Epilepsy Surgery in Patients with Tuberous Sclerosis

Summary

With a few exceptions patients with tuberous sclerosis (TS) suffering from drug-resistant epilepsies have potentially epileptogenic lesions within both hemispheres. Until one decade ago in general such a constellation was an exclusion criteria for considerations with respect to epilepsy surgery. However experience has shown that it is not so rare to find patients in whom over the years seizures are generated from just one single focus and that these patients can be good candidates for epilepsy surgery. Almost revolutionary was the further development: multi-step procedures in patients with bilateral epileptogenic lesions – with promising results in terms of postoperative seizure outcome. Also, with increasing experience, it becomes more and more possible to differentiate already non-invasively which lesions could be epileptogenic and which are rather not the source of the seizures. The most important achievement of epilepsy surgery in TS however is that in selected cases early surgical intervention is able to prevent severe mental retardations, which are often the main burden for families who have members with this peculiar disease.

Key words: Tuberous Sclerosis Complex, epilepsy, mental retardation, epilepsy surgery

Epilepsiechirurgie bei Patienten mit Tuberöser Sklerose

Personen mit Tuberöser Sklerose, welche an Pharmaka-resistenten Epilepsien leiden, haben in der Regel mehrere potenziell epileptogene Läsionen – verteilt in beiden Hirnhälften.

Bis vor ca. 10 Jahren war eine solche Konstellation noch ein Ausschlusskriterium bezüglich Überlegungen in Richtung eines möglichen epilepsiechirurgischen Eingriffs. Die Erfahrung hat aber gezeigt, dass es nicht wenige Betroffene gibt, bei welchen über die Jahre konstant lediglich nur ein Herd epileptische Anfälle generiert, und dass diese Patienten gute Kandidaten für eine Operation sein können. Nahezu revolutionär war dann als nächste Weiterentwicklung die Einführung mehrstufiger Vorgehensweisen bei Personen mit Herden in beiden Hemisphären – mit guten postoperativen Ergebnissen.

Mit wachsender Erfahrung ist es auch immer mehr möglich, bereits nicht-invasiv und relativ verlässig epileptogene Läsionen von nicht-epileptogenen Läsionen zu unterscheiden.

Der wahrscheinlich wichtigste Fortschritt ist aber darin zu sehen, dass in ausgewählten Fällen schwere mentale Retardierungen, welche bei Kindern mit TS zu beobachten sind, wenn die Epilepsie früh beginnt und schwer verläuft, durch frühzeitige Operationen verhindert werden können.

Schlüsselwörter: Tuberöse Sklerose, Epilepsie, mentale Retardierung, Epilepsiechirurgie

Chirurgie de l’épilepsie chez des patients avec sclérose tubéreuse

Les personnes atteintes de sclérose tubéreuse et souffrant d’épilées pharmacorésistantes présentent en général plusieurs lésions potentiellement épilepto-gènes, réparties dans les deux hémisphères cérébrales.

Il y a environ 10 ans, un tel cas de figure était encore un critère d’exclusion dans toute réflexion orientée vers une éventuelle chirurgie de l’épilepsie. Depuis, l’expérience a toutefois montré que les cas n’étaient pas rares où les crises épileptiques étaient constamment générées pendant des années par un seul foyer et que ces patients pouvaient être de bons candidats à une opération. L’innovation suivante, quasi révolutionnaire, a été l’introduction de procédures en plusieurs étapes chez des patients présentant des foyers dans les deux hémisphères – avec de bons résultats postopératoires.

A cela s’ajoute qu’avec l’expérience, on est toujours
Introduction on Epilepsy Surgery

