



Surgical treatment for refractory epileptic spasms: The Detroit series

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SUMMARY

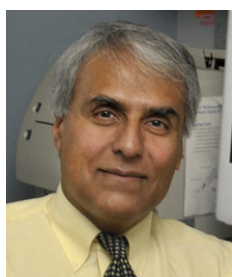
Objective: We reviewed our experience of surgery for epileptic spasms (ES) with or without history of infantile spasms.

Methods: Data were reviewed from 65 (33 male) patients with ES who underwent surgery between 1993 and 2014; palliative cases were excluded.

Results: Mean age at surgery was 5.1 (range 0.2–19) years, with mean postsurgical follow-up of 45.3 (6–120) months. Mean number of anticonvulsants used preoperatively was 4.2 (2–8), which decreased to 1.2 (0–4) postoperatively ($p < 0.0001$). Total hemispherectomy was the most commonly performed surgery ($n = 20$), followed by subtotal hemispherectomy ($n = 17$), multilobar resection ($n = 13$), lobectomy ($n = 7$), tuberectomy ($n = 6$), and lobectomy + tuberectomy ($n = 2$), with International League Against Epilepsy (ILAE) class I outcome in 20, 10, 7, 6, 3, and 0 patients, respectively (total 46/65 (71%); 22 off medication). Shorter duration of epilepsy ($p = 0.022$) and presence of magnetic resonance imaging (MRI) lesion ($p = 0.026$) were independently associated with class I outcome. Of 34 patients operated <3 years after seizure onset, 30 (88%) achieved class I outcome. Thirty-seven (79%) of 47 patients with lesional MRI had class-I outcome, whereas 9 (50%) of 18 with normal MRI had class I outcome. Positron emission tomography (PET) scan was abnormal in almost all patients [61 (97%) of 63 with lateralizing/localizing findings in 56 (92%) of 61 patients, thus helping in surgical decision making and guiding subdural grid placements, particularly in patients with nonlesional MRI. Fifteen patients had postoperative complications, mostly minor.

Significance: Curative epilepsy surgery in ES patients, with or without history of infantile spasms, is best accomplished at an early age and in those patients with lesional abnormalities on MRI with electroencephalography (EEG) concordance. Good outcomes can be achieved even when there is no MRI lesion but positive PET localization.

KEY WORDS: Seizure, Epilepsy surgery, Epileptic spasms, FDG-PET, West syndrome.



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The triad of epileptic spasms,¹ developmental arrest, and a pattern of hypsarrhythmia on electroencephalography (EEG) is referred to as West syndrome; however, epileptic spasms (ES) can occur without hypsarrhythmia.² The recommended initial medical treatment of ES is either vigabatrin or adrenocorticotrophic hormone (ACTH).³ If these agents fail to suppress the spasms (and hypsarrhythmia, when present), the ketogenic diet or various anticonvulsants may be tried with variable success.³

When ES are refractory to medical management, a surgical option is recommended in selected patients who mani-

KEY POINTS

- Curative epilepsy surgery in patients with epileptic spasms (ES), with or without history of infantile spasms, is best accomplished in those with abnormal MRI
- Good outcomes can be achieved even when there is no MRI lesion but positive PET localization
- Surgical outcome is extremely good in children who were operated on within 3 years of presentation with ES
- Postoperative complications, although not negligible and certainly serious in some cases are, in general, acceptable (considering the gravity of intractable ES)

fest focal findings on neuroimaging and EEG. Although there had been several case reports of spasms ceasing after surgical removal of a lesion,^{4–6} the first reported *series* consisted of 10 patients with ES and porencephalic cysts in whom neurosurgical marsupialization of the cysts and fenestration to the ventricular system resulted in resolution of the spasms.⁷ Epilepsy surgery for ES in the *absence* of a visible lesion on magnetic resonance imaging (MRI) was reported in 1990,⁸ followed by a larger series from the same investigators.⁹ Both of these series focused on subjects without lesions visible on MRI but with metabolic foci detected using glucose metabolism positron emission tomography (PET) scanning. Since then, there have been many studies reporting successful epilepsy surgery for the amelioration of intractable ES.^{10–13}

The best outcomes with surgery for intractable epilepsy in general are achieved when the patients harbor a single lesion detected on MRI and/or PET and there is general concordance with ictal/interictal EEG recordings. Although many centers have gained experience in surgery for intractable ES when there is an MRI visible lesion, there is still a general reluctance to perform surgery guided exclusively by PET and EEG findings, that is, MRI-negative cases. At our center, we have placed great emphasis on PET imaging in localizing metabolic foci, which, if concordant with ictal EEG and when resected, have resulted in excellent outcomes. Sometimes, the MRI scans are interpreted initially as normal, but with focal PET findings determined objectively, the MRI is reinterpreted and subtle abnormalities corresponding to the PET localization are discovered in retrospect.¹⁴

The present study was conducted to review our experience with ES epilepsy surgery with the intent of investigating who might be surgical candidates. Herein, we report our findings in 65 infants and children with intractable ES who were treated with intended curative surgical resections. We have included both MRI-positive and MRI-negative cases, and compared their surgical outcomes.

