Surgical treatment of refractory status epilepticus in children

Clinical article

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Object. Refractory status epilepticus (RSE) is a life-threatening neurological emergency associated with high morbidity and mortality. Affected patients often require prolonged intensive care and can suffer multiple complications. Surgical intervention to control RSE is rarely used but can obviate the risks of prolonged seizures and intensive care treatment. Authors of the present study analyzed their experience with the surgical management of patients suffering from RSE.

Methods. The Epilepsy Surgery Database at Miami Children’s Hospital was reviewed for patients who had undergone surgery for RSE. Clinical presentation, electrophysiological profile, radiological data, surgical details, and postoperative course were evaluated.

Results. Between 1990 and 2012, 15 patients underwent surgery for uncontrolled seizures despite high-dose medical suppressive therapy. The mean preoperative duration of status epilepticus was 8 weeks. Ictal SPECT and FDG-PET imaging in conjunction with intraoperative electrophysiological studies helped to outline the extent of resection. Surgical intervention controlled seizures in all patients and facilitated the transition out of intensive care. Adverse events related to a prolonged intensive care unit stay included sepsis and respiratory complications. Four patients had worsened neurological function, developing hemiparesis and dysphasia. There was no operative mortality.

Conclusions. Surgical intervention can successfully control refractory partial status epilepticus, prevent associated morbidity, and decrease intensive care unit stay. Ictal SPECT and PET are valuable in guiding resection.

Key Words • refractory status epilepticus • intractable seizure • epilepsy surgery • emergency

Status epilepticus (SE), defined as seizures lasting 30 minutes or longer, is a common life-threatening medical emergency in adults and children and is associated with high morbidity and mortality. More than 150,000 new cases occur annually in the US, which result in 22,000–42,000 deaths.13,15 Refractory status epilepticus (RSE) is associated with 12.9% neurological morbidity after the first episode of SE and 29.2% morbidity after recurrent SE.13,25

The management of SE is typically staged with medical treatment gradually escalated to bring seizures under control.29 Most patients with the disorder respond to first-line treatment with phenytoin, barbiturates, or levetiracetam. High-dose benzodiazepines, such as midazolam, pentobarbital, or propofol, are typically introduced when seizures are uncontrolled by the first-line medications.10 Intravenous propofol, lidocaine, valproate, ketamine, and even electroconvulsive therapy have been used to suppress SE;14,28,32 however, a small number of cases are refractory to all medical treatment, or respond only briefly and continue in SE for prolonged periods of time, sometimes for weeks or months.17 By this point in the course of the disease, patients are often critically ill, requiring intensive medical treatment and cardiorespiratory support. Prolonged coma and respiratory problems account for more than 50% of deaths.13

Refractory status epilepticus, defined as SE unresponsive to benzodiazepines and intravenous anticonvulsants, including phenytoin or levetiracetam, occurs in 30% of patients with SE.17 Those affected typically have a focal electrophysiological onset, yet neurosurgical intervention is rarely performed. Studies on the surgical treatment of RSE are therefore limited to single case reports or small series involving cortical resection, callosal sectioning, multiple subpial transections (MSTs), hemispherectomy, and vagus nerve stimulation.1,3,4,9–12,16,17,19,20,24 There is no consensus on how or when to surgically manage this medical emergency.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
Surgery for refractory status epilepticus

We describe our experience in patients with RSE who underwent surgery on an urgent basis after high-dose medical suppressive therapy (HDST) failed.

Methods

We conducted a retrospective review of the Epilepsy Surgery Database at the Brain Institute of Miami Children’s Hospital for the period from 1990 to 2010. Patient data were de-identified, and study approval was obtained from the hospital research committee. The decision to perform surgery in all cases was based on careful evaluation of patient clinical semiology, electrophysiological data, radiological studies, and a high suspicion of a focal electrophysiological onset. All cases had been discussed in multidisciplinary epilepsy surgery conferences, and informed consent had been obtained from the parents.

Relevant demographic information, seizure semiology, structural and functional imaging studies, electroencephalography (EEG) features, and follow-up data were reviewed.

