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Review

Reoperation after failed resective epilepsy surgery

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ABSTRACT

Purpose: Resection of the seizure focus leads to sustained seizure-freedom in intractable focal epilepsy in up to 80% of selected populations. However, surgery fails to help in a considerable proportion of patients. Reevaluation and reoperation may be considered in a selected group of patients with an unfavorable postsurgical outcome. Here, we reviewed 15 case series on reoperation after failed resective epilepsy surgery in adults in order to identify factors associated with a good chance of benefitting from a second operation.

Methods: Literature review of case series describing the outcome of epilepsy surgical re-operations.

Results: Overall, 3.8–14% of all patients who had resective epilepsy surgery underwent a second operation. A total of 402 reoperated patients were included. Reoperation was performed in average between 2 and 5.5 years after the first surgery. 36.6% of all patients were seizure-free with a minimal follow-up of 6 months to 4 years after the second operation. Postsurgical complications were observed in 13.5% and mainly consisted of visual field defects and, less frequently, of hemiparesis. The causes of failed first epilepsy surgery were heterogeneous and included incorrect localization or incomplete resection of the seizure focus, presence of additional seizure foci or progression of the underlying disease. Some features appear to indicate successful reoperation, such as concordance of postsurgical imaging and electroclinical findings as well as absence of brain trauma and cerebral infection prior to epilepsy onset.

Conclusion: Reoperation after thorough assessment of all available clinical, imaging and EEG findings can be an efficacious and reasonably safe treatment option which can achieve sustained seizure control after failed resective epilepsy surgery.

1. Introduction

Resective epilepsy surgery can lead to sustained seizure control in up to 70–80% of selected patients with medically refractory focal epilepsy.[1] This means, in turn, that up to 20–30% of operated patients will suffer from recurrent seizures after surgery. Epilepsy surgery is commonly considered as a failure if patients continue to have disabling seizures (more than "rarely" occurring disabling seizures, usually classified as class III and IV according to the Engel classification or outcome class 3–6 according to the ILAE classification).[2] People with recurrent postsurgical seizures, however, may achieve full seizure control later on whether spontaneously by the "running down" phenomenon,[3] by continuation, reinstitution or modification of anticonvulsant drugs as well as by alternative treatment options such as vagal nerve stimulation or stimulation of the anterior thalamic nucleus.[4–8] Given this variability in the disease course after a first operation, it appears difficult to define after how many seizures and after what time interval following surgery one can assume recurrence of epilepsy. The situation is further complicated by the sparse knowledge of the best time point of reevaluation and reoperation, of selection criteria for appropriate candidates, of potential indicators and predictors for favorable and unfavorable seizure-outcome after second surgery, and of efficiency and safety of a second surgery.

Taken together, it remains to be elucidated which diagnostic and therapeutic strategy is appropriate in people after failed epilepsy surgery. Here, we reviewed pertinent literature and suggest a practical approach which may allow efficient work-up and may help in the clinical decision-making when facing people after surgical failure.

2. Methods

We have considered articles in peer-reviewed scientific journals published between January 1980 and January 2013 in English dealing with reoperation after failed resective epilepsy surgery in adult patients with medically refractory focal epilepsy.

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Abstracts and book chapters have not been included in this review. The following terms were searched on PubMed: reoperation, second operation, failed epilepsy surgery, focal epilepsy, refractory epilepsy, and human.

3. Review of the literature

3.1. General characteristics, reevaluation and reoperation rates

Fifteen case series with a total of 402 reoperated patients fulfilled inclusion criteria and were analyzed in this review. Overall, 3.8–14% of all patients in whom a resective epilepsy surgery was performed underwent a second operation.[9–16] The time interval between the first and second surgical intervention ranged in average between 2 and 5.5 years (Table 1). Most patients suffered from temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) of heterogeneous etiologies as well as hypothalamic hamartomas in one series (Table 1). Neurosurgical techniques for the first epilepsy surgery varied according to epilepsy type and underlying pathology (Tables 1 and 2). Following failed resective epilepsy surgery (commonly reported as class III and IV according to the Engel classification or ILAE classification class 3–6), 32–100% of the patients were reevaluated.[9,12,15,17] Of these, 22.1–73.3% patients proceeded to a second operation,[6,9,12,15,17] leading to reoperation rates between 35.9 and 65.2% in patients with unfavorable outcome after epilepsy surgery.[9,12,15,17] The reasons for not performing a reoperation included the presence of inconsistent MRI and EEG findings, bilateral independent interictal epileptiform discharges (IED), a widespread seizure focus, overlap of the seizure focus with eloquent cortex, a compulsory intracranial study before second surgery (which was considered difficult or refused by the patient) or simply because the patient did not want a second surgery.