METHODS

Subjects

We reviewed the records of >500 infants and children with ES evaluated between January 1993 and December 2014 at the Children's Hospital of Michigan, Wayne State University in Detroit, Michigan. Most of them were not considered for surgery due to resolution of spasms with medical treatment or were not good surgical candidates due to bilateral ictal EEG onsets, phenotype of severe developmental delay with no gains in skills over a protracted period, spastic quadriplegia, microcephaly, severe muscle wasting, and so on, suggesting an underlying neurogenetic condition. Such patients typically had severe bilateral symmetric hypometabolism on PET, and some had an underlying inoperable genetic mutation (e.g., *ARX*, *CDKL5*, *SCN2A*, and *STXBPI*). During this time period, 98 of these infants and children underwent surgical treatment. Of these, one third were excluded from the present series for the following reasons: (1) patients who had <6 months follow-up, (2) patients who underwent a "palliative resection" (designated as palliative prior to surgery¹⁵), and (3) patients whose seizures had evolved to atonic/tonic semiology and who underwent corpus callosotomy. Complete clinical data from the remaining 65 subjects are described in the present study (Table S1). Backgrounds of patients were Caucasian (n = 44), African American (n = 10), Hispanic (n = 4), Middle Eastern (n = 4), and Asian (n = 3). Included in the 65 patients are 11 children who were reported in a recent publication on "subtotal hemispherectomy."¹⁶ All 65 had been diagnosed with ES, which remained refractory despite aggressive treatment.

Diagnostic testing

All patients were evaluated with scalp interictal and ictal video-EEG, MRI, and glucose metabolism PET scans. Developmental assessments were performed when feasible. Some children also received PET scans with ¹¹C-flumazenil (FMZ) or ¹¹C-alpha-methyl-L-tryptophan (AMT) under research protocols. In particular, all patients with tuberous sclerosis complex (TSC) underwent AMT-PET scans to localize epileptogenic tubers.¹⁷ Genetic testing had been performed by referring physicians in some patients, but none showed a known mutation (at that time) to be associated with ES. Following presurgical evaluation, the patients were presented in a weekly held multidisciplinary epilepsy surgery conference for discussion and consensus regarding surgical candidacy.

Although PET plays an important role in our surgical program, it is used only as a guide for intraoperative or chronic subdural electrocorticography (ECoG) sampling, and the actual extent of cortical resection is typically based on the ECoG data. None of the patients in our study was operated based on PET imaging only. However, subtle ictal EEG changes were often considered more

seriously if supported by PET localization/lateralization. On the other hand, patients with structural lesions seen on the MRI scans (e.g., middle cerebral artery infarct in utero) were operated on even if the EEG was discordant due to dipole distortion.

Surgical placements of subdural electrodes

A craniotomy was performed over the location suspected to be epileptogenic based on the results of presurgical investigations. Various combinations of platinum grid and strip subdural electrodes (interelectrode distance: 1 cm) were placed over the region of brain to be sampled with ECoG. When appropriate, electrode placements included the precentral and postcentral gyri as well as medial temporal regions.¹⁸ To avoid movement of subdural electrodes after placement, all electrode plates were stitched to adjacent plates or the edge of the dura mater. To minimize the risk of infection, electrode leads were then tunneled about an inch from the main wound. Using a digital camera, intraoperative photographs were taken prior to dural closure. Following dural closure in a semi-watertight fashion, the bone flap was replaced but not secured. A subgaleal drain was placed to minimize postoperative scalp swelling. All electrodes were subsequently displayed on the three-dimensional brain surface reconstructed from high-resolution MRI.¹⁹

Extraoperative ECoG recording

Patients who had a two-stage surgery underwent extraoperative video-ECoG recordings for 2–5 days (Fig. 1). In extraoperative (chronic) ECoG recording, habitual seizures were captured, and visual assessment determined the seizure-onset zones, defined as the sites initially exhibiting ictal ECoG changes associated with each seizure event. In all patients, ictal ECoG patterns of epileptic spasms were characterized by widespread fast-wave discharges (>30 Hz) with or without a preceding spike.^{20,21} Ictal ECoG patterns of focal seizures were characterized by either repetitive spike-wave discharges or focal fast wave discharges.¹⁸ In addition to the seizure-onset zones, we visually marked the sites showing frequent interictal spike discharges. Following analysis of the ECoG data, the results were discussed with the parents/guardians and the recommendation was made that the extent of resection should include the presumed epileptogenic zones consisting of the seizure-onset zones, as well as frequent spiking zones not accounted for by propagation from the seizure-onset zone and neuroimaging abnormalities surrounding the seizure-onset zones. Thereby, we intended to preserve the eloquent areas defined by electrical stimulation mapping as well as their associated vascular structures.¹⁴ In the event that the presumed epileptogenic zones overlapped with the eloquent areas, resection margin was determined, on a case-by-case basis, after intense discussion with the family of a given patient regard-

ing the pros and cons of complete resection of the presumed epileptogenic zones.

