Epilepsy surgery in tuberous sclerosis: The Dutch experience

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Summary

Introduction: Epilepsy associated with tuberous sclerosis complex (TSC) is drug resistant in more than half of the patients. Epilepsy surgery may be an alternative treatment option, if the epileptogenic tuber can be identified reliably and if seizure reduction is not at the expense of cognitive or other functions. We report the presurgical identification of the epileptogenic tuber and post-surgical outcome of patients with TSC in The Netherlands.

Methods: Twenty-five patients underwent the pre-surgical evaluation of the Dutch Comprehensive Epilepsy Surgery Programme, including a detailed seizure history, interictal and ictal video EEG registrations, 3D FLAIR MRI scans and neuropsychological testing. Suitability of the candidates was decided in consensus. Seizure outcome, scored with the Engel classification, and cognition were reassessed at fixed post-surgery intervals.

Results: Epilepsy surgery was performed in six patients. At follow-up, four patients had Engel classification 1, two had classification 4. Improved development and behaviour was perceived by the parents of two patients. Epilepsy surgery was not performed in 19 patients because seizures were not captured, ictal onset zones could not be localised or were multiple, interictal EEG, video EEG and MEG results were not concordant, or
Introduction

Cortical tubers, the hallmark of tuberous sclerosis complex (TSC) are associated with a variety of neurological symptoms including epilepsy and mental retardation. Epilepsy is often the presenting symptom and seizures occur in the majority of patients. The manifestation of epilepsy is age-related, with the highest incidence in the first year of life. In children with infantile spasms (IS) TSC accounts for 10—30% of cases. Focal seizures are the main seizure type in older patients with TSC, but these can also occur in children with TSC-related IS. Only few studies have reported long term follow up in TSC. Although a good short-term outcome has been described, relapses are frequent and long-term outcome is unfavourable with respect to the severity of epilepsy and mental status.

Adequate treatment of the seizures is mandatory. Despite ongoing development of new anti-epileptic drugs, epilepsy in TSC is often medically intractable. Other treatment options are the ketogenic diet, vagal nerve stimulation and epilepsy surgery. Successful epilepsy surgery in patients with TSC was published for the first time in 1964. Subsequently, many authors have reported good seizure outcome after epilepsy surgery in series of selected patients with TSC. We performed a systematic review of the published cases from observational studies regarding epilepsy surgery in patients with TSC. Studies were included if they at least reported quantitative seizure outcome and description of the type of surgery. Seizure freedom was achieved in 101 of the 177 patients (57%) and seizure frequency reduced by >90% in another 32 patients (18%) (total of good seizure outcome in 75% of patients).

Methods

Between 1999 and 2006, 25 patients diagnosed with TSC according to revised diagnostic criteria, in 21 patients confirmed by DNA analyses (10 TSC1 and 11 TSC2), were examined at the outpatient department of Paediatric Neurology (Sylvia Töth Centre) and Neurology, UMC, Utrecht, The Netherlands, and referred for pre-operative work-up to the Dutch Comprehensive Epilepsy Surgery Programme.

Pre-operative evaluation included: detailed (seizure) history and physical examination, cerebral MRI scans, high resolution (HR) EEG, seizure recording with long-term video EEG, and a comprehensive neuropsychological assessment. Additionally, magnetoencephalography (MEG) recording was performed if cooperation was expected. When appropriate a Wada test, for evaluation of language and memory networks, was performed at a second stage.

MR images were processed on a Philips Gyroscan ACS-NT 1.5 T whole body system (Philips Medical Systems, Best, The Netherlands). All patients underwent a transaxial or coronal Fluid Attenuated Inversion Recovery (FLAIR) and a transaxial T1 scan. Slice thickness was 1.5 mm. without interslice gap. Scan parameters were: repetition time (TR), 11,000 ms; echo time (TE), 125 ms; inversion time (TI), 2600 ms. Tubers were automatically segmented with use of a KNN segmentation technique.

