



Tuber or Not Tuber: The Question of Epileptogenic Lesions in Tuberous Sclerosis Complex (TSC)

Intrinsic Epileptogenicity of Cortical Tubers Revealed by Intracranial EEG Monitoring.

Mohamed AR, Bailey CA, Freeman JL, Maixner W, Jackson GD, Harvey AS. *Neurology* 2012;79:2249–2257.

OBJECTIVE: We sought to identify intracranial EEG patterns characteristic of epileptogenic tubers and to understand the contribution of perituberal cortex. **METHODS:** Twenty-three intracranial EEG monitoring studies were reviewed from 17 children aged 1.3–7.7 years with tuberous sclerosis complex and intractable multifocal epilepsy, 14 with a history of epileptic spasms. Interictal epileptiform discharges and ictal rhythms for 60 electroclinically distinct seizures (EDS) were analyzed in relation to 162 sampled tubers. **RESULTS:** Localized, tuber-related, ictal rhythms were seen in 49/60 EDS, most commonly as low voltage fast activity recruiting to rhythmic spiking, then diffuse slowing or bursts of ripple range activity. Ictal onset in localized EDS involved only tubers in 57% and tubers with perituberal cortex in 31%. Ictal fast ripples (FR) noted at seizure onset in 15/38 localized EDS were confined to tubers in 73% and involved tuber with perituberal cortex in 27%. Intraictal activation occurred during seizure propagation in 19 localized EDS, being to tubers in 63% and to tubers with perituberal cortex in 37%; 63% of activated tubers generated independent EDS. Trains of periodic sharp waves on an attenuated background were seen interictally at 36/162 tubers, with 67% of those tubers generating EDS ($p = 0.0001$). Interictal FR, when present, involved tubers more commonly than perituberal cortex but were not associated with EDS. **CONCLUSION:** The study demonstrates interictal and ictal intracranial EEG findings characteristic of epileptogenic tubers, suggests that tubers play a greater role in seizure genesis than perituberal cortex, and suggests tubectomy may be a sufficient surgical approach in a number of patients.

Commentary

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



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 tuberectomies 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 tuberectomies.

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

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