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WHEN SURGICAL TREATMENT IN PHARMACORESISTANT EPILEPSY IS NOT AN OPTION?

Abstract: Epilepsy surgery is considered the most effective way to control seizures in patients with pharmacoresistant focal epilepsy, leading to improvements in cognition, behaviour and overall quality of life. However, in certain cases due to increased risk of serious adverse events and deterioration of clinical status, surgical treatment in these patients is not considered an optimal therapeutical option. The aim of this work was to, by analyzing currently available data, give an overview of the criteria on surgical treatment in pharmacoresistant epilepsy and possibly define the most common exclusion criteria for surgical tretment in epilepsy.

Key words: *pharmacoresistant epilepsy, surgical treatment, exclusion criteria*

INTRODUCTION

Drug responsiveness of a patient's epilepsy should be regarded as a dynamic process rather than a fixed state. Namely, instead of being constant, the course of epilepsy sometimes fluctuates. [1] Since epilepsy surgery is considered the most effective way to control seizures in patients with pharmacoresistant focal epilepsy, leading to improvements in cognition, behaviour and overall quality of life [2], the basic issue in even considering surgical treatment in epilepsy is to define pharmacoresistant epilepsy. In that line, in order to improve patients care and facilitate clinical research, the International League Against Epilepsy (ILAE) appointed a Task Force to formulate a consensus definition of drug resistant epilepsy. The overall framework of the definition has two „hierarchical" levels. The first level provides a general scheme to categorize outcome („seizure-free", „treatment failure", „undetermined") to each therapeutic intervention (whether pharmacologic or nonpharmacologic), including a minimum dataset of knowledge about the intervention that would be needed. The second level provides a core definition of drug resistant epilepsy, using a set of essential criteria based on the categorization of response (from Level 1) to trials of antiepileptic drugs. Hence, as a testable hypoth-

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esis, it is proposed that drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [3].

It has been shown that in patients with pharmacoresistant epilepsy, preoperative epilepsy evaluation and subsequent epilepsy surgery can lead to a significant improvement in seizure control, as well as improovment in overall quality of life and social participation. Furthermore, in this setting, proportion of seizure-free patients increases. [4] However, the effectiveness of surgical treatment depends on epilepsy type, underlying pathology and accurate localization of the epileptogenic brain region by various clinical, neuroimaging, and neurophysiological investigations. Substantial progress has been made in the methods of preoperative assessment, particularly in patients with normal features on MRI. Still, the evidence is scarce for the indication and effect of most preoperative investigations, with no biomarker precisely delineating the epileptogenic zone. Therefore, a priority for the development of epilepsy surgery is the generation of high-level evidence to promote the harmonization and dissemination of best practices. [2]

The only way to minimise the risks of serious adverse events and deterioration of clinical status after epilepsy surgery is a carefull selection of patient-candidates. [2] Namely, in certain cases, surgical treatment in patients with pharmacoresistant epilesy is not considered an optimal therapeutical option, which is why it is necessary to define the most common exclusion criteria for epilepsy surgery.

AIM

The aim of this work is to, by analyzing currently available data, give an overview of the criteria on surgical treatment in pharmacoresistant epilepsy and possibly define the most common exclusion criteria for surgical tretment in epilepsy.

METHODOLOGY

A systematic review and meta-analysis of the evidence on this topic was performed. To provide evidence-based estimates of longterm results of various types of epilepsy surgery and to identify sources of variation in results of published studies, Medline, Index Medicus, the Cochrane database, bibliographies of reviews, original articles and book chapters to identify articles published from 1990. were searched.

DISSCUSION

Before seizures are deemed intractable, it is necessary to be certain that the correct drugs have been used in the correct amounts for adequat seizure type. Focal seizures are more likely to be intractable than primarly generalized forms of epilepsy. [5] Prevalence of intractable idiopathic generalized seizures (IGE) is 10–30%

and mostly due to delayed or inappropriate treatment. [6] In a large cohort of IGE patients, EEG focalities were found in 56% and localized mostly to anterior regions. [7, 8] Furthermore, in a series of IGE patients studied with video-EEG, focal interictal epileptiform discharges and semiologic features of focal seizure onset were observed in 35% of cases, but no seizures with focal EEG onset were seen. Studies have reported EEG focalities in 30–55% of patients with JME. [9] The reported frequency of focal or lateralized EEG abnormalities in patients with absence seizures ranges from 16–35%. [10] Based on the results of multiple studies, it appears that focal interictal EEG abnormalities are found among one third of patients with IGE, which can leed to inapropriate diagnosis of focal epilesy. [7]

The main idea of preoperative epilepsy evaluation is to define the chance of complete seizure freedom and the likelihood of inducing new neurological deficits in a given patient. As epilepsy surgery is an elective procedure, quality standards are particularly high. Quality control relates to seven different domains: (1) establishing centers with a sufficient number of sufficiently and specifically trained personnel, (2) minimum technical standards and equipment (video electroencephalography monitoring – VEM, high resolution MRI, neuropsychology department,…), (3) continuing medical education of employees, (4) surveillance by trained personnel during the VEM, (5)systematic acquisition of clinical and outcome data, (6) the minimum number of preoperative evaluations and epilepsy surgery procedures and (7) cooperation of epilepsy centers. Most centers decided to make these standards obligatory for predicting good postoperative seizure outcome. [11] Currently, non-invasive tests are providing information regarding positioning of invasive electroencephalography (EEG) electrodes, with possibility to replace intracranial EEG in at least some patients, if they are able to accurately locate a seizure focus. Most studies reported fluorodeoxyglucose positron emission tomography (PET) influencing the decision for or against surgery in 70–80% of patients, which can lead to beter postsurgical outcome. [11]

