

## RESEARCH ARTICLE

# Surgical evaluation in children <3 years of age with drug-resistant epilepsy: Patient characteristics, diagnostic utilization, and potential for treatment delays

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**Abstract**

**Objective:** Drug-resistant epilepsy (DRE) occurs at higher rates in children <3 years old. Epilepsy surgery is effective, but rarely utilized in young children despite developmental benefits of early seizure freedom. The present study aims to identify unique patient characteristics and evaluation strategies in children <3 years old who undergo epilepsy surgery evaluation as a means to assess contributors and potential solutions to health care disparities in this group.

**Methods:** The Pediatric Epilepsy Research Consortium Epilepsy Surgery Database, a multicentered, cross-sectional collaboration of 21 US pediatric epilepsy centers, collects prospective data on children <18 years of age referred for epilepsy surgery evaluation. We compared patient characteristics, diagnostic utilization, and surgical treatment between children <3 years old and those older undergoing initial presurgical evaluation. We evaluated patient characteristics leading to delayed referral (>1 year) after DRE diagnosis in the very young.

**Results:** The cohort included 437 children, of whom 71 (16%) were <3 years of age at referral. Children evaluated before the age of 3 years more commonly had abnormal neurological examinations ( $p = .002$ ) and daily seizures ( $p = .001$ ). At least one ancillary test was used in 44% of evaluations. Fifty-nine percent were seizure-free following surgery ( $n = 34$ ), with 35% undergoing limited focal resections. Children with delayed referrals more often had focal aware ( $p < .001$ ) seizures and recommendation for palliative surgeries ( $p < .001$ ).

**Significance:** There are relatively few studies of epilepsy surgery in the very young. Surgery is effective, but may be disproportionately offered to those with severe presentations. Relatively low utilization of ancillary testing may contribute to reduced surgical therapy for those without evident lesions on magnetic resonance imaging. Despite this, a sizeable portion of patients have favorable outcome after focal epilepsy surgery resections.

**KEYWORDS**

childhood epilepsy, epilepsy surgery, pharmacoresistant

**1 | INTRODUCTION**

Incidence of epilepsy is highest in the first years of life.<sup>1-3</sup> Drug-resistant epilepsy (DRE) occurs in one third of all people with epilepsy, with higher than average rates in children <3 years of age, ranging from 35% to 65%, possibly due to specific etiologies presenting in early childhood, such as structural brain abnormalities, early onset neurogenetic and metabolic disorders, and perinatal brain injury, each highly associated with intractability.<sup>4-7</sup> Age at seizure onset of <1 year and preexisting developmental delays predict development of DRE, yet one quarter of children without these characteristics will develop DRE within 1 year of seizure onset.<sup>6</sup> Early recognition and resolution of DRE is essential to optimize developmental

**Key Points**

- Epilepsy surgery in children <3 years of age is effective, leading to substantial seizure reduction in most patients
- Children evaluated for epilepsy surgery at very young age may disproportionately represent the most severe cases of drug-resistant epilepsy at that age
- Young candidates for palliative procedures may experience delay to surgical evaluation, yet experience outcomes equal to or better than other treatment options

outcome, as uncontrolled seizures at this critical period of brain development can result in developmental decline.<sup>6</sup>

Surgical therapy, consisting of localization and subsequent resection or ablation of the epileptogenic zone, can result in seizure freedom in appropriately chosen candidates, yet surgical therapy is less commonly utilized in children <3 years old.<sup>8</sup> Limited series have demonstrated epilepsy surgery is safe and effective in this age group, achieving seizure freedom in 60%–90% of patients, with evidence of improved developmental outcomes.<sup>4,9–11</sup> The paucity of epilepsy surgery in this age group is in part related to the unique challenges surrounding presurgical evaluation, surgical planning, and decision-making, given perceived risks from physiologic immaturity and limited blood volume.<sup>12</sup>

