22. Imbach P, Morrell A: Idiopathic thrombocytopenic purpura (ITP): Immunomodulation by intravenous immunoglobulin (IVIg). *Int Rev Immunol* 1989;5:181–188.
23. Leung DY: The immunologic effects of IVIG in Kawasaki disease. *Int Rev Immunol* 1989;5:197–202.
24. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association: Guidelines for the diagnosis of rheumatic fever. Jones criteria, 1992 update. *JAMA* 1992;268:2069–2073.
25. Danjani AS, Bisno AL, Chung KJ, et al: Prevention of rheumatic fever. A statement for health professionals by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. *Circulation* 1988;78:1082–1086.
26. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW: Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat Med* 2003;9:914–920.
27. Asbahr FR, Negrao AB, Gentil V, et al: Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: A prospective 6-month study. *Am J Psychiatry* 1998;155:1122–1124.
28. Aronson N, Douglas HS, Lewis JM: Cortisone in Sydenham's chorea. Report of two cases. *JAMA* 1951;145:30–33.
29. Glaser GH, Merritt HH: Effects of corticotropin (ACTH) and cortisone on disorders of the nervous system. *JAMA* 1953;148:898–904.
30. Dixon ASJ, Bywaters EGL: Methods of assessing therapy in chorea with special reference to the use of ACTH. *Arch Dis Child* 1952;27:161–166.
31. Ghram N, Allani C, Oudali B, et al: [Sydenham's chorea in children]. *Arch Pediatr* 1999;6:1048–1052.
32. Wilmsmeyer W, Ukena D, Wagner TO, Sybrecht GW: First-time treatment with steroids in bronchial asthma: Comparison of the effects of inhaled beclomethasone and of oral prednisone on airway function, bronchial reactivity and hypothalamic-pituitary-adrenal axis. *Eur Respir* J 1990;3:786–791.
33. Woo WK, McKenna KE, Robinson JD, et al: Iatrogenic adrenal gland suppression from use of a potent topical steroid. *Clin Exp Dermatol* 2003;28:672–673.
34. Robinson JD, Angelini BL, Krahnke JS, Skoner DP: Inhaled steroids and the risk of adrenal suppression in children. *Exp Opin Drug Saf* 2002;1:237–244.
35. Quirolo KC: Transfusion medicine for the pediatrician. *Pediatr Clin North Am* 2002;49:1211–1238.

Original Article

Epilepsy Surgery Outcome in Children With Tuberous Sclerosis Complex Evaluated With α-[^{11}C]Methyl-L-Tryptophan Positron Emission Tomography (PET)

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ABSTRACT

Tuberous sclerosis complex is commonly associated with medically intractable seizures. We previously demonstrated that high uptake of α-[^{11}C]methyl-L-tryptophan (AMT) on positron emission tomography (PET) occurs in a subset of epileptogenic tubers consistent with the location of seizure focus. In the present study, we analyzed the surgical outcome of children with tuberous sclerosis complex in relation to AMT PET results. Seventeen children (mean age 4.7 years) underwent epilepsy surgery, guided by long-term videoelectroencephalography (EEG) (including intracranial EEG in 14 cases), magnetic resonance imaging (MRI), and AMT PET. AMT uptake values of cortical tubers were measured using regions of interest delineated on coregistered MRI and were divided by the value for normal-appearing cortex to obtain an AMT uptake ratio. Based on surgical outcome data, tubers showing increased AMT uptake (uptake ratio greater than 1.00) were classified into three categories: (1) epileptogenic (tubers within an EEG-defined epileptic focus whose resection resulted in seizure-free outcome), (2) nonepileptogenic (tubers that were not resected but the patient became seizure free), or (3) uncertain (all other tubers).

Increased AMT uptake was found in 30 tubers of 16 children, and 23 of these tubers (77%) were located in an EEG-defined epileptic focus. The tuber with the highest uptake was located in an ictal EEG onset region in each patient. Increased AMT uptake indicated an epileptic region not suspected by scalp EEG in four cases. Twelve children (71%) achieved seizure-free outcome (median follow-up 15 months). Based on outcome criteria, 19 of 30 tubers (63%) with increased AMT uptake were epileptogenic, and these tubers had significantly higher AMT uptake than the nonepileptogenic ones ($P = .009$). Tubers with at least 10% increase of AMT uptake (in nine patients) were all epileptogenic. Using a cutoff threshold of 1.02 for AMT uptake ratio provided an optimal accuracy of 83% for detecting tubers that needed to be resected to achieve a seizure-free outcome. The findings suggest that resection of tubers with increased AMT uptake is highly desirable to achieve seizure-free surgical outcome in children with tuberous sclerosis complex and intractable epilepsy. AMT PET can provide independent complementary information regarding the localization of epileptogenic regions in tuberous sclerosis complex and enhance the confidence of patient selection for successful epilepsy surgery. (*J Child Neurol* 2005;20:429–438).

Tuberous sclerosis complex is a neurocutaneous disorder characterized by tumorous growths that involve multiple organs, including the brain, retina, kidney, heart, and skin.[1] It is inherited as an autosomal dominant trait with a high degree of penetrance and a high spontaneous mutation rate, now known to result from mutations in at least two different genes, *TSC1* on chromosome 9 and *TSC2* on chromosome 16.[2,3] Approximately 70% to 90% of patients with tuberous sclerosis complex have seizures,[4,5] and the seizures are often refractory to anticonvulsant drugs.

Patients with tuberous sclerosis complex and intractable epilepsy typically have multiple cortical tubers that can result in a complex seizure pattern.[6] For this reason, surgical treatment in patients with tuberous sclerosis complex was previously restricted to surgical resection of subependymal giant cell astrocytomas, which can cause obstructive hydrocephalus secondary to blockage of cerebrospinal fluid pathways but are not considered to be epileptogenic.[7–9] With the recent advances of electrophysiologic monitoring techniques and multimodality neuroimaging, which can improve the detection of epileptogenic foci in tuberous sclerosis complex, several investigators have reported successful cases of surgical treatment following resection of tuber and surrounding epileptogenic tissue.[6,10–14] Anatomic neuroimaging with computed tomography and magnetic resonance imaging (MRI), especially fluid-attenuated inversion recovery images, can demonstrate accurately the locations of tubers and calcifications.[15–18] A recent preliminary study has also suggested that diffusion-weighted MRI might be able to identify epileptogenic tubers.[19] Functional neuroimaging with fluorodeoxyglucose (FDG) positron emission tomography (PET) shows decreased interictal glucose metabolism corresponding to the location of tubers and calcifications.[20,21] However, FDG PET cannot differentiate between epileptogenic and nonepileptogenic tubers. Furthermore, even in cases with lobar seizure onset as defined by scalp ictal electroencephalographic (EEG) recordings, it is difficult to identify the precise location of epileptogenesis.

We recently demonstrated that PET with α-[^{11}C]methyl-L-tryptophan (AMT), a tracer of serotonin synthesis and tryptophan metabolism via the kynurenine pathway, is able to identify a subset of tubers with high tracer uptake consistent with the location of seizure onset defined by seizure semiology and ictal EEG in two thirds of patients with tuberous sclerosis complex and intractable epilepsy, whereas the remaining (nonepileptogenic) tubers showed low uptake of AMT.[22,23] However, surgical outcome following resection of the presumed epileptic focus is the ultimate criterion to verify accurate delineation of the epileptogenic zone. In the present study, we analyzed the surgical outcome at our center in children with tuberous sclerosis complex in whom AMT PET assisted in identification of epileptic foci during presurgical evaluation.

