Current Management of Tuberous Sclerosis Complex

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Tuberous Sclerosis

• **Tuberous sclerosis complex (TSC)**; a neurocutaneous syndrome characterized by skin lesions (adenoma sebaceum, etc), benign tumors in various organs, early-onset epilepsy, and mental retardation.
Benign Tumors in Various Organs

- Brain cortical tubers / SE nodules /
  - SE giant cell astrocytoma (SEGA)
- Cardiac rhabdomyoma
- Retinal nodular harmartoma / achromic patch
- Renal angiomyolipoma / cysts
- Lung lymphangioleiomyomatosis
- Periungual fibroma
- Gingival fibroma
- Non-renal hamartoma
- Bone cysts
- Hamartomatous rectal polyps

Major & Minor features in TSC Diagnostic Criteria.
# Genetics of TSC; TSC1 and TSC2

<table>
<thead>
<tr>
<th></th>
<th>TSC1</th>
<th>TSC2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal location</td>
<td>9q34</td>
<td>16p13.3</td>
</tr>
<tr>
<td>Size</td>
<td>55 kb</td>
<td>40 kb</td>
</tr>
<tr>
<td>Number of exons</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>Transcript size</td>
<td>8.6 kb</td>
<td>5.5 kb</td>
</tr>
<tr>
<td>Mutation occurrence</td>
<td>10-15% of sporadic cases</td>
<td>75-80% of sporadic cases</td>
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<tr>
<td>Prevailing mutations</td>
<td>Small truncations (mostly</td>
<td>Large deletions and/or</td>
</tr>
<tr>
<td></td>
<td>nonsense mutations and small</td>
<td>rearrangements involving PKD1,</td>
</tr>
<tr>
<td></td>
<td>deletions), lack of hotspots</td>
<td>small truncations</td>
</tr>
<tr>
<td></td>
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<td>(mostly missense mutations</td>
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<tr>
<td></td>
<td></td>
<td>or deletions), lack of</td>
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<td></td>
<td></td>
<td>hotspots</td>
</tr>
<tr>
<td>LOH in affected</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>Hamartin</td>
<td>Tuberin</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Less severe</td>
<td>More severe</td>
</tr>
</tbody>
</table>
Genetics and Pathogenesis

- **TSC** results from mutation of **Hamartin or Tuberin**, *which together inhibit* the *phosphatidyl inositol 3-kinase (PI3) signaling pathway*, involving the *mammalian target of rapamycin (mTOR)* and a cascade of other downstream kinases and translational factors that stimulate protein translation, cell growth and proliferation.

- **Mutations of hamartin or tuberin in TSC** leads to *hyperactivation of the mTOR and downstream signaling pathways* result in *increased cell growth, proliferation and abnormal gene expression*.

- **These alterations are associated with widespread hamartomas in several organs, including the brain, heart, skin, eyes, kidney, lung, and liver.**

  → **Epilepsy, mental retardation, cutaneous lesions (adenoma sebaceum, etc), and tumors in various organs** will develop as a result.
Neurobiology of TSC

TSC

TSC1/TSC2

Hamartin

Tuberin

↑

mTOR

↑

S6K/S6, eIF4E

↑

Protein synthesis

↑

↑

Tumorigenesis

↑

Epileptogenesis
소아 결절성 경화증 환자에 동반된 간질의 경과에 대한 임상적 고찰
울산대학교 의과대학 서울아산병원 소아청소년과
이은혜 · 정민희 · 고태성

Study of Clinical Course of Epilepsy in Children with Tuberous Sclerosis Complex
Eun Hye Lee, MD, Min Hee Jeong, MD, and Tae-Sung Ko, MD
Department of Pediatrics, Asan Medical Center, Ulsan University College of Medicine, Seoul, Korea
## Seizure types according to onset age (AMC)