When surgical therapy is employed in children <3 years old with DRE, treatment frequently targets lesional epilepsy, and the abnormalities are more likely to be large multilobar or hemispheric pathologies. Prior studies have shown >80% of children <3 years of age with DRE offered surgical therapy had a lesional magnetic resonance imaging (MRI) and >50% underwent hemispherectomy or multilobar resections.<sup>9,13–16</sup> Given the underlying etiologies, these patients have high seizure burdens and significant developmental delays at the time of surgical referral. Nonetheless, among children <3 years of age with DRE, 48% have normal MRI and 26% are typically developing.<sup>6,17</sup> This disconnect suggests that surgical therapy in children <3 years old is disproportionately offered to those with the most severe epilepsy presentations, whereas those who stand to have the most developmental benefit from early seizure freedom are delayed or even excluded from surgical therapy. Given the relative infrequency of epilepsy surgery in children <3 years old, few studies have specifically examined epilepsy surgery in this age group.<sup>9,11–16</sup> Most are retrospective in design and performed by single surgical centers, which can be limited by local policies, small cohorts, available technology, and referral bias. Identifying favorable surgical candidates and potential barriers to referral would improve utilization, seizure freedom, and developmental outcomes in this age group. The present study, based on prospectively collected data from a large multicenter consortium, aims to define patient characteristics, evaluation strategies, and surgical techniques utilized in children <3 years of age referred for epilepsy surgery evaluation and to explore potential contributors to decreased surgery referrals and/or utilization in this population.

## 2 | MATERIALS AND METHODS

The Pediatric Epilepsy Surgery Database, a project of the Pediatric Epilepsy Research Consortium (PERC; [www.pediatricerc.org](http://www.pediatricerc.org)), is a collaboration of 21 US pediatric epilepsy centers prospectively enrolling children (0–18 years of age) referred for evaluation of surgical therapy for epilepsy. Sites identify patients for enrollment if they are (1) admitted for presurgical epilepsy evaluation, (2) discussed in a multidisciplinary epilepsy surgery conference, or (3) undergo epilepsy surgery during the enrollment period. Patients are enrolled regardless of whether they ultimately progress to surgical therapy. Database enrollment began January 2018 and has continued consecutively since. Sites obtain institutional review board approval prior to data collection; thus, sites initiate data contribution at varied start times following project inception. For this project, patients enrolled from January 2018 to April 2020 were submitted for analysis. Although all participating sites are designated as Level 4 centers by the National Association of Epilepsy Centers, total surgical volume varies between centers. The mean number of pediatric epilepsy surgeries performed per site during the enrollment period for this study was 24 (range = 3–60) in 2018 and 25 (range = 1–69) in 2019.

One hundred twelve common data elements are entered by local research staff into a shared Research Electronic Data Capture (REDCap) database housed at Cook Children's Medical Center.<sup>18,19</sup> REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources. A site identification number is combined with a consecutive 4-digit patient ID to create the unique PERC ID, cross-referenced at each site to the patient's medical record number. No protected health information is stored in the shared database. Sites maintain data locally and upload on a quarterly basis to the shared database for analysis and review of completeness. Study staff issue queries quarterly to be reconciled by local staff.

All sites utilize a manual of operations defining individual data elements to ensure data consistency. Although data are collected prospectively from enrollment, some data regarding epilepsy history and prior evaluation are collected retrospectively through review of records and patient interview. Baseline patient demographics collected include gender, race, ethnicity, referral source, insurance, and geographical distance from the treating epilepsy center. Epilepsy characteristics include age at onset, seizure types according to International League Against Epilepsy definitions,<sup>20</sup> seizure frequency, failed therapies, and examination findings. Neurological

