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Review

Is there a place for surgical treatment of nonpharmacoresistant epilepsy?

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ABSTRACT

Epilepsy surgery has been shown to be the best possible treatment in well-defined and difficult-to-treat epilepsy syndromes, such as mesial temporal lobe epilepsy with unilateral hippocampal sclerosis, even early in the course of the disease if pharmacoresistance is proven.

This review addresses the question if epilepsy surgery may be justified today even in nonpharmacoresistant cases. There are two possible groups of patients: first, there are epilepsy syndromes with a benign spontaneous course or with a potentially good treatment prognosis under appropriate antiepileptic drug (AED) treatment. Second, there are epilepsies with potentially worse AED treatment prognosis in which appropriate AED treatment has not yet been applied because of the short course of the disease, tolerability problems that prevented usually effective dosing, or adherence issues.

In group one, the good spontaneous prognosis or the usually satisfying course under AED treatment in line with the commonly generalized underlying epileptogenesis does not suggest that epilepsy surgery is a realistic alternative, not even in cases with distinct focal clinical and/or electroencephalography (EEG) patterns like in Rolandic epilepsy with centrotemporal spikes.

In the second group, the recent International League Against Epilepsy (ILAE) definition should allow assessment of individual pharmacoresistance early after the onset of the disease in order to avoid any delay. Concerns about a potential disease-specific or drug-specific cognitive decline that could be avoided in early surgery are speculative, a matter of controversial discussion, and certainly not relevant, if pharmacoresistance is consequently addressed in time according to the ILAE recommendations. One should also not forget that even in typically pharmacoresistant epilepsy syndromes that are suitable for surgical procedures, satisfying courses do exist that would not require early or any epilepsy surgery.

Therefore, in almost any instance, epilepsy surgery as initial treatment or immediately after a first AED is still not recommended although, especially in cases with nonadherence to AEDs, it may be occasionally considered in order to outweigh the risks of ongoing seizures and epilepsy if surgery is not performed.

1. Introduction

In many instances, epilepsy turns out to be a life-long chronic burden. The aim of any epilepsy therapy is seizure freedom without treatment-associated adverse events [1].

The gold standard of epilepsy treatment is permanent drug treatment with antiepileptic drugs (AEDs) based on the concept of prophylactic suppression of seizure activity and thus the reduction or even elimination of the risk of further seizures in people with the susceptibility of recurrent seizures [2]. The general consensus is that seizures in around 2/3 of patients with epilepsy are sensitive to AED treatment and they may expect complete or almost complete seizure freedom. Interestingly, this has not been considerably influenced by the introduction of newer AEDs since the early 1990s [3–6]. Thus, seizures in approximately 1/3 of people with epilepsy (PWE) will be more difficult to treat. According to a recent definition of the International League Against Epilepsy (ILAE), AED resistance 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" [7]. Therefore, the condition of PWE who become seizure-free with the first two treatment options or in which the first two treatment options have not yet been applied may be considered as at least potentially nonpharmacoresistant.

Whether AED treatment is promising or not is substantially influenced by the underlying epilepsy syndrome and etiological constellation [8]. It is somewhat astonishing that most studies that address the prognosis of AED therapy do not systematically cover this crucial aspect [9].

Of course, AED treatment as an approach that is symptom-oriented but not causally effective is not the only treatment option we have. Epilepsy surgery offers a potentially curing treatment option in PWE with ongoing seizures. Basic requirements for epilepsy surgery comprise the

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diagnosis of epilepsy along with not only the well-substantiated hypothesis of a uniregional epileptogenic zone that might be resected without inacceptable potential postoperative deficits but also phamarcoresistance and inacceptable quality of life under the conditions of the best-established AED therapy [1, 10].

It is tempting to speculate whether this attitude may have changed so that epilepsy surgery could be supposed as the primary epilepsy treatment even in patients with not yet proven pharmacoresistant epilepsy as a causative alternative to ongoing AED treatment. This is the topic of this paper presented at the 11th International Epilepsy Colloquium at Frankfurt, Germany, in March of 2018.