3.2. Reassessment after failed surgery

A common problem in clinical practice is to define recurrence of epilepsy after epilepsy surgery. Occurrence of the first and second postoperative seizure within 6 months after surgery along with an unprovoked initial recurrence and ipsilateral IED 6 months after surgery is associated with a poor postsurgical seizure outcome, and may therefore predict failed epilepsy surgery.[18] The decision to initiate reevaluation, however, is commonly taken on an individual basis and depends, among other factors, on the actual seizure control, seizure severity and the patients' wish. Reassessment requires a comprehensive review of pre- and postsurgical clinical, EEG and imaging findings.

The first step usually includes the reappraisal of clinical, MRI and EEG findings obtained prior to first surgery. A number of features are associated with the seizure-outcome after a first resective epilepsy surgery, potentially providing explanations for a failed surgery. For instance, the exclusive presence of ipsilateral IED, a clear pathology on brain MRI as well as the concordance of MRI and electroclincial findings predict a favorable outcome, whereas the presence of frequent contralateral IED, a normal brain MRI, disconcordant MRI and electroclinical findings as well as frequent secondarily generalized tonic-clonic seizures appear to predict an unfavorable outcome after a first surgery.[5,15,19–21] Importantly, the absence of specific neuropathological findings of the resected tissue is also associated with a poorer outcome.[22] Altogether, thorough revision of all findings related to the first surgery may give insights into the causes of insufficient postsurgical seizure control.

In a second step, postsurgical cerebral MRI is commonly performed to estimate the quality and extent of the first surgical intervention. In a high proportion of patients after a first failed epilepsy surgery, MRI demonstrated residual cerebral structures including retained mesial, lateral or posterior brain tissue in people with TLE.[9,11,13,15,23,24] It is often challenging to judge whether the neurosurgical intervention has been performed as intended based on MRI criteria. When the patient is seizure-free after epilepsy surgery, the seizure focus has obviously been successfully removed or the ictogenic network has been sufficiently disturbed by removal of a certain tissue volume. In mesial TLE, this "critical mass" appears to be rather individual, explaining the wide range of controversial findings of various authors and working groups investigating the optimal extent of resection.[25] There is, however, good evidence that e.g. in the case of selective amygdalohippocampectomy, a sufficient technique consists of removal of the major parts of the uncus and amygdala, the hippocampus and the parahippocampal gyrus with a posterior extent of about 2.5 cm.[26] The clinical value of further imaging studies using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) remains to be confirmed, but first reports on the use of e.g. alpha-[^{11}C]methyl-L-tryptophan PET in the reevaluation after surgical failure are promising.[27,28]

Finally, video-EEG telemetry with seizure recording is repeated. To date, it remains to be elucidated after which time interval following the first operation and in whom video-EEG monitoring should be performed. Jehi and co-workers have addressed these issues in patients after unsuccessful TLE surgery and found that seizure recurrence within the first postoperative year along with a "higher" seizure frequency (at least 4 seizures per month) predict successful identification of the seizure focus.[6] Importantly, in those patients who displayed seizure recurrence within the first 6 months, the seizure focus was distant to the original site of surgery,[6] suggesting that the initial localization of the seizure generator was wrong or that additional seizure generators were present. Furthermore, patients with contralateral IED prior to a standard temporal lobectomy (first surgery) were more likely to have seizure recurrence from the contralateral temporal lobe, strengthening the importance of thorough reappraisal of all findings (see first step). In contrast to a standard temporal lobectomy, people with more limited resections were more likely to undergo repeat EEG recordings with intracranial electrodes (Table 2).[6] The use of intracranial electrodes was reported in 7.5–73.3% of the patients before second surgery without increased complication rates (Tables 1 and 2).[9,10,16,23,29] In some of the patients, intracranial EEG recordings were even performed during both the first and second pre-surgical assessment without difficulties.[30]