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Onset age</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>≤12 m</td>
<td>&gt;12 m</td>
</tr>
<tr>
<td>No change group</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>(70.1%)</td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>CPS</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>GTS</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>SPS</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Change group</td>
<td>15</td>
<td>2</td>
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<tr>
<td></td>
<td>(29.8%)</td>
<td></td>
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<tr>
<td>IS → LGS</td>
<td>3</td>
<td>0</td>
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<tr>
<td>IS → CPS</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>IS → GTS</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>CPS → IS</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>CPS → GTCS</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Atonic seizure → CPS</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44 (77.1%)</strong></td>
<td><strong>13 (22.8%)</strong></td>
</tr>
<tr>
<td>Seizure type</td>
<td>Seizure frequency</td>
<td>F/U loss</td>
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<tr>
<td>--------------------</td>
<td>-------------------</td>
<td>----------</td>
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<tr>
<td></td>
<td>free</td>
<td>≥1/m</td>
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<tr>
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<td>8</td>
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<tr>
<td>CPS</td>
<td>9</td>
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<tr>
<td>GTS</td>
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<tr>
<td>Change group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS → LGS</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IS → GTS</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CPS → IS</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CPS → GTCS</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Atonic seizure → CPS</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td><strong>26 (50%)</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>

M, month; w, week; D, day; F/U, follow-up; IS, infantile spasms; CPS, complex partial seizure; GTS, generalized tonic seizure; SPS, simple partial seizure; LGS, Lennox-Gastaut syndrome; GTCS, generalized tonic clonic seizure.
• Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review. (Hancock E, Osborne JP. J Child Neurol. 1999)
  – 313 patients without TSC, 170 (54%) had complete cessation of their infantile spasms,
  – 77 patients with TSC, 73 (95%) had complete cessation of their seizures.
# Epilepsy Surgery (AMC)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Seizure type</th>
<th>Interictal EEG</th>
<th>Ictal EEG</th>
<th>Brain MRI</th>
<th>Postop. F/U</th>
<th>Notes</th>
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<tbody>
<tr>
<td>1</td>
<td>2 m/M</td>
<td>GTS head drop</td>
<td>Rt. F-T area spike and wave</td>
<td>Diffuse generalized Cortical spike and slow wave and fast activities in Rt. F-T area</td>
<td>Right F-T area</td>
<td>Seizure free</td>
<td>52 m</td>
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<tr>
<td>2</td>
<td>6 m/M</td>
<td>IS → LGS</td>
<td>Multifocal spike discharges (O2, O1, C4, T4) and generalized epileptiform discharges</td>
<td>Fast activities from Rt. F-C area</td>
<td>Generalized spike and slow wave discharges</td>
<td>25 m</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15 m/F</td>
<td>Drop attack</td>
<td>Generalized epileptiform discharges, Rt. P-O areas and Lt. C area</td>
<td>Generalized slowings → theta slowings over Rt. C-P-T area</td>
<td>MRI absent</td>
<td>Seizure free</td>
<td>23 m</td>
</tr>
<tr>
<td>4</td>
<td>57 m/M</td>
<td>CPS</td>
<td>Focal slowings and spike from Lt. T-P areas</td>
<td>Rt. T-P delta → Lt. hemispheric spike, Lt. side delta → Lt. hemispheric spike</td>
<td>MRI absence</td>
<td>Seizure free → Recurred after 4 years</td>
<td>106 m</td>
</tr>
</tbody>
</table>

M, male; F, female; m, months; IS, infantile spasms; LGS, Lennox-Gastaut syndrome; GTS, generalized tonic seizure; CPS, complex partial seizure; EEG, electroencephalography; MRI, magnetoencephalography; P, parietal; O, occipital; T, temporal; C, central; Lt., left; Rt., right; F/U, follow-up.
AMT PET imaging


Figure 4.
(A) 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography (FDG PET) image of a child with tuberous sclerosis complex (TSC) showing multiple areas of cortical glucose hypometabolism representing multiple cortical tubers (thin arrows). (B) Alpha-[11C]methyl-L-tryptophan positron emission tomography (AMT PET) of the same child showing a single tuber which showed increased AMT uptake (thick arrow). The patient underwent left temporoparietal resection, including the tuber with increased AMT uptake. He became seizure-free for 15 months. After 4 years of follow-up, he achieved Engel class II A outcome.