HR EEG recording (85 channel; BioSemi Mark-6, Brainstar system 4.0) was performed at a sampling rate of 1024 Hz, using a cap containing Sn electrodes (ElectroCap Inc.). The electrodes of the HR EEGs were positioned according to the 10% system accepted by the American EEG society. Electrode positions were registered using a magnetic tracking device (Polhemus, Colchester, VT, USA). In addition, three anatomical marker points (e.g. nasal and pre-auricular) and head-shape were measured, which allowed matching with MRI and MEG markers.

Video EEG was planned in all with 21-channel recordings with electrode positions according to the 10—20 system. Registration of at least two seizures from each seizure type was required for continuation of the pre-surgical programme.
Neuropsychological tests were selected from a fixed battery according to the widely varying age and abilities of the patients. Every patient underwent at least a test of intelligence or of mental development. The other tests covered major domains of cognition, i.e. intelligence, vocabulary, memory and learning, graphical construction, executive functioning, attention, speed and fine motor functions. The following tests were performed: Dutch versions of Wechsler Adult Intelligence Test, Wechsler Intelligence Scales for Children-Revised or Wechsler Preschool and Primary Scales of Intelligence, Wechsler Memory Scale, Visual Retention Test, California Verbal Learning Test, Controlled Oral Word Production, Wisconsin modified Card Sorting Test, Trail Making Parts A and B, Reaction times, and Manual tapping. Administration and scoring were according to the test manuals. The results (quotient scores, centiles or standard scores) were converted to a general scale with the values 1 (extremely below average), 2 (below average), 3 (average) and 4 (above average). In case of cut-off scores, scale values 1 and 3 were used. We assigned a 'cognition index' to each patient by adding her/his scale values and dividing the sum by her/his number of tests (maximum of 10). When calculating the cognition index from the scaled values, differences in the number of tests used to assess the domains were allowed for by granting a factor 3 to intelligence scores and a factor 0.5 to both California Verbal Learning Test scores. The cognition index could vary between 1.00 and 4.00.

MEG, using 151 axial gradiometers arranged as a helmet (Omega 151, CTF system Inc., Port Coquitlam, British Columbia, Canada), were recorded at a sampling rate of 625 Hz, inside a magnetically shielded chamber (Vacuumschmelze GmbH, Hanau, Germany). Head position with respect to the helmet and, after each recording session, electrode positions and head-shape were recorded, using four magnetic localising coils. The signals were (software) bandpass filtered between 0.7 and 70 Hz.

When performing the Wada test, effectiveness of the amobarbital injection was EEG-controlled. Language processing was screened by asking the patient to name five visually presented everyday objects such as spoon and toothbrush, to describe the 'Cookie theft' Picture and to execute four items from the 'Token test'. Results were qualitatively judged. With respect to memory screening, the patient was asked to look at a picture of a everyday subject, a photograph of a person, a playing card, a card with the name of a country, and a card with a Dutch saying for recall 15 min later. A passing score of 60% recall was required.

Results of the above mentioned investigations were evaluated in the Dutch Collaborative Epilepsy Surgery Programme. Patients in whom seizure semiology, interictal EEG recording, localisation of the ictal onset zone, and localisation of the target tuber were concordant were considered eligible for epilepsy surgery. Image guided surgery was performed using Stealth Station (Medtronic). With the results of the video EEG recording and if available the MEG results, the target tuber was identified. This epileptogenic tuber was demarcated on T2 weighted images. Electrocorticography (ECoG) tailored the resection.

Outcome was evaluated with neurological examination at 3, 6 and 12 months and at the end of follow-up (most recent visit to outpatient clinic). A postoperative MRI was performed at 3 months and neuropsychological examinations followed at 6, 12 and 24 months. Post-operative seizure outcome was scored using the Engel classification.

Results

Table 1 summarizes demographic and pre-surgical illness variables of the 25 TSC patients.

