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"Epilepsy surgery recipes galore": in quest for the epileptogenic tuber in tuberous sclerosis complex

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Tuberous sclerosis complex (TSC) is a genetic disease, the life-long neurological morbidity of which is usually defined early in life, by epilepsy and cognitive delay that typically go hand in hand. Early onset of epilepsy is the one of the important risk factor for continuing seizures and cognitive disability later in life (Curatolo *et al*. 2008). Early and aggressive treatment of epilepsy is, therefore, critical. It is generally accepted that most seizures in TSC are partial onset seizures. Like in any other refractory partial epilepsy, when medical treatment fails, evaluation for the possibility of epilepsy surgery should be considered early in every patient with TSC. Seizure freedom or effective control of debilitating seizures after epilepsy surgery is crucial in improving quality of life in patients with TSC. However, two key rules for planning surgical strategy, localization of the epileptogenic zone (EZ) and minimizing risk of a permanent new postoperative deficit(s), pose additional challenges unique to TSC. These challenges emanate from multiple factors, often age-related, and in complex interaction with each other. First, the presence of multiple bilateral tubers, sometimes partially or nearly confluent, on the brain MRI portrays a possibility of multiple epileptogenic lesions. The tubers often intermingle with white matter abnormalities and defy accurate identification of margins even on a high resolution brain MRI making anatomical delineation for surgery inaccurate. Second, the patient is frequently a child or a cognitively disabled young adult with stereotypic non-focal seizure semiology (epileptic spasms, bland seizures with behavior arrest, tonic or atonic seizures with falls) and a scalp video EEG that often shows overwhelming generalized or multiregional interictal abnormalities and non-localizable ictal onset. Considering recent reports of a single epileptogenic lesion on the brain MRI leading to generalized and multiregional interictal and ictal abnormalities on scalp EEG, a scenario of multiple epileptogenic lesions with such an EEG appears to be an insurmountable condition for epilepsy surgery (Gupta *et al*. 2007). Third, young age along with cognitive delay and behavior issues render cooperation for noninvasive mapping of eloquent functions, whenever necessary, challenging or even impractical. And lastly, lack of long-term longitudinal post operative outcome studies make family counseling before surgery imprecise as there is always a potential concern for emergence of epileptogenicity from the non-resected tubers. No wonder, in the quest for a successful surgical strategy in TSC, multiple presurgical investigative tools in various combinations and recipes have been reported in the published case series from various centers.

In this issue of *Epileptic Disorders*, Unterberger *et al*. (2009) highlight one such surgical approach. In their patient, a 21-year-old intellectually normal woman who presented with seemingly generalized motor seizures, authors made a strong hypothesis for surgery based on the video EEG evaluation that showed lateralizing semiology in the presence of right temporal interictal spikes and ictal onset during all the recorded seizures. From multiple bilateral tubers on the brain MRI in their patient, based on the scalp video EEG findings, authors were able to narrow the inventory of potential epileptogenic tuber(s) to the right lateral mid temporal, parietal, and posterior frontal regions. Their approach highlights the importance of careful video EEG in every patient, not withstanding the lack of auras, lateralizing seizures or the presence of seemingly generalized seizures in the history. In the absence of any further localization of the EZ by nuclear imaging studies, authors proceeded with the implantation of subdural grids and depth electrodes in this patient. Using a customized coverage of brain with an array of grids and depth electrodes, authors (Unterberger *et al*. 2009) elegantly show further localization of the EZ based on the interictal and ictal subdural and depth EEG recordings as well as a surgical strategy after excluding any eloquent function (low risk for language) in the vicinity of the planned resection by direct electric cortical stimulation. Clearly, this patient's ability to cooperate and communicate was critical to obtain and interpret all the data to execute a precise surgical plan that led to seizure freedom.

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Despite the existence of complex factors unique to TSC as outlined above, epilepsy surgery is an effective treatment for epilepsy in TSC at all ages. Published series on epilepsy surgery in TSC have reported high rates of success in alleviating or significantly improving seizures in most patients who under go surgery. In a systematic review of literature published between 1960 and 2006, Jansen *et al*. (2007) reviewed a sample of 177 TSC patients who underwent epilepsy surgery, and were subjects in 25 published articles in peer reviewed journals. Not surprisingly, authors found these observational case series incomparable due to extreme variability in the collection and reporting of data (Jansen *et al*. 2007). However, in a composite analysis, 75% TSC patients were either seizure free (57%; 0.1-47 [mean 3.7] years follow-up) or > 90% improved in seizure frequency (18%; 0.5-20 [mean 4.2] years follow-up). Such high success rates after surgery in TSC parallel seizure outcome after a single lesion extratemporal lobe epilepsy surgery. Also of interest was the finding that a large number of TSC patients who underwent surgery had generalized and multiregional interictal scalp EEG abnormalities (48%) and non-localizable ictal onset (46%) findings, however, the presence of focal *vs* non focal scalp EEG abnormalities had no statistically significant relationship to seizure remission after surgery. Obviously, these patients were selected for epilepsy surgery based on other (not studied in the paper) criteria(s) such as semiology, functional deficits, dominant tuber(s) on the brain MRI, nuclear imaging studies, or magnetoencephalogram (MEG), again highlighting the point that generalized and multiregional EEG abnormalities on the scalp video EEG does not preclude surgical candidacy in a child with a solitary or multiple lesions (such as in TSC). Use of multimodal pre-surgical tools such as 18F flurodeoxyglucose (FDG) positron emission tomography (PET), alpha-[(11)C] methyl-L-tryptophan (AMT) PET, ictal single photon emission computed tomography (SPECT), and MEG coregistered to the brain MRI have been used in varying combinations with claims of success, however, there is no perfect formula in identification of the epileptogenic tuber, and neither does any tool(s), alone or in combination, been shown to improve the rate of seizure freedom after surgery (Jansen *et al*. 2007). A logical step by step by investigation tailored to each patient remains the corner stone of presurgical evaluation in TSC. Recently, in patients with unidentifiable EZ (epileptogenic tuber(s)) on multimodal noninvasive investigations, bilateral subdural and depth electrode implantation encompassing wide regions of brain bilaterally followed by a focused search for the epileptogenic tuber(s) with staged resection(s) has been reported from one center (Weiner *et al*. 2008). Palliative procedures, such as corpus callostomy or partial or complete resection of the "most" epileptogenic tuber (cause of most frequent or most severe seizures), could also help in some patients with TSC where surgery is done to minimize injuries, abolish the most disabling seizures with falls and loss of consciousness, and prevent episodes of life threatening status epilepticus.

In conclusion, epilepsy surgery in TSC poses unique challenges specific to the disease. The investigation to find the culprit tuber (and define the epileptogenic zone) is best individualized to each patient considering all aspects of their clinical condition and goals of epilepsy surgery. No formula fits all TSC patients. Generalized seizure semiology on history and generalized or multiregional abnormalities on a routine scalp EEG should not preclude a thorough evaluation for epilepsy surgery. Every TSC patient with refractory epilepsy should undergo presurgical evaluation using a customized approach. □

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Epileptic Disorders Case Records, published under the heading "Anatomo-electro-clinical correlations" are expected to provide to the reader a comprehensive approach of pre-surgicalevaluation and epilepsy surgery strategies. Authors are expected to provide supplemental data for publication on the DVD to allow further discussion on the surgical approach chosen.

Epileptic Disorders will published all documented comments, critics and suggestions discussing the approach taken by the authors. The readers are invited to submit their eventual comments in the online submission system as « Letter to the Editor » with reference to the Case Records' number.

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