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Study concept or design: P.S., F.Z.; drafting/revising of manuscript: all the authors; analysis of interpretation: all the authors.

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METAPLASTIC BONE IN A CORTICAL TUBER OF A YOUNG PATIENT WITH TUBEROUS SCLEROSIS COMPLEX

Cortical tubers are the most common brain lesions of the tuberous sclerosis complex (TSC).¹ They vary widely in size, location, and appearance, may have a cystic or a calcified component, and are often epileptogenic.^{2,3} Histologically, tubers are hypomyelinated hamartomas, which are characterized by abnormal cortical lamination and are typically composed of giant or balloon cells, dysplastic neurons, and reactive astrocytes.⁴ We report the radiologic and pathologic findings of a resected calcified tuber identified as an epileptogenic focus.

Case report. The patient is a 19-year-old right-handed woman with a known spontaneous TSC1 mutation. She was the product of a normal pregnancy. Seizure onset occurred at the age of 9 months and led to a diagnosis of TSC. Neuropathologic features include numerous cortical tubers and subependymal giant cell tumors (SGCT). The patient has experienced daily seizures since their onset. Multiple antiepileptic medications and other anticonvulsant treatments were tried without significant seizure control. The patient has a history of global developmental impairment.

As part of the presurgical evaluation for neurosurgical intervention, an MRI showed SGCT, multiple tubers located in bilateral frontal, parietal, and occipital lobes, and a large (22 mm) T2 hypointense calci-

fied lesion deep to the left superior frontal sulcus (figure). Review of prior scans revealed that the calcified component of this lesion was not visible when the patient was 2 years 4 months old and was first visible on MRI when the patient was 4 years old (figure). Fluorodeoxyglucose PET revealed numerous bilateral frontal and parietal foci of cortical hypometabolism corresponding to cortical tubers on coregistered MRI. There was also a single focus of asymmetric hypermetabolism in the left middle frontal gyrus located deep to the large calcified cortical tuber described. Although the EEG was multifocal, discharges were more prominent over the left frontocentral region. At age 19, the patient underwent a left frontal craniotomy and intraoperative electrocorticography, which demonstrated frequent interictal epileptiform abnormalities in the tissue surrounding the large frontal lobe calcified tuber that had been suspected to be the source of her more problematic partial seizures. The tuber and its immediately surrounding tissue were excised. Subsequently, she has had a significant improvement in both the number and severity of seizures.

The resection specimen consisted of a 5.4 × 2.6 × 1.7 cm aggregate of brain tissue. A dominant fragment had a heterogeneous cut surface and central mineralization (figure, B.a). Histology demonstrated a tuber clearly delineated from overlying white matter, which was diffusely gliotic, suggesting that the adjacent tuber tissue had chronically compressed the

(A) Progression over years of the left frontal tuber on MRI scans. Axial T2 fast spin-echo (FSE) (a) and axial fluid-attenuated inversion recovery (FLAIR) (b) are presented chronologically. MRI shows that the calcified left frontal tuber does not appear on T2 FSE sequence at the age of 2 years and 4 months. FLAIR was not available for review at this age. The calcified lesion remains stable over time as shown on T2 FSE and FLAIR images from age 9 years 11 months, 17 years 1 month, and 19 years 1 month. (B) Gross and histopathology of tuber resection specimen. (a) The largest fragment of the resection specimen is bisected and demonstrates a firm tan cut surface with a central area of mineralization (arrows) and the in situ position of the surgical electrode. (b) The bone in the specimen is sharply demarcated from the adjacent gliotic white matter which contains numerous small calcifications (top of field). Architecturally, the bone is cortical-like and has scattered haversian-like canals, which enclose blood vessels (hematoxylin & eosin [H&E], 10×). (c) The surface of the bone that borders the brain tissue is lined by flattened osteoblasts (arrowheads). The bone is lamellar in pattern with scattered small osteocytes (arrows) that have delicate canaliculi (H&E, 20×). (d) Small foci of woven bone (arrow) are deposited on preexisting lamellae and extend into and encompass some of the small calcifications (H&E, 40×).

white matter. The area of mineralization corresponded to a $0.5 \times 0.3 \times 0.3$ cm fragment of mature cortical-like bone surrounded by punctuate calcifications. The bone had lamellar architecture, haversian-

like canals, which enclosed small capillaries, and small osteocytes with delicate canaliculi. The bone surface was sharply demarcated from adjacent gliotic white matter by a rim of flattened osteoblasts (IIB,

IIC). In limited areas, small foci of woven bone extended from the surface into and encompassed some of the microscopic calcifications (IID).

Discussion. A calcified component of tubers has been reported to contribute to epileptogenicity,^{5,6} but this relationship has not been consistently observed.⁷ In the present case, the significant improvement in seizure frequency after the surgery suggests that the lesion was involved in the epileptogenic zone. However, the relationship of the calcification to the epileptogenicity is unclear, particularly since the patient's seizure onset occurred years before the tuber appeared calcified. The calcification of tubers in TSC is poorly understood, and it is not known if seizure activity perhaps promotes an inflammatory response in tubers, which leads to calcification, or if instead some other process leads to calcification, which then by unknown mechanisms contributes to epileptogenicity.

The pathophysiology leading to calcification of tubers in TSC is also unclear, and has been thought to be a form of dystrophic calcification. Prospective and retrospective studies are currently underway to better understand the etiology of bone formation in the cortical tuber as well as to characterize its frequency and possible relationships to dystrophic calcifications frequently seen in tubers. So far, tissue from 7 resected calcified tubers has been reviewed and all show dystrophic calcification without the presence of lamellar bone. The presence of lamellar bone in the current case raises interesting questions regarding the cell origin and biology of cortical tubers.

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