There is most likely no other etiology by which it is possible to demonstrate more impressively how much progress has been made over the last decade in the field of epilepsy surgery then in TSC. Since the advent of MRI the few patients with single epileptogenic tubers and drug resistant seizures were always considered to be candidates for epilepsy surgery, but for a long time it was beyond the imagination of epileptologists that patients with multiple such lesions in both hemispheres could possibly benefit from surgery on the long run. In fact there is a drop in the rate of seizure free patients comparing the rate on ≤ 2 years follow up (64.5% in Engel’s Class I) with the rate on > 2 years follow up (43.6% in the review by Madhavan et al. [24], but that difference did not reach statistical significance in the multi-variant analysis. In a series from Beijing reported by Liang et al. [25], 72% were seizure free at 1 year follow up, 60% at 2 years and still 54.5% at the 5 years follow up – a figure not very much different (if different at all) from long term outcome figures in patients with other etiologies who have undergone epilepsy surgery. 12 out of 18 children operated on at UCLA became seizure free – with an average length of follow up of 4.1 years! The length of follow up was not different between seizure free and not seizure free patients in the meta-analysis by Jansen et al. [26]. 177 operated patients with TSC were included in this comprehensive review; 57% became seizure free and a seizure reduction by more than 90% was achieved in another 18%. Out of these 177 patients 71 underwent focal resections, 74 lobar resections and 16 multilobar resections. In another meta-analysis 53% were in Engel’s outcome class I and 11% in Class II [24]. In both studies duration of the epilepsy and the number of tubers had no influence on seizure outcome. A younger age at onset of epilepsy and bilateral interictal spikes were risk factors for seizure recurrence in the review by Madhavan et al. [24] but not in the analysis by Jansen et al. [26], in which mental retardation and spasms were associated with a less favorable outcome. In contrast to the data in the review by Madhavan et al. [24] a younger age at surgery and a shorter duration of epilepsy were associated with a more favorable outcome in the pediatric series from UCLA [27]. The highest risk factor for seizure recurrence in the meta-analysis by Jansen et al. [26] was “multifocal SPECT-findings”.

Until several years ago epilepsy surgery was offered only to patients in whom a single focus in one hemisphere could be identified (the “principle tuber”, the one and only “epileptogenic tuber”). In recent years boundaries in epilepsy surgery for patients with TSC have been pushed forward dramatically, from 2 step procedures for patients with foci in each hemisphere [28] to single step invasive recordings with subdural grids over both hemispheres in patients with multiple epileptogenic lesions within both hemispheres, (as identified by prior non-invasive investigations) [29], to the implantation of subdural grids bilaterally in search of foci in patients in whom the results of non-invasive evaluations did not provide a hypothesis with respect to the localization of the epileptogenic regions [30]. It is somewhat astonishing that outcome with respect to postoperative seizure control can be as good in patients with multiple foci and surgeries in both hemispheres as it is in patients with single, unilateral foci [29, 25], although there are other reports that multifocality is negatively correlated with seizure outcome [31].

At our center, over a period of 12 years, 10 children with TSC have been operated, including one girl with epileptogenic foci in both hemispheres (who has been
operated on in a multistep approach after evaluations with subdural grids both times); 6 are seizure free, 1 is in Engel’s Class II, 3 are in Engel’s Class 3 (worthwhile improvement). Despite all the progress the selection of patients with severe epilepsies caused by TSC however remains a challenge; and it cannot be emphasized enough that the decision whether a patient with TSC is a candidate for epilepsy surgery or not has to be made by the epilepsy specialists working at epilepsy centers with a large experience in epilepsy surgery — and not by the referring source [32]. On the other hand, for an optimal management of patients with TSC and drug resistant seizures, it is mandatory that physicians who are taking care of the patients “at home” and specialists at centers where the evaluation for epilepsy surgery is done are communicating closely with each other; e.g. a reconfirmation by the referring source that the electro-clinical picture which has been captured during a presurgical evaluation by means of a prolonged EEG-/Video-monitoring would fit well with what has been documented over months and years before, is extremely helpful in the decision making process. Nevertheless, in a number of patients it will be necessary to repeat investigations, e.g. by carrying out a second EEG-/Video-monitoring (which can sometimes be of shorter duration than the first prolonged EEG-/Video-monitoring) in order to document that one is dealing with a stable focus. Because of the nature of the disease it is not surprising that the ratio operated patients/patients evaluated for epilepsy surgery is not always as favorable as it is in other etiologies, e.g. as in Benign Tumors, Focal Cortical Dysplasia or Mesial Temporal Lobe Epilepsy.