examination is described as normal or abnormal and further categorized as cognitive/developmental delay, motor deficit, sensory deficit, or visual deficit. If available, age at DRE diagnosis is provided. We define DRE as the failure of two appropriate antiseizure medications (ASMs) used in adequate trials determined at each site. If the age at second ASM failure is not available, the age is recorded as “unknown.” The methods of presurgical evaluation are unique to each patient and are determined at the discretion of the treating center. Electroencephalographic (EEG) results are categorized as single seizure focus, multifocal, generalized, mixed generalized/focal, or indeterminate. Presence or absence of additional testing as part of the evaluation is recorded along with results categorized as follows: congruent, defined as imaging localization within the same hemisphere and lobe as EEG localization of seizure onset; discordant, defined as localization outside of the hemisphere and lobe of EEG localization; and normal. MRI results are recorded as abnormal if a lesion is present and reasonably felt to be the source of epilepsy. MRI findings such as global atrophy and nonspecific white matter changes are regarded as normal. Sites determine categorization of results and surgical candidacy for their patients, typically following multidisciplinary review in an epilepsy surgery conference attended by epileptologists, neurosurgeons, neuroradiologists, neuropsychologists, and other, ancillary staff. If surgery is offered, the type of surgery offered and whether invasive monitoring is required are recorded, as well as intent of the procedure, categorized as definitive (intended to result in seizure freedom) or palliative. For patients denied surgery, the reason for denial is categorized as inadequate data for localization, multifocal onset, risks outweighing benefit, or parent/patient declined. Outcome is collected at subsequent clinical follow-up and recorded based on Engel classification.<sup>21</sup>

For the purposes of this study, patients undergoing an initial presurgical evaluation were included. Patients previously evaluated for surgery and presenting for repeat evaluation and those with prior epilepsy surgery were excluded. To describe characteristics unique to children <3 years old referred for surgical evaluation, the cohort was initially divided into patients <3 years of age at referral for epilepsy surgery evaluation and those older. Patient characteristics, evaluation strategies, and surgical outcomes were described and compared by age at the time of referral ( $\leq 3.0$  vs.  $> 3.0$  years). Categorical variables were compared using Pearson chi-squared analysis, and continuous variables were compared using independent *t*-test. All statistical analysis was completed using IBM SPSS software, and level of significance was set at  $< .001$  following Bonferroni correction for multiple variables. After identifying characteristics of meaningful

difference between patients referred at  $< 3$  years and those older, we sought to determine factors that may delay epilepsy surgery despite DRE diagnosis at  $< 3$  years of age. We define early DRE as DRE diagnosed before the age of 3 years. Early referral for epilepsy surgery was defined as when a child was referred for evaluation within 1 year of DRE diagnosis. Among all children with seizure onset at  $< 3$  years of age, we compared patient and epilepsy characteristics of those with early DRE with those diagnosed as intractable later. To account for loss of data for patients where age at DRE diagnosis was unknown, we compared characteristics of those with unknown age at DRE to those with known age for meaningful differences. Patients with early DRE and early referral were compared to those with referral  $> 1$  year from DRE diagnosis for characteristics leading to delayed evaluation. Finally, among children referred at age  $< 3$  years, we compared children who were seizure-free to those not seizure-free following surgery to identify characteristics that may predict outcome.

### 3 | RESULTS

#### 3.1 | Patient characteristics

At the time of this analysis, the PERC Epilepsy Surgery Database included 602 children evaluated for epilepsy surgery. After excluding patients with prior presurgical evaluations or prior epilepsy surgery, 437 were included in this cohort. Patients referred for epilepsy surgery were equally distributed by gender (201 female/236 male), with the majority of White race (334/437, 76%) and non-Hispanic ethnicity (373/437, 85%). Most had private insurance (59%) and lived within 100 miles of a participating epilepsy center (69%). The majority had focal onset seizures (85%) with weekly or daily (69%) seizure frequency and abnormal MRIs (71%). The most common etiology (54%) was a structural abnormality such as cortical malformation or dysplasia.