*Epilepsia © ILAE*
A 3-year-old girl with tuberous sclerosis complex began having seizures at age 7 weeks. She did not have infantile spasms. Her seizures consisted of 8 to 10 complex partial seizures daily, lateralized to the left hemisphere without further clear localization within that hemisphere. Many abnormal interictal findings included diffuse slowing during wakefulness, intermittent slowing over the left anterior quadrant, and spike discharges seen independently over the left central and frontal regions as well as right central, frontal, and temporal regions. Her brain MRI (A) showed greater than 20 tubers over both hemispheres, and her $^{18}$fluorodeoxyglucose PET (FDG-PET) (not shown) showed multiple focal areas of moderate to severe decreased glucose metabolism.
Multi-staged Multifocal Resection

Epilepsy Surgery in Young Children With Tuberous Sclerosis: Results of a Novel Approach

Howard L. Weiner, MD\textsuperscript{a,b,c,d}, Chad Carlson, MD\textsuperscript{d,e}, Emily B. Ridgway, MD\textsuperscript{d}, Josiane LaJoie, MD\textsuperscript{c,d,e}, Orrin Devinsky, MD\textsuperscript{b,d,e}

\textsuperscript{a}Division of Pediatric Neurosurgery, Department of Neurosurgery, New York University; University Medical Center, New York, New York; \textsuperscript{b}Department of Pediatrics, New York; New York University Medical Center, New York, New York; \textsuperscript{c}Department of Neurology; \textsuperscript{d}Pediatrics, 2006

\textbf{ABSTRACT}

\textbf{OBJECTIVE.} Tuberous sclerosis complex (TSC) is associated with medically refractory epilepsy and developmental delay in children and usually results from cortical tubers. Seizures that begin in young patients are often refractory and may contribute to developmental delay. Functional outcome is improved when seizures are controlled at an early age. Previous reports have shown modest benefit from surgical resection of single tubers/seizure foci in older children; however, many children with TSC develop uncontrolled seizures before age 1. To identify patients who might benefit from surgery and to maximize outcome, we used a novel surgical approach in young children that consists of invasive intracranial monitoring, which is typically 3-staged and often bilateral.

\textbf{METHODS.} Of 110 consecutive children who underwent epilepsy surgery by a single surgeon in the past 6 years, 25 patients (9 boys and 16 girls) had TSC. At the time of their first surgery at our institution, they were a median age of 4.0 years. A total of 31 separate admissions for epilepsy surgery in these 25 patients were identified. Bilateral electrode placement was performed in 13 children whose seizures could not be lateralized definitively preoperatively, and 22 patients underwent 3-stage surgeries.

\textbf{RESULTS.} At 6 months or longer after the initial resection, 21 (84\%) children were class I, 2 (8\%) children were class II, and 2 (8\%) children were class IV. At a mean follow-up of 23 months, 17 (68\%) children were class I, 6 (24\%) were class II, and 2 (8\%) were class III. Four of the 5 children who initially were rejected as surgical candidates because of multifocality and who required initial bilateral electrode study are now seizure-free.

