Seizure Remission and Antiepileptic Drug Discontinuation in Children With Tuberous Sclerosis Complex

Steven P. Sparagana, MD; Mauricio R. Delgado, MD; Lori L. Batchelor, RN; E. Steve Roach, MD

Background: Epilepsy is a common neurologic complication of tuberous sclerosis complex (TSC) and it is often refractory to treatment. Therefore, treating physicians are often reluctant to discontinue antiepileptic drugs (AEDs) in individuals with TSC who have attained seizure remission. To our knowledge, seizure remission and AED discontinuation in children with TSC has not been studied.

Objective: To characterize seizure remission and AED discontinuation in children with TSC.

Methods: Retrospective medical record and neuroimaging analysis of 15 children with TSC and epilepsy who had seizure remission, with a subsequent trial of discontinuation of AED treatment.

Results: The seizure remission rate for the group of patients with TSC and epilepsy was 14.2%. From the group of 15 patients who had a remission, the absolute relapse rate was 26.7% after a mean follow-up of 5 years 7 months. Patients with sustained remission were more likely to have normal intelligence and only a few cortical or subcortical lesions on neuroimaging.

Conclusions: The proportion of children with TSC and epilepsy who achieve seizure remission is small. Nevertheless, some do attain seizure remission, and AEDs may be successfully discontinued. Mild cerebral involvement is a general clinical marker for seizure remission. The relapse rate in those who have undergone a trial of discontinuation of AED therapy is comparable with the rate in the general pediatric population with epilepsy.

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Tuberous Sclerosis complex (TSC) is a genetic disorder with a variable phenotypic presentation. Some individuals have minimal stigmata and complications, and others have involvement of multiple organ systems. In TSC, there are many potential neurologic complications, including epilepsy. Epilepsy in TSC is symptomatic, with seizures arising from epileptogenic cortical tubers (hamartias) or from an epileptogenic area surrounding certain tubers. The severity of epilepsy in this disorder ranges from mild to catastrophic.

There are potential risks in treating epilepsy with an antiepileptic drug (AED). Consequently, the general approach is to discontinue AED therapy once a child’s seizures are in remission (with remission defined as being seizure free for 2-5 years). To our knowledge, there have been no detailed reports on the likelihood of achieving seizure remission or on subsequent discontinuation of AED therapy in children with TSC. We report on our experience at Texas Scottish Rite Hospital for Children (Dallas).

We conducted a retrospective medical record review of all children with a definite diagnosis of TSC (as defined by the Tuberous Sclerosis Complex Consensus Conference, 1998) actively followed up in the Tuberous Sclerosis Clinic at Texas Scottish Rite Hospital for Children between 1990 and 2002. All children with a history of epilepsy or febrile seizures were identified. From the group of children with a history of epilepsy, patients who had undergone an attempt to taper AEDs were further selected. Medical records of these patients were analyzed in detail for demographic information, specific information about the nature of the child’s epilepsy and AED therapy, and information on the attempt to discontinue AED treatment. Criteria for the determination of intelligence included educational level, neurologic examination, and in a few cases, formal IQ testing. Four patients underwent cranial magnetic resonance imaging and 11 underwent cranial computed tomography, and these studies were reviewed. This project was approved by the institutional review board at the University of Texas Southwestern Medical Center (Dallas).
RESULTS

There were 122 children with definite TSC, ranging in age from 2 months to 18 years. Fourteen patients (11.5%) had no history of seizures of any type, and there was a history of epilepsy in 106 (86.9%). Two patients had a history of isolated febrile seizures. They were not treated with AEDs, and they have not developed epilepsy to date.

There were 15 patients (9 girls, 6 boys) (14.2%) who had seizure remission and a subsequent trial of discontinuation of AEDs. Five (33.3%) of these 15 patients had a relapse of seizures, and AED treatment was restarted. In one girl who relapsed, AEDs were subsequently successfully tapered, and she remains seizure free. Thus, for this subgroup of patients with TSC and epilepsy, the total sustained remission rate was 73.3% (11 of 15), and the absolute relapse rate was 26.7% (4 of 15).