SUBJECTS AND METHODS

Subjects

Between November 1996 and March 2003, 87 patients who fulfilled the diagnostic criteria for definite tuberous sclerosis complex[1] and intractable epilepsy underwent AMT PET scanning at the Children's Hospital of Michigan PET Center. All studies were performed in accordance with the regulations of the Wayne State University Human Investigation Committee, and informed consent of the patient, parent, or legal guardian was obtained. From these 87 patients with tuberous sclerosis complex, 40 patients were followed and evaluated for epilepsy surgery in our center, whereas 47 patients were referred from other centers and were evaluated for surgery elsewhere. Seventeen of the 40 patients evaluated by us have undergone surgery thus far (8 males and 9 females; mean age at surgery 4.7 ± 3.7 years; age range 4 months–12.3 years; Table 1). Ten patients did not undergo epilepsy surgery because a consensus of the patient selection criteria for surgical treatment[24] was not reached.

Fourteen of the 17 patients underwent two-stage surgery with subdural grid electrodes placement, followed by focal cortical resection or lobectomy. One-stage resective surgery was performed in the remaining three patients, who showed an extensive hemispheric tuber (patients 8 and 13) and large tubers with calcification remote from the eloquent area (patient 9). Patients with one-stage surgery underwent intraoperative electrocorticography to define the extent of resection. Two patients (2 and 10) had repeated surgery, and in such cases, the outcome is reported after the second surgery. Surgical outcome was assessed using Engel's modified classification scheme[25]: class I, seizure free; class II, rare seizures; class III, worthwhile improvement; class IV, no worthwhile improvement.

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EEG Evaluation

All patients underwent long-term video-EEG monitoring with scalp/zygomatic electrodes to identify the location of seizure onset and to characterize the ictal semiology. Scalp EEG electrodes were placed according to the International 10-20 system. To further delineate the cortical areas to be resected and to identify sensorimotor cortex, 14 patients underwent subdural electrode placement, the locations of which were guided by seizure semiology, seizure onset zone as determined by scalp EEG, and the location of tubers defined by MRI and FDG and AMT PET abnormalities. Subsequently, intracranial video-EEG monitoring for 2 to 5 days was performed to record ictal events and interictal activity. In every patient, at least three habitual seizures were captured and analyzed. Seizure onset electrodes were defined as electrodes involved in ictal EEG onset consisting of sustained rhythmic discharges or periodic spiking discharges with frequency > 2 Hz showing spatial evolution, which are visually distinguishable from background activity and not attributed to the state of arousal.[26]

MRI Scanning Protocol

MRI studies were performed on a GE 1.5 Tesla Signa unit (GE Medical Systems, Milwaukee, WI). The protocol includes four multiplane acquisitions with different contrasts and orientations. First, a T_2-weighted fast spin echo series employing a 16 echo-train length is performed in axial plane with a repetition time of 4900 milliseconds, an echo time of 85 milliseconds, and a 256 × 192 matrix for a field of view of 220 mm in the frequency direction and 165 mm in the phase direction. The second scan is a volumetric T_1-weighted spoiled gradient echo sequence obtained with 124 contiguous coronal slices of 1.5 mm thickness and no gap to cover the entire head using the following image parameters: repetition time/echo time = 35/5 milliseconds, flip angle = 35 degrees, matrix = 256 × 128, and field of view = 240 mm. The third MRI series corresponds to an axial spin-echo T_1-weighted acquisition with a repetition time/echo time of 450/9 milliseconds, 2 excitations, field of view of 220 mm in the frequency direction and 165 mm in the phase direction, slice thickness of 5 mm, a 50% gap, and a matrix of 256 × 192. Finally, a fluid-attenuation inversion recovery coronal series was performed with an inversion time of 2400 milliseconds and the following sequence parameters: repetition time/echo time = 9600/150 milliseconds, slice thickness = 5 mm, 50% gap, field of view = 220 mm, matrix = 256 × 192, and 2 excitations.

PET Scanning Protocol

PET studies were performed using the CTI/Siemens EXACT/HR (Knoxville, TN) whole-body positron tomograph. This scanner generates 47 image planes with a slice thickness of 3.125 mm. The reconstructed image in-plane resolution obtained is 5.5 ± 0.35 mm at full width at half-maximum and 6.0 ± 0.49 mm in the axial direction (reconstruction parameters: Shepp-Logan filter with 1.1 cycles/cm cutoff frequency) for the FDG PET scan and 7.5 ± 0.38 mm at full width at half-maximum and 7.0 ± 0.49 mm in the axial direction (reconstruction parameters: Hanning filter with 1.26 cycles/cm cutoff frequency) for the AMT PET scan. The FDG and AMT PET scans were performed on different days. Sedation with intravenous nembutal (3 mg/kg) or midazolam (0.2–0.4 mg/kg) and fentanyl (1 μg/kg; maximum 50 μg) was used, if necessary. For FDG studies, sedation was administered during the scanning period only.

FDG PET Scan

Patients were fasted for 4 hours prior to the PET study. Scalp EEG electrodes were placed according to the International 10-20 system, and the EEG was monitored throughout the tracer uptake period. All scans reported in this study were performed interictally. One venous line was established for injection of FDG (0.143 mCi/kg) synthesized using a CTI/Siemens RDS-11 cyclotron. Calculated attenuation correction was applied according to the method of Bergstrom et al.[27]

AMT PET Scan

Patients were fasted for 6 hours prior to the PET study to obtain stable plasma tryptophan levels during the course of the study. Scalp EEG was monitored continuously. The tracer AMT (0.1 mCi/kg) was injected intravenously as a slow bolus over 2 minutes. Twenty-five minutes following tracer injection, a dynamic emission scan of the brain (7 × 5 minutes) was acquired in three-dimensional mode. Measured attenuation and decay correction were applied to all images. The standard uptake value method for semiquantitative analysis of tracer accumulation was used.[28] The standard uptake value represents tissue activity concentration normalized to the injected activity per kilogram of body weight. As all patients received a standardized dose based on their weight (0.1 mCi/kg), calibrated images (μCi/cc) directly depict the standard uptake value.[29]

Definition of Cortical Tubers

In the present study, the term "tuber" includes all cortical lesions imaged because the exact histology is not known based on neuroimaging alone. Nodular lesions in the cortex that were hyperintense or heterointense with calcification on the fluid-attenuated inversion recovery or T_2-weighted images and focal nodular cortical hypometabolic regions on the FDG PET images were counted as cortical tubers. The number and location of cortical tubers were visually identified on the fluid-attenuated inversion recovery or T_2-weighted MRIs and FDG PET scans. Because the exact borders of some of the lesions can be difficult to delineate, all scans were enlarged on a 19-inch monitor, and the contrast was adjusted to optimize the separation of the identified lesion from the surrounding normal-appearing cortex. A complex consisting of a focal nodular lesion and the cortex overlying the focal nodular lesion was counted as a cortical tuber when the overlying cortex appeared to be dysplastic on MRI (usually associated with hypometabolism on FDG PET). Hyperintense lesions within the white matter, such as subcortical heterotopias or radial migration lines, were not considered cortical tubers. AMT PET scans were coregistered with MRI and FDG PET scans by using MPI-tool (Advanced Tomo Vision, Erftstadt, Germany), a software package employing a multipurpose three-dimensional registration technique.[30] The coregistration method is highly interactive and is based on the simultaneous alignment of image contours that are exchanged in three orthogonal cuts through the brain. The maximal misregistration error is 0.5 mm for the PET/MRI coregistration.[30]

Regions of Interest

Regions of interest for the cortical tubers and normal-appearing cortex were delineated on fluid-attenuated inversion recovery or T_2-weighted images, as described previously,[23] using a semiautomated threshold-based software program written in IDL 5.1 (Research Systems, Boulder, CO), similar to that described by Kennedy et al.[31] The regions of interest were directly copied to the coregistered AMT PET images (Figure 1, A and B). The average standard uptake value for regions of interest was determined as a weighted average over all planes showing the region.