Seizure semiology

Median age at seizure onset was 0.6 years, range 0.1—14 years. At onset 14 patients had infantile spasms (IS), 6 had complex partial seizures (CPS), 4 had secondary generalised tonic clonic seizures (sGTCS), and 1 had tonic seizures (TS). At time of examination 19 patients had CPS (the sole seizure type in 12), 7 had TS (the sole type in 2), 6 had sGTCS (the sole type in 2), 2 had myoclonic seizures (MS) and 1 patient had atonic seizures. Seizure frequency was daily in 13 patients, weekly in 9 patients and less frequent in 3 patients.

MRI scans

Multiple tubers were found in all patients. The median number of tubers (assessed in 22 patients) was 27, range 8—58. Median tuber/brain volume ratio (calculated by dividing total tuber volume by total brain volume, excluding CSF) was 1.2, range 0.2—5.1%.

Interictal EEG

In one patient interictal epileptiform activity was absent. The interictal epileptiform activity could be localised to one region in seven patients and was multifocal in the other 17, involving both hemispheres in 13 patients.
## Table 1 Presurgical evaluation of 25 patients with tuberous sclerosis and drug resistant epilepsy

<table>
<thead>
<tr>
<th>Patient/age (years)</th>
<th>Age at onset (years)</th>
<th>Seizure type at onset</th>
<th>Semiology</th>
<th>Seizure frequency</th>
<th>CI</th>
<th>Interictal EEG</th>
<th>Ictal EEG</th>
<th>Tuberous no./volume ratio</th>
<th>MEG</th>
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</thead>
<tbody>
<tr>
<td>1/19</td>
<td>0.6</td>
<td>IS</td>
<td>sGTCS</td>
<td>Weekly</td>
<td>2.3</td>
<td>R posterior temporal, L frontotemporal</td>
<td>L frontotemporal</td>
<td>18/0.34</td>
<td>R parieto-temporal</td>
</tr>
<tr>
<td>2/10</td>
<td>1.2</td>
<td>TS</td>
<td>TS, CPS</td>
<td>Daily</td>
<td>1.0</td>
<td>R parietal, R temporal, L temporal</td>
<td>No seizures</td>
<td>20/0.18</td>
<td></td>
</tr>
<tr>
<td>3/10</td>
<td>0.9</td>
<td>sGTCS</td>
<td>CPS</td>
<td>Weekly</td>
<td>2.0</td>
<td>R hemisphere, L posterior temporal</td>
<td>Multiple onset zones</td>
<td>20/1</td>
<td>Few spikes</td>
</tr>
<tr>
<td>4/27</td>
<td>9</td>
<td>sGTCS</td>
<td>CPS</td>
<td>Weekly</td>
<td>3.4</td>
<td>R frontotemporal</td>
<td>L mesiotemporal</td>
<td>53/1.0</td>
<td>Few spikes</td>
</tr>
<tr>
<td>5/4</td>
<td>0.1</td>
<td>sGTCS, TS</td>
<td>TS</td>
<td>Daily</td>
<td>1.0</td>
<td>R frontotemporal, L frontocentral, L temporal</td>
<td>L central</td>
<td>29/2.52</td>
<td></td>
</tr>
<tr>
<td>6/24</td>
<td>0.6</td>
<td>IS</td>
<td>sGTCS, CPS, CPS</td>
<td>Daily</td>
<td>2.0</td>
<td>L hemisphere, R frontopolar</td>
<td>L central</td>
<td>24/1.49</td>
<td></td>
</tr>
<tr>
<td>7/17</td>
<td>5</td>
<td>IS</td>
<td>CPS</td>
<td>Weekly</td>
<td>3.8</td>
<td>R and L ant. temporal, R posterior temporal</td>
<td>R temporal</td>
<td>19/0.34</td>
<td>R temporal</td>
</tr>
<tr>
<td>8/3</td>
<td>0.2</td>
<td>IS</td>
<td>TS, MS, CPS</td>
<td>Daily</td>
<td>1.0</td>
<td>Multifocal, R frontotemporal</td>
<td>R frontotemporal</td>
<td>27/1.69</td>
<td></td>
</tr>
<tr>
<td>9/22</td>
<td>0.8</td>
<td>IS</td>
<td>sGTCS</td>
<td>Monthly</td>
<td>1.4</td>