Seventy-one patients (16%) were  $< 3$  years of age at the time of presurgical referral. Within this cohort, the mean age at seizure onset was .7 years ( $n = 71$ ,  $SD = .62$ ), mean age at DRE diagnosis was 1.2 years ( $n = 54$ ,  $SD = .81$ ), mean age at referral for surgical evaluation was 1.5 years ( $n = 71$ ,  $SD = .86$ ), and mean age at surgery was 1.8 years ( $n = 34$ , range = .3–3.8 years,  $SD = .98$ ). The characteristics of patients  $< 3$  years old at referral compared to those older at initial referral are shown in Table 1. There were no significant differences in gender, race, ethnicity, or insurance type between the two groups; however, those referred prior to age 3 years lived in closer proximity to referral centers ( $p = .05$ ).

Whereas the type of seizures and number of failed ASMs were similar between the groups, children referred at age <3 years more commonly had abnormal neurological examinations ( $p = .002$ ), daily seizures ( $p = .001$ ), abnormal MRI results ( $p = .042$ ), and known etiologies ( $p = .04$ ) at the time of referral.

### 3.2 | Evaluation strategies

Specific evaluations performed by age at referral are presented in Table 2. Compared to children referred after the age of 3 years, those referred at younger age underwent less ancillary testing. MRI was obtained as part of the evaluation in all children <3 years of age. Of these, 55 (77%) were performed using 3-T MRI and 15 (21%) using 1.5-T MRI, and 64 (90%) included at least one thin slice (i.e., 1 mm) sequence. The mean age at MRI was 1.4 years (SD = .85), with the majority of MRI studies done after the age at referral for Phase I evaluation. Eleven MRIs interpreted as normal were obtained at a mean age of 1.35 years (SD = .35). Sixty children <3 years old had abnormal MRI findings; 33 (55%) were multilobar or hemispheric (22 cortical malformations, four encephalomalacia, seven other), whereas 27 (45%) were unilobar abnormalities (20 focal cortical dysplasias [FCDs], four tumors with/without FCD, three vascular lesions). Of the unilobar lesions, 13 were frontal, 10 temporal, two parietal, one occipital and one unilobar was missing localization data. Among children <3 years at referral, 34 (48%) had only MRI/video-EEG, 31 (44%) had one other ancillary test, and six (8%) had more than one ancillary test. When ancillary testing was used, it was more often used in children with normal MRI or those without unilobar malformations. Fluorodeoxyglucose positron emission tomography was used most commonly and with similar frequency compared to older children. Although other neuroimaging (single photon emission computed tomography, magnetoencephalography [MEG], functional MRI [fMRI], other) was used less frequently in children <3 years of age, only fMRI was used significantly less compared to older children. A similar number of children were offered and underwent surgical treatment regardless of age at initial referral. At the time of data analysis for this study, 56 (79%) patients referred at age < 3 years had a surgical decision rendered; 45 (80%) were recommended for surgery. Thirty-four (76%) had completed surgery. Seventy-three percent of children <3 years old at referral underwent single stage procedures. When invasive monitoring was required, methods of evaluation were similar regardless of age at referral. Twelve children <3 years old were recommended for invasive monitoring, and nine underwent subsequent resective surgery (eight lesionectomies/

lobectomies, 50% Engel I at mean 24 months; one hemispherectomy, Engel IV at 26 months). All cases using invasive monitoring had abnormal MRIs, with the majority ( $n = 8$ , 66%) having unilobar lesions. Three of the four cases with multifocal lesions undergoing invasive monitoring underwent multilobar resective procedures (33% Engel I at mean 26 months).

Although surgery was performed at similar rates regardless of age at referral, children <3 years old more often underwent large procedures (i.e., hemispherectomy), whereas older children more commonly underwent neuromodulation or thermal ablation procedures, although this did not meet the stated level of significance. As a result, pathological specimens were more commonly available for children <3 years old. Malformations of cortical development were more commonly reported in children <3 years old, likely owing to the size of malformations and the tendency to offer resections in this age group. Surgical procedures were intended to be definitive in the majority of patients regardless of age, although palliative procedures were less common in children <3 years old. Type of surgery related to MRI findings is described in Table 3. When patients were denied surgery, the reasons were similar between the groups.