Details of epilepsy and discontinuation of AEDs are presented in Table 1. One child had a positive family history of epilepsy (first-degree relative), and 3 patients had a positive family history of epilepsy and TSC. All of the patients had fundamentally normal results on neuro-

Table 1. Profiles of Children With Tuberous Sclerosis and Epilepsy Who Have Discontinued Antiepileptic Drug Therapy*

<table>
<thead>
<tr>
<th>Patient/ Sex</th>
<th>Family Hx</th>
<th>Epilepsy</th>
<th>Intelligence</th>
<th>Age at First Seizure</th>
<th>Seizure Type(s)</th>
<th>Drug Therapy</th>
<th>Time Until Seizure Control</th>
<th>Time Seizure Free Prior to AED D/C</th>
<th>Age at AED D/C</th>
<th>EEG at AED D/C</th>
<th>Duration of AED Taper</th>
<th>Duration of F/U After AED D/C</th>
<th>Time to Seizure Relapse</th>
<th>Seizures Controlled After Relapse</th>
<th>Duration of F/U After Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>10 mo</td>
<td>IS</td>
<td>Mono</td>
<td>1 wk</td>
<td>3 mo</td>
<td>1 y 1 mo</td>
<td>11 y 10 mo</td>
<td>Focal epileptiform activity</td>
<td>2 mo (Abrupt)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/M</td>
<td>−</td>
<td>−</td>
<td>Mild MR</td>
<td>3 mo</td>
<td>IS</td>
<td>Mono</td>
<td>3 y 11 mo</td>
<td>7 y 8 mo</td>
<td>1 y 1 mo</td>
<td>11 y 10 mo</td>
<td>Focal epileptiform activity</td>
<td>2 mo (Low dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/M</td>
<td>+</td>
<td>+</td>
<td>NL</td>
<td>1 y</td>
<td>CPS w/GTCS</td>
<td>Mono</td>
<td>NA</td>
<td>12 y</td>
<td>17 y 2 mo</td>
<td>NL</td>
<td>4 mo</td>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/M</td>
<td>−</td>
<td>−</td>
<td>Mild MR</td>
<td>2 y 9 mo</td>
<td>CPS w/GTCS</td>
<td>Duo</td>
<td>3 y 7 mo</td>
<td>2 y 10 mo</td>
<td>9 y 1 mo</td>
<td>NL</td>
<td>2 mo</td>
<td>6 y 7 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/F</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>7 mo</td>
<td>IS</td>
<td>Mono</td>
<td>1 y 5 mo</td>
<td>1 y 11 mo</td>
<td>4 y 4 mo</td>
<td>NA</td>
<td>2 mo</td>
<td>1 y 4 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/M</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>1 y 5 mo</td>
<td>CPS w/GTCS</td>
<td>Mono</td>
<td>3 y 9 mo</td>
<td>1 y 9 mo</td>
<td>7 y</td>
<td>NL</td>
<td>1.5 mo</td>
<td>2 y 4 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/F</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>6 mo</td>
<td>IS</td>
<td>Mono</td>
<td>2 mo</td>
<td>1 y 2 mo</td>
<td>2 y</td>
<td>NL</td>
<td>NA</td>
<td>12 y 8 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/F</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>5 y 8 mo</td>
<td>CPS w/GTCS</td>
<td>Mono</td>
<td>2 y 2 mo</td>
<td>2 y 2 mo</td>
<td>13 y 5 mo</td>
<td>Focal epileptiform activity</td>
<td>4 mo</td>
<td>5 y 11 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/F</td>
<td>+</td>
<td>−</td>
<td>Mod MR</td>
<td>3 mo</td>
<td>IS</td>
<td>CPS w/GTCS</td>
<td>Mono</td>
<td>3 y 3 mo</td>
<td>1 y 1 mo</td>
<td>4 y 7 mo</td>
<td>Focal epileptiform activity</td>
<td>2 mo</td>
<td>12 y 9 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/F</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>9 mo</td>
<td>CPS w/GTCS</td>
<td>Mono</td>
<td>1 y</td>
<td>3 y 10 mo</td>
<td>5 y 6 mo</td>
<td>Focal epileptiform activity</td>
<td>1.5 mo</td>
<td>10 y 5 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/F</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>1 y 2 mo</td>
<td>CPS w/GTCS</td>
<td>Mono</td>
<td>6 mo</td>
<td>2 y 9 mo</td>
<td>4 y 1 mo</td>
<td>Mild slowing</td>
<td>3 mo</td>
<td>3 y 11 mo 3 y 11 mo Yes</td>
<td>10 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/F†</td>
<td>+</td>
<td>+</td>
<td>NL</td>
<td>11 mo</td>
<td>IS</td>
<td>Mono</td>
<td>NA</td>
<td>4 y</td>
<td>5 y 3 mo</td>
<td>NA</td>
<td>1 mo</td>
<td>3 y 2 mo 3 y 2 mo Yes</td>
<td>6 yo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/F</td>
<td>−</td>
<td>−</td>
<td>Mild MR</td>
<td>2 mo</td>
<td>CPS w/GTCS</td>
<td>Mono</td>
<td>8 y</td>
<td>3 y 6 mo</td>
<td>10 y 6 mo</td>
<td>Multifocal epileptiform activity</td>
<td>8 mo</td>
<td>5 y</td>
<td>No</td>
<td>1 y 11 mo</td>
<td></td>
</tr>
<tr>
<td>14/M</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>5 mo</td>
<td>IS</td>
<td>Mono</td>
<td>1 mo</td>
<td>1 y 1 mo</td>
<td>1 y 7 mo</td>
<td>Focal epileptiform activity</td>
<td>A abrupt (low dose)</td>
<td>3 y 4 mo 3 y 4 mo No</td>
<td>1 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/F</td>
<td>+</td>
<td>+</td>
<td>Mild MR</td>
<td>7 mo</td>
<td>CPS, SPS</td>
<td>Duo</td>
<td>1.5 mo</td>
<td>1 y 6 mo</td>
<td>2 y 6 mo</td>
<td>NA</td>
<td>2 mo</td>
<td>10 y 6 mo 10 y 6 mo Yes</td>
<td>5 y 3 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drug; CPS, complex partial seizures; D/C, discontinuation; EEG, electroencephalogram, ellipses, not applicable; F/U, follow-up; GTCS, generalized tonic-clonic seizures; Hx, history; IS, infantile spasms; MR, mental retardation; Mod, moderate; NA, data not available; NL, normal; SPS, simple partial seizures; −, absent; +, present.

