Successful surgery in late onset epilepsy with tuberous sclerosis complex

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ABSTRACT – [Case records of Epileptic Disorders. Anatomo-electro clinical correlations. Case 01-2009]. Tuberous sclerosis complex (TSC) is a multisystem genetic disorder with variable phenotypic expression, caused by mutations in one of the two tumor suppressor genes, TSC1 or TSC2. Epilepsy is the most common neurological presentation and seizures are often medically intractable. Definition of the epileptogenic zone during presurgical evaluation is challenging given the multiple potentially epileptogenic lesions visible on MRI. However, TSC patients may nevertheless achieve seizure freedom, when preoperative evaluation yields concordant results. The strategies used in these patients vary substantially among different epilepsy surgery centres. We present a 21-year-old right-handed, intellectually not impaired woman with TSC and medically intractable seizures since the age of 15 years. Careful multi-stage presurgical evaluation, including prolonged video-EEG-monitoring, cerebral high resolution MRI, ictal and interictal [99m Tc]HMPAO-SPECT, [18 F]FDG-PET and further invasive recordings with subdural and depth electrodes led to the identification of an epileptogenic tuber with concordant seizure onset zone in the right neocortical temporal lobe. A tailored resection was performed leading to excellent surgical outcome (follow-up 12 months, Engel class I).

Key words: epilepsy, tuberous sclerosis complex, epilepsy surgery

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder with variable phenotypic expression, caused by mutations in one of the two tumor suppressor genes, TSC1 on chromosome 9, (codes hamartin), or TSC2 on chromosome 16, (codes tuberin). The majority of patients have TSC as a result of spontaneous genetic mutations while in one-third of the patients TSC is inherited in an autosomal-dominant trait (Curatolo et al. 2006). TSC causes abnormal cellular differentiation and proliferation along with abnormal neuronal migration (Sparagna and Roach 2000), which leads to characteristic widespread development of benign tumors, so-called hamartomas, in multiple organ systems including brain, kidneys, lungs and skin. The revised diagnostic criteria of TSC propose major and minor clinical features, identifying definite, probable or possible cases of TSC (Roach et al. 1998). Brain abnormalities comprise cortical and subcortical tubers,
subependymal nodules and subependymal giant cell astrocytomas. Epilepsy in 80-90%, developmental delay in 40-80% and neuropsychiatric disorders in 25-50% of cases are the main neurological features of TSC (Holmes et al. 2007). One third of patients have seizure onset in the first year of life with infantile spasms. Other seizure types include simple partial seizures, complex partial seizures or secondary generalized tonic-clonic seizures. The seizures are medically intractable in more than half of patients, especially when infantile spasms are present. Intractable seizures are accompanied by progressive developmental and cognitive deterioration (Holmes et al. 2007). Hence, epilepsy surgery is an option for TSC patients with medically intractable seizures. Surgical management is challenging since tubers are often multifocal, bilateral and can overlap with eloquent cortex. The success of surgery depends on the identification of the epileptogenic zone and its correspondence to a single tuber, the so-called “epileptogenic tuber”. Concordant preoperative clinical, electrophysiological and imaging findings determine the excellent postoperative seizure control, comparable to other focal etiologies (Jarar et al. 2004, Lachhwani et al. 2005).

We report a 21-year-old intellectually not impaired woman with late onset of epileptic seizures in TSC as an illustrative case report to highlight the importance of a multi-stage presurgical evaluation process. This approach has been reported by several authors who demonstrated excellent postsurgical outcomes in these patients.