Results

Clinical Profile

More than 750 children had undergone surgery for intractable epilepsy; 15 were treated between 1990 and 2010 on a semi-urgent basis after aggressive medical therapy for RSE had failed. Eight boys and 7 girls had well-localized seizure onsets (Table 1). The median age at presentation with SE was 10 years (range 4 months–19 years), and the median age at epilepsy onset was 4 years (range 0.1–14 years). All patients were treated in the intensive care unit and had persistent seizures despite HDST with multiple anticonvulsant drugs. The duration of SE ranged from 2 to 24 weeks (mean 8 weeks). Seizures were focal in all patients and secondarily generalized in 12; epilepsy partialis continua occurred in 3 patients. No one had electrical SE during sleep.

Scalp EEG studies revealed seizures arising focally or lateralized to one cerebral hemisphere in all patients. Focal seizure onset occurred in 12 patients and was evident when the seizures recurred during the weaning phase of HDST. Seizure onset was generalized or intermittently bilateral in 3 patients. Intercital EEG revealed focal epileptiform discharges and polymorphic slowing in 10 patients; 5 patients had multifocal epileptiform discharges.

All patients underwent MRI using our institutional epilepsy protocol, which was performed using minimum field strength of 1.5 T. Scans were normal in 2 patients. Seven patients had malformations of cortical development, including focal cortical dysplasia or hemimegalencephaly. Six patients had nonspecific changes, including atrophy (diffuse or focal peri-rolandic), hippocampal signal change, or periventricular leukomalacia. These nonspecific findings were noted on the initial MRI study that predated the onset of RSE, thus indicating remote insults.

Functional imaging for seizure localization was performed using SPECT or FDG-PET to detect local hyperperfusion or metabolic abnormalities, respectively. All but 2 patients had either an ictal SPECT or FDG-PET study: one had hemimegalencephaly and the other demonstrated peri-rolandic focal atrophy corresponding to the region of ictal onset, thus obviating the need for functional imaging in both patients. Ictal SPECT scans were obtained in 12 patients, and localized hyperperfusion was seen in 10. In the remaining 3 patients, FDG-PET scans were obtained: 2 patients had focal hypometabolism, and 1 showed focal hypermetabolism suggesting a localized ictal onset (Fig. 1). Functional imaging data were used to guide electrocorticography (ECoG) and subsequent resection.

All patients were in uncontrolled SE at the time of surgery, and had failed an adequate trial of HDST. The HDST included more than one pharmacological agent (pentobarbital, midazolam, valproate, fosphenytoin, ethosuximide, topiramate, lorazepam, clonazepam, and/or levetiracetam) in mono- or polytherapy, followed by barbiturate infusion to achieve burst suppression. The duration of RSE before surgical intervention ranged from 2 weeks to 4 months. Eight patients were in pentobarbital coma before surgery; 4 were transferred to our institution after HDST at outside institutions had failed.

Histopathology revealed focal cortical dysplasia in 9 patients. Seven patients had Type II dysplasia, 4 had Type IIa, and 3 had Type Ib. One patient had Type Ia dysplasia. No histopathological data were available in 1 patient. Three patients had encephalitis (one of whom had cortical dysplasia along with encephalitis), and 1 patient each had focal ischemic necrosis, hemimegalencephaly, and mycoplasma encephalitis. One patient had Rasmussen encephalitis.

Surgical Management

Surgical intervention was considered for patients with persistent SE or those unable to be weaned from HDST. To be considered for surgery, a patient had to have a well-localized seizure onset that had progressed to SE. However, the extent of cortical resection needed to control seizures was often difficult to determine, as the precise extent of the epileptogenic zone and the relationship with eloquent cortex was difficult to outline in the setting of persistent SE or pentobarbital coma; therefore, we used multimodal functional imaging via SPECT and/or PET in conjunction with ECoG monitoring to plan cortical resections.

Three patients underwent 2-stage extraoperative monitoring to identify the epileptogenic zone and map eloquent cortex. Two of them (Cases 1 and 2), who were the first patients in this series, had seizures arising from the left hemisphere; MR images were normal in both of these patients. Both patients initially underwent MSTs as seizure onset was localized to eloquent cortex. While this intervention successfully halted SE in 1 patient, subsequent central resection was required in the second patient to achieve complete seizure freedom. The third (Case 14) underwent intra cranial EEG monitoring for seizure localization and functional mapping after relapsing into continuous seizures once the patient was weaned from a barbiturate coma.