2. Conceptual considerations

If we discuss patients with nonpharmacoresistant epilepsies, there are two principal groups: first, there are PWE whose syndrome has a benign spontaneous course with a potentially good treatment prognosis under appropriate AED treatment. Second, there are PWE with potentially worse AED treatment prognosis, in whom appropriate AED treatment has not yet been applied because of the short course of the disease, tolerability problems that prevented usually effective dosing, or adherence issues. These two groups will be discussed separately in the following sections.

3. PWE whose syndrome has a benign spontaneous course with a potentially good treatment prognosis under appropriate AED treatment

Numerous papers addressed the prognosis of epilepsy in general and of various epilepsy syndromes [11–18].

Long-term observations report a general remission rate of children with epilepsy between around 50–60% [15, 16] and up to around 80% [11, 12, 18]. Among others, Rolandic epilepsy with centrotemporal spikes, Panayiotopulos syndrome, and benign familial neonatal infantile seizures have been reported to have an excellent spontaneous prognosis and outcome [15]. Examples for epilepsy syndromes with very good prognosis with and sometimes without sustained AED treatment are the classical idiopathic generalized epilepsy syndromes such as childhood and juvenile absence epilepsy, epilepsy with generalized tonic–clonic seizures, or juvenile myoclonic epilepsy [1, 8]. Primarily generalized epilepsy syndromes are looked upon as a relative contraindication for epilepsy surgery [10]. Since these epilepsy syndromes either remit spontaneously or do not offer a realistic surgical approach because of the underlying generalized epileptogenesis, surgical treatment, with its inevitable risk of morbidity and mortality, is and will certainly be not a realistic treatment option in these patients. Even if focal and distinct epileptogenesis is apparent like in Rolandic epilepsy with centrotemporal spikes, the usually benign self-limiting course and the nonlesional etiology certainly do not suggest epilepsy surgery as a realistic alternative therapeutic option. Neural stimulation techniques like vagal nerve or intracranial stimulation or surgical approaches such as corpus callosotomy were only considered and performed in cases with generalized epileptogenesis and a proven difficult course in spite of appropriate AED treatment [19–22].

4. PWE with potentially worse AED treatment prognosis in which appropriate AED treatment has not yet been applied because of the short course of the disease, tolerability problems that prevented usually effective dosing, or adherence issues

Several epilepsy syndromes and clinical constellations are possible if we consider epilepsy surgery. Exactly as with AED treatment in every individual case, the treatment decision needs to be based on a careful individual risk–benefit evaluation of the available options. The overall objective is to ensure the best possible quality of life according to the patient's individual circumstances [2]. For this brief review, we believe that it might be somewhat counterproductive to list every etiology and syndrome that might be suitable for epilepsy surgery and to outweigh in every potential syndrome whether the individual risk–benefit ratio might justify a surgical approach prior to proven pharmacoresistance. In order to emphasize the methodological problem of potential surgical treatment in PWE and still not pharmacoresistant epilepsy, we want to concentrate on epilepsy syndromes with impaired prognosis under AED treatment and promising prognosis with epilepsy surgery and to outweigh perspectives and possible burdens of conventional AED versus surgical treatment.

Epileptic syndromes or diagnostic constellations for which the possibility of epilepsy surgery may be suggested are shown in Table 1.