Partial volume effects, which are related to underlying subresolution heterogeneity (gray and white matter in brain tissue), as well as spillover between regions owing to the limited spatial resolution of PET, lead to incorrect estimation (under- and overestimation) of the true regional concentrations of radioactivity.[32] Contamination of tracer activity from adjacent cortex can distort the AMT uptake value in cortical tubers. Although the partial volume effects associated with tubers with large and circular structures are small, partial volume effects associated with small, thin, and irregularly shaped tubers can cause large distortions of AMT uptake values.[33] To test

Table 1. Clinical and α-[^{11}C]Methyl-L-Tryptophan Positron Emission Tomographic Data of the 17 Patients

Patient No./ Age/Sex	Age at Onset	History of IS	Interictal Scalp EEG Epileptiform Activity	Seizure Onset on Scalp EEG	Ictal Intracranial EEG Seizure Focus	Number of Tubers	Location of Tubers With Increased AMT Uptake (Value)		Surgery	Outcome	Follow-up
							Ipsilateral to Focus	Contralateral to Focus			
1/1.2 yr/F	3 mo	+	Rt F, P Lt F	Rt F, T	Rt F	9	Rt F (**1.17**),* Rt P (1.02)†		Rt F lobectomy	I	22 m
2/12.3 yr/F	1 wk	+	Rt T-P, F Lt F	Rt T-P	Rt T-P	37	Rt T-P (**2.02, 1.45, 1.08**),* Rt P (**1.10**)*	Lt P (1.02)†	Rt hemispherectomy	I	19 m
3/9 yr/M	2 yr	−	Lt T-P, F Rt F, T	Generalized or Lt T-P	Lt T-P	12	None		Lt T-P resection	IV	55 m
4/5.3 yr/M	1.5 yr	−	Lt T Rt F	Lt T	Lt T, P	4	Lt T (**1.07**)*	Rt T-O (1.01)†	Lt T, P resection	I	9 m
5/6.3 yr/M	7 mo	+	Rt T-P, F Lt F	Rt T-P	Rt T-P	10	Rt T (**1.17**),* rt T-P (**1.13**)*	Lt F (1.03)†	Rt T-P resection	I	28 m
6/1.7 yr/F	5 mo	+	Lt T-P	Lt T-P-O	Lt F, T, P	14	Lt F-T-P (**1.01**),* lt F (**1.02**)*		Lt F-T-P resection	I	43 m
7/2.3 yr/M	3 mo	+	Lt T, P, rt T Generalized	Lt > rt hemisphere	Lt T-P	11	Lt T-P (1.04)‡		Lt T-P resection	IV	13 m
8/4 mo/M	4 d	−	lt T-P	Lt posterior	Not performed	1	Lt T-P-O (**1.51**)*		Lt T-P-O resection	I	9 m
9/8.1 yr/F	16 hr	+	Lt T-P, rt F-T Generalized	Lt. T-P, posterior	Not performed	18	Lt O (**1.09**)	Rt F (1.07)	Lt T-P-O resection	III	58 m
10/7.8 yr/M	5 mo	+	Lt posterior, T-P Rt T-P	Lt T-O, P	Lt T, P, O	9	Lt O (**1.02**)*		Lt T-P-O resection	I	7 m
11/7.5 yr/F	1.2 yr	−	Lt F, P Rt F-T	Lt F	Lt F, P	6	Lt F (**1.04**),* lt P (**1.11**)*	Rt T (1.02)†	Lt F, P resection	I	38 m
12/2.3 yr/F	2 wk	+	Lt F, T-P, O Rt F, T-P	Lt hemisphere	Lt F, T-P	9	Lt T-P (**1.03**)*	Rt F (1.01)†	Lt subhemispherectomy	I	7 m
13/11 mo/F	2 wk	−	Lt F, T-P-O Rt F, T, P	Lt hemisphere	Not performed	3	Lt F-T-P (**1.4**)*		Lt hemispherectomy	I	12 m
14/9.3 yr/F	3.5 yr	−	Lt T-P	Lt T-P, F	Lt F-T-P	1	Lt T-P (**1.06**)‡		Lt F-T-P resection	III	15 m
15/1.7 yr/M	4 mo	+	Rt F, T, P Lt T	Rt F-T	Rt F-T Rt interictal spiking	21	Rt P (**1.01**)		Rt F-P resection	IV	33 m
16/1.9 yr/F	3.5 mo	+	Rt hemisphere Lt F	Rt T	Rt T, P-O	4	Rt T (**1.11**),* rt P (**1.03**)*		Rt T, P-O resection	I	10 m
17/1.4 yr/M	13 d	+	Lt F-P	Lt F-P	Lt F-P	10	Lt F-P (**1.04**)*		Lt F-P resection	I	5 m

AMT = α-[^{11}C]-methyl-L-tryptophan; EEG = electroencephalographic; F = frontal; IS = infantile spasm; O = occipital; P = parietal; T = temporal.
Based on comparisons with outcome, *epileptogenic and †not epileptogenic (patients became seizure free despite nonresection of these tubers), whereas the rest of the tubers could not be clearly classified based on outcome criteria.
If the value of the AMT uptake ratio is bold, the tuber was surgically resected. ‡Tuber in eloquent cortex, partially resected.

the effect of such distortions on our calculations, initially, AMT uptake ratios of two of such small tubers (in patients 4 and 11) were measured and the calculated uptake ratios were 1.09. However, visual inspection of the AMT PET images did not reveal any obvious increases compared with the surrounding cortex (Figure 2), whereas other larger tubers clearly showed up on visual evaluation when their calculated uptake ratio values exceeded 1.05 (> 5% increase compared with surrounding normal cortex). Both of these small tubers were located in the hemisphere contralateral to the epileptic focus whose resection alleviated seizures. Therefore, to minimize the partial volume effects, very small (tubers whose size is less than spatial resolution of the AMT PET scan) and thin (seen only in one plane of images) tubers were not considered.

Data Analysis

We previously reported that the AMT uptake ratios of tubers localized in the epileptic lobe were higher than those in the nonepileptic lobe, and even the tubers with mild increases in AMT uptake could be related to the epileptiform activity.[23] Therefore, to obtain AMT uptake ratios for each tuber, standard uptake values determined in cortical tubers were divided by standard uptake values determined in surrounding normal cortex. Tuber uptake ratios of tubers located in frontal, temporal, and parietal regions of interest were calculated with values obtained from surrounding normal frontal, temporal, and parietal cortex, whereas uptake ratios of tubers located in the occipital lobe were calculated using the standard uptake values obtained from normal occipital cortex. This is necessary because AMT uptake in the occipital cortex is higher than in other cortical regions, which show a relatively homogeneous pattern of activity.[34] AMT uptake ratios of the cortical tubers were calculated in all patients. As in previous studies,[23] we defined the tubers with increased AMT uptake as regions with the AMT uptake ratio > 1.00 (typically, most tubers show AMT uptake much less than that of surrounding cortex, with an uptake ratio < 1.00). Only tubers showing increased AMT uptake were included into further analysis for comparisons with ictal EEG findings and surgical outcome data.

Tubers with increased AMT uptake were considered to be in the EEG-defined seizure onset zone if at least one subdural electrode overlying the tuber participated in seizure onset or, in the three patients with no intracranial EEG monitoring, if the tuber was located in a lobe showing seizure onset on scalp ictal EEG recording.