The remaining 12 patients underwent 1-stage resections guided by intraoperative ECoG. Electrocorticography was performed using subdural grid or strip electrodes. Anesthesia was maintained with less than 0.5%
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Presentation</th>
<th>Duration of RSE (wks)</th>
<th>Semiology</th>
<th>EEG During RSE</th>
<th>Ictal SPECT</th>
<th>PET</th>
<th>MRI</th>
<th>Surgery</th>
<th>Result</th>
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<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>UK</td>
<td>SP2G</td>
<td>nonlocalizing</td>
<td>+</td>
<td>ND</td>
<td>normal</td>
<td>It frontal MSTs after 2-stage extraop monitoring</td>
<td>SE stopped; Szs persist, &lt;50% reduction</td>
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<td>2</td>
<td>5</td>
<td>24</td>
<td>EPC</td>
<td>it central</td>
<td>+</td>
<td>ND</td>
<td>normal</td>
<td>It frontal MSTs, then central resection after 2-stage extraop monitoring</td>
<td>SE stopped; Szs free</td>
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<tr>
<td>3</td>
<td>10</td>
<td>6</td>
<td>EPC, SP2G</td>
<td>it central?</td>
<td>+</td>
<td>ND</td>
<td>atrophy</td>
<td>It frontopolar corticectomy</td>
<td>SE stopped; Szs persist, 50% reduction</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>3</td>
<td>GS</td>
<td>rt frontal</td>
<td>+</td>
<td>ND</td>
<td>cortical dysplasia</td>
<td>frontal resection, then frontal &amp; insular lobectomy</td>
<td>SE stopped; no Szs now</td>
</tr>
<tr>
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<td>6</td>
<td>16</td>
<td>EPC</td>
<td>burst suppression</td>
<td>ND</td>
<td>ND</td>
<td>focal atrophy</td>
<td>rolandic resection</td>
<td>SE stopped; &gt;90% Sz reduction</td>
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<td>16</td>
<td>FS2G</td>
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<td>ND</td>
<td>bilat hippocampal</td>
<td>TPO resection, then hemispherectomy</td>
<td>SE stopped; occasional GS</td>
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<td>7</td>
<td>6</td>
<td>12</td>
<td>CPSs</td>
<td>burst suppression, nonlocalizing</td>
<td>−</td>
<td>ND</td>
<td>rt atrophy</td>
<td>It frontal lobectomy, corticectomy</td>
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<td>+</td>
<td>ND</td>
<td>hippocampal signal change</td>
<td>temporal lobectomy, then hemispherectomy</td>
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<td>fast rhythm it central</td>
<td>+</td>
<td>ND</td>
<td>cortical dysplasia</td>
<td>rolandic resection</td>
<td>SE stopped; no Szs</td>
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<td>10</td>
<td>0.4</td>
<td>12</td>
<td>clusters of CPSs</td>
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<td>−</td>
<td>ND</td>
<td>hemimegalepalephaly</td>
<td>hemispherectomy</td>
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<td>+</td>
<td>ND</td>
<td>cortical dysplasia</td>
<td>It frontal corticectomy, resection, then lobectomy</td>
<td>SE initially persisted, but stopped after reop; no Szs thereafter</td>
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<tr>
<td>12</td>
<td>5</td>
<td>3</td>
<td>CPSs</td>
<td>it ant</td>
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<td>cortical dysplasia</td>
<td>frontal corticectomy</td>
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<td>13</td>
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<td>it frontal</td>
<td>+</td>
<td>ND</td>
<td>hypometab</td>
<td>cortical dysplasia</td>
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<td>3.5</td>
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<td>+</td>
<td>ND</td>
<td>hypometab</td>
<td>cortical dysplasia</td>
<td>frontal lobectomy</td>
</tr>
</tbody>
</table>