3.3. Success rates and indicators for favorable and unfavorable seizure outcome after reoperation

The success rates (defined as the proportion of seizure-free patients) following a second surgery varied considerably between the published case series and ranged from 9.5 to 57.1%.[11,15] Across all studies, 36.6% of the reoperated patients became seizure-free (Table 1). This relatively high success rate has to be considered with caution, because the case series included highly selected patients who were judged eligible for a second operation with a good chance of getting seizure free. The criteria for eligibility are likely to vary from center to center and may include type of epilepsy and underlying pathology as well as postsurgical MRI findings. For instance, it might appear more intuitive to reoperate a patient with retained mesial structures after a first surgery for mesial TLE with associated hippocampal sclerosis on brain MRI, than a patient suffering from a non-lesional mesial TLE assessed by intracranial video-EEG telemetry. It would be helpful to dispose of specific features which identify candidates with a good chance of getting seizure-free after reoperation, but unequivocal predictors

Table 1
Review of case series on reoperation after failed resective epilepsy surgery in adults.

Reference	Type of epilepsy (pathology)	Seizure recurrence after 1st surgery	No. of re-operated and analyzed pts.	Favorable seizure outcome after 2nd surgery (no. of pts.)[a]	Complications related to 2nd surgery (no. of pts.)	Minimum follow-up after 2nd surgery (mean)	Mean time interval between 1st and 2nd surgery	Indicators/predictors of favorable seizure outcome after 2nd surgery (as highlighted by the authors)	Indicators/predictors of unfavorable seizure outcome after 2nd surgery (as highlighted by the authors)
Siegel et al.[16]	Mixed (about two third TLE)	In 89% within the first year	64	I: 22 II: 5	10 pts.: 9 pts. visual field defects 1 pt. hemiparesis	1 yr (4.0 yrs)	5.5 yrs	Epilepsy duration $\leq$5 years prior to first surgery (odds ratio 3.18, 95% CI 1.03, 9.90); focal IED[b] prior to first surgery (odds ratio 4.45, 95% CI 1.22, 16.18)	
González-Martínez et al.[29]	Heterogeneous population (FCD, HS, tumors, dual pathology, nonspecific lesions)	71% within the first year	57	I: 22 II: 8	12 pts.: 8 pts. quadrantanopsia 4 pts. hemiparesis	2 yrs (10.6 yrs)	4.4 yrs	Tumors as initial pathology better outcome than FCD or HS	
Germano et al.[23]	TLE	60% of the patients within 6 months, and 90% of the pts. within the first 2 years after surgery	40	I: 21 II: 4	0 pt.	2 yrs (4.8 yrs)	5.5 yrs		EEG abnormalities in multiple brain areas
Salanova et al.[14]	FLE (nontumoral)	Not reported	39	1 of 35 seizure-free 6 of 35 seizure-free after early postoperative seizures	3 pts.: 1 hemiparesis 1 paresis of leg 1 facial weakness	4 yrs (19 yrs)	Not reported	Absence (or significant reduction) of spiking in ECog after resection	Combined fronto-temporal resections (in contrast to frontal resection alone)
Wyler et al.[31]	Mixed (mostly TLE)	Not reported	31	I: 15	3 pts.: 2 pts. quadrantanopsia 1 pt. hemiparesis	Not reported	Not reported	Residual structural lesions; extension of the first surgery; invasive EEG recordings prior to first surgery in non-lesional epilepsies	
Schulz et al.[13]	Mesial TLE (HS)	Not reported	22	I: 9	2 pts.: 1 pt. hemianopia 1 pt. dyslexia/ quadrantanopsia	2 yrs (3.6 yrs)	4.95 yrs		Secondary propagation of ictal activity to the contralateral hemisphere; small quantity of lateral temporal lobe resection
Holmes et al.[10]	Mixed	Not reported	21	I: 9	0 pt.	1 yr (3 yrs)	2 yrs	Concordance of preoperative focal MRI findings with ictal EEG onset before and after the first failed surgery	History of CNS infection prior to epilepsy onset
Schwartz and Spencer[46]	Heterogeneous population (FCD, HS, tumors, others)	Not reported	21	I: 4	Not reported	1 yr (3.5 yrs)	Not reported	Removal of recurrent tumors, repeated invasive monitoring to correct a prior sampling error	