\textbf{CONCLUSIONS.} This approach can help to identify both primary and secondary epileptogenic zones in young TSC patients with multiple tubers. Multiple or bilateral seizure foci are not necessarily a contraindication to surgery. Long-term follow-up will determine whether this approach has durable effects.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Surgery Stage 1</th>
<th>Surgery Stage 2</th>
<th>Surgery Stage 3</th>
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<tbody>
<tr>
<td>1</td>
<td>3.8</td>
<td>Bilateral strips</td>
<td>Removal of electrodes</td>
<td>Left posterior frontal and temporal regions (posterior to resection)</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>Left frontal tuber resection then left grid and strips</td>
<td>Left frontal resection from operculum to mesial cortex and temporal resection</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6.5</td>
<td>Right grid and strips</td>
<td>Right frontal and temporal resection (tubers) with premotor/SMA approach</td>
<td></td>
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<tr>
<td>4</td>
<td>0.6</td>
<td>Left grid and strips/right strips</td>
<td>Left temporal tuber resection</td>
<td>Extension of left temporal resection</td>
</tr>
<tr>
<td>5</td>
<td>7.1</td>
<td>Left grid and strips/right strips</td>
<td>Left frontal tuber resection</td>
<td>Left posterior frontal (additional tuber) and left temporal resection</td>
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<tr>
<td>6</td>
<td>10.4</td>
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<td>Left focal anterior frontal resection and MST posteriorly</td>
<td>Extension of frontal resection and posterior MST</td>
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<td>7</td>
<td>1.1</td>
<td>Right grid and strips/left strips</td>
<td>Right frontoparietal tuber resection</td>
<td>Extension of right frontoparietal resection</td>
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<td>8</td>
<td>6.7</td>
<td>Right grid and strips</td>
<td>Right anterior frontal tuber resection</td>
<td>Extension of stage 1 resection as well as a right frontocentral tuber (presumed motor area) resection</td>
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<td>9</td>
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<td>Right grid and strips/left strips</td>
<td>Right frontal tuber resection (× 2) and right anterior temporal resection</td>
<td>Resection of remaining right frontal and temporal tubers</td>
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<td>10</td>
<td>4.1</td>
<td>Bilateral strips</td>
<td>Removal of electrodes</td>
<td>Extension of right frontal resection with parietal, posterior insular, and posterior temporal resection</td>
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<td>11</td>
<td>4.3</td>
<td>Right grid and strips</td>
<td>Right frontal resection</td>
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<td>12</td>
<td>4.7</td>
<td>Left grid and strips</td>
<td>Left temporal resection (anterior and posterior tubers) extending mesially</td>
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</tr>
<tr>
<td>10</td>
<td>3.6</td>
<td>Right grid and strips/left strips</td>
<td>Right posterior frontal tuber resection</td>
<td>Right temporal tuber resection</td>
</tr>
<tr>
<td>11</td>
<td>4.6</td>
<td>Bilateral strips</td>
<td>Removal of electrodes</td>
<td>Right superior frontal tuber resection</td>
</tr>
<tr>
<td>11</td>
<td>5.9</td>
<td>Right grid and strips</td>
<td>Right frontal resection</td>
<td>Right parietal and supplementary motor area resection</td>
</tr>
<tr>
<td>12</td>
<td>2.4</td>
<td>Right grid and strips/left strips</td>
<td>Right parieto-occipital tuber resection</td>
<td>Left parietal and left anterolateral temporal lobectomy involving 2 tubers</td>
</tr>
</tbody>
</table>
Epilepsy Surgery

• Previously published studies (Old Surgical Strategy); the best seizure control is obtained when a single tuber and associated epileptogenic zone is documented and targeted surgically.

• **Epilepsy surgery in tuberous sclerosis: a systematic review.** *(Jansen FE, van Huffelen AC, Algra A, van Nieuwenhuizen O. Epilepsia. 2007)*
  - 25 articles since 1960. (177 patients)
  - Seizure freedom in 101 patients (57%). Seizure frequency improvement by > 90% in 32 patients (18%).

  - 70 patients
  - Associations between younger age at seizure onset, present/prior history of infantile spasms, interictal focality (bilateral versus unilateral), and absence of residual postoperative predominant tuber, and poorer postoperative outcome (p < 0.01).

• Advances in EEG techniques, functional neuroimaging, and invasive cortical mapping are changing this view and allowing an increased number of TSC patients to be evaluated for resective surgery.

  → (Emerging Surgical Strategy); Intracranial electrode recordings, Multi-staged or bilateral surgery.
• **Tuberous sclerosis complex and the ketogenic diet.** (Kossoff EH, Thiele EA, Pfeifer HH, McGrogan JR, Freeman JM. *Epilepsia*. 2005)
  – 11/12 (92%) children had a >50% reduction in their seizures at 6 months on the diet, and 8/12 (67%) had a >90% response.

  – 2/3 patients became seizure-free within 2 months on the diet. In the third patient drop attacks decreased significantly. On follow-up the diet was well accepted and without adverse effects.
Vagal Nerve Stimulation

- **Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex.** *(Major P, Thiele EA. Epilepsy Behav. 2008)*
  - 16 patients (mean age at VNS implantation= 15 years, mean duration of follow-up= 4 years)
  - Outcome; class I (>80% seizure frequency reduction) in 3 (19%), class II (50-79% reduction) in 5 (31%), class III (<50% reduction) in 2 (13%), class IV (magnet benefit only) in 1 (6%), and class V (no improvement) in 5 (31%) patients.