The most common causes of non-surgical candidates after presurgical evaluation for epilepsy surgery were patients and their families giving up intracranial invasive EEG positioning for various reasons (42/112, 37.5%). Namely, patients and their families still have doubts about the surgical risks, costs and effectiveness. [12] Long-term follow-up studies of temporal lobe epilepsy surgery revealed a narrower range of seizure-free rates (59–89%). However, long-term studies in parietal and occipital lobe surgery both reported a 46% seizure-free rate. But, resections of frontal lobe produced the worst long-term seizure-free rates among the resective surgeries (mean 27%, median 34%), although they were highly heterogeneous (ranging from 9% to 80%). Poorer outcomes may relate to inability to resect the entire epileptogenic area due to its proximity to functionally important cortex. In addition, the epileptogenic area may be larger in the frontal lobe and seizure spread may be particularly rapid and extensive. [13]

Bilateral or multifocal abnormalities on MRI are another relative contraindication for epilepsy surgery. Conventional surgical approaches to intractable epilepsy with bilateral frontal or multifocal injury may be limited to palliative procedures

like *vagus* nerve stimulation and corpus callosotomy. [14] What is more, a number of studies support the hypothesis that neurosurgery after viral encephalitis may be a triggering factor for viral infection and seizure reactivation. [15,16]

Patients with epilepsy who are magnetic resonance imaging negativ (MRI -) can be successfully treated with surgery. Improved sensitivity of MRI will indeed improve the outcomes of presurgically studied patients. Surgical failures in patients without histopathological lesions mostly result from extensive epileptogenic areas. Overall, the odds of being seizure-free after surgery were 2.5 times higher in patients with lesions on MRI or histopathology (OR 2.5, 95% CI 2.1–3.0, $p < 0.001$). In patients with temporal lobe epilepsy surgery, the odds were 2.7 times higher in those with lesions (OR 2.7, 95% CI 2.1–3.5, $p < 0.001$). In patients with extratemporal epilepsy surgery the odds were 2.9 higher in those with lesions (OR 2.9, 95% CI 1.6- 5.1, $p < 0.001$). Outcomes were similar in children and adults. [18,19]

Another possible exclusion factor for epilepsy surgery are psychiatric disorders. They are called „hidden" contraindications for presurgical VEEG and neurosurgical treatment of farmacoresistent epilepsy. Studies have highlighted the necessity of psychiatric evaluation for these patients, especially for those with refractory temporal lobe epilepsy with mesial temporal sclerosis who are surgical candidates, because of the risk of negative behavioral events. [15] The presence of pre-surgical depression (OR 3.32; $p = 0.008$), pre-surgical interictal psychosis (OR 4.39; $p = 0.009$) and epileptiform discharges contralateral to the epileptogenic zone (OR 2.73; $p = 0.01$) were risk factors associated with post-surgical psychiatric disorders. Relatively high psychiatric comorbidities observed in surgical candidates and their possible negative impact on post-surgical outcomes requires a careful pre-surgical evaluation of clinical, socio-demographic and psychiatric factors. [20,21] Available data suggest that outcomes for people with mixed psychogenic nonepileptic seizures/epileptic seizures are not promising, due to often persisting epileptic seizures, while some patients even had worsening or new-onset psychogenic nonepileptic seizures. Therefore, psychogenic nonepileptic seizures should also remain a relative contraindication for epilepsy surgery. [22]

CONCLUSION

Most centers decided to set up quality standards for preoperative monitoring particularly high and obligatory, in order to predict good postoperative seizure outcome. Studies demonstrated the feasibility of extending high resolution MRI and PET to all diagnostic strategies with good cost-effectiveness results, if available.

It seems that the common causes of non-surgical candidates after presurgical evaluation for epilepsy surgery might be: giving up of invasive intracranial EEG, multifocal or extensive epileptogenic zones, generalized seizures, epileptogenic zone in functional areas, as well as, psychiatric disorders and pseudoseizures.

Epilepsy surgery is also less likely in patients with the history of severe encephalitis and perinatal brain injury associated to extensive and/or multifocal lesions and diffuse, multiple, bilateral abnormality on cranial MRI.

The presence of pre-surgical depression, pre-surgical interictal psychosis and epileptiform discharges contralateral to the epileptogenic zone were risk factors associated with post-surgical psychiatric disorders. Furthermore, psychogenic nonepileptic seizures are also a relative contraindication for epilepsy surgery.

Apart from all mentioned, other risks of epilepsy surgery could be divided into three groups. The first one refers to risks associated with surgery, since surgery may lead to infection and bleeding, as well as the risk of an allergic reaction to the anesthesia. The second is associated to the risk of postoperative neurological deficits. Namely, it has been shown that surgery can worsen existing problems or create new problems with neurological deficits, including loss of functions such as vision, speech, memory or movement. The third one are risks of surgery failure, since even with careful pre-surgical evaluation, surgery may not eliminate or reduce seizures. That is why before undergoing surgery, doctors have to discuss and inform both the patient and the family about the potential risks and benefits of the procedure.

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