<td>R frontotemporal, L temporal, R frontoparietal</td>
<td>No seizures</td>
<td>35/1.24</td>
<td>Few spikes</td>
</tr>
<tr>
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<td>IS</td>
<td>CPS</td>
<td>Daily</td>
<td>1.0</td>
<td>L posterior temporal, L and R parietal</td>
<td>No seizures</td>
<td>29/2.69</td>
<td></td>
</tr>
<tr>
<td>11/30</td>
<td>0.4</td>
<td>IS</td>
<td>CPS</td>
<td>Monthly</td>
<td>1.9</td>
<td>L centroparietal</td>
<td>Not performed</td>
<td>58/1.68</td>
<td>Few spikes</td>
</tr>
<tr>
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<td>IS</td>
<td>TS, aTS, CPS, MS CPS</td>
<td>Daily</td>
<td>1.0</td>
<td>R hemisphere, L parietal</td>
<td>Not localising</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/5</td>
<td>0.5</td>
<td>IS</td>
<td>CPS</td>
<td>Daily</td>
<td>1.0</td>
<td>L frontoparietal/temporal, R anterior temporal</td>
<td>Not localising</td>
<td>32/1.48</td>
<td></td>
</tr>
<tr>
<td>14/5</td>
<td>0.2</td>
<td>IS</td>
<td>CPS</td>
<td>Daily</td>
<td>1.0</td>
<td>L parieto-occipital</td>
<td>L parietal</td>
<td>8/0.17</td>
<td></td>
</tr>
<tr>
<td>15/3.5</td>
<td>0.5</td>
<td>IS</td>
<td>CPS with myoclonias</td>
<td>Daily</td>
<td>2.0</td>
<td>R parieto-occipital</td>
<td>R temporo-occipital</td>
<td>17/0.19</td>
<td></td>
</tr>
<tr>
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<td>0.3</td>
<td>IS</td>
<td>CPS</td>
<td>Monthly</td>
<td>1.0</td>
<td>L parietal, L temporal</td>
<td>No seizures</td>
<td>34/5.14</td>
<td></td>
</tr>
<tr>
<td>17/3</td>
<td>0.2</td>
<td>IS</td>
<td>TS</td>
<td>Daily</td>
<td>1.0</td>
<td>R hemisphere</td>
<td>Not localising</td>
<td>20/0.32</td>
<td></td>
</tr>
<tr>
<td>18/23</td>
<td>0.3</td>
<td>sGTCS</td>
<td>CPS</td>
<td>Daily</td>
<td>3.0</td>
<td>R frontopolar</td>
<td>R frontopolar</td>
<td>5</td>
<td>R frontal/ frontalopolar</td>
</tr>
<tr>
<td>19/5</td>
<td>2.3</td>
<td>CPS</td>
<td>CPS</td>
<td>Weekly</td>
<td>1.8</td>
<td>R posterior temporal</td>
<td>R posterior temporal</td>
<td>26/0.52</td>
<td></td>
</tr>
<tr>
<td>20/22</td>
<td>0.3</td>
<td>IS</td>
<td>CPS, sGTCS</td>
<td>Daily</td>
<td>1.0</td>
<td>No epileptiform activity</td>
<td>Not localising</td>
<td>24/1.49</td>
<td></td>
</tr>
<tr>
<td>21/28</td>
<td>14</td>
<td>sGTCS</td>
<td>sGTCS, TS, CPS</td>
<td>Weekly</td>
<td>1.0</td>
<td>L frontocentral</td>
<td>Not localising</td>
<td>L frontal</td>
<td></td>
</tr>
<tr>
<td>22/36</td>
<td>0.9</td>
<td>CPS</td>
<td>Weekly</td>
<td>2.4</td>
<td>R frontotemporal</td>
<td>R mesiotemporal</td>
<td>34/1.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23/34</td>
<td>0.8</td>
<td>IS</td>
<td>CPS, sGTCS</td>
<td>Weekly</td>
<td>1.2</td>
<td>R and L temporal, parasaggital</td>
<td>Multiple onset zones</td>
<td>30/1.08</td>
<td></td>
</tr>
<tr>
<td>24/9</td>
<td>0.3</td>
<td>IS</td>
<td>CPS, MS</td>
<td>Daily</td>
<td>1.0</td>
<td>R hemisphere, L temporal</td>
<td>L centroparietal</td>
<td>18/0.32</td>
<td></td>
</tr>
<tr>
<td>25/3</td>
<td>1.5</td>
<td>CPS</td>
<td>Weekly</td>
<td>3.0</td>
<td>R central, L temporal</td>
<td>No seizures</td>
<td>10/0.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Video EEG recording