Because seizure-free surgical outcome is the ultimate goal for defining epileptic brain tissue, we have classified each tuber with increased AMT uptake as epileptogenic, nonepileptogenic, and uncertain epileptogenicity, based on outcome criteria. The criteria for this categorization were as follows:

1. Epileptogenic tubers were defined as tubers whose resection was followed by seizure-free outcome. The uptake ratios of epileptogenic tubers are indicated with an asterisk in Table 1.
2. Nonepileptogenic tubers were defined as tubers with increased AMT uptake that were not resected, but the patient became seizure free after resection of other areas.
3. Tubers with uncertain epileptogenicity included all other tubers with increased AMT uptake. These included tubers with increased AMT uptake occurring in patients who did not become seizure free after resection.

AMT uptake ratios in epileptogenic versus nonepileptogenic tubers were compared using the Mann-Whitney *U* test. A *P* value < .05 was considered significant. Furthermore, to determine an optimal tuber uptake ratio for detection of epileptogenic tubers based on the above-described surgical outcome criteria, a receiver operating characteristic analysis was applied to the tubers with increased AMT uptake, which could be classified as either epileptogenic or nonepileptogenic. Tubers with uncertain epileptogenicity were not included in this analysis. We computed sensitivity (epileptogenic tubers above a cutoff threshold/all epileptogenic tubers) and specificity (nonepileptogenic tubers below a cutoff threshold/all non-epileptogenic tubers), using varying cutoff thresholds of the tuber uptake ratio.

Surgical Planning

For each patient, findings of video-EEG monitoring, MRI, neuropsychologic testing, and FDG PET and AMT PET were presented and discussed at a multidisciplinary surgical planning meeting, and the combined localizing information provided by these data was used to decide surgical resection and to design the location and extent of subdural grid coverage. Patients with nonlocalizing AMT PET were not rejected from surgery if electroclinical findings provided sufficient localization. In cases with intracranial EEG recording, this EEG information was used to tailor the resection, targeting areas involved in seizure onset, early spread, and areas showing frequent (in general, > 10 spikes/minute) interictal spiking, unless they occurred in eloquent cortex.

RESULTS

MRI and FDG PET Findings

In the 17 patients, 179 tubers (mean 11 ± 9 per patient; range 1–37) were identified on MRI. In all but 2 patients, multiple cortical tubers were found in both hemispheres. Two patients (8 and 14) exhibited a single tuber. On the other hand, two patients (8 and 13) had a giant tuber occupying almost the entire hemisphere. Interictal FDG PET images revealed foci of decreased glucose metabolism in cortical regions corresponding to the location of cortical tubers and surrounding dysplastic cortices.

Scalp EEG Findings

The EEG results are summarized in Table 1. Interictal scalp EEG showed multifocal spike and wave discharges or generalized discharges in both hemispheres in 13 of the 17 patients (76%) and focal interictal epileptiform activity in 4 patients (6, 8, 14, and 17). Ictal scalp EEG showed prominent focal or regional abnormality (seizure onset involved one or two adjacent lobes) in eight patients, multifocal but clearly unihemispheric abnormality in five patients (6, 8, 9, 10, and 14), one hemisphere involved without further localization in two patients (12 and 13), and bilateral onset with dominance over one hemisphere in two cases (3 and 7).

AMT PET Findings

Thirty tubers (30 of 179; 16.8%) had increased AMT uptake (ratio at least 1.01) in 16 patients. Seven patients showed a single region of increased AMT uptake, six patients showed two regions, and three patients showed three or more regions with increased AMT uptake (see Table 1). One patient (5) showed an obvious increase in AMT uptake in cortex adjacent to a tuber but not in the tuber itself (Figure 3, A–C); the value measured in the adjacent cortical region (rather than the tuber value itself) is included in the table. Resective surgery included both the tuber and surrounding cortex. The cortex with increased AMT uptake adjacent to the tuber showed cortical dysplasia with balloon cells, as confirmed by pathologic examination (Figure 3, D and E). However, cortical dysplasia was also present in resected cortical tissue, which did not show increased AMT uptake.

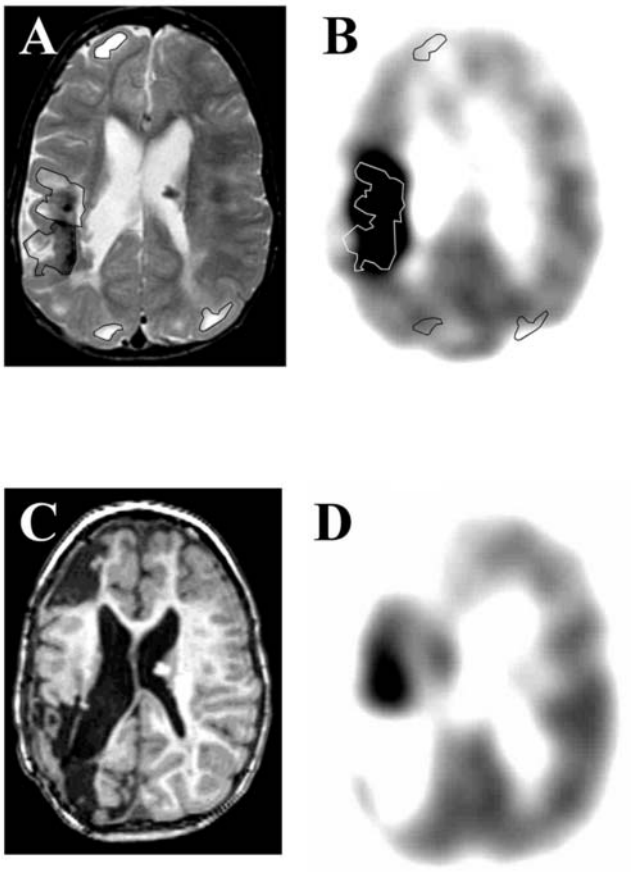

Figure 1. Magnetic resonance images (MRIs) and α-[^{11}C]methyl-L-tryptophan (AMT) positron emission tomographic (PET) scans in a 12-year-old girl with tuberous sclerosis complex (patient 2). *A,* Preoperative T_2-weighted MRI shows several cortical tubers in which regions of interest are delineated using a semiautomated program. *B,* AMT PET image with regions of interest copied from the MRI. One of the tubers showed increased AMT uptake, whereas other, smaller tubers showed decreased AMT uptake. There were other regions that were possibly abnormal but did not show a cortical tuber. T_1-weighted MRI (*C*) and AMT PET scan (*D*) after resective surgery shows a residual region of increased AMT uptake at the border of the right frontoparietal resection. Although this patient had class III outcome after the first surgery, she became seizure free following a second surgery after resection of the residual epileptogenic area with increased AMT uptake.

Relationship Between Ictal EEG and AMT PET Results

Twenty-four tubers showed increased AMT uptake ipsilateral to the epileptic focus, and 23 of these occurred in a region showing seizure onset, confirmed by intracranial EEG monitoring for 20 tubers (and only by scalp EEG in the remaining three patients who did not undergo intracranial EEG monitoring) (Figure 4). Thus, altogether, 77% (23 of 30) of the tubers with increased AMT uptake were located in the EEG-defined seizure onset area(s), and tubers with AMT uptake ≥ 1.08 (at least 8% increase) were all in seizure onset regions (13 of 13; 100%). Increased tuber AMT uptake correctly detected additional areas with seizure onset not found on ictal scalp EEG but confirmed by intracranial EEG in three patients (6, 11, and 16). In addition, one tuber (in patient 15, with a right frontotemporal focus) showed a mild increase (uptake ratio 1.01) in a region (right parietal) that was not involved in onset of seizures but showed frequent interictal spiking on intracranial EEG. Another tuber (in patient 1) showed a mild increase (1.02) ipsilateral to the epileptic focus but outside the lobe showing ictal EEG onset, which contained a tuber with an increased uptake ratio of 1.17.