- **Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery.** *(Elliott RE, Carlson C, Kalhorn SP, Moshel YA, Weiner HL, Devinsky O, Doyle WK. Epilepsy Behav. 2009)*
  - 19 patients (mean age at VNS implantation= 14.7 ± 12 years), 1 patient; F/U loss
  - Mean reduction of seizure frequency = 72%
  - 2 patients = Engel Class I (18%), 1 = Class II (9%), 7 = Class III (64%), and 1 = Class IV (9%) outcome.
  - In total, 8 of 10 (80%) patients experienced improved seizure control following intracranial surgery (mean reduction: 65%, range: 0-100%, P<0.05).
mTOR Inhibitor
“Rapamycin”
• **Rapamycin (Sirolimus)**
  - Originally developed as an antifungal agent but was abandoned.
  - Potent immunosuppressive and antiproliferative properties.
  - Immunosuppressant drug to prevent rejection in organ transplantation (ex. Kidney transplants) and in the treatment of certain cancers.
Intervention points: mTOR (mammalian Target of Rapamycin)

- TSC
  - TSC1/TSC2
    - Hamartin
    - Tuberin
      - mTOR
        - S6K/S6, eIF4E
          - Protein synthesis
            - Tumorigenesis
            - Epileptogenesis

Rapamycin
• **Treatment with the mTOR inhibitor “Rapamycin”**
  – improve cognitive function in TSC2 heterozygous mutant mice (Ehniger et al., 2008)
  – prevent (early treatment) or reduce (late treatment) seizures in TSC1 mutant mice (Zeng et al. 2008)
  – Suggesting that abnormal activation of this pathway in TS is responsible for both learning deficits and seizures.
### Epileptogenesis and Antiepileptogenic/Antiepileptic Drugs

#### Brain Injury
- Head trauma
- Stroke
- Hypoxia-Ischemia
- Prolonged febrile seizure
- Tumor
- Cortical Malformation
- Genetic disease

#### Latent Period (Epileptogenesis)
- Cell signaling pathways
- Gene regulation/transcription
- Protein synthesis
- Synaptic reorganization
- Neuronal death
- Neurogenesis
- Astrogliosis
- Inflammation
- Vascular changes

#### Seizures (Epilepsy)
- Membrane excitability
  - Ion channels
- Synaptic transmission
  - Neurotransmitters
  - Neurotransmitter Receptors

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**Primary prevention**

**“Anti-epileptogenic” drugs**

**“Anti-epileptic” drugs**
Potential Antiepileptogenic Effects of mTOR Inhibitors

- **mTOR inhibitors** prevented epilepsy and the underlying histological and molecular mechanisms of epileptogenesis in glial-selective KO mouse model of TSC, representing a true anti-epileptogenic action (Zeng et al. 2008).

- mTOR inhibitors also block histological abnormalities and possibly seizures in another mouse model of TSC, involving primarily neuronal abnormalities (Meikel et al., 2008).

- mTOR inhibitors also decrease seizures and histological abnormalities in a mouse model involving **PTEN** inactivation, a gene upstream from the **TSC** genes, which have phenotypical similarities to TSC (Kwon et al., 2003; Ljundberg et al., 2009; Zhou et al., 2009).

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**Rapamycin Reduces Seizure Frequency in Tuberous Sclerosis Complex**

Jennifer Muncy, BA, Ian J. Butler, MB, BS, FRACP, and Mary Kay Koenig, MD

The authors present a 10-year-old girl with tuberous sclerosis complex who has been receiving rapamycin for 10 months for seizure control. She was started at 0.05 mg/kg/d and titrated to an effective dose of 0.15 mg/kg/d. There was a dramatic reduction in seizure frequency with rapamycin therapy. Further studies are needed to objectively investigate the benefits of rapamycin in tuberous sclerosis complex and to clarify its mechanism of seizure control.

**Keywords:** tuberous sclerosis; rapamycin; seizures
• **mTOR pathway** is activated by pilocarpine status epilepticus in rats and **mTOR inhibitors** suppress subsequent development of mossy fiber sprouting (Buckmaster et al. 2009).

• **mTOR pathway** is activated by kainate status epilepticus in rats and **mTOR inhibitors** also decrease subsequent mossy fiber sprouting, neuronal death, and the progression of epilepsy (Zeng et al., 2009).

• **mTOR pathway** is activated by traumatic brain injury in rats (Chen et al., 2007) and **mTOR inhibitors** decrease neuronal death following TBI (Erlich et al., 2007), although effects on posttraumatic epilepsy have not yet been reported.
• **mTOR inhibitors** reversed spatial learning deficits in Tsc2+/- mutant mice (Ehninger et al., 2007).