Intraoperative ECoG recording

In intraoperative ECoG recordings, we sampled ECoG signals generously from the areas potentially epileptogenic based on the findings of noninvasive presurgical evaluations including scalp video-EEG and neuroimaging. Somatosensory-evoked potentials (SSEPs) were intraoperatively recorded as needed. Surgical resection generally included the regions showing neuroimaging abnormalities as well as frequent spiking on ECoG. If a given patient had profound motor deficits associated with massive structural lesions, we generally recommended hemispherectomy. Otherwise, we generally preserved the normal-appearing cortex as well as the sensorimotor areas determined by intraoperative SSEPs and anatomic landmarks.

Resection procedure

Resective surgery was tailored to the presumed epileptogenic zones. All procedures were performed using a large fronto-temporoparietal osteoplastic craniotomy based on the temporalis muscle. Trans-sylvian approach was used to perform hemispherectomy (n = 20) and subtotal hemispherectomy sparing the primary sensorimotor cortex (n = 17). In patients with epileptiform activity involving the primary sensorimotor cortex, extensive multiple subpial transections (MSTs) were performed perpendicular to the sulci. A strip of cortex along the center of the involved gyrus was first coagulated along the entire extent, and then MSTs were performed at 5 mm intervals.

Histopathology

All surgical specimens were examined in detail by one of the authors (WJK) after the samples were stained with hematoxylin and eosin, cresyl-violet, Luxol fast-blue, and glial fibrillary acidic protein (GFAP) antibody. If indicated for further clarification, the specimens were also stained with periodic-acid Schiff, Bielschowsky, Bodian, Congo red, and various immunostains.

Statistical analysis

Follow-up ranged from 6 to 120 months (mean 45.3 months). The surgical outcome was reported based on the International League Against Epilepsy (ILAE) classification.²² Values are reported as mean \pm standard deviation (SD) for normally distributed continuous variables, median and range for skewed continuous variables, and frequencies and percentages for categorical variables. A multivariate logistic regression analysis was performed to determine if surgical outcome was independently associated with “age at surgery,” “duration of epilepsy,” “number of antiepileptic drugs,” and “presence of MRI lesion.” A p-value of ≤ 0.05 was considered statistically significant. SPSS 21.0 (SPSS Inc, Chicago, IL, U.S.A.) was used for the data analyses.