Six patients had a single tuber with increased AMT uptake (uptake range 1.01–1.07) in the hemisphere contralateral to the epileptic focus on EEG. However, in all patients with multiple tubers with increased AMT uptake (including these six with bilateral increases), the tuber with the highest uptake always occurred in an EEG-defined epileptic region. Further, in patients with a single tuber with AMT increase, this tuber was always located in an EEG-defined epileptic region.

The EEG-defined epileptic cortex extended beyond the lobe(s) containing tuber(s) with increased AMT uptake in seven patients (4, 9, 10, 12, 14, 15, and 16), including three of five patients with class III or IV outcome.

Surgical Outcome

The surgical outcome for each patient is shown in Table 1. The follow-up period ranged from 5 to 58 months (median 15 months; mean 22.5 ± 17 months). Twelve patients (12 of 17; 71%) achieved seizure-free outcome (class I), including two patients (2; see Figure 1, C-D, and patient 10) who required more extensive resection following the first surgery (performed at another center in patient 10), and two patients had class III outcome. In three of the five patients who continued to have seizures postoperatively (classes III and IV), cortical tubers with increased AMT uptake and/or the adjacent cortex had been incompletely resected owing to the involvement of eloquent cortex (patients 7 and 14), or a number of tubers were present in the contralateral homologous area (patient 15). Among three patients with class IV outcome, one patient (15) achieved considerably improved cognitive function following surgery. These outcome data indicate that surgical treatment was of benefit in 15 patients (88%). The remaining two patients did not show any improvement in seizure frequency or cognitive function following surgical treatment.

Relationship Between Surgical Outcome and AMT PET Findings

All 12 patients with seizure-free outcome had cortical tuber(s) with increased AMT uptake in the region of the seizure focus, concordant with the ictal EEG localization. Based on the outcome criteria, 19 tubers with increased AMT uptake were epileptogenic and 6 tubers were nonepileptogenic, whereas the epileptogenicity of the remaining 5 tubers with increased AMT uptake (in 4 patients who continued to have seizures after surgery) remained uncertain. Mean AMT uptake was significantly higher in epileptogenic tubers (1.18 ± 0.24) than in nonepileptogenic tubers with increased AMT uptake (1.03 ± 0.08; $P = .009$). Further, tubers with AMT uptake of at least 1.10 (ie, ≥ 10% increase compared with surrounding normal cortex; $n = 11$ tubers in nine patients) were unequivocally epileptogenic, whereas all nonepileptogenic tubers showed an increase of less than 4% (uptake ratio between 1.01 and 1.03). Consistent with this, the receiver operating characteristic analysis showed that a cutoff threshold of AMT uptake ratio of 1.03 resulted in a specificity of 100% for detecting epileptogenic tubers and a sensitivity of 74% (82% accuracy). A further increase in the cutoff threshold decreased sensitivity, whereas a cutoff threshold of 1.02 provided 83% sensitivity and 84% specificity (83% accuracy) for detecting epileptogenic tubers as defined by outcome.

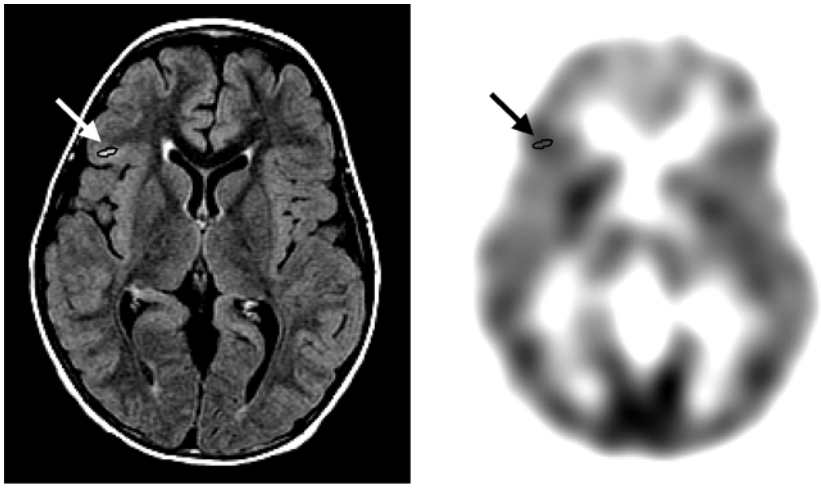

Figure 2. A very small tuber (location denoted by arrows) delineated on fluid-attenuated inversion recovery magnetic resonance imaging in patient 11. Although the calculated α-[11C]methyl-L-tryptophan uptake ratio was 1.09, no apparent increase was seen on visual evaluation. Because a similar phenomenon was observed in other cases, very small tubers were not included in the final analysis.

AMT PET Findings in Nonsurgical Patients or Patients Who Underwent Surgery in Other Centers

Of the 70 patients who had AMT PET performed but did not undergo surgery in our center, 32 were known to be not considered for resective epilepsy surgery owing to a lack of convincing electroclinical data to justify focal cortical resection. In these 32 nonsurgical patients, none of the tubers showed increased AMT uptake in 22 (69%) patients, 5 (15.5%) patients had bilateral, multifocal increases, and only 5 (15.5%) patients had one or more tubers with increased AMT uptake on one side of the brain. However, these were all mild increases, with only one tuber exceeding the AMT ratio of 1.03. In the remaining 38 of the 70 children, AMT PET showed one or more tubers with increased AMT uptake in all but 3 cases. Twelve of these patients are known to have undergone surgery in other institutions: seven had Engel class I or II outcome after 12 to 53 months of follow-up, three showed worthwhile improvement (after 2, 28, and 48 months), and two patients had class IV outcome (including one with no increased AMT uptake). The surgical decision is still pending, or no follow-up data were available for the other 26 patients.

DISCUSSION

Our study confirms that a considerable proportion of children with tuberous sclerosis complex and intractable epilepsy can be rendered seizure free after careful presurgical evaluation using multimodality imaging. In our series, seizure freedom was achieved in 71% (12 of 17) of patients with tuberous sclerosis complex and intractable epilepsy. This outcome figure is probably an underestimation because three subjects did not have complete resection of the epileptic region identified by increased AMT uptake owing to their location in eloquent cortex or the presence of tubers in the contralateral homologous region. If these three patients are not considered in the analysis of outcome, there would be 12 seizure-free patients of 14 (86%) with class I outcome. The vast majority of tubers with increased AMT uptake were epileptogenic by both intracranial EEG and outcome criteria, and tubers with at least a 10% increase in uptake were all epileptogenic using the seizure-free outcome criterion. On the other hand, patients with nonlocalizing AMT PET are less likely to be candidates for successful resective epilepsy surgery.