*The first group of 10 subjects have remained in seizure remission. The second group of 5 subjects have had a relapse.
†Reattained seizure remission and are currently seizure free (without taking AEDs) for 4 years 8 months.
logic examination. Ten patients had normal intelligence, and 5 had mild or moderate mental retardation, of whom also had mild autistic behaviors.

None of the patients undergoing a trial of discontinuation of treatment with AEDs had a history of febrile seizures. Three had infantile spasms only. Four others had a history of infantile spasms, with subsequent evolution to other seizure types (complex partial, simple partial, or complex partial with secondary generalization). Eight patients had complex partial seizures, simple partial seizures, or complex partial seizures with secondary generalization. The age at the first seizure ranged from 2 months to 3 years 8 months, with 11 patients having seizures beginning before age 12 months. The mean age at onset of seizures of all types was 13.8 months, and 6.4 months for those with infantile spasms.

The mean time to gain seizure control was 25.8 months for the whole group, although those with infantile spasms alone achieved seizure control at a mean of 4 weeks. The duration of seizure remission prior to discontinuation of AED therapy ranged from 3 months to 12 years (mean for the whole group, 3.2 years; median, 2 years 2 months). For those with infantile spasms only, the mean seizure-free period prior to discontinuation of AEDs was 10 months. The mean age at AED discontinuation was 6 years 9 months (range, 13 months to 17 years 2 months). For those with infantile spasms only, the mean age at AED discontinuation was 19 months.

Electroencephalographic results at the time of AED discontinuation were normal in 5 patients, abnormal in 7, and not available in 3. Five of 7 patients had focal epileptiform activity. Mild slowing was seen in 3 patients, and multifocal epileptiform activity was seen in 1 child.

Prior to AED discontinuation, 12 patients had been receiving AED monotherapy, and 3 had been receiving duotherapy. The AED taper period ranged from abrupt discontinuation to as long as 8 months (mean, 2.3 months). The follow-up period after AED discontinuation ranged from 6 months to 12 years 8 months (mean, 5 years 7 months; median, 5 years).

All of the patients had evidence of subependymal nodules and cortical and subcortical lesions on neuroimaging. Most of the patients (11 of 15) underwent head computed tomography, and while computed tomography is not the best method to determine lesion number and volume, a review of the scans permitted a broad categorization into those with few (≤5) and those with multiple (>5) cortical and subcortical lesions. Most of the patients (12 [80%] of 15) had few cortical and subcortical lesions. Of the 3 with multiple lesions, 2 were in the sustained remission group and only 1 was in the relapse group. Three patients had evidence of a subependymal giant cell astrocytoma (SEGA). One child had an intraventricular mass surgically resected, and it was confirmed to be a SEGA. Two patients in the relapse group had small, stable probable SEGAs that have not to date grown to dimensions warranting resection.