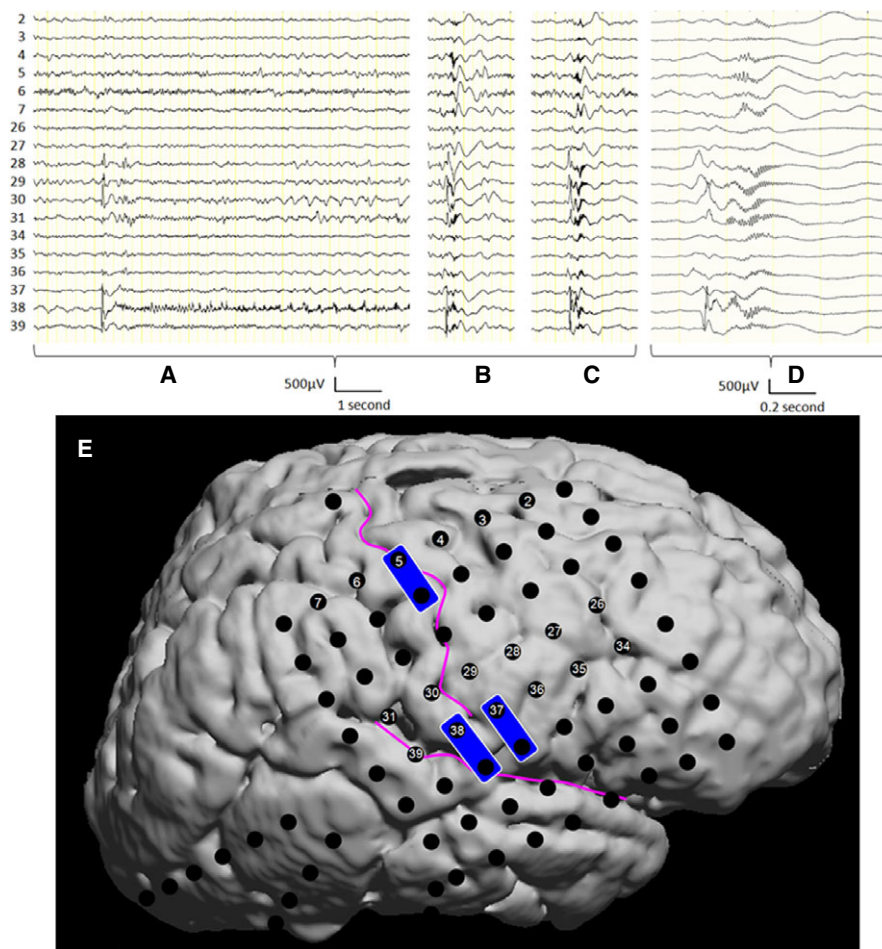


Figure 1.

Ictal ECoG traces in a patient with intractable seizure and epileptic spasms (patient 5). (A) The focal seizure was associated with a single spike discharge with the maximum amplitude at channel 38 in the inferior rolandic region, followed by prolonged fast-wave discharges intermixed with periodic sharp waves in the surrounding regions. (B and C) Forty seconds after the onset of the focal seizure, a cluster of epileptic spasms took place; each of the spasms was associated with a leading focal spike followed by widespread fast-wave discharges involving the superior rolandic region including channels 4 and 5. (D) Ictal ECoG traces shown in (C) are enlarged; ictal fast wave discharges at channels 4 and 5 were delayed compared to those in the inferior rolandic region. (E) The locations of subdural electrodes are presented on the surface-rendered image. Electrical stimulation of channels 5 and 13 elicited left-hand twitching, whereas that of channels 37 and 45 as well as 38 and 46 induced mouth movement. Surgical resection included the inferior rolandic cortex and frontal lobe containing the cortical tubers, seizure-onset zones, as well as regions independently showing independent spike discharges. The sensorimotor hand area underlying channels 5 and 13 was preserved.

Epilepsia © ILAE

RESULTS

There were 65 patients (33 male); mean age of seizure onset was 1.08 ± 1.4 (median 0.5, range 0.1–7) years, and mean age at surgery was 5.1 ± 4.4 (median 3.5, range 0.2–19) years. The mean duration of postsurgical follow up was 45.3 ± 30.4 (median 30, range 6–120) months, and mean duration between seizure onset and surgery was 4.21 ± 3.8 (median 3.0, range 0.05–18.9) years. The mean number of anticonvulsants being taken prior to surgery (including vigabatrin) was 4.22 (range 2–8). Seizure frequency at the time of surgery was multiple daily in 58 patients and at least weekly in the remaining 7 patients.

Seizure types

Out of the 65 patients, 46 patients had onset of spasms in infancy and 19 patients had late-onset spasms ranging from 1.4 to 11 years. At the time of surgery, 37 of the 65 were experiencing active spasms and 28 had a recent history of spasms. Although the onset of spasms ranged from 1 month to 7 years, most patients had early onset with a median age of 0.7 year (mean 1.4 ± 1.6). Indeed, of the 28 patients with recent spasms, 18 had spasm onset in infancy ranging from 1 to 12 months. The average duration for age of spasm offset in these 28 patients was 4.1 ± 3.3 years (median 3.0, range 1–14 years).

Fifteen of the 65 had manifested only spasms, whereas 50 had multiple seizure types, including spasms and focal seizures in 38 patients, spasms and generalized seizures (including tonic/myoclonic) in 7 patients, and spasms, and focal and generalized seizures in 5 patients (Table S1).

Types of resection

The results from the presurgical evaluations are shown in the Table S1. The surgery was performed based on these data and intraoperative ECoG when applicable ($n = 23$), as well as further data obtained from extraoperative ECoG recordings ($n = 42$). Surgery was extensive, with total ($n = 20$) or subtotal ($n = 17$) hemispherectomy along with multilobar resection ($n = 13$) performed in the majority of patients (Table 1). Patients who underwent one-stage hemispherectomy ($n = 18$) had a major structural abnormality and were already significantly hemiparetic. Two patients underwent extraoperative ECoG recording prior to hemispherectomy (patients 16 and 54), since the degree of hemiparesis was subtle/mild and there was a reasonable chance to preserve the sensorimotor cortex. In these two patients, the primary sensorimotor cortex was very much involved in the presumed epileptogenic zone based on the results of extraoperative ECoG recordings; therefore, hemispherectomy was performed.

In addition to the various resections described earlier, MSTs were performed on 10 patients (5, 17, 23, 34, 35, 37, 38, 39, 43, and 60) to preserve motor function. One of the children (patient 26) underwent a partial corpus callosotomy in addition to right multilobar resection. There were seven patients (9, 1, 23, 26, 42, 43, and 51) who underwent two sets of surgeries (reoperations). Three patients came to us with a history of surgery performed elsewhere and four patients required two sets of surgery at our center.