* ant = anterior; CPS = complex partial seizure; EPC = epilepsy partialis continua; FS2G = focal seizures with secondary generalization; GS = generalized seizure; hydroceph = hydrocephalus; hypermetab = hypermetabolism; hypometab = hypometabolism; ND = not done; PVL = periventricular leukomalacia; SP2G = simple partial seizures with secondary generalization; Sz = seizure; TPO = temporoparietoccipital; UK = unknown; + = localized hyperperfusion; − = no localized hyperperfusion; ? = reflects uncertainty regarding findings.
Surgery for refractory status epilepticus

Sevoflurane and supplemented with propofol infusions. Given that widespread EEG abnormalities are expected in patients with prolonged SE, intraoperative ECoG was never used in isolation but rather in conjunction with the scalp EEG and imaging data. Magnetic resonance imaging was performed to identify anatomical abnormalities. Ictal SPECT scans were obtained to identify the area of presumed epileptogenic zone. We relied on focal interictal discharges, runs of repetitive spikes, or focal burst suppression along with ictal onset to guide the extent of resection. These discharges were noted at the time of initial presentation and deterioration into SE or during periods when the seizure status was transiently controlled. Multifocal random spikes or widespread background slowing was ignored. While a more aggressive approach using extraoperative recording may have improved outcomes, we believed that the pre- and intraoperative data were sufficient and that this group’s clinical status, repeated seizures, poor mental state, and inability to cooperate for reliable brain mapping did not justify chronic intracranial EEG recording. As shown in Fig. 1, resection was limited to the area of the presumed epileptogenic zone and anatomically involved cortex, as it was believed that a more extended resection in the absence of an ability to outline eloquent cortex with brain mapping would carry the risk of inadvertent neurological deficits.

With regard to surgical procedure, 2 patients underwent MSTs of eloquent cortex guided by functional imaging studies and electrophysiological data (both EEG and intraoperative ECoG). Both patients had normal MRI studies (Cases 1 and 2; Table 1). The patient in Case 2 continued to have frequent seizures from the motor strip and subsequently underwent a tailored peri-rolandic resection after extraoperative monitoring. The initial resection included corticectomy in 13 patients, following failed MST in 1 patient, and 6 of these 13 patients had complete lobectomy. The remaining 7 patients underwent limited corticectomy. One patient underwent hemispherectomy for hemimegalencephaly.

Patient Outcomes

All patients had been followed up for at least 12 months at the time of this report. Status epilepticus resolved in 14 patients after the initial resection. The last patient, who remained in SE, had extensive left frontal cortical dysplasia, and the ictal SPECT scan had shown concordant hyperperfusion in the same region; however, the initial frontal cortical resection was limited because of an inability to map expressive language. The patient had repeat surgery during which the frontal lobectomy was completed, as were MSTs of the Broca area and precentral gyrus (Fig. 2). The patient was seizure free thereafter. Thus, surgical intervention ultimately controlled RSE in all patients. Postoperatively, all patients were extubated, weaned from HDST, and successfully transferred to a rehabilitation facility.

Four patients continued to have frequent intermittent seizures (but not SE) and required additional surgical intervention after the initial corticectomy (lobar resection [2 patients], hemispherectomy [2 patients]). Decisions...
to perform these procedures were made after a detailed workup that included video EEG to characterize the seizures and define seizure onset. Magnetic resonance imaging and ictal SPECT scanning were also repeated to identify the extent of remaining cortical abnormality and define areas of ictal hyperperfusion. Postoperative follow-up ranged from 12 months to 5 years. Final outcome was seizure freedom (Engel Class I) in 7 patients, 90% seizure reduction (Engel Class II) in 4 patients, and persistent seizures in 4 patients (Engel Class III or IV).

No patient had an isolated corpus callosum or vagus nerve stimulator placement to control SE.

Seven patients had postoperative hemiparesis, and 1 patient had prolonged postoperative expressive dysphasia, which was evident when she was extubated after seizures ceased. Hemiparesis improved in 3 patients. Neurological deterioration in the remaining 4 patients was related to worsening weakness and dysphasia. One patient (Case 15) had prolonged postoperative benzodiazepine withdrawal symptoms. There was no postoperative mortality. Neither did postoperative wound infection, meningitis, hematoma, or hydrocephalus requiring CSF diversion develop in any patient. Four patients underwent a tracheostomy following prolonged intubation and respiratory failure. Additional complications included respiratory infection (3 patients), urinary tract infection (2 patients), and pancreatitis, electrolyte imbalance, and decubitus ulcer (1 patient each).