Table 1 (*Continued*)

Reference	Type of epilepsy (pathology)	Seizure recurrence after 1st surgery	No. of re-operated and analyzed pts.	Favorable seizure outcome after 2nd surgery (no. of pts.)[a]	Complications related to 2nd surgery (no. of pts.)	Minimum follow-up after 2nd surgery (mean)	Mean time interval between 1st and 2nd surgery	Indicators/predictors of favorable seizure outcome after 2nd surgery (as highlighted by the authors)	Indicators/predictors of unfavorable seizure outcome after 2nd surgery (as highlighted by the authors)
Salanova et al.[15]	TLE	Not reported	21	I: 12 II: 5	Not reported	1 yr (range 1–16 yrs)	5.2 yrs	Anterior temporal localization of seizure focus, abnormal brain imaging	
Pati et al.[11]	HH	Not reported	21	I: 2	12 pts.: 1 pt. symptomatic stroke 5 pts. hyperphagia 1 pt. panhypopituitaris 4 pts. hypernatremia 1 pt. communicating hydrocephalus	6 months (median 9 months)	Not reported		
Jung et al.[17]	TLE	Immediately after operation (16 pts.)	17	I: 5	Not reported	1 yr (6.3 yrs)	Not reported		History of traumatic brain injury
Awad et al.[9]	Mixed (mostly TLE)	87% within the first 6 months	15	I: 7	0 pt.	8 months (1.5 yrs)	3.2 yrs		
Jehi et al.[18]	TLE	69% within the first year, 31% after the first year	15	I: 6	Not reported	Not reported	Not reported	Recurrence of seizures within the ipsilateral (to original operation site) basal and mesial temporal lobe	
Abosch et al.[44]	Mesial TLE	Not reported	13	4 seizure-free	Not reported	Not reported	2.6 yrs		
Ramos et al.[12]	Mesial TLE	All within the first year	5	I: 2 II: 1	Not reported	Not reported	Not reported		
Summary (all)			402	147 seizure-free (36.6%)	42/310 pts. (13.5%)				
Summary (without HH)			381	145 seizure-free (38%)	30/289 pts. (10.4%)				

ECoG: electrocorticography; FCD: focal cortical dysplasia; FLE: frontal lobe epilepsy; HH: hypothalamic hamartoma; HS: hippocampal sclerosis; IED: interictal epileptiform discharges; pts.: patients; SAHE: selective amygdalohippocampectomy; TLE: temporal lobe epilepsy.

[a] At last follow-up according to Engel classification.

[b] Opposite to regional, bilateral or generalized IED.

Table 2
Reassessment and surgical techniques applied in the reviewed case series.