Surgical outcome

The mean follow-up period after surgery was 45.3 months (range 6–120 months). Forty-six patients were completely seizure-free (Table 1); 22 of them were no longer taking any anticonvulsants, whereas 24 remained on medication. It appeared that patients with larger surgical resection had better surgical outcome (Table 1). The 19 patients with seizure recurrence had class III, IV, or V outcomes and remained on medication. The time of seizure relapse ranged from 1 month to 4.5 years (mean 1.5 ± 1.3 years; median 1.0). Two of these 19 patients had

been seizure-free for 4 years prior to recurrence of their seizures. The median value number of anticonvulsants being taken by these children decreased to 1 (range 0–4) after surgery, compared to 3 (range 2–8) before surgery.

Lesional versus nonlesional on MRI

The underlying etiology was somewhat diverse including malformations of cortical development ($n = 21$), neurocutaneous syndrome (Klippel-Trenaunay-Weber syndrome, 1; linear nevus sebaceous syndrome, 1; and tuberous sclerosis, 17), infections ($n = 2$), chromosomal abnormalities ($n = 4$), ischemia/hemorrhagic stroke secondary to in utero stroke, methicillin-resistant *Staphylococcus aureus* (MRSA) meningitis, aneurysm, methylene tetrahydrofolate reductase (MTHFR) mutation, factor V Leiden mutation, autoimmune thrombocytopenia ($n = 12$), tumors such as mixed glial tumor and dysembryoplastic neuroepithelial tumour (DNET) ($n = 2$), perisylvian syndrome ($n = 1$), and Down syndrome ($n = 1$). The imaging findings were diverse with varied pathologies including malformations of cortical development (focal cortical dysplasia, hemimegalencephaly, schizencephaly, polymicrogyria, and pachygyria), multiple hamartomas including subependymal giant cell astrocytoma, encephalomalacic changes secondary to ischemic/hemorrhagic stroke, meningitis/encephalitis, and tumors.

Based on the MRI scans, 47 of the 65 patients were considered to have a lesion concordant with ictal EEG localization. Of these 47 lesional cases, 37 had a class I outcome (79%), 4 had class III, and 6 had class IV outcomes. The MRI scans did not show lesions in 18 subjects, and in this nonlesional group, 9 had class I outcome (50%), 4 had class III outcome, 3 had class IV outcome, and 2 had class V outcome. The chance of class I outcome was 1.6 times greater in lesional than in nonlesional cases. The pathology of the resected tissues in 18 patients with nonlesional epilepsy (as defined by imaging) revealed focal cortical dysplasia (FCD) in five, of which four had class I outcome. These included patient 1 (class I outcome), patient 38 (class I), patient 43 (class V), patient 48 (class I), and patient 60 (class I). In 16 patients identified as having MCD including FCD by imaging and pathology, 14 had favorable class I outcomes.

PET findings

PET scan was abnormal (showed multifocal and widespread abnormalities) in almost all patients (61 [97%] of 63), with lateralizing/localizing findings in 56 (92%) of 61 patients. This greatly helped in surgical decision making and guiding in subdural grid placement, particularly in patients with normal MRI and bilateral EEG abnormalities (Fig. 2).

Postoperative complications

Of the 65 patients, 15 patients (3, 7, 18, 19, 20, 23, 24, 26, 28, 31, 32, 38, 51, 53, and 54) had postoperative complica-

Table 1. Surgical detail and seizure outcome

Surgery	No.	ILAE outcome – No. of patients
Total hemispherectomy	20	I–20
Subtotal hemispherectomy	17	I–10; 3–3; 4–4
Multilobar resection	13	I–7; 3–4; 5–2
Lobectomy	7	I–6; 3–1
Tuberectomy	6	I–3; 4–3
Lobectomy + tuberectomy	2	4–2

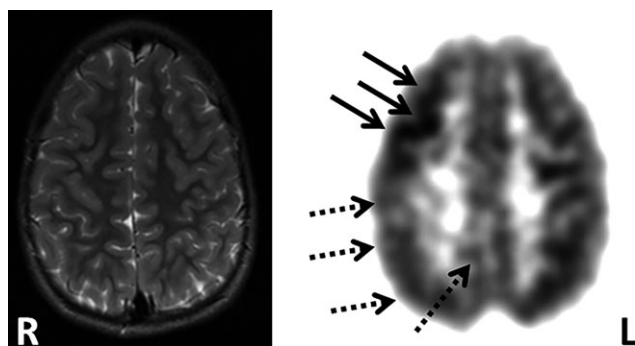


Figure 2.