With AED treatment as the gold standard, some of the syndromes shown in Table 1 almost never allow achievement of sustained seizure freedom as the primary goal of epilepsy therapy. Examples are mesial temporal epilepsy with hippocampal sclerosis, Rasmussen's encephalitis, or other syndromes with large unihemispheric lesions [1, 2, 8, 10, 15]. While the latter are candidates for functional hemispherectomies that nowadays lead to sustained seizure freedom in more than 80% of operated patients [23], the former are candidates for selective amygdalohippocampectomy or anterior temporal lobe resections, both of which are also associated with rates of complete or almost complete seizure freedom in at least 70% [24–30]. Although in severe encephalopathies such as Rasmussen's encephalitis, postoperative improvement of cognitive functions has been described along with a favorable seizure outcome [23], it is certainly not justified to address a potential favorable cognitive development independent of seizures as a somewhat psychosurgical approach prior to the proof of pharmacoresistance. Nobody would proceed with hemispherectomy just to improve cognition. Less favorable though still convincing results compared with appropriate AED treatment are reached by epilepsy surgery in patients with extratemporal lesions or nonlesional cases [27, 31].

Mesial temporal lobe epilepsy with hippocampal sclerosis may therefore serve as a good paradigm to address the question of whether pharmacoresistance is definitely required to be proven in every single case prior to the decision to proceed with presurgical diagnostics and epilepsy surgery.

Is AED treatment, which is the accepted gold standard of epilepsy treatment in general, really the gold standard in mesial temporal epilepsy with hippocampal sclerosis and is epilepsy surgery really the

Table 1
Epileptic syndromes and diagnoses for which epilepsy surgery may be suggested [10].

Patients who may be selected only by noninvasive presurgical diagnostics
Mesial temporal lobe epilepsy associated with hippocampal sclerosis
Circumscribed epileptogenic lesions (not near eloquent areas)
Benign neoplasms
Ganglioglioma
Dysembryoplastic neuroepithelial tumor
Low-grade astrocytoma
Oligodendroglioma
Vascular malformations
Atrophic scars
Large unihemispheric epileptogenic lesions (for hemispherotomy)
Hemiconvulsion Hemiplegia Epilepsy (HHE)
Sturge–Weber syndrome
Rasmussen's encephalitis
Hemimegalencephaly
Epileptic encephalopathies and multifocal disease (for corpus callosotomy)
Lennox–Gastaut syndrome
Epileptic syndromes and diagnoses for which epilepsy surgery may be suggested only after additional invasive presurgical diagnostics
Temporal lobe epilepsy with discordant electroclinical data
Bilateral mesial temporal sclerosis
Normal MRI
Extratemporal circumscribed epileptogenic lesions close to eloquent area
Malformations of cortical development
Dual pathologies

second choice treatment in these cases? Patients with mesial temporal epilepsy and hippocampal sclerosis are less likely to respond to AEDs than patients with other focal epilepsies [32]. According to Semah et al. [17], only 11% of patients with mesial temporal epilepsy with hippocampal sclerosis will become seizure-free with AEDs whereas the chance to achieve seizure freedom by means of epilepsy surgery is at least 70%, [24–30] even if we consider only pharmacoresistant cases as it is still the rule if epilepsy surgery is performed [1, 10, 26].

On the other hand, we assume that data about treatment success with AEDs in patients with mesial temporal epilepsy and hippocampal sclerosis might be negatively biased by the overrepresentation of tertiary epilepsy centers that contribute their data to outcome investigations [32].

In a recent European survey that covered 767 patients, the probability of achieving seizure freedom for at least 12 months varied depending on the AED. Still, with carbamazepine as the most effective AED in this study, the rate of seizure freedom was only 11% and lower than 11% with all the other 9 AEDs that were investigated. Adverse drug reactions with their additional impact on quality of life were observed in 47.6% of patients [32]. Interestingly, this study confirmed that in patients with mesial temporal epilepsy and hippocampal sclerosis, the response rates were highest during the initial AED treatment and dropped with the following alternative AED treatments [32] as it is seen in general: in a long-term syndrome-independent follow-up study of 133 children, 73% became seizure-free with the first AED [18]. In a monocenter study of 253 patients with mesial temporal epilepsy and hippocampal sclerosis, 9% achieved seizure freedom with AED treatment after one year of observation [33].