One patient feared the surgical procedure and discontinued the pre-surgical programme before ictal registration. In nine patients, one region of seizure origin was found. Seizures were not captured in five patients. Multiple regions of seizure onset were found in two patients. Seizure origin was diffuse in five patients and multifocal in three patients.

Cognition index was calculated in 24 patients. The cognition index was above average in only one patient, average in three, below average in six and extremely below average in 13 patients. Cognition was not assessed in one patient.

MEG was performed in 11 patients. In four patients too few spikes were identified and source localisation could not be applied. Unifocal epileptiform activity was seen in six patients. Results were concordant with interictal EEG activity in five of these patients, identifying the target tuber.

A Wada test was performed bilaterally in two patients with the epileptogenic tuber in the right temporal lobe (nos. 7 and 22), because post-operative memory deficit was feared. Both showed language representation in the left hemisphere. With respect to memory, recall after amobarbital injection in the right carotid artery was 100% in patient 7 and 80% in patient 22, which rendered them suitable candidates for right temporal lobe surgery.

Epilepsy surgery was not performed in 19 patients (Fig. 1), including the patient who discontinued the programme and the five patients in whom video EEG recording failed to capture seizures. In two patients (patients 1 and 23) results of interictal EEG, video EEG recording and MEG were not concordant. In five patients the ictal onset zone could not be localised (patients 12, 13, 17, 20 and 21). Video EEG recording revealed multiple ictal onset zones in three patients (patients 3, 6, and 24). Invasive recording was not expected to identify one epileptogenic tuber because eight of these patients had multiple seizure types clinically. In two patients surgery was postponed because seizure burden diminished after a change in medication (patients 4 and 5). Deliberations have not yet been closed for one patient (patient 14). Six patients underwent epilepsy surgery (Table 2). Seizure semiology had been consistent over time in five of them, but had changed in patient 8. Further, results of interictal, ictal, and MEG recordings (performed in four of the surgical patients) and the location of one or a cluster of tubers were all concordant. Patients for whom surgery was considered an option differed from those for whom surgery was rejected in cognition index only (means in the surgical patients versus those for whom surgery was rejected 2.3 versus 1.5, difference 0.8; 95% confidence interval −1.6 to −0.03).

Surgery

The identified epileptogenic tuber was localised in the right hemisphere in all surgical candidates (in the temporal region in four, the frontal in one and the parieto-occipital region in one patient). All four patients with temporal lobe epilepsy had multiple tubers located in this area. ECoG tailored the resection, resulting in a temporal lobectomy in three (ECoG tailored the posterior resection border) a posterior temporal resection in one, a tuberectomy in the right parieto-occipital region in one and a right-sided frontal corticectomy in one patient. Intra-operative ECoG patterns consisted of a continuous spiking pattern, recruiting activity, bursts of spikes and a sporadic spiking pattern, according to the criteria published previously.30 ECoG after resection showed bursts of spikes in the parieto-temporal region in patient 8 and sporadic spikes over the precentral gyrus in patient 18.