MRI and fluorodeoxyglucose (FDG)-PET scan in a 7-year-old right-handed boy (patient 60) with uncontrolled seizures and cluster of epileptic spasms. Although MRI was normal (left side), FDG-PET (right side) revealed an area of hypometabolism in the right lateral and medial parietal cortex (broken arrows), as well as hypermetabolism (solid arrows) in the right lateral frontal cortex. The patient underwent right frontoparietal cortical resection, which turned out to be cortical dysplasia on histopathology. The child is seizure-free at two and a half years follow-up and is doing well.

Epilepsia © ILAE

tions, which include isolated hydrocephalus (patients 3, 18, 19, 20, 26, 28, 32, 38, and 54), anoxic brain injury with hydrocephalus (patient 7), wound and bone flap infection (patient 53), hydrocephalus accompanied by postshunt cerebrospinal fluid (CSF) leak with bone flap infection (patient 51), subgaleal fluid collection (patients 23), epidural hematoma (patients 31), and CSF fluid leak after head trauma (patients 24). The most severe of these was in one child (patient 7) with left hemiplegia and a history of right middle cerebral artery infarct in the newborn period associated with meningoencephalitis. She had a cardiac arrest intraoperatively after completion of scalp closure, resulting in mild extrapyramidal rigidity, but nevertheless became seizure-free. Of the 11 patients who required ventricular shunts, the types of surgeries were hemispherectomy (n = 7), subtotal hemispherectomy (n = 2), multilobar resection (n = 1), and tubectomy (n = 1).

Statistical results

A receiver operating characteristic (ROC) curve analysis explored the relationship between the age of surgery and the risk of failing to achieve ILAE class I outcome. This analysis revealed that the age cutoff of 3 years resulted in the most accurate prediction of seizure outcome; namely, patient age of >3 years was associated with a greater risk of failure to achieve ILAE class I outcome, with sensitivity of 0.95 and specificity of 0.52 (Table 2). In other words, patients who had surgery within 3 years of seizure onset showed a more favorable outcome than those operated >3 years after seizure onset. Of the 34 patients operated prior to 3 years of seizure onset, 30 (88%) had a class I outcome. The remaining 31 patients underwent surgery more

Table 2. Effect of seizure duration on surgical outcome

Duration between seizure onset and surgery (years)	No. of patients	ILAE outcome – No. of patients
<1	15	I–14, 3–1
1–2	8	I–8
2–3	11	I–8; 3–2; 4–1
>3	31	I–16; 3–5; 4–8; 5–2

than 3 years after seizure onset and these had variable outcomes (Table 2). This observation does not clarify if the surgical outcome was associated with “patient age” or “duration of epilepsy.” To address this issue, we performed multivariate logistic regression analysis. This analysis revealed that both longer duration of epilepsy (p = 0.022; odds ratio [OR] 1.56, 95% confidence interval [CI] 1.07–2.28) and lack of MRI lesion (p = 0.026; OR 4.54, 95% CI 1.20–17.2) were independently associated with a larger risk of failing to achieve ILAE class I outcome in our patient cohort. Patient age (p = 0.19) and number of antiepileptic drugs (p = 0.98) were not independently associated with surgical outcome in our patient cohort.

DISCUSSION

Several major observations are clear from the present study. First, the presence of an MRI-visible lesion in patients with intractable ES is associated with a better surgical outcome than when no lesion can be detected on MRI (79% vs. 50% ILAE class I). However, the fact that up to 50% of MRI-negative cases still had ILAE class I outcome indicates that epilepsy surgery is worth pursuing in this group, if all medical treatments have failed, considering the very poor overall prognosis of intractable ES.¹² Second, children who were operated on within 3 years of presentation with ES had an extremely good result, with 30 (88%) of 34 achieving ILAE class I outcome. Third, postoperative complications, although not negligible and certainly serious in some cases, are, in general, acceptable (considering the gravity of intractable ES) and not too different from those reported in other published series on pediatric epilepsy surgery.

Lesional versus nonlesional based on MRI

Prior to the first cases of resective surgery for ES, these seizures were believed to be of generalized onset rather than localization related. That notion was challenged when focal resections guided by PET studies of glucose metabolism and intraoperative ECoG revealed underlying FCD not detected on the relatively low-resolution MRI scans used at that time.^{8,9} Initially, there was much controversy as to whether surgical resections for ES (a “generalized” epilepsy) could be justified based on metabolic imaging,²³ but this skepticism has gradually subsided.²⁴ It is notable that Sankar and colleagues²⁵ subsequently demonstrated that

MRI scans, if performed in the first year of life at the presentation of West syndrome, may not detect cortical dysplasia in the region of the PET abnormality because poor gray–white matter differentiation may not yet be obvious at this age; however, repeat MRI scans later in the second or third years will often reveal evidence of cortical dysplasia previously missed.²⁵