### 3.3 | Early DRE and time to surgery referral

Having identified characteristics unique to children <3 years of age at time of epilepsy surgery referral, we sought to identify characteristics in children intractable at this age responsible for delayed surgery. There were 202 patients with early life epilepsy (onset at <3 years) who were referred for surgical evaluation. Of these, 176 (87%) qualified as having DRE at the time of referral.

The age at DRE diagnosis was known for 143 (81.3%); 79 (55%) had early DRE diagnosis, and 64 (45%) were older than 3 years at diagnosis of DRE. We were unable to determine the age at DRE diagnosis in 33 (18.8%) patients due to lack of adequate retrospective records or parental recall. Patients with unknown age at DRE diagnosis had older mean age at the time of referral (7.2 vs. 5.5 years,  $p = .03$ ), had longer duration between seizure onset and referral (6.2 vs. 4.6,  $p = .04$ ), and had failed fewer ASMs (2.4 vs. 3.5,  $p = .001$ ). For children in whom age at becoming drug resistant was unknown, they were less often African American ( $p = .043$ ), lived further away from the surgical center ( $p = .023$ ), and more often had focal seizures ( $p = .028$ ). There were no significant differences among children with epilepsy onset at <3 years with early DRE compared to those with later DRE diagnosis.

**TABLE 1** Baseline patient characteristics compared by age at referral

Characteristic	<3 years at referral, n = 71	>3 years at referral, n = 366	p
Demographics			
Gender, M:F	33:38	168:198	.93
Race			
White	51 (72%)	283 (77%)	.31
Black	11 (15%)	33 (9%)	
Other	9 (13%)	50 (14%)	
Ethnicity			
Hispanic	12 (17%)	40 (11%)	.13
Non-Hispanic	59 (83%)	314 (86%)	
Unknown	0	12 (3%)	
Insurance type			
Private	35 (49%)	222 (61%)	.29
Public	35 (49%)	138 (38%)	
Self-pay	1 (2%)	4 (1%)	
Distance to surgical center			
<50 miles	44 (62%)	181 (49%)	.05
51–100 miles	15 (21%)	63 (17%)	
101–500 miles	10 (14%)	109 (30%)	
>500 miles	2 (3%)	13 (4%)	
Epilepsy characteristics			
Type of seizure			
Focal	65 (92%)	307 (84%)	.06
Generalized	4 (6%)	44 (12%)	
Unknown	2 (1%)	13 (4%)	
Frequency of seizure			
Daily	43 (61%)	122 (33%)	.001
Weekly	14 (20%)	123 (34%)	
Monthly	8 (11%)	73 (20%)	
>Monthly	6 (8%)	46 (13%)	
Abnormal neurological exam	48 (68%)	165 (45%)	.002
Mean number of failed ASMs	2.66 (SD = 1.9)	3 (SD = 1.9)	.16
Abnormal MRI	60 (85%)	253 (69%)	.04

Abbreviations: ASM, antiseizure medication; F, female; M, male; MRI, magnetic resonance imaging.

Finally, we sought to determine patient characteristics that may contribute to delayed surgical referral in a child with early onset DRE. Of the 79 children with early DRE, 49 (62%) were referred within 1 year of DRE diagnosis and the rest had delayed referrals. There were significant differences between those referred early versus late with regard to mean age at referral (1.5 vs. 5.9 years,  $p < .001$ ), duration from seizure onset to referral (.9 vs. 5.2 years,  $p < .001$ ), and number of failed ASMs prior to referral (2.7 vs. 5.2,  $p < .001$ ). Children with delayed referrals for epilepsy surgery were more likely to have abnormal

neurological examinations ( $p = .037$ ) and generalized ( $p = .03$ ) or focal aware ( $p < .001$ ) seizure types, and to be recommended for surgeries that were intended to be palliative ( $p < .001$ ).