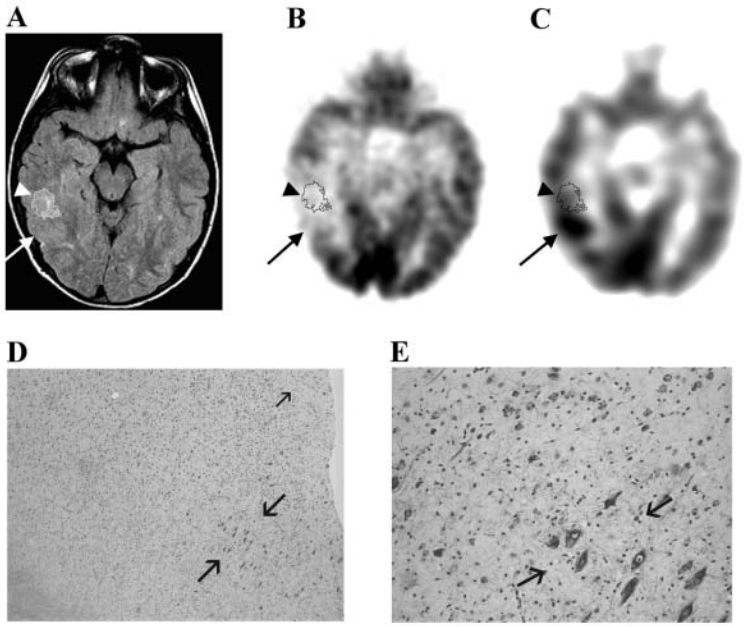

Figure 3. Fluid-attenuated inversion recovery magnetic resonance images (MRIs), fluorodeoxyglucose (FDG) positron emission tomography (PET), α-[11C]methyl-L-tryptophan (AMT) PET, and histology in a 6.3-year-old boy (patient 5) with tuberous sclerosis complex and intractable epilepsy. *A,* Fluid-attenuated inversion recovery MRI shows a single cortical tuber (*delineated area with arrowhead*) in the right temporal region. *B,* FDG PET scan shows extensive cortical hypometabolism in the region of tubers seen on MRI (*circled area with arrowhead*), as well as the dysplastic cortex adjacent to a tuber (*arrow*). *C,* AMT PET scan shows more prominent increase of AMT uptake in the dysplastic cortex (*arrow*; AMT uptake ratio 1.17) adjacent to the tuber than in the region of the right temporal cortical tuber (*delineated area with arrowhead;* AMT uptake ratio 1.0). *D,* An area of dysplastic cortex showing poor definition of laminar architecture, irregularly arranged large neurons in layer four (*larger arrows*), and clusters of small neurons in lamina 1 (*smaller arrow*). No tuber is present in this area (Luxol fast blue/cresyl violet; original magnification, ×25). *E,* Details of large dysplastic neurons (*arrows*) in layer four (Luxol fast blue/cresyl violet; original magnification, ×100).

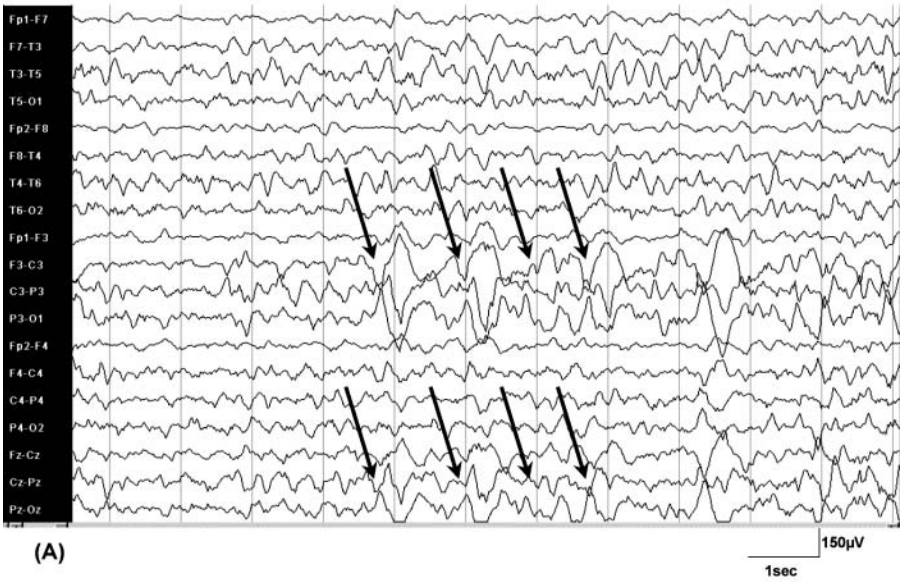

Figure 4. A 1-year-old boy (patient 17) with tuberous sclerosis complex and uncontrolled focal seizures. *A,* Scalp ictal electroencephalographic (EEG) recording showed sustained, irregular, rhythmic, slow-wave activity (arrows) at electrodes C3, P3, Pz, and Cz, with the highest amplitude at C3–P3.

Outcome of Epilepsy Surgery in Tuberous Sclerosis

Recent studies on surgical outcome in tuberous sclerosis complex reported that approximately half of the patients could be rendered seizure free without use of multimodality imaging techniques during presurgical evaluation. Avellino et al reported that 6 of 11 patients with tuberous sclerosis complex who underwent surgical resection became seizure free after surgery.[11] Guerreiro et al described 18 patients with tuberous sclerosis complex undergoing surgical treatment.[12] Seven of these patients underwent corpus callosotomy, and the remaining 11 patients underwent resective surgery. The outcome of the 11 patients treated by resection was seizure free in 5 patients (45%). In a more recent study, Jarrar et al reported 59% seizure freedom 1 year after surgery, which decreased to 42% in those who had been followed for at least 5 years.[14]

The major difficulty of localizing and completely resecting epileptogenic regions in patients with tuberous sclerosis complex is that despite the common presence of multiple and bihemispheric cortical tubers, seizures can arise from restricted regions related to a single tuber.[10] MRI and interictal FDG PET abnormalities cannot typically distinguish between epileptogenic and nonepileptogenic tubers. Ictal studies using single photon emission computed tomography have sometimes been helpful in this regard,[13,14,35,36] Still, ictal studies are often difficult to accomplish in children with tuberous sclerosis complex because their seizures are typically brief. A strong advantage of AMT PET is that it is performed in the interictal state and can identify epileptogenic cortical tuber(s) despite multifocal EEG abnormalities and multiple neuroimaging abnormalities.

In the present series, five patients continued to have seizures postoperatively. Three of these had incomplete surgical resection of the cortical tubers with increased AMT uptake. Two of the 12 patients who achieved class I outcome became seizure free only after a second resection. These included patient 2, who underwent a right frontoparietal resection and temporal lobectomy at our center following AMT PET scanning but continued to have seizures. Repeat AMT PET showed residual areas of increased AMT uptake in the anterior

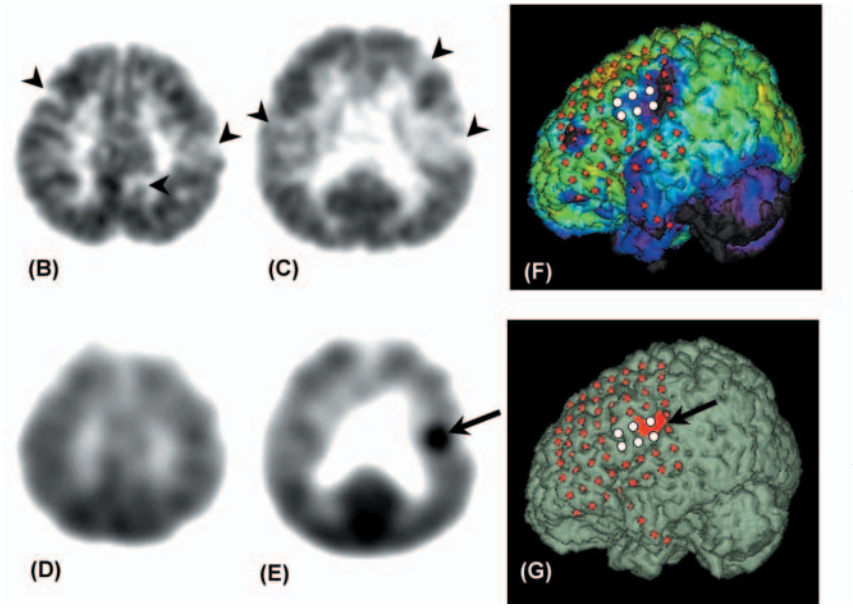

Figure 4. *B* and *C,* Interictal fluorodeoxyglucose (FDG) positron emission tomographic (PET) scan showed multifocal nodular hypometabolic regions, including the left inferior and medial parietal regions (*arrowheads*). Based on the ictal EEG and FDG PET findings, possible epileptogenicity in the left medial parietal region could not be ruled out. *D* and *E,* Increased α-[^{11}C]methyl-L-tryptophan (AMT) uptake confined to the left inferior lateral parietal region (*arrow*); this finding enhanced the confidence of localizing the epileptogenic tuber. *F* and *G,* Three-dimensional reconstructed surface magnetic resonance images superimposed with subdural electrodes. *F,* Nodular glucose hypometabolic areas are indicated by encircled violet areas in the left inferior parietal and frontal regions. *G,* Increased AMT uptake is indicated by a red area in the left inferior parietal region (*arrow*). Ictal subdural EEG recording showed seizure onset originating from the left primary sensory face area (*white electrodes*).