In the children who had a relapse of seizures, the time to relapse ranged from 3 years 2 months to 10 years 6 months (mean, 5 years 2 months). Seizures were readily controlled with AED reinitiation in 3 of the 5 patients. Patient 12 attained remission, and AEDs were subsequently discontinued. She remained seizure free for 4 years 8 months. Patient 13 underwent a previous attempt at discontinuation of AEDs but her seizures reoccurred prior to completion of the AED taper. To date, she continues with suboptimal control of her seizures.

Individuals with TSC have an 84% to 92% chance of having at least 1 seizure during their lives. With the inclusion of 2 children who had isolated febrile seizures, the incidence of having at least 1 seizure in this study was 88.5%. The incidence of epilepsy (ie, a condition with recurrent nonfebrile seizures) was 86.9%.

Epilepsy in TSC is often refractory, and there is often a bias among treating physicians to continue epilepsy treatment even after an individual has had a sustained seizure remission. In our population of children with TSC, only 14.2% had a remission of seizures of significant duration and character to permit a trial of AED discontinuation. The figure approximates the 12.9% to 14% remission rate for children with epilepsy due to complications of cerebral palsy.

Despite the overall low remission rate, our data show that AEDs may be successfully discontinued in children with TSC who have had a remission of seizures. The absolute relapse rate of 26.7% compares well with the relapse rate of 25% to 31% for all children with epilepsy who have discontinued AEDs.

While our children with TSC and seizure remission are few in number, several trends are noted. Children who had remission of seizures appeared to have a milder presentation within the clinical spectrum of TSC. All had normal results on neurologic examination, and 67% had normal intelligence (compared with the usual figure of 50% quoted for TSC). Those with some degree of mental retardation were mildly to moderately affected. Additionally, the group as a whole had minor cerebral involvement, with 80% having few cortical and subcortical tubers on neuroimaging. It is well recognized that cortical tuber count is a reliable biomarker for severity of cerebral dysfunction. Some patients with multiple tubers, and others with SEGAs, were also able to achieve remission. Seizure type varied, and 7 patients had infantile spasms. Many patients (47%) with abnormal findings on electroencephalogram still achieved seizure remission.

The group of patients who had a relapse of seizures is admittedly small; however, some notable characteristics were the 4:1 girl-boy ratio, and the group had a higher proportion of abnormal findings on electroencephalogram (Table 2). The mean age at relapse for the girls was 11 years 3 months; hence, one possibility is that the biological changes of puberty may be a factor in seizure relapse. There was also a slightly higher percentage of mental retardation in the relapse group (40%) compared with the sustained remission group (30%). Two patients with small stable SEGAs also had relapse of seizures. It is not clear whether the SEGAs were significant contributing factors in the relapse of these patients. Three of the 5 patients who relapsed gained excellent control of the seizures after reinitiating AEDs.
A very young age at seizure onset is often associated with a poor seizure prognosis.7 Eleven (73%) of the 15 patients had seizure onset at or prior to 12 months of age. Therefore, early age at seizure onset does not necessarily result in a poor outcome for this subgroup of children with TSC.

A history of infantile spasms is not a contraindication to stopping AEDs. Infantile spasms typically constitute a catastrophic epilepsy syndrome and are usually associated with mental retardation, although some patients may have normal intelligence.8 However, in this subgroup of children, infantile spasms did not characteristically evolve into refractory seizures, and most of the group (71%) remarkably developed with normal intelligence. Six of the 7 patients with a history of spasms (including patient 12) were ultimately seizure-free after discontinuation of AEDs.

In summary, AEDs may be successfully tapered in some children with TSC and a history of epilepsy after seizure remission is attained. As a whole, those achieving seizure remission had mild neurologic findings, and the group with sustained remission was more likely to have normal intelligence, a greater likelihood of having a normal finding on electroencephalogram at the time of discontinuation, and few cortical and subcortical tubers on neuroimaging. The relapse rate is comparable with the relapse rate in the general pediatric population with epilepsy. Therefore, in carefully selected children with TSC and seizure remission of sufficient duration, it is reasonable to consider discontinuation.

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