### 3.4 | Unique populations

There were 11 children with normal MRIs referred for epilepsy surgery evaluation prior to the age of 3 years. Of these, only one had been offered surgery and was Engel

**TABLE 2** Diagnostic utilization and surgical treatment

Diagnostic test	<3 years at referral, <i>n</i> = 71	>3 years at referral, <i>n</i> = 366	<i>p</i>
Ictal data on EEG			
Single focus	39 (55%)	180 (49%)	.44
Multifocal	11 (15%)	66 (18%)	
Generalized	0	21 (6%)	
Mixed generalized	5 (7%)	24 (7%)	
Indeterminate	3 (4%)	14 (4%)	
Blank	13 (18%)	61 (17%)	
Ancillary testing			
1 ancillary test	31 (44%)	118 (32%)	.75
>1 ancillary test	6 (8%)	108 (30%)	
PET	33 (46%)	188 (51%)	
SPECT	5 (7%)	88 (24%)	
MEG	6 (8%)	70 (19%)	
fMRI	0 (0%)	99 (27%)	
Other <sup>a</sup>	1 (1%)	25 (7%)	<.001
Surgery			
Surgical decision rendered	56 (79%)	283 (77%)	.77
Surgery offered	45 (80%)	219 (77%)	.90
Surgery denied	11	64	.70
Inadequate data	4	25	
Multifocal	2	17	
Nonepileptic	1	2	
Risks/benefit	1	6	
Other	5 <sup>b</sup>	13 <sup>c</sup>	
Invasive monitoring	12 (27%)	99 (45%)	.07
Grids/strips	3 (25%)	10 (10%)	
SEEG	6 (50%)	77 (77%)	
Depths	2 (17%)	2 (2%)	
Grids/strips and SEEG	0	2 (2%)	
Patient declined	0	3 (3%)	
Missing data	1 (8%)	5 (5%)	
Surgery performed	34 (76%)	162 (74%)	.85
Type of surgery			
Lesionectomy	11 (32%)	42 (23%)	.01
Lobectomy	12 (35%)	35 (22%)	
Hemispherectomy	9 (26%)	19 (12%)	
Laser ablation	0	19 (12%)	
Corpus callosotomy	0	9 (6%)	
Neuromodulation	1 (3%)	32 (20%)	
Other	1 (3%)	6 (6%)	
Other	1 (3%)	6 (6%)	
Intent of surgery			
Definitive	28 (82%)	105 (67%)	.11
Palliative	6 (18%)	57 (35%)	

(Continues)

**TABLE 2** (Continued)

Diagnostic test	<3 years at referral, <i>n</i> = 71	>3 years at referral, <i>n</i> = 366	<i>p</i>
Pathology <sup>d</sup>			
Inflammatory	0	5 (3%)	.001
Malformation	22 (65%)	25 (15%)	
MTS	0	12 (7%)	
Tumor	6 (18%)	20 (12%)	
Vascular	2 (6%)	4 (2%)	
Other	8 (24%)	43 (27%)	
No pathology sent	4 (12%)	71 (44%)	

Abbreviations: EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MTS, mesial temporal sclerosis; PET, positron emission tomography; SEEG, stereo-EEG; SPECT, single photon emission computed tomography.

<sup>a</sup>Wada test, transcranial magnetic stimulation, and Curry source localization.

<sup>b</sup>Other comprised two seeking care elsewhere, two needing additional testing, and one declining.

<sup>c</sup>Other comprised three needing additional testing, two still considering surgery, and eight declining.

<sup>d</sup>May have >1 pathology reported.

**TABLE 3** Type of surgical treatment based on MRI findings

MRI finding	Type of surgery	Seizure-free, <i>n</i> (%), mean duration in months
Abnormal MRI, <i>n</i> = 33		
Hemispheric/multilobar, <i>n</i> = 13	6 hemispherectomy	4 (66%), 22.2
	6 lesionectomy/ lobectomy	2 (30%), 26.7
	1 neuromodulation	0, 12
Unilobar, <i>n</i> = 20	17 lesionectomy/ lobectomy	11 (64%), 21.4
	3 hemispherectomy	1 (33%), 27.3
	Lobectomy	1 (100%), 24