**Discussion**

Van Ness first reported the surgical management of SE in a patient with an acute intracerebral hematoma that precipitated RSE. Multiple case series subsequently documented the role of surgical intervention for RSE. Interventions included focal cortical resection, hemispherectomy, MST, vagus nerve stimulation, and callosotomy. Ng et al. described 5 patients with RSE successfully treated with neurosurgical intervention: 3 who underwent focal cortical resection and 1 each who underwent hemispherectomy and transcallosal resection of a hypothalamic hamartoma. Four became seizure free and the fifth patient had a more than 90% reduction in seizure frequency. Three of these patients had been documented earlier as isolated case studies.

Vendrame and Loddenkemper et al. recently reviewed the existing literature on children surgically treated for RSE and noted that surgery may be an option if there is strong evidence of electrographic and/or structural focal abnormality. The majority of patients had either generalized discharges or nonfocal lateralized electroencephalographic features. Lateralized MRI findings also helped to localize the area of seizure onset.

Ma et al. described 3 patients with RSE successfully treated using focal resection, MSTs, or callosal section. More recently, Mohamed et al. documented the successful use of magnetoencephalography (MEG) to localize
Surgery for refractory status epilepticus

Two patients each underwent temporal lobectomy and tailored cortical resection and 1 underwent hemispherectomy. All patients were relieved of RSE and 2 became seizure free. Alexopoulos et al.1 resected epileptogenic lesions in 10 patients with RSE after 2 weeks of HDST had failed. Status epilepticus was acutely controlled in all patients. Six patients underwent hemispherectomy. At a median follow-up of 7 months, 7 patients were seizure free and the rest had significant improvement.

Our findings corroborate those in prior studies, confirming the role and efficacy of surgical intervention in carefully selected patients with RSE. However, unlike in previous reports, our resections were tailored to the electrographic abnormalities and concordant anatomical and physiological imaging data to avoid more radical hemispheric resections. The precise extent of resection can be difficult to determine, as the ability to map eloquent cortex and define the adjacent epileptogenic zone without chronic extraoperative monitoring is challenging in RSE. Recall that patients with this disorder are often critically ill, are supported by a ventilator, and may have normal or nonlocalizing MRI abnormalities (8 patients in the present study).

The extent of resection in our series of patients was guided by preoperative electroencephalographic data, anatomical neuroimaging findings, preoperative ictal SPECT and FDG-PET scans, and the intraoperative demonstration of repetitive bursts or focal burst suppression accompanying ictal onset. Widespread slowing and multifocal random spikes were not used to determine the extent of resection. Chronic extraoperative recording was performed in only 3 patients whose seizures arose in the left frontal region. Two underwent MSTs and a limited frontal resection as the initial procedure.

With our approach, 13 of 15 patients had resolution of RSE; the 2 remaining patients (Cases 2 and 11) required extended resections in the postoperative period to achieve complete control of SE. Persistent postoperative seizures in 4 patients (Cases 1, 3, 13, and 15) mandated extended resections for seizure control. Importantly, only 3 patients required hemispherectomy. This finding contrasts with data in the literature review by Vendrame and Loddenkemper34 in which 14 of 32 patients had a hemispherectomy. Recall that patients with this disorder are often critically ill, are supported by a ventilator, and may have normal or nonlocalizing MRI abnormalities (8 patients in the present study).

In summary, patients with RSE should be evaluated for evidence of focal onset of seizure abnormalities and anatomical abnormalities on MRI and should be considered for physiological imaging via ictal SPECT or FDG-PET. Surgical intervention should also be considered to control SE when it becomes refractory to HDST.

Conclusions

In summary, patients with RSE should be evaluated for evidence of focal onset of seizure abnormalities and anatomical abnormalities on MRI and should be considered for physiological imaging via ictal SPECT or FDG-PET. Surgical intervention should also be considered to control SE when it becomes refractory to HDST.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bhatia, Ragheb, Mor-
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