Case Study

A 21-year-old, right-handed intellectually not impaired woman of turkish origin experienced her first generalised tonic-clonic seizure (GTCS) at the age of fifteen years during the night sleep. She did not experience any aura. Initial investigations, including cerebral MRI were reportedly normal. The patient was referred for further diagnostic evaluation at the age of 18 years because the seizures became medically intractable (at least one GTCS/month). Pregnancy and birth history were uneventful, psychomotor development was normal and family history for epilepsy and TSC was negative. Neurological examination was normal. The patient attended a regular school. She underwent an extensive presurgical epilepsy work-up during in-patient video-EEG-monitoring. Six subclinical seizures and three habitual secondary GTCS with lateralizing signs to the right hemisphere (version to the left, right-sided asymmetric seizure termination) were recorded during the video-EEG-monitoring. Ictal EEG exhibited rhythmic theta activity over the right midtemporal area with a rapid propagation of less than ten seconds to the anterior temporal and frontal regions. Interictal EEG demonstrated right midtemporal periodic sharp waves. High-resolution MRI showed multiple cortical and subcortical tubers with high-signal in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (left frontopolar, precentral and occipital, right frontolateral, parieto-occipital and temporal neocortical) and subependymal hamartomas with low-signal in T1- and T2-weighted sequences (figure 1B-D). A cerebral CT scan identified characteristic calcified subependymal nodules (figure 1A). Brain imaging findings led to the diagnosis of TSC. Further organ screening detected mild shagreen spots and facial angiofibroma and mild lung involvement with an early stage of lymphangioleiomyomatosis. A cerebral [18 F] FDG-PET did not reveal increased tracer uptake. Neuropsychological testing detected mild deficits in alertness, frontal-executive function and figural memory.

Although the seizure onset on scalp EEG was localized to the right midtemporal area, a rapid spread of the ictal EEG as well as the multiplicity of the tubers in right frontal and parietal areas suggested a multifocal involvement. We performed an ictal [99m Tc] HMPAO-SPECT study, which revealed a widespread hyperperfusion involving not only the right temporal neocortex, but also areas of the frontal and parietal neocortices (figure 1E). All available data were reviewed at an interdisciplinary patient management conference. At this stage, there were at least two possible opportunities open for discussion. First, to remove the MRI-visible lesion on the right temporal area without further knowledge of the epileptogenic network or second, to further investigate the patient with invasive EEG recording. Our decision pro implantation was based on a) the widespread hyperperfusion pattern on the ictal SPECT, b) the multiplicity of the MRI lesions over the right hemisphere and c) the rapid temporal and extratemporal spread of the ictal EEG. A subdural grid was placed over the right temporal and parietal neocortex, subdural strips were implanted over the right frontolateral cortex (one electrode), the right temporal pole (one electrode), the right temporobasal regions (two electrodes) and the occipital neocortex (one electrode). In addition, one depth electrode was stereotactically placed tangentially to the temporal neocortical lesion in a posterior-anterior direction. Another depth electrode was placed in the right hippocampus for ruling out a possible mesial seizure onset with the spread to the neocortical areas (figure 2). We recorded thirteen subclinical seizures. Ictal EEG onset was localized by spike wave activity, consecutive attenuation and rhythmic thirteen Hz activity over an extended area over the right mid- to posterior temporal neocortex (figure 3B). Concordantly, periodic interictal spikes were recorded over the same regions (figure 3A). We performed an intracranial electrical stimulation (according to our standard protocol starting with 1 mA up to 13 mA in steps of 1 mA; rectangular impulses, 200 μsec, 50 Hz) in order to test cortical function and excitability. Stimulation was stopped when a habitual seizure was evoked. A subclinical seizure was recorded by
stimulation of the electrodes placed over the seizure onset zone. Cortical stimulation provided a clear separation of eloquent motor and sensory cortex from seizure onset zone. The patient was tested for visual neglect taking into consideration the location of the lesion, although no eloquent cortical areas were found. Based on the results

Figure 1. A) Axial CT with calcified subependymal nodule. B) Axial T2 MRI, right lateral temporal cortical area with increased signal, thick cortex and blurred gray-white matter junction (arrow). C) Axial FLAIR MRI; the same area as in B with increased MR signal (arrow). D) Coronal FLAIR MRI with multiple cortical tubera (black arrows); right lateral temporal tuber was resected (white arrow). E) Ictal SPECT: hyperperfusion in right lateral temporal, frontal, parietal cortical area (arrows); injection time: fifteen seconds after clinical seizure onset and 20 seconds after ictal EEG onset, respectively. F) Axial T2 post-surgical MRI. G) Coronal T2 post-surgical MRI.