Indeed, current higher resolution 3-Tesla MRI scanners and advanced scanning sequences are able to detect even very subtle lesions corresponding to the focal metabolic abnormalities shown on PET, and this improvement in MRI technology probably accounts for the relatively larger number of MRI-positive cases (47/65 or 72%). A higher number of patients with MRI-visible lesions achieved seizure freedom (79%) compared to those who relied more on PET for neuroimaging localization (50% of these had class I outcome). This is not surprising in view of multiple studies on pediatric epilepsy surgery in general, where nonlesional cases typically showed a lower seizure-free outcome compared to lesional cases.²⁶ It is likely that the MRI-negative group is heterogeneous, including patients with cortical dysplasia not evident on MRI as well as patients with yet-undiagnosed underlying genetic mutations as the etiology for their ES. The notion that mutations causing epilepsy in children may present with focal seizures is exemplified in patients with *SCN1A* mutations, which may be associated with both focal and generalized epilepsy.²⁷ Still, 50% of MRI-negative cases in the present study attained seizure freedom and, considering that intractable ES is associated with a very poor outcome,¹² surgery is well worth pursuing in such cases. A multimodal approach to delineate the epileptogenic zone is often required,²⁸ as evidenced by the contribution of PET in the present cohort. Indeed, PET scan was lateralizing in almost all patients (92%), and this greatly aided in subdural grid placement, particularly in patients with normal MRI and bilateral EEG abnormalities, and in subsequent surgical decision making, such as the extent of surgical resection, and need for total or subtotal hemispherectomy, which perhaps resulted in better than expected surgical outcomes.

It has been argued, and is now generally accepted, that ES are initiated as cortical epileptic discharges that, during a “critical” developmental period, undergo secondary generalization in an age-dependent mechanism to emerge as spasms.²⁹ Perhaps one of the strongest arguments to support such a concept is the observation that focal seizures may trigger a cluster of ES. This was first reported by Dalla Bernardina et al.³⁰ in the Italian literature, and subsequently replicated by others.^{31,32} In this latter study, it was noted that of the 16 patients with clusters of bilateral ES preceded by focal seizures, 3 had complete agenesis of the corpus callosum, suggesting that propagation (or secondary generalization) of the focal seizures to emerge as spasms was not through the corpus callosum in these population. This observation is consistent with the notion that corpus callosotomy

is not an effective treatment for ES. In addition, ES can be seen in patients with agenesis of the corpus callosum, such as children with Aicardi syndrome. ECoG on 15 children with subdural electrodes revealed that spasms were associated with either a “leading” spike followed by fast-wave bursts, or fast-wave bursts without a “leading” spike, and that the “leading” spike originated in proximity to the PET abnormality.²⁰ Furthermore, failure to resect cortex showing the “leading” spike was associated with poor surgical outcome, indicating that the leading spike may be a biomarker of the trigger zone leading to the spasms.

Occasionally, the epileptogenic zone may be very large and involve much of the hemisphere. If the patient does not exhibit significant hemiparesis, we have elected in such cases to perform a “subtotal” hemispherectomy in order to preserve the primary motor and sensory cortex. We recently reported our experience with this operation in 23 patients with intractable epilepsy, 11 of whom had ES as their major seizure type.¹⁶ MRI scan showed focal abnormalities in 12 of the 23 children, whereas PET showed focal/lateralized hypometabolism in all but one child. An ILAE class I outcome was achieved in 17 (74%) of the 23 subjects after a mean follow-up period of 65 months in that study. In the present study, 17 of the 65 subjects underwent a “subtotal” hemispherectomy. Ten (58.8%) had class I outcome, three showed class III outcome, and the remaining 4 had class IV outcome.

All too often, however, there are multiple foci seen on the MRI and/or PET, thus precluding a surgical approach. In some instances of multiple cortical epileptic foci, a palliative surgery can be offered if the majority of seizures emanate from one of the foci. We believe that it is important to designate and declare palliative cases prior to surgery in order to analyze surgical results accurately; in the present series, we have excluded such cases. We have recently analyzed our results on palliative epilepsy surgery in children (including 7 cases of ES), and the outcome appears to be quite favorable, with 11 (61.1%) of 18 patients showing seizure reduction and 8 (44%) of 18 children achieving seizure freedom, including 3 of the 7 with ES.¹⁵

Although lesional and nonlesional outcomes in epilepsy surgery are well described,³³ there are few such data on patients specifically with ES in this regard. The new information from the current study suggests that ES subjects without an MRI lesion but with a positive fluorodeoxyglucose (FDG)–PET can still be epilepsy surgery candidates if there is concordance with the EEG, and seizure freedom can still be achieved in half of such subjects. It would be important if the current study were to stimulate a multicenter collaboration of lesional and nonlesional ES cases coming to epilepsy surgery.