border of the right frontoparietal resection (Figure 1). Further resection of the right frontal cortex resulted in class I outcome. On the other hand, patient 10 underwent resective surgery at another hospital without AMT PET evaluation, but his seizures returned 4 weeks after the surgery. AMT PET showed increased AMT uptake region adjacent to the previously resected area. He also achieved class I outcome after the removal of the increased AMT uptake area. These results further suggest that favorable seizure outcome can be obtained if tubers with increased AMT uptake are resected completely.

Interestingly, six patients (2, 4, 5, 9, 11, and 12) had unresected tuber(s) with increased AMT uptake contralateral to the seizure focus, without clear ictal EEG correlate. Five of these tubers, however, showed minimal (1–3%) increases, and all proved to be nonepileptogenic based on surgical outcome. This finding, together with the findings of the receiver operating characteristic analysis, suggests that resection of cortical tubers with such mild increases in AMT uptake is not necessarily required. Comparison between AMT PET and epileptiform EEG findings can help determine whether tubers with mild increases of AMT uptake should be evaluated by intracranial EEG and should indeed be included in the surgical resection to optimize outcome. Also, use of other imaging modalities, such as diffusion-weighted MRI,[19] might be helpful to further characterize potential epileptogenicity of such tubers.

Considerations for Optimal Interpretation of AMT PET in Tuberous Sclerosis

The outcome definition of epileptogenic tubers with high uptake in this study has some limitations. First, resection of a tuber unrelated to epileptic seizures could result in seizure-free outcome if the resection extends beyond this tuber and includes truly epileptic areas (this could happen, for example, in cases of large multilobar resections). Another potential limitation of this outcome definition is that in six patients (1, 2, 5, 6, 11, and 16), multiple (two to four) tubers were resected from the same hemisphere. In such cases, it remains unclear whether resection of all of these tubers was truly necessary to achieve seizure freedom. Still, in all of these six cases, ictal intracranial EEG was recorded and showed that all of these tubers were located in a seizure onset area.

Another limitation is accurate assessment of AMT uptake values for small tubers owing to partial volume effects. Region of interest–based analysis of AMT uptake can give false-positive results for tubers whose diameter falls below the resolution of the images (approximately 7 mm in the present study); therefore, calculated increases should be assessed further by visual inspection.

A further consideration is that increased AMT uptake can occur adjacent to a tuber in the surrounding epileptogenic cortex (as shown in Figure 3), which we have previously reported.[22] This could indicate the presence of dysplastic cortex adjacent to a tuber; seizure activity on intracranial EEG can be localized to such perituberal cortex.[22,37] Recent studies indeed suggest a pathogenic relationship between certain forms of focal cortical dysplasia and mosaic *TSC* gene mutations.[38] This suggests that too restricted resection of the visible cortical tuber (pure lesionectomy) can result in unfavorable seizure outcome. Dysplastic abnormalities in the cortex might or might not be detected on MRI.[39–41] A tuber-based region of interest analysis could also miss such epileptogenic dysplastic cortical regions. The only practical way of detecting such tubers is a visual screening of the AMT PET images and application of additional, perituberal regions of interest wherever visual inspection raises the possibility of perituberal increases in AMT uptake. FDG PET in such cases might help by showing hypometabolism extending beyond the tuber. However, hypometabolic areas seen on FDG PET usually extend beyond the epileptogenic regions, and not all cortical areas showing decreased glucose metabolism are necessarily epileptogenic.[42–45] Therefore, in such cases, perituberal regions of interest should be confined to areas that appear to show increased AMT uptake on visual inspection; this makes this type of analysis less objective than the tuber-based region of interest approach. Nevertheless, with these limitations in mind, the applied method has approximately 80% sensitivity and specificity (by using the cutoff threshold of 1.02 for AMT uptake ratio) for identifying tubers that need to be resected for seizure freedom.

It should also be noted that detection of tuber(s) with increased AMT uptake can provide additional localizing information, even when the scalp EEG results were not precisely localizing (see Figure 4). First, owing to its limited spatial resolution, scalp EEG is not sufficient to differentiate between epileptogenic and nonepileptogenic tubers located in close proximity. This issue is particularly important if such tubers are close to eloquent cortex. Furthermore, ictal EEG results in children with brief seizures or infantile spasms are often difficult to interpret, and it is particularly difficult to lateralize and localize seizure foci located close to the midline or far from the scalp (eg, medial or inferior temporal regions or deep in the insula). Therefore, it is clinically often very useful and desirable to obtain independent imaging data to confirm the location of the presumed epileptic focus, to enhance the confidence of patient selection for epilepsy surgery, and, in some cases, to raise the possibility of additional epileptic regions missed by scalp EEG (such as in patients 11, 15, and 16 in the present series). AMT PET can help optimize subdural electrode placement in such cases.

In summary, surgical treatment can be highly effective in alleviating seizures and improving cognitive function in selected patients with tuberous sclerosis complex and intractable epilepsy. Surgical resection of the cortical tubers with an AMT uptake of at least 10% greater than the mean cortical AMT uptake is highly desirable to achieve a favorable surgical outcome, whereas tubers with smaller increases should be resected if there is concordance with ictal epileptiform activity. AMT PET provides complementary localizing information regarding potentially epileptogenic regions and improves patient selection for successful surgery in conjunction with other localization techniques.

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References

1. Roach ES, DiMario FJ, Kandt RS, Northrup H: Tuberous Sclerosis Consensus Conference: Recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. *J Child Neurol* 1999;14:401–407.
2. Fryer AE, Chalmers A, Connor JM, et al: Evidence that the gene for tuberous sclerosis is on chromosome 9. *Lancet* 1987;i:659–661.
3. Kandt RS, Haines JL, Smith M, et al: Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease. *Nat Genet* 1992;2:37–41.