• **mTOR inhibitors** reversed social deficits, suggestive of autistic behavior, in *PTEN* KO mice (Zhou et al., 2009).
Sirolimus for Angiomyolipoma in Tuberous Sclerosis Complex or Lymphangioleiomyomatosis

John J. Bissler, M.D., Francis X. McCormack, M.D., Lisa R. Young, M.D., Jean M. Elwing, M.D., Gail Chuck, L.M.T., Jennifer M. Leonard, R.N., Vincent J. Schmitthorst, Ph.D., Tal Laor, M.D., Alan S. Brody, M.D., Judy Bean, Ph.D., Shelia Salisbury, M.S., and David N. Franz, M.D.

METHODS

We conducted a 24-month, nonrandomized, open-label trial to determine whether sirolimus reduces the angiomyolipoma volume in patients with the tuberous sclerosis complex or sporadic lymphangioleiomyomatosis. Sirolimus was administered for the first 12 months only. Serial magnetic resonance imaging of angiomyolipomas and brain lesions, computerized tomography of lung cysts, and pulmonary-function tests were performed.

RESULTS

Of the 25 patients enrolled, 20 completed the 12-month evaluation, and 18 completed the 24-month evaluation. The mean (±SD) angiomyolipoma volume at 12 months was 53.2±26.6% of the baseline value (P<0.001) and at 24 months was 85.9±28.5% of the baseline value (P=0.005). At 24 months, five patients had a persistent reduction in the angiomyolipoma volume of 30% or more. During the period of sirolimus therapy, among patients with lymphangioleiomyomatosis, the mean forced expiratory volume in 1 second (FEV₁) increased by 11.8±33.0 ml (P=0.06), the forced vital capacity (FVC) increased by 39.0±57.0 ml (P<0.001), and the residual volume decreased by 43.9±49.3 ml (P=0.02), as compared with baseline values. One year after sirolimus was discontinued, the FEV₁ was 62±41.1 ml above the baseline value, the FVC was 346±712 ml above the baseline value, and the residual volume was 333±570 ml below the baseline value; cerebral lesions were unchanged. Five patients had six serious adverse events while receiving sirolimus, including diarrhea, pyelonephritis, stomatitis, and respiratory infections.

CONCLUSIONS

Angiomyolipomas regressed somewhat during sirolimus therapy but tended to increase in volume after the therapy was stopped. Some patients with lymphangioleiomyomatosis had improvement in spirometric measurements and gas trapping that persisted after treatment. Suppression of mTOR signaling might constitute an ameliorative treatment in patients with the tuberous sclerosis complex or sporadic lymphangioleiomyomatosis. (ClinicalTrials.gov number, NCT00457380.)
Rapamycin Causes Regression of Astrocytomas in Tuberous Sclerosis Complex

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Objective: Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the formation of hamartomas in multiple organs. Five to 15% of affected individuals display subependymal giant cell astrocytomas, which can lead to substantial neurological and postoperative morbidity due to the production of hydrocephalus, mass effect, and their typical location adjacent to the foramen of Monro. We sought to see whether therapy with oral rapamycin could affect growth or induce regression in astrocytomas associated with TSC. Methods: Five subjects with clinically definite TSC and either subependymal giant cell astrocytomas (n = 4) or a pilocytic astrocytoma (n = 1) were treated with oral rapamycin at standard immunosuppressive doses (serum levels 5–15ng/ml) from 2.5 to 20 months. All lesions demonstrated growth on serial neuroimaging studies. Magnetic resonance imaging scans were performed before and at regular intervals following initiation of therapy. Results: All lesions exhibited regression and, in one case, necrosis. Interruption of therapy resulted in regrowth of subependymal giant cell astrocytomas in one patient. Resumption of therapy resulted in further regression. Treatment was well tolerated. Interpretation: Oral rapamycin therapy can induce regression of astrocytomas associated with TSC and may offer an alternative to operative therapy of these lesions.

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Conclusion

- Although refractory epilepsy is common in TSC patients, vigabatrin is regarded as the treatment of choice in the short-term treatment of infantile spasms.
- Multi-disciplinary managements, using multimodality neuroimaging and epilepsy surgery, have important role in achieving seizure control in some of TSC patients.
- Recent clinical trials using inhibitors of the mammalian target of rapamycin (mTOR) showed possibility of targeted therapies for seizures, cognitive function, astrocytomas, angiofibromas, and angiomyoliomas, etc. in TSC patients.
- Cognitive and epilepsy outcome of TSC will be improved in the future.