In all patients histopathological findings indicated a disorder of cortical lamination and showed the presence of ballooning cells in the surrounding white matter, consistent with the diagnosis of tuberous sclerosis. In patient 18 an asymptomatic giant cell astrocytoma was present as well and was partly resected.

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**Figure 1** Scheme showing consensus decision of 25 TSC patients evaluated for epilepsy surgery.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at surgery (y)</th>
<th>EcoG</th>
<th>Surgery</th>
<th>PA</th>
<th>Outcome</th>
<th>f-u (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>17</td>
<td>pre: continuous spiking pattern R; midtemporal neocortex and hippocampus; post: no epileptiform activity</td>
<td>R temporal lobectomy; R amygdalohippocampectomy</td>
<td>BC, DN</td>
<td>Engel 1a; CI: 3.8</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>pre: continuous spiking pattern R anterior temporal; burst and recruiting pattern posterior temporal; post: burst and continuous spikes posterior temporal</td>
<td>R temporal lobectomy; R amygdalohippocampectomy</td>
<td>BC</td>
<td>Engel 4; CI: 1.0</td>
<td>34</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>pre: continues spiking pattern over tuber region; post: few isolated spikes border resection</td>
<td>R parieto-occipital tuberectomy</td>
<td>GC, BC</td>
<td>Engel 1a; CI: 2.0</td>
<td>14</td>
</tr>
<tr>
<td>18</td>
<td>23</td>
<td>pre: continuous pattern R frontobasal; burst of spikes subfrontal; post: sporadic spikes R precentral</td>
<td>R frontopolar resection</td>
<td></td>
<td>Engel 4</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>pre: continuous spiking pattern border resection; extensive region of sporadic spikes R frontal; post: sporadic spikes R precentral</td>
<td>R frontalcorticectomy</td>
<td>GC, BC</td>
<td>Engel 4; CI: 3.0</td>
<td>37</td>
</tr>
<tr>
<td>19</td>
<td>5</td>
<td>pre: recruiting pattern R parieto-temporal; post: sporadic spikes border resection</td>
<td>R posterior temporal resection</td>
<td>DN, BC</td>
<td>Engel 1a; CI: 2.0</td>
<td>76</td>
</tr>
<tr>
<td>22</td>
<td>36</td>
<td>pre: sporadic spikes R anterior temporal and hippocampus; post: sporadic spikes border resection</td>
<td>R temporal lobectomy; R amygdalohippocampectomy</td>
<td>BC, MTS</td>
<td>Engel 1b</td>
<td>15</td>
</tr>
</tbody>
</table>

At the end of follow-up (9–71 months) Engel class 1 was achieved in four patients (67%, of whom three patients had Engel 1a). One of the seizure free patients has been taken off medication after two years seizure freedom. The period of follow up is relatively short in two patients who are still on antiepileptic drugs. Seizure frequency improved in the first three months by >50% in patient 8 but worsened again resulting in no improvement at the end of follow-up. A re-resection was considered, but postponed because no general agreement was reached which tuber should be considered epileptogenic.

Postoperative MRI findings showed incomplete tuber resection even after a re-resection for recurrent seizures in patient 18. By the re-resection no improvement of seizure pattern was achieved. Cognition index was assessed at 6, 12 and 24 months in patients 7, 8, 18 and 19, and at 6 months only in patient 15. Post-surgical neuropsychological examination is planned in patient 22. The measured postoperative cognition index was stable over time in all but one patient (nr 19). In this patient, cognition index had improved slightly at 6 months (cognition index of 2), deteriorated at 12 months (cognition index of 1.3) and was back at the initial level post-surgical level at 24 months (cognition index of 2). Parents of this patient perceived improvement of both development and behaviour postoperative. Parents of patient 8 perceived improved development during the first three months (period of improved seizure control), but an arrest was perceived when seizure frequency was back at the pre-surgical level.

Postoperative complications consisted of quadrant hemianopia in patients 7, 19 and 22.