4. Gomez MR. Neurologic and psychiatric features, in Gomez MR (ed): *Tuberous Sclerosis*, 2nd ed. New York, Raven Press, 1988, 21–36.
5. Webb DW, Fryer AE, Osborne JP: Morbidity associated with tuberous sclerosis: A population study. *Dev Med Child Neurol* 1996; 38:146–155.
6. Baumgartner JE, Wheless JW, Kulkarni S, et al: On the surgical treatment of refractory epilepsy in tuberous sclerosis complex. *Pediatr Neurosurg* 1997;27:311–318.
7. Sinson G, Sutton LN, Yachnis AT, et al: Subependymal giant cell astrocytomas in children. *Pediatr Neurosurg* 1994;20:233–239.
8. Di Rocco C, Iannelli A, Marchese E: On the treatment of subependymal giant cell astrocytomas and associated hydrocephalus in tuberous sclerosis. *Pediatr Neurosurg* 1995;23:115–121.
9. Cuccia V, Zuccaro G, Sosa F, et al: Subependymal giant cell astrocytoma in children with tuberous sclerosis. *Childs Nerv Syst* 2003;19:232–243.
10. Bebin EM, Kelly PJ, Gomez MR: Surgical treatment for epilepsy in cerebral tuberous sclerosis. *Epilepsia* 1993;34:651–657.
11. Avellino AM, Berger MS, Rostomily RC, et al: Surgical management and seizure outcome in patients with tuberous sclerosis. *J Neurosurg* 1997;87:391–396.
12. Guerreiro MM, Andermann F, Andermann E, et al: Surgical treatment of epilepsy in tuberous sclerosis. Strategies and results in 18 patients. *Neurology* 1998;51:1263–1269.
13. Koh S, Jayakar P, Dunoyer C, et al: Epilepsy surgery in children with tuberous sclerosis complex: Presurgical evaluation and outcome. *Epilepsia* 2000;41:1206–1213.
14. Jarrar RG, Buchalter JR, Raffel C: Long-term outcome of epilepsy surgery in patients with tuberous sclerosis. *Neurology* 2004;62:479–481.
15. Roach ES, Williams DP, Laster DW: Magnetic resonance imaging in tuberous sclerosis. *Arch Neurol* 1987;44:301–303.
16. Nixon JR, Houser OW, Gomez MR, Okazaki H: Cerebral tuberous sclerosis: MR imaging. *Radiology* 1989;170:869–873.
17. Cusmai R, Chiron C, Curatolo P, et al: Topographic comparative study of magnetic resonance imaging and electroencephalography in 34 patients with tuberous sclerosis. *Epilepsia* 1990;31:747–755.
18. Takanashi J, Sugita K, Fujii K, Niimi H: MR evaluation of tuberous sclerosis: Increased sensitivity with fluid-attenuated inversion recovery and relation to severity of seizures and mental retardation. *AJNR Am J Neuroradiol* 1995;16:1923–1928.
19. Jansen FE, Braun KP, van Nieuwenhuizen O, et al: Diffusion-weighted magnetic resonance imaging and identification of the epileptogenic tuber in patients with tuberous sclerosis. *Arch Neurol* 2003;60:1580–1584.
20. Szelies B, Herholz K, Heiss WD, et al: Hypometabolic cortical lesions in tuberous sclerosis with epilepsy: Demonstration by positron emission tomography. *J Comput Assist Tomogr* 1983;7:946–953.
21. Rintahaka PJ, Chugani HT: Clinical role of positron emission tomography in children with tuberous sclerosis complex. *J Child Neurol* 1997;12:42–52.
22. Chugani DC, Chugani HT, Muzik O, et al: Imaging epileptogenic tubers in children with tuberous sclerosis complex using α-[^{11}C] methyl-L-tryptophan positron emission tomography. *Ann Neurol* 1998;44:858–866.
23. Asano E, Chugani DC, Muzik O, et al: Multimodality imaging for improved detection of epileptogenic foci in tuberous sclerosis complex. *Neurology* 2000;54:1976–1984.
24. Asano E, Chugani DC, Juhász C, et al: Surgical treatment of West syndrome. *Brain Dev* 2001;23:668–676.
25. Engel J Jr, Van Ness PC, Rasmussen TB, Ojemann LM: Outcome with respect to epileptic seizures, in Engel J Jr (ed): *Surgical Treatment of the Epilepsies*, 2nd ed. New York, Raven Press, 1993, 609–621.
26. Spencer SS, Guimaraes P, Katz A, et al: Morphological patterns of seizures recorded intracranially. *Epilepsia* 1992;33:537–545.
27. Bergstrom M, Litton J, Eriksson L, et al: Determination of object contour from projections for attenuation correction in cranial positron emission tomography. *J Comput Assist Tomogr* 1982;6:365–372.
28. Woodard HQ, Bigler RE, Freed B: Expression of tissue isotope distribution, letter. *J Nucl Med* 1975;16:958–959.
29. Chugani DC, Muzik O, Chakraborty P, et al: Human brain serotonin synthesis capacity measured in vivo with alpha-[^{11}C]-methyl-L-tryptophan. *Synapse* 1998;28:33–43.
30. Pietrzyk U, Herholz K, Fink G, et al: An interactive technique for three-dimensional image registration: Validation for PET, SPECT, MRI and CT brain studies. *J Nucl Med* 1994;35:2011–2018.
31. Kennedy DN, Filipek PA, Caviness VS Jr: Anatomic segmentation and volumetric calculations in nuclear magnetic resonance imaging. *Trans Med Imaging* 1989;8:1–7.
32. Aston JA, Cunningham VJ, Asselin MC, et al: Positron emission tomography partial volume correction: Estimation and algorithms. *J Cereb Blood Flow Metab* 2002;22:1019–1034.
33. Mazziotta JC, Phelps ME, Plummer D, Kuhl DE: Quantitation in positron emission computed tomography: 5. Physical-anatomical effects. *J Comput Assist Tomogr* 1981;5:734–743.
34. Javoy-Agid F, Scatton B, Ruberg M, et al: Distribution of monoaminergic, cholinergic, and GABAergic markers in the human cerebral cortex. *Neuroscience* 1989;29:251–259.
35. Tamaki K, Okuno T, Iwasaki Y, et al: Regional cerebral blood flow in relation to MRI and EEG findings in tuberous sclerosis. *Brain Dev* 1991;13:420–424.
36. Koh S, Jayakar P, Resnick T, et al: The localization value of ictal SPECT in children with tuberous sclerosis complex and refractory partial epilepsy. *Epileptic Disord* 1999;1:41–46.
37. Asano E, Chugani DC, Juhász C, et al: Epileptogenic zones in tuberous sclerosis complex: Subdural EEG versus MRI and FDG PET, abstract. *Epilepsia* 2000;41(Suppl 7):128.
38. Becker AJ, Urbach H, Scheffler B, et al: Focal cortical dysplasia of Taylor's balloon cell type: Mutational analysis of the *TSC1* gene indicates a pathogenic relationship to tuberous sclerosis. *Ann Neurol* 2002;52:29–37.
39. Chugani HT, Shields WD, Shewmon DA, et al: Infantile spasms: I. PET identifies focal cortical dysgenesis in cryptogenic cases for surgical treatment. *Ann Neurol* 1990;27:406–413.
40. Chugani HT, Shewmon DA, Shields WD, et al: Surgery for intractable infantile spasms: Neuroimaging perspectives. *Epilepsia* 1993;34:764–771.
41. Desbiens R, Berkovic SF, Dubeau F, et al: Life-threatening focal status epilepticus due to occult cortical dysplasia. *Arch Neurol* 1993;50:695–700.
42. Theodore WH, Newmark ME, Sato S, et al: [^{18}F]Fluorodeoxyglucose positron emission tomography in refractory complex partial seizures. *Ann Neurol* 1983;14:429–437.
43. Sadzot B, Debets RM, Maquet P, et al: Regional brain glucose metabolism in patients with complex partial seizures investigated by intracranial EEG. *Epilepsy* Res 1992;12:121–129.
44. Henry TR, Mazziotta JC, Engel J Jr: Interictal metabolic anatomy of mesial temporal lobe epilepsy. *Arch Neurol* 1993;50:582–589.
45. Juhász C, Chugani DC, Muzik O, et al: Relationship of flumazenil and glucose PET abnormalities to neocortical epilepsy surgery outcome. *Neurology* 2001;56:1650–1658.