Identification of the epileptic region in TSC

Non-invasive EEG and semiology: The selection for epilepsy surgery is not so difficult in patients who, over years, have just one single stable focus in their EEG, despite multiple tubers on imaging [33 - 35]. Within the context of the decision making process pro or against a proposal for surgery the interpretation of findings like interictal multifocal sharp waves, more than one focal seizure pattern, “generalized” EEG-seizure pattern, more than one clinical seizure type etc. can be extremely difficult. But there is consensus that patients with TSC and severe epilepsies, who present with such more “complex” electro-clinical pictures should not be excluded from considerations for surgery. More and more patients with more than one focus are now becoming seizure free post surgery (see previous paragraph).

Even in patients with a high number of tubers and other pathological signal changes and “diffuse” and “chaotic” electro-clinical pictures attempts must be made to correlate such findings with each other: epileptiform activities over brain areas, which look totally normal (cortical and subcortical level) are most likely representing “irritative” phenomena, e.g. as a result of (frequent) seizure spread. Generalized EEG-pattern, and generalized seizures (or spasms in association with generalized seizure pattern) are no indication for a callosotomy; this procedure will not lead to seizure freedom [26]; in TSC these signs and symptoms are always reflecting seizure spread or a kind of secondary generalization and the chance to find a resectable epileptogenic region which is the primary source of the seizures is not so bad.

**MRI, epileptogenic tubers, non-epileptogenic tubers and epileptogenic regions:** MRI-changes in patients with TSC are so characteristic that the diagnosis will not be missed. Only in patients with a single tuber the differential diagnosis from FCD type Ib can be sometimes more difficult. When seizures cannot be controlled by medication and when there are several tubers visible on MRI, the key question then is whether one is able to come up with a hypothesis from which region(s) seizures are most likely generated from — without knowing any other symptoms and signs, and without knowing the results from other tests. Indeed this question can be answered positively despite the fact that there is little data in the literature in support of this statement. Up to now centers have studied mainly the predictive value of (non-invasive) ancillary tests like PET, SPECT, MEG, MSI etc. for the identification of the “principle tuber(s)” (see next paragraph). But searching for “principle tubers”, in our opinion, is a concept which neglects the fact that it is not so rare that the epileptogenic region is located outside from or even distant from tubers [36; own experience]. There is a variety of imaging features: one set of tubers consists of hypomyelinated hamartomas, which show a highly increased signal on T2- and are hypodense on T1-images. There is no epileptogenic tissue within the core of this tuber type, as it has been documented by means of invasive recordings [37] and these tubers are not epileptogenic when located strictly intracortical (at first glance – juxtacortical with no signal changes within the surrounding white matter may be more correct), even when their size is large. Epileptogenic are tubers who are surrounded by FCD — and theses changes are visible on T2- and on Flair-images and are appreciated as FCD by the experts (“white matter changes with features of FCD”; [38, 39; authors own experience]; but this view is not shared by all centers [40]. Focal Cortical Dysplasia is the underlying pathology of epileptogenic regions outside/distant from tubers (own experience) and the pathological substrate of the epileptogenic “non-tuber-areas” as reported by Wang et. al. [36]. Another set of tubers, showing the characteristic “transmantle sign” [41] resembles in all imaging aspects the type II b - FCD. Surprisingly, in TSC, only a minority of this lesion type is epileptogenic, which is in sharp contrast to the situation in patients with FCD. The explanation for this puzzling observation is most likely that the “transmantle-lesions in TSC”, despite their similarity with respect to
imaging aspects, are somewhat different in terms of cellularity from the “transmantle lesions in FCD”: in TSC balloon-cells are outnumbering dysmorphic neurons, whereas in FCD type IIb with the transmantle sign dysmorphic neurons are outnumbering balloon cells [42] — and it has been shown by several authors that seizures are more associated with the presence of dysmorphic neurons and less with the presence of balloon cells [43 – 46]. Yet two other tuber types too seem to be associated more often with the generation of seizures: “calcified tubers” and “cyst-like-tubers” [38].

Such a sub-classification of different tuber types is missing in 2 recent papers, both addressing the question of seizure generation within tubers vs. seizure generation within peri-tuberal cortex: according to Mohamed et al. [41] most seizures in their series were generated from inside the tubers, whereas Ma et al. [47] reported “heterogenous” situations – seizure onset zones within and outside from tubers (= inside of perituberal cortex).