Reference	Reassessment including MRI and seizure recording	Invasive extraoperative EEG recordings prior to 1st surgery (no. of pts.)	Invasive extraoperative EEG recordings prior to 2nd surgery (no. of pts.)	Repeated invasive recordings	Surgical techniques applied in first surgery	Surgical techniques applied in second surgery
Siegel et al.[16]	Yes	3 pts.	6 pts.	Not specified	Lesionectomy (33 pts.), temporal lobe resection (28 pts.), extratemporal resection (3 pts.)	Reoperation was mostly confined to the same lobe as first operation (55 pts.)
González-Martínez et al.[29]	Yes	15 pts.	26 pts.	9 pts.	Lesionectomy (tumor, FCD), ATL (for mesial TLE, 9 pts.) and SAHE (1 pt.)	Extension of the previous operation (54 pts.)
Germano et al.[23]	Yes	6 pts.	3 pts.	Not specified	Anterior temporal lobe resections (37 pts.), SAHE (2 pts.), resection of arachnoid cyst (1 pt.)	Extension of first operation (removal of mesiotemporal structures (amgydala, hippocampus up to the level of superior colliculus in 30 pts.)
Salanova et al.[14]	In some of the pts.	No	No	N.A.	Electrocorticography-guided resection (26 pts.), more than one third underwent extensive removal of frontal lobe including orbital cortex and anterior cingulate areas	Extension of first operation (26 pts.)
Wyler et al.[31]	Yes	12 pts.	No	No	Focal resection (31 pts.)	Mostly extension of first operation (30 pts.)
Schulz et al.[13]	Yes	1 pt.	No	No	Keyhole resection of mesiobasal structures after removal of temporal pole; standard en bloc resection via the anterior temporal or lateral subtemporal approach; SAHE via transsylvian or lateral temporal approach; miminal invasive resection of the hippocampal formation through a stereotactically guided working sleeve	Extension of first operation
Holmes et al.[10]	Yes	8 pts.	11 pts.	Not specified	Tailored resection (strictly temporal resections 11 pts.; temporal and extratemporal resections 10 pts.)	Mostly extension of first operation (17 pts.)
Schwartz and Spencer[46]	Yes	11 pts.	7 pts.	6 pts.	No overlap with functional cortex: total removal of entire ictal onset zone; overlap with functional cortex: subtotal resection and/or multiple subpial transsections or stereotactic radiosurgery or total resection; Mesial temporal sclerosis: standard anterior medial temporal resection and total amygdalahippocampectomy;	Extension of first operation (e.g. neocortical resection in mesial TLE), resection of recurrent tumors, and others
Salanova et al.[15]	Yes	9	No	No	ECoG-guided en-bloc temporal resections or lesionectomies	ECoG-guided extension of first operation
Pati et al.[11]	Yes	No	No	N.A.	Different techniques (resection via endoscopic, transcallosal, orbitozygomatic approach, radiosurgery)	Mostly removal of residual HH
Jung et al.[17]	Yes	2 pts.	No	No	SAHE, anterior medial temporal or tailored temporal lobe resections	Anterior medial temporal (16 pts.), SAHE (1 pt.) on the same side as first surgery
Awad et al.[9]	Yes	Not reported	11 pts.	N.A.	Temporal or frontal lobectomy (7 pts.), anterior temporal lobectomy (2 pts), SAHE (2 pts.), topectomy (2 pts.), anteriomesial temporal lobectomy (1 pt.), parietal lesionectomy (1 pt.),	Mostly extension of first operation
Jehi et al.[18]	Yes	Not specified	Not specified	Not specified	Standard ATL (dominant: 4–4.5 cm; non-dominant: 5–5.5 cm; hippocampus removed as far back as the level of superior colliculus) including removal of mesial structures, temporal tip, parahippocampal and inferior or temporal gyri) (53 pts.); SAHE transsylvian or transsulcal, 3 cm hippocampus resected (5 pts.); lesionectomy (4 pts.); "tailored" resections (6 pts.)	Extension of first operation (basal and mesial parts)

Table 2 (*Continued*)

Reference	Reassessment including MRI and seizure recording	Invasive extraoperative EEG recordings prior to 1st surgery (no. of pts.)	Invasive extraoperative EEG recordings prior to 2nd surgery (no. of pts.)	Repeated invasive recordings	Surgical techniques applied in first surgery	Surgical techniques applied in second surgery
Abosch et al.[44]	Yes	Not specified	6 pts. (?)	Not specified	Transcortical SAHE (removal of hippocampus, amygdala, entorhinal cortex and uncus)	Extension of first operation or cortico-amygdalahippocampectomy
Ramos et al.[12]	Yes	No	No	N.A.	Selective anterior mesial temporal resection with removal of hippocampus and parahippocampus to the level of the superior colliculus, resection of the uncus and partial resection (> 80%) of the amygdala via a transcortical approach (superior and middle temporal gyri preserved)	ECoG-guided extension of first operation

ATL: anterior temporal lobectomy; ECoG: electrocorticography; FCD: focal cortical dysplasia; FLE: frontal lobe epilepsy; HH: hypothalamic hamartoma; HS: hippocampal sclerosis; IED: interictal epileptiform discharges; SAHE: selective amygdalohippocampectomy; TLE: temporal lobe epilepsy.