Figure 2. A) Implantation schemes of subdural grid over the right parietal and temporal neocortex (GR, sixty-four leads), subdural electrodes over the right frontal neocortex (FPR, eight leads), the right temporal (TPR, TBAR, TBBR, each eight leads) and the right occipital region (TOR, six leads), red lines: seizure onset zone. B) Hippocampal (Tra, eight leads) and right temporooccipital (Trb, twelve leads) depth electrodes. C) Position of subdural grid and subdural electrodes (grid, FPR, TPR, TBAR, TBBR), red dots: seizure onset zone.
of invasive recordings and the concordant imaging findings, a tailored resection of the right mid- to posterior temporal neocortex was performed (figure 1F, G) without any peri- or postsurgical complications, leading to a seizure freedom (Engel class I). Histopathology of the surgical specimen showed typical features of TSC. Postoperative follow-up at 12 months revealed a non-compromising left sided quadrantic hemianopia without any further disability.
Discussion

Our patient is paradigmatic for the relationship of multiple possible epileptogenic lesions and the seizure onset zone which may pose several puzzling questions during the presurgical evaluation.

Over the past years a multi-stage approach including invasive EEG recording has been used successfully to determine seizure onset zone in these patients (Romanelli et al. 2002). Concordant preoperative electroclinical and imaging findings determine the excellent postoperative seizure control (Jarrar et al. 2004, Lachhwani et al. 2005). Patients without MRI lesions are less likely to be considered candidates for epilepsy surgery. Hence, finding an epileptogenic lesion is the best predictor for good postsurgical outcome. However, especially in TSC patients, where lesions are often multifocal and bilateral, the question arises, which may be the leading one? Astonishingly, the initial MRI was reported as normal in our patient. It has been shown, that the sensitivity of non-expert reports of standard MRI for focal lesions is much lower compared to expert reports. Moreover, an epilepsy dedicated MRI allows identifying focal epileptogenic lesions in more than half of standard MRI failures (Von Oertzen et al. 2002). Our patient underwent a high-resolution MRI at our institution, which clearly demonstrated multiple lesions, comprising of cortical and subcortical tubers and subependymal calcified nodules, leading to the definite diagnosis of TSC. When looked by an expert radiologist, these lesions were also visible in the first MRI, supporting the importance of expert reading in specialised centers.

In our patient, the first non-invasive examinations revealed a concordance between the scalp EEG and the real temporal neocortical tuber, but the rapid ictal spreading pattern and multiple other tubers in the right hemisphere led to further investigations. Some authors favor the high diagnostic yield of interictal PET with [11 C] AMT (Luat et al. 2007), which is not available at our institution. Ictal SPECT may be another method to further investigate the seizure onset zone leading to correct localization in up to 90% of temporal lobe epilepsies and 80% of extratemporal epilepsies (Spencer et al. 1995). However, it may falsely localize the seizure onset zone or not localize it at all (Koh et al. 2000). The widespread ictal hyperperfusion pattern in our patient involving temporal, parietal and frontal areas further supported multilobar involvement.

Our implantation scheme was extensive covering the right temporo-parietal and frontal neocortex, additionally we placed depth – electrodes in the right hippocampus and in the proximity of the right temporal tuber to explore the relationship between hippocampus and neocortical areas. This approach was successful in our patient, where a restricted seizure onset zone over the right mid- to posterior temporal neocortex could be clearly demonstrated. Consecutive tailored resection rendered the patient seizure free.

The most predictive factor in successful epilepsy surgery is the concordance of electroclinical and imaging findings. Non-invasive methods may be sufficient in many patients even when multiple lesions are present. Some patients may, however, undergo invasive recordings to achieve sufficient precision in delineating the seizure onset zone and its relationship to the epileptogenic lesion.

Disclosures.
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