Studies that included newly diagnosed mesial temporal epilepsy with hippocampal sclerosis reported markedly higher success rates with AED-responsive patients at rates of 15%, 29%, and 31%, respectively [34–36]. If some of these patients had been operated very early, postoperative seizure freedom might have been falsely ascribed to epilepsy surgery although seizure freedom would have been achieved by AED treatment (or even because of the spontaneous course). In a recent trial, seizure freedom with AEDs for more than 12 months was observed in 24.7% of patients with mesial temporal epilepsy and hippocampal sclerosis. Newer AEDs did not alter the success rate [37] so we should not expect a better treatment chance for these patients despite the latest AED developments.

When considering a seizure-free period of at least 12 months as the criterion for effective treatment, one has to be careful. Long-term studies show that both delayed but sustained seizure freedom and fluctuations between periods of seizure freedom and relapse are possible in the long-term [5, 38] and that relapse-remitting patterns with periods longer than two years occurred in 30% of 122 patients with mesial temporal epilepsy and hippocampal sclerosis [39].

Randomized controlled trials clearly showed the superiority of epilepsy surgery at least concerning the short-term outcome for the following 12 months in pharmacoresistant cases of temporal lobe epilepsy in adults [40, 41] as well as in general drug-resistant childhood epilepsy [42]. Most likely, surgical results would be even better if patients with mesial temporal lobe epilepsy and hippocampal sclerosis would have been included without proven pharmacoresistance. On the other hand, the inclusion of such cases in the randomized trials mentioned here could have had a positive influence on the performance of the nonoperated group in these studies.

Thus, because of a lack of data of real comparative trials, the question of whether epilepsy surgery is justified prior to proven pharmacoresistance in syndromes such as mesial temporal lobe epilepsy with hippocampal sclerosis cannot be answered solely on the basis of available scientific data.

5. Discussion

Epilepsy is usually a chronic disease — at least in most of the adult patients with ongoing seizures. The therapeutic gold standard is chronic prophylactic therapy with AEDs. If sustained seizure freedom is achieved in an individual case, the epilepsy in this case is apparently not pharmacoresistant. The potential burden of long-term tolerability issues with ongoing AED therapy has been extensively discussed in the literature. In nonpharmacoresistant epilepsy cases, the potential burden of AED-induced long-term adverse events would probably still not suggest epilepsy surgery as a possible alternative since many of all long-term seizure-free patients deny an alternative AED treatment (and probably also epilepsy surgery) even in case of adverse events because they do not want to risk a seizure relapse [43]. Furthermore, in many epilepsy syndromes with good spontaneous or AED treatment prognosis, a distinct and removable lesion is not the underlying cause so the electroclinical profile does not fit the methodological requirements we postulate in suitable epilepsy surgery candidates, which means that epilepsy syndromes such as classical idiopathic generalized epilepsies are looked upon as relative contraindication for epilepsy surgery [10] beyond the usually very good prognosis under appropriate AED therapy [1, 8, 43].

Considering PWE with potentially worse AED treatment prognosis in which appropriate AED treatment has not yet been applied because of the short course of the disease, tolerability problems that prevented usually effective dosing, or adherence issues, one still has to be careful to apply epilepsy surgery too early because at least mesial temporal epilepsy as the underlying syndrome associated with hippocampal sclerosis as the probable epileptogenic lesion [44] should be proven in every single case. It is certainly not justified to suggest a potential mesial temporal lobe epilepsy or even an imminent and later probably AED-resistant epilepsy just because of the diagnosis of hippocampal sclerosis by means of magnetic resonance imaging (MRI). We know that hippocampal sclerosis may be associated with other epilepsy syndromes and even occur in otherwise healthy people [45].

It is certainly helpful in the context of this paper that the ILAE has clearly defined pharmacoresistance in order to avoid previous uncertainties [5]. The diagnosis of a pharmacoresistant epilepsy is thus justified in case of a “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” [7]. This means that in PWE whose epilepsy might turn out as pharmacoresistant, we do not have to wait for an unacceptably long period to know whether our first or second AED strategy failed or not.