of favorable seizure outcome after a second surgery have not been established yet (Table 1). It is tempting to hypothesize that the site of reoperation and contiguity of the recurrent seizure focus to the first operation site is a relevant predictor of good seizure outcome.[6,31] In most studies, however, the majority of reoperations consisted of a surgical extension of the first operation, so that it is impossible to relate seizure outcome to the site of operation (Table 1). In one study, tumors as underlying pathology were associated with a better seizure outcome than focal cortical dysplasia and hippocampal sclerosis.[29] Furthermore, duration of epilepsy $\leq$5 years before first surgery and the presence of focal IED prior to first surgery appeared to predict good seizure outcome after reoperation.[16] Potential indicators for unfavorable seizure outcome after a second surgery include EEG abnormalities in multiple brain areas, secondary propagation of ictal activity to the contralateral hemisphere as well as history of encephalitis and brain trauma before first onset of epilepsy (Table 1).[10,13,17,23] Interestingly, 4.7–14.1% of the patients who were reoperated without success were operated a third time and achieved seizure-freedom in 44.4–100% of the cases.[10,16,23,29,32]

3.4. Complications related to reoperation

Complication rates related to the second surgery ranged from 0% in reoperated TLE patients to 57.1% in patients reoperated for hypothalamic hamartoma with an overall complication rate of 13.5% across all studies (42 of 310 patients, Table 1).[11,23] Complications mainly included postoperative visual field deficits and less frequently mild to moderate hemiparesis.

4. Discussion

4.1. Limitations of this review and the included studies

This review is based on retrospective case series published from 1989 to 2013, from different epilepsy centers in different countries, using different imaging and EEG techniques, dealing with very heterogeneous study populations (e.g. differing localization of the lesions or operation site as well as variable etiologies such as hippocampal sclerosis, brain tumor, focal cortical dysplasia, hypothalamic hamartomas, cavernomas and unspecific lesions) being evaluated by many epileptologists and operated and reoperated by many neurosurgeons with different neurosurgical techniques. These inherent differences among the cited studies are mirrored by the high variability of seizure outcomes and illustrate that it is difficult to draw valid and reliable conclusions on predictors of successful reevaluation and reoperation after failed resective epilepsy surgery.

The most important advances in the last decade (and thus the most important limitations of some of the previous studies) are probably the development of high resolution MRI and postprocessing techniques allowing e.g. the detection of subtle focal cortical dysplasia or bilateral involvement of mesiotemporal structures (which have probably not been detected in some of the older studies because of insufficient, low-resolution imaging techniques) as well as the discovery of novel disease entities such as autoimmune-mediated epilepsies and the identification of genetic epilepsies which can cause signs of focal epilepsies (e.g. SCN1A mutations).[33–35] Furthermore, the criteria to stratify chances and risks of epilepsy surgery are likely to vary between tertiary epilepsy centers, and epileptologists and neurosurgeons from different centers may request a variable level of consistency of MRI and electroclinical findings before proceeding to surgery (e.g. the decision to operate may be solely based on a MRI-lesion along with consistent focal IEDs).[36] Another important problem is the lack of a unified strategy on when and how to taper off anticonvulsant

drugs after successful surgery. Thus, there might be a bias in some of the studies due to differences in the planned discontinuation of anticonvulsant drugs in seizure-free patients.[4] A general problem is the difficulty to determine the actual seizure outcome. Seizure frequencies are commonly reported by the patients (who may be unaware of some seizure types or amnesic afterwards, or who do not report seizures for personal reasons), the relatives and the caretakers. This method, however, does not provide accurate seizure counts, and may be biased by seizure types and side of seizure activity.[37] Finally, people may suffer from new onset psychogenic, non-epileptic seizures after surgery, mimicking seizure recurrence and failed surgery.[38,39]