Age at surgery

In general, early surgery is advocated in children with medically refractory epilepsy due to greater plasticity and ability to reorganize functions in the developing brain

compared to a more mature brain. A review of cognitive outcome following epilepsy surgery in children revealed that the strongest predictors of long-term cognitive outcome were duration of epilepsy, preoperative cognitive status, and postoperative seizure freedom.³⁴ However, many other factors, including age at surgery and underlying etiology, also were related to a change in postoperative cognitive scores.

In the present series, we found that children with intractable ES who had surgery within 3 years of presentation had an excellent outcome. Indeed, of the 34 children in this category, 30 (88%) achieved a class I outcome. This surgical success is higher than average success rates in our own previous series⁹ as well as recent studies from other centers,^{10,12,13,35} although the numbers of subjects in most of those reports are small compared to the present series. For example, Lee et al.³⁵ reported that 9 (60%) of 15 children with ES became seizure-free following surgery. In one relatively large series of 30 children with ES and cortical dysplasia who underwent cortical resection, 22 (73.3%) became seizure-free.¹² Of interest, that same study found no difference in surgical outcome between MRI-positive and MRI-negative cases before age 1 year.

The reason for a better seizure-free outcome (as distinct from cognitive outcome) in younger compared to older children in the present study is not clear, and we can only speculate as to why this might be. A possible explanation is that since the seizures (and interictal spiking) in patients with ES usually occur with high frequency, the tendency to establish a large epileptic network and secondary epileptic foci from an active primary focus within a short period may be greater than with other seizure types. The results of multivariate logistic regression analysis in the present study support this notion. Another possibility could be that the smaller brain is more easily covered by subdural electrodes and hence there may be less sampling error than with larger brains. In addition, there is a tendency to perform larger resections in younger infants with the advantage of a more complete removal of epileptogenic brain tissue.

The optimal timing of epilepsy surgery in the pediatric population has been in debate for some time, as the extent and timing of cortical resection is determined “case by case” based on the intractability, developmental concerns, and after extensive discussion with the family regarding the pros and cons of surgical resection. The choice of 3 years in our paper was somewhat arbitrary, as we explored different time scales. However, it can be safely recommended that earlier surgery can provide early relief from catastrophic epilepsy and may allow resumption of developmental progression during critical stages of brain maturation. From a clinical perspective, our experience is that surgery should be performed no later than 3–4 years, although this has not been rigorously tested. Clearly, large multicenter studies with standardized approaches will be required to address this issue.

Limitations

Limitations of our study include its retrospective design, and short duration of follow-up in some patients. Larger prospective studies with multicenter collaboration could reveal clinically relevant associations and correlate presurgical variables with outcomes.

Postoperative complications

Although early surgery is increasingly being advocated for children with intractable focal epilepsy, and certainly supported by data from the present study, intraoperative and postoperative complications are also the highest in the youngest surgical candidates. In a report of 15 infants who were operated at 6 months of age or younger for intractable severe epilepsy, the most frequently encountered complication was blood loss, with a median estimated blood loss of 63% of the total blood volume (range 3–214%). One infant had an intraoperative acute ischemic infarct resulting in hemiparesis, yet 46% of the infants became seizure-free.³⁶ In a recent analysis of 552 hemispherectomies performed in the United States between 2000 and 2009, in-hospital mortality occurred in five subjects (0.9%) and ventricular shunt placement during the surgical admission increased over time from 6.7% to 16.5%.³⁷

The most severe complication encountered in the present study was in a child (patient 7) who had a cardiac arrest following right hemispherectomy after scalp closure. Even so, this child became seizure-free but manifested mild extrapyramidal rigidity on follow-up examinations. Other complications are not different from what has been reported previously. There were no differences in postoperative complications between the MRI-positive and MRI-negative groups: 11/47 (23.4%) lesional and 4/18 (22.2%) nonlesional patients had postsurgical complications. Furthermore, 12/15 (80%) of them had class I outcome, suggesting no effect of postsurgical complication on surgical outcome. Due to the typical large multilobar resections or even hemispherectomies performed in young children with ES, it is anticipated that some of them will acquire hydrocephalus and require a shunt. In the present series, 11 (16.9%) of the 65 children required CSF shunting. This number is consistent with the results from a very large multicenter study conducted by the Post-Hemispherectomy Hydrocephalus Workgroup on 690 children who underwent hemispherectomy where 23% required shunt treatment for hydrocephalus.³⁸ Most of the patients had improvement in behavior and developmental parameters, including language and social skills with better seizure control.^{39,40} Postoperative development was not negatively affected by the surgery. For example, some patients with tuberous sclerosis remained delayed but were no worse. In contrast, most patients made significant developmental gains after surgery.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Detailed clinical and demographic data.