The typical diagnostic findings in a frequently pharmacoresistant syndrome like mesial temporal lobe epilepsy with hippocampal sclerosis are well-defined and easy to diagnose [5]. Therefore, it should not be difficult to diagnose it early in the course of the disease so that appropriate treatment can also be initiated as early as possible. Under these circumstances, it should be possible to fulfill the minimum requirements for the diagnosis of pharmacoresistant epilepsy [7] within a short period. If pharmacoresistance is evident according to these criteria, at least in temporal lobe epilepsy and for a limited follow-up, epilepsy surgery is the first-line therapy, not an alternative to further and modified AED treatment [41].

It is mandatory that in the case of a syndrome like mesial temporal lobe epilepsy with hippocampal sclerosis and pharmacoresistance, unnecessary delays are avoided [5]. In many epilepsy centers like ours, many patients with clearly defined pharmacoresistant focal epilepsy had to wait for decades until they were successfully operated on [31]. The longer pharmacoresistant mesial temporal lobe epilepsy with unilateral hippocampal sclerosis lasts without surgical intervention, the more its progressive nature may become apparent concerning memory decline, recruitment of additional epileptogenic tissue, reduced chances of successful epilepsy surgery over time, and accumulated sudden unexpected death in epilepsy (SUDEP) risk [5, 46–49]. Therefore, one should certainly not wait longer with appropriate presurgical diagnostics if pharmacoresistance is shown according to the definition of the ILAE [7] because the increased risks mentioned above caused by a longer duration of a pharmacoresistant epilepsy syndrome that is suitable for a

surgical approach are certainly higher than the risks of surgery itself. For temporal resections, recent publications report a mortality rate below 1% [26, 27, 50] and a risk of permanent morbidity between 1% and 2.5% [27, 50].

If new-onset epilepsy is associated with a lesion with questionable prognosis like a tumor, early tumor-related surgery may be justified and even crucial to avoid any further deterioration beyond epileptic seizures as a consequence of such a lesion.

One last and crucial aspect has to be considered if we discuss epilepsy surgery in nonpharmacoresistant epilepsy: about thirty years ago, when the renaissance of epilepsy surgery started, there were well-known doubters within the community of epileptologists who had to be convinced that this therapeutic approach is effective, safe, and justified. Because of the global development and recognition of epilepsy surgery during the last decades, its standing is certainly different today. With the experience we have nowadays, it may be justified to consider and perform epilepsy surgery in certain cases even if pharmacoresistance is not proven. One matter of questionable adherence may be the burden of a sustained AED therapy with its potential acute and chronic safety hazards. Epilepsy surgery may offer the cure instead of the satisfying treatment of epilepsies. On the other hand, many of our successfully operated patients finally decided to stay on AEDs postoperatively [31], and 85% of our seizure-free patients, irrespective of surgery or successful drug treatment, refuse discontinuation of AEDs because of their fear of seizure relapses [43]. Still, there might be individual situations where very early epilepsy surgery may be justified. For instance, we are discussing extensively the case of a patient at our center who clearly fulfills all criteria of an ideal candidate for selective amygdalohippocampectomy but does not fulfill the criteria of pharmacoresistance because of a lack of adherence. In this case, it will be very difficult to finally prove true pharmacoresistance. On the other hand, there is undoubtedly an elevated risk of epilepsy-related morbidity and mortality if we wait longer with surgery that offers the patient a high chance of 70% to become seizure-free, even without further AED treatment [5]. Still, even if we proceed with surgery in this case, careful and well-documented information and informed consent are mandatory because such an approach is not yet consistent with official guidelines that mention pharmacoresistance as a crucial requirement for epilepsy surgery [51]. We are possibly approaching a new era of outweighing the burden of AED treatment and the potential benefit of very early epilepsy surgery. However, the time of different recommendations for early surgery prior to proven pharmacoresistance has not yet come.

Declaration of interest

None.

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