4.2. Pathophysiology and causes of failed epilepsy surgery

Failure of epilepsy surgery has many potential sources.[40–42] It could be due to a wrong initial hypothesis and incorrect localization of the seizure focus because of disconcordant MRI and electroclincal findings or a spatial sampling bias during intracranial EEG recordings. Seizures may also reoccur because of a planned limited resection due to contiguity of the seizure focus to functional cortex or because of an insufficient neurosurgical technique with a partially retained epileptogenic lesion. For instance, in people with mesial TLE, residual entorhinal cortex was found in 9 of 10 patients who did not become seizure-free after selective amygdalohippocampectomy, as compared to 10 patients who were seizure-free and in whom there was no evidence of residual entorhinal cortex.[24] Seven of the 9 patients with residual entorhinal cortex were seizure-free after reoperation with resection of the mesiotemporal structures. In one study assessing causes of failed epilepsy surgery, however, residual hippocampus was found in 5 patients with mesial TLE, but thought to be the cause of postsurgical seizure recurrence in one patient only.[43] In another study, there was no significant difference in seizure outcome in mesial TLE patients with or without residual mesiotemporal structures following selective amygdalohippocampectomy.[44] These results suggest that failed epilepsy surgery could also be due to inherent properties of more widespread ictogenic networks. These networks involve e.g. not only mesiotemporal structures (amygdala, hippocampus, entorhinal cortex and parahippocampal gyrus) in the case of mesial TLE, but also neocortical or subcortical areas of the ipsilateral temporal lobe or hemisphere, possibly due to widespread modifications caused by recurrent seizure activity, traumatic brain injury or encephalitis. Some authors have also suggested the term "temporal plus epilepsy" to describe an entity which clinically mimics a "pure" TLE, but which involves brain areas in conjunction with the temporal lobe (such as the orbito-frontal cortex, the frontal and parietal operculum, the insula and the temporo-parieto-occipital junction), ultimately leading to incorrect or incomplete localization of the seizure focus.[45] The presence of a dual pathology, e.g. hippocampal sclerosis together with focal cortical dysplasia in the same temporal lobe, has become frequently apparent with the advent of high resolution MRI, and is an additional cause of surgical failure.[46,47] Finally, the nature of the underlying disease can lead to a recurrent seizure focus (e.g. tumor recurrence) or new seizure foci (e.g. involvement of the contralateral hippocampus in mesial TLE). This may be partially due to recently described genetic and inflammatory mechanisms such as SCN1A mutations or autoimmune-mediated limbic encephalitis in association with TLE and hippocampal sclerosis.[33,34] The underlying genetic and inflammatory processes may have not been detected before surgery and could prevent favorable postsurgical seizure outcome at least in some of the operated patients. For instance, people with SCN1A mutations occasionally display hippocampal sclerosis, but commonly suffer from generalized or multifocal epilepsies, suggesting that the sclerotic hippocampus is not the only seizure focus.[35,48] More generally, co-existence of two syndromes such as TLE and idiopathic generalized epilepsy which has not been detected before epilepsy surgery or incidental lesions in the context of symptomatic generalized epilepsies may cause postsurgical failure. In limbic encephalitis, the more diffuse pathophysiology with possible affection of both mesiotemporal structures appears to lower chances of postsurgical seizure-freedom. A selected group of patients (particularly those with unilateral hippocampal sclerosis), however, may benefit from resective epilepsy surgery, as recently suggested.[49] It remains to be elucidated whether e.g. specific antibodies define subgroups of patients with limbic encephalitis which benefit from resective epilepsy surgery in a disease phase where the underlying inflammatory process has ceased.

4.3. Practical approach to reoperation after failed epilepsy surgery

According to the analyzed case series, the overall chance of getting seizure-free with a second resective operation amounts to 36.6% with an overall complication rate of 13.5%. This relatively high success rate is encouraging, but might be not very meaningful for clinical practice, given the heterogeneous etiologies and surgical techniques. Thus, these retrospective case series can only provide some cautious clues to reoperation strategies after failed epilepsy surgery and general conclusions may not be valid. The individual medical constellation together with the patient's desire to proceed to a second operation should be taken into account when counseling people after surgical failure. Bearing these limitations in mind, systematic assessment of the following features may be helpful to identify those candidates who benefit most from a second surgery.