Discussion

In the last few decades, a dozen series have reported favourable seizure outcome after epilepsy surgery in TSC.10–12,16–19,20,31–35 Seizure outcome in our series of patients (67% Engel class 1) is comparable to those reported by others.

Epilepsy surgery is often not considered when bilateral epileptogenic zones are present or when a progressive epileptic encephalopathy is feared. Severe mental retardation is often regarded another contraindication for epilepsy surgery because retardation is frequently associated with diffuse cerebral dysfunction. For those reasons, and because—often numerous—tubers are not always clearly demarcated and may be located in eloquent cortex, the option of epilepsy surgery has long been refused to patients with TSC and pharmaco logically intractable epilepsy.

Insights have changed and several studies have proven that even in the presence of multiple bilateral tubers the epileptogenic zone and one or two tuber regions consistently coincide, especially when partial seizures are the clinical manifestation.9,16,21 Our results add that even a number of 30 tubers and more is no impediment for good seizure outcome, if one or two tubers can be resected. Shifting foci are often feared, but little evidence is available to support the hypothesis of an epileptogenic potential of every tuber, rather, consistent electroencephalographic patterns are found over time.36

Experience taught that surgical outcome is best for patients in whom semiology, EEG and MRI findings concordantly point to a surgically accessible location.1 The favourable outcome in the admittedly small number of suitable patients makes every attempt to identify the primary epileptogenic zone worthwhile. Factors related to post-surgical recurrence of seizures are: tonic seizures, the presence of multiple regions of abnormal HMPAO uptake on SPECT imaging, a corpus callosotomy (in comparison to resective surgery), and moderate or severe intellectual disability.21 The latter is in agreement with our observation as one of the patients with poor seizure outcome had severe intellectual disability.

Despite the considerable variation in duration of follow up, many studies have shown that other tubers do not become epileptogenic after removal of the main epileptogenic region and associated tuber. This is in agreement with the hypothesis that after resection of a primary focus the secondary focus may be eliminated or silenced.37 The assumption of a poor outcome in case of multiple seizure types with early onset, multiple cortical tubers and multifocal or generalised epileptogenicity is not (yet) empirically supported, which calls for the consideration of epilepsy surgery in all TSC patients with drug resistant epilepsy.

In complex cases, additional information may be obtained with MEG, subtraction SPECT, [11C] methyl-L-tryptophan ([11C] AMT) PET, or invasive EEG recording. A single localisation of epileptiform activity was detected more often by MEG than EEG. In addition, MEG sources were closer to presumed epileptogenic tubers than EEG sources.39 [11C] AMT PET has been able to distinguish between epileptogenic and non-epileptogenic tubers.9,16 Above all, ECoG is essential to tailor the resection of the epileptogenic zone after the target tuber is removed. The excision should be extended in non-eloquent cortex if a continuous pattern of spikes, recorded with ECoG, persists after initial tuberectomy. Although our series of patients is too small to draw firm conclusions, sporadic spike activity in other regions than the...
border of the resection, and incomplete resection of the tuberal region(s) appear to be related to recurrent seizures. When multiple epileptogenic tubers are identified in distant brain regions epilepsy surgery has proven to be very successful with the proposed technique of multistage surgery. The perspective of future seizure recurrence should be weighed against that of a (temporary) relief of severe epilepsy, e.g. during a critical period of neurodevelopment. Although parents of two children in our series evaluated development and behaviour to have ameliorated, psychometric follow up indicated neither catch up nor — for that matter — decay.

In conclusion, we suggest that surgical treatment should be considered in every TSC patient with drug resistant epilepsy. Although seizure freedom is an unrealistic aim in patients with severe cognitive disability, the chance of substantial seizure reduction renders surgery a compelling option if seizure semiology, interictal HR EEG, ictal EEG, and MRI findings are concordant. In complex patients, without clear identification of the epileptogenic tuber, more efforts with multimodal non-invasive techniques (MEG, AMT PET, subtraction SPECT) are necessary and worthwhile.

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References


