In any form of epilepsy associated with distinct anatomical lesions within the brain, questions arise as to whether the lesional tissue alone is epileptogenic, whether perilesional cortex is also epileptogenic, or whether even more remote cortical regions that appear structurally normal may serve as independent epileptic foci. In disorders associated with multiple distinct lesions, these questions become progressively more complex yet are potentially critical to answer when patients with such lesions who have medically refractory epilepsy are considering the possibility of resective surgery as a treatment option.

The paper by Mohamed et al. from Melbourne, Australia, provides us with detailed and well-reported data that suggest important answers to these questions for patients with tuberous sclerosis complex, which is one of the archetypal examples of multilesional epilepsy in pediatrics (1) but for which we have only limited direct evidence regarding epileptogenicity (2, 3). The authors report on a total of 23 intracranial EEG monitoring studies performed in 17 children with TSC-associated refractory epilepsy, most of whom had epileptic spasms and all of whom had at least two distinct seizure foci by scalp EEG monitoring. Individually tailored intracranial electrode paradigms included subdural grids and strips overlying cortical tubers and perituberal cortex and, in some patients, depth electrodes implanted into tubers themselves. The authors present details on the ictal and interictal epileptiform activity seen in this cohort (which included a total of 60 electroclinically distinct seizures), as well as the specific relationship of this activity to the anatomical lesions themselves.

The highlights of their findings are:

1. Most seizures arose from tubers alone, but in a minority of cases, tubers and perituberal cortex were involved together at ictal onset. Perituberal cortex alone and cortex that was remote from tubers were sites of ictal onset only uncommonly.

2. The ictal EEG pattern usually consisted of low-voltage fast activity, evolving into rhythmic spiking, followed by periodic spikes or slow waves.

3. When seen, interictal trains of periodic sharp waves on an attenuated background tended to signify tubers that were involved in ictal onset.

Surgery in these children, all of whom underwent tuberectomies (often of multiple tubers, but all sparing perituberal
Epileptogenic Lesions in TSC

cortex), rendered 35% of them seizure free with a median follow up of 19 months, an impressive outcome considering that not all epileptogenic tubers were able to be resected. In fact, additional tuberecorties after the study period in several of the children who had not become seizure-free led to further improvements in seizure control. Postoperative patients who were not seizure-free had video-EEG monitoring that variably implicated either unresected tubers or sites of previous tuberecorties.

The implications of this work for our understanding and management of medically refractory epilepsy in TSC are obvious. Not only are these highly informative data regarding the typical ictal and interictal EEG patterns expected when recording from epileptogenic tubers, but the identification of tubers as clearly more important in independently generating seizures than perituberal cortex is very valuable. These findings will help those taking care of TSC patients to interpret the results of what are often complicated intracranial EEG recordings and plan what are often complicated resective surgeries, many of which are manifestly undertaken as palliative procedures, done with the understanding that not all seizure foci will be necessarily addressed.

An unanswered question, however, is how these findings should affect our approach to other forms of epilepsy that are also associated with multiple discrete lesions, either acquired (as in posttraumatic epilepsy) or developmental (as in nodular heterotopia, for example). In some of these other conditions, there is growing evidence to support the notion that development of aberrant connectivity—which may lead to hyperexcitable neuronal circuits—is a critical substrate of epileptogenesis (4), and successful surgery may require resections that extend beyond mere lesionectomies (5).

Ultimately, it would be useful to integrate the electrophysiological findings reported here with a more detailed appreciation of anatomical and functional connectivity in TSC, as demonstrated through diffusion tensor tractography and other forms of connectivity imaging (6). Though patients generally had positive surgical results in this cohort, it is possible that the outcomes for TSC patients could be improved with a more nuanced preoperative understanding of abnormal circuits and connections. In particular, tuber–tuber and tuber–cortical connections that may involve remote or even contralateral regions could be demonstrated fairly readily on imaging; such findings might help to plan the placement of intracranial EEG electrodes. Where to put the electrodes is an especially critical question in multilesional disorders, for which the usual caveat applies more than ever: One can see activity only from where the electrodes are. Indeed, one of the limitations of this paper is that the cortical tubers themselves had very good electrode coverage but perituberal cortex (and especially remote cortex) somewhat less so.

These days, in any patient with focal epilepsy, high-resolution neuroimaging is used to look for underlying lesions that might be responsible for the seizures. But when lesions are found and the seizures remain uncontrolled, the question becomes whether the lesions are solely—or even primarily—responsible for seizure genesis, and thus whether taking them out alone will be sufficiently helpful. This paper shows us that in TSC, the answer from intracranial EEG recording may be “yes” in many instances.

by Bernard S. Chang, MD, MMSc

References

Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

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3. Are you the Main Assigned Author?  ☒ Yes  ☐ No

If no, enter your name as co-author:

4. Manuscript/Article Title: Tuber or not Tuber

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