4.3.1. History taking and features of postsurgical seizures

- History of encephalitis or traumatic brain injury prior to onset of epilepsy (may indicate a lower chance of getting seizure free due to more widespread seizure focus).
- Late onset of epilepsy (may be caused by an autoimmune-mediated limbic encephalitis, which possibly indicates an unfavorable outcome).
- Associated learning disabilities (could be due to genetic causes such as mitochondriopathy or SCN1A mutations which are potential indicators for an unfavorable outcome).
- Semiology of recurrent seizures (persistence of habitual aura as a hint that the seizure focus has not completely been removed; persistence of habitual aura, but novel semiologic aspects after surgery indicating new propagation pathways; postsurgical onset of novel initial symptoms suggestive for the development of a new seizure focus or the activation of a pre-existing, but inactive seizure focus before surgery; new onset of inhabitual or bizarre symptoms possibly indicating psychogenic, non-epileptic seizures).
- Time point of seizure recurrence (an early recurrence suggests that the predominant seizure focus has not been removed, or that the focus of recurrence is distant to original surgical bed).[6]
- Postsurgical seizure frequency (high seizure frequency increases the likelihood of identifying the seizure focus during repeat video-EEG telemetry; low seizure frequency may suggest favorable outcome by additional anticonvulsant drug treatment or the running-down phenomenon; low frequency, however, may also indicate a marked and sustained improvement after the first operation and could be an important factor in convincing the patient and the surgeon to attempt further surgery).[3,6]

4.3.2. Interictal and ictal scalp EEG features after failed surgery

- ○ EEG abnormalities exclusively ipsilateral to the side of first operation (potential indicator for a favorable outcome).
- ○ Contralateral IED or ictal patterns recorded after surgery (potential indicator for an unfavorable outcome).
- ○ Secondary propagation of seizure activity to the contralateral hemisphere e.g. in mesial TLE (potential indicator for an unfavorable outcome).[13]

4.3.3. Neuropathology

- ○ Consistency of neuropathological findings with MRI diagnosis prior to first surgery (e.g. hippocampal sclerosis, focal cortical dysplasia, benign tumor).

4.3.4. Postsurgical MRI

- ○ Presence of residual and putatively epileptogenic lesions.
- ○ Detection of new lesions (e.g. signs of contralateral hippocampal sclerosis, recurrent brain tumor).

According to the resulting features, individual postsurgical constellations could be classified into the following three categories:

Category I with a good chance of favorable seizure outcome after reoperation: Patients display consistent electroclinical and MRI findings prior to first surgery, postsurgical EEG abnormalities ipsilateral to the side of first surgery and residual structures on postsurgical MRI.

Category II with a moderate chance of favorable seizure outcome after reoperation: Patients display consistent electroclinical and cerebral imaging findings (with a visible lesion on MRI or without a clear pathology on MRI, but a unilateral regional hypometabolism in cerebral ^{18}F-fluorodeoxyglucose positron emission tomography and subsequent confirmative intracranial video-EEG telemetry) prior to first surgery, an apparently sufficient surgery according to postsurgical MRI and seizure-onset in the same region of or in close vicinity to the site of the initial operation (e.g. in a patient with recurrent seizures after a complete selective amygdalohippocampectomy, the second surgery could consist of an extension to the lateral neocortex or an anterior temporal lobectomy).

Category III with a poor chance of favorable seizure outcome after reoperation: Patients display inconsistencies of electroclinical and MRI findings prior to first surgery, a new seizure semiology, multifocal or widespread EEG abnormalities, an apparently sufficient surgery according to postsurgical MRI and a seizure-onset contralateral to the side of the initial operation, novel (or newly diagnosed) epileptogenic lesions, a limited resection due to overlap of seizure-focus with eloquent cortex or the postsurgical diagnosis of underlying genetic or inflammatory diseases.

This classification is, of course, arbitrary and incomplete, and thought to provide a practical approach to reoperation strategies. Patients of category I most likely benefit from a second resective epilepsy surgery early after recurrence of epilepsy. Patients of category II may require (repeated) invasive video-EEG telemetry, additional laboratory investigations (e.g. genetics or determination of antibodies associated with autoimmune encephalitis) or further PET- or SPECT-imaging studies. These patients may wait one or two years after failed surgery to appreciate the natural course (“running down” – phenomenon, efficacy of additional best medical treatment) before invasive reevaluation and reoperation. Patients of category III are unlikely to benefit from a reoperation, and alternative treatments (novel anticonvulsants, vagal nerve stimulation and stimulation of the anterior thalamic nucleus) may be considered.

In summary, reoperation appears to be an efficacious and reasonably safe option to achieve sustained seizure control in a selected group of patients after failed epilepsy surgery. Reevaluation requires thorough assessment of all available clinical, imaging and EEG findings in order to identify suitable candidates for reoperation. The decision to perform reevaluation and reoperation is individually taken and based on the entire medical constellation and the patient’s wish.

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