With increasing experience in the judgement of the various changes in the MRI of patients with TSC one can expect that more publications will address the meaning of different tuber types and other signal changes as far as the non-invasive identification of the epileptogenic region is concerned. In addition Gallagher et al. [48] have shown that different tuber types can also have a predictive value for variables other then epilepsy surgery. Withholding early surgery because the epilepsy a patient with TS is suffering from seems not to be so severe (“considering how his MRI looks like”) is a doubtful approach. In an investigation “heterogenous” situations – seizure onset zones within and outside from tubers (= inside of perituberal cortex).

Ancillary tests – PET, SPECT, MEG, Magnetic Source Imaging (MSI):

There is no generally accepted protocol on when and how to use additional tests (additional to prolonged EEG-/Video-monitoring and MRI) in the determination of the epileptogenic region in TSC. For many years, one pediatric center (Detroit) has been heavily relying on AMT-PET [49 – 52], because of the relative low yield of FDG-PET in an etiology characterized by multiple lesions [53], others believe in the value of ictal SPECT [54, 55] or MEG [56]. There is reason to assume that regarding postoperative seizure outcome, combinations of these tests may have a higher positive predictive value than single tests alone, like it is the case when Magnetic Source Imaging (MSI) is combined with PET/co-registered with MRI [27].

Timing of epilepsy surgery in Tuberous Sclerosis – Prevention of severe mental retardation

Like in patients with other etiologies a referral for a presurgical evaluation is indicated when seizures are not controlled after the administration of 2 appropriate antiepileptic drugs and when the epilepsy has a negative impact on the patient’s quality of life. The reality however looks different. Early referrals are rather the exception. Because of anticipated difficulties in the identification of the epileptogenic region and a widely spread scepticism regarding their chances by surgery, patients with TS usually get numerous AED’s prior to a formal presurgical evaluation, an attitude which often delays surgery for years. This kind of treatment might be justified as long as mental development is not impaired but it is the wrong approach when patients do not develop well. The main risk factors for a permanent mental retardation are early onset of epilepsy/onset within the first year of life, a presentation with infantile spasms and even worse the occurrence of a West Syndrome and duration of a West Syndrome. A high tuber count is another risk factor as are bilateral tubers and tuber localization within the temporal lobes [57 – 62, 20]. But there are also patients with TS who are mentally normal despite a high tuber count; these are persons without epilepsy or with well controlled seizures [63]. Therefore, when suffering from drug resistant seizures, also patients with large numbers of tubers deserve a responsible discussion with respect to a possible early epilepsy surgery. Jansen et al. [64] presented data showing that most likely not the number of tubers is so relevant regarding mental development but the total brain volume, occupied by tubers. Withholding early surgery because the epilepsy a patient with TS is suffering from seems not to be so severe (“considering how his MRI looks like”) is a doubtful approach. In an investigation of children (with a variety of etiologies) with and without infantile spasms (IS) who had undergone epilepsy surgery Jonas et al. [65] were able to show that patients with IS, who had had lower IQ-scores prior to surgery than the children in the other group but who had been operated on at younger ages than patients without IS (in whom the epilepsies prior to surgery had been milder and who had developed better before surgery) had bypassed the other children in terms of mental development on follow up investigations !! Prompt cessation of seizures is a key point in the attempt to prevent a permanent mental retardation – and to keep a West Syndrome as short as possible is most important [66, 24, 67] – whether this is achieved by medication or by surgery seems to be not so decisive.

Risk factors for Autism Spectrum Disorders (ASD) in patients with TSC by and large overlap with the risk factors for mental retardation [68, 60, 69, 70]. Unfortunately expectations that patients with TS might recover from ASDs post successful epilepsy surgery (successful in terms of seizure control) must be kept low; this is a problem in general in epilepsy surgery; variables other then the epilepsy (e.g. tubers within both temporal lobes,) seem to play greater role. What can be seen sometimes are minor positive changes which however might not be so minor for the quality of life of the whole family of a patient with TSC.
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