% of the pediatric cases [37, 38, 39, 40]. Engel II outcome has been reported in 15% of pediatric cases [39].

Other important factors to discuss when reporting outcomes after resective surgery using pediatric SEEG evaluation are the etiology and type of resection. Children who received a unilobar resection had Engel I outcome in 67% of cases, and for multilobar resection, 33% had Engle 1 outcome [38]. The best SEEG outcomes are associated with the pathology of focal cortical dysplasia, with lower chances of seizure freedom for gliosis, post encephalitis, and absence of clear pathology [38, 14].

SEEG has a low complication rate. Intracranial hemorrhage without functional deficit is found in 2-25% of pediatric cases [38, 39, 14]. Intracranial hemorrhages leading to permanent deficit have been reported in 1.5% of the cases [38].

In conclusion, SEEG is a technique with a low risk of complications and offers a unique opportunity to patients who may benefit from a tridimensional neurophysiological evaluation, especially those with deep seating lesions.

When the epilepsy surgery is not an option

There are circumstances where surgery is not an option (e.g., epileptogenic zone in eloquent areas or multiple epileptogenic areas), but there are other alternatives for children who are not candidates for epilepsy surgery (see Table 1) [13].

Neuromodulation is a rapidly evolving field, and it is used in a variety of clinical settings, including epilepsy. The potential side effects are fewer than standard surgical approaches [21]. Nevertheless, there is usually a need for device implantation. Procedures include less invasive methods, such as vagus nerve stimulation (VNS), to more invasive techniques used for deep brain stimulation (DBS), reactive or responsive neurostimulation (RNS), and chronic subthreshold cortical stimulation (CSCS) and transcranial direct current stimulation (tDCS) [22]. A transcranial magnetic stimulation device (TMS) is another noninvasive option.

VNS is the best-studied and most widely used neuromodulatory modality in pediatric epilepsy. It is safe, effective, and approved by FDA [14]. Its efficacy has been demonstrated in children and adults, with more than a 50% seizure reduction in 50%

Table 1. Alternative treatments when surgery is not possible

Intervention	Type	Indications
Invasive Neuromodulation	Vagus nerve stimulation (VNS)	Focal, multifocal epilepsy, drop attacks (tonic/atonic seizures), Lennox-Gastaut syndrome, tuberous sclerosis complex (-related multifocal epilepsy, and unsuccessful resective surgery [24]
	Deep brain stimulation (DBS)	There are no randomized controlled trials for DBS use in pediatric patients with epilepsy [25]. DBS is an alternative or adjuvant treatment for children with DRE [26].
	Reactive or responsive neurostimulation (RNS)	Focal onset seizures, epilepsy with two seizure onset zones [27].
	Chronic subthreshold cortical stimulation (CSCS)	Seizure onset in the eloquent cortex [28]
Noninvasive Neuromodulation	Transcranial magnetic stimulation device (TMS)	No available data on the efficacy of TMS for the treatment of pediatric or adult epilepsy [25].
	Transcranial direct current stimulation (tDCS)	The level of evidence to support its use in epilepsy is limited [25].
Stereotactic approaches	Laser interstitial thermal therapy (LiTT)	Hypothalamic hamartoma, periventricular heterotopia, and deep focal cortical dysplasias [29].
Other minimally invasive	Magnetic resonance guided focused ultrasound (FUS)	Still in experimental stage – some cases have been reported, and a pilot study is available in patients with mesial temporal lobe epilepsy, frontal epilepsy, and cingulate gyrus [30, 31].

of the patients. Elliott et al. concluded that VNS is effective and safe for children younger than 12 years [41], and it seems a feasible therapy in children under the age of 5. Responder rate, impact on quality of life, and psychomotor development are not influenced by age at implantation; however, more extensive studies looking at outcomes of children with early VNS implantation are needed [42].

DBS can be directed at different targets, but clear indications for use in children have not yet been established. A systematic study, including 40 pediatric patients implanted with DBS, showed that 12.5% obtained an ILAE I outcome, and the remaining group had some reduction in seizure frequency [11].

RNS is distinct from other types of neurostimulation. It involves continuous monitoring of a focal brain region via intracranial electrodes placed over the ictal onset zone with "responsive" cortical stimulation (based on computer analysis of EEG signal input) to abort seizures [43]. The cortical stimulation can be modified using a continuous feedback loop [44]. Studies have already demonstrated the efficacy and safety of RNS. About half of patients can achieve a 75% seizure reduction. The main reported side effect is infection [45].

With CSCS, the objective is to alter local neuronal function to reduce seizure probability while preserving or perhaps enhancing cortical function. One study showed that 10 of 13 patients (76.9%) had improvement in both epilepsy severity and quality of life following chronic stimulation. Most patients experienced more than 50% seizure reduction and a significant decrease in the burden of interictal epileptiform discharges [37].

Transcranial direct current stimulation (tDCS), a non-invasive method of electrical stimulation of the brain using a weak direct current applied to the scalp through electrodes has been used in children. A study including 36 children reported some reduction in the frequency of seizures, and this procedure was well tolerated [46]. A decrease in the frequency of seizures has also been reported in children with Lennox Gastaut syndrome [29].

Laser interstitial thermal therapy (LiTT) and other stereotactic approaches are novel and valuable surgical techniques when standard surgical access is difficult or impossible, e.g., hypothalamic hamartoma (HH), periventricular heterotopia (PVHT), and deep focal cortical dysplasias (FCDs) [47].

Lastly, magnetic resonance guided focused ultrasound (FUS), a minimally invasive modality, can be used for tissue ablation using real-time MR thermography monitoring [44].

Conclusion

Even today, many children continue to be refractory to treatment, and sometimes this diagnosis is inappropriate due to various factors. Epilepsy surgery continues to be the most effective treatment for these patients. Nevertheless, the underutilization of this alternative is the general rule, particularly in less-income countries, so it is important to establish epilepsy surgery pro-

grams in these countries. In addition to the "traditional evaluation" schemes, nowadays, advances in methodologies, including stereotaxy, allow the use of the stereoelectroencephalography (sEEG) technique, which involves neurophysiological evaluation in a permitted three-dimensional manner. Likewise, other technologies are feasible, including laser ablation, different types of neurostimulation, and other technologies that can improve the results and minimize the risks.

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Competing interests

None.

Author contributions

Juan Carlos Pérez-Poveda has been involved in drafting the manuscript and revising it critically for important intellectual content and has given final approval of the version to be published.
Loreto Rios-Pohl has made substantial contributions to conception and design, data acquisition, analysis, and interpretation; has been involved in drafting the manuscript or revising it critically for important intellectual content and has given final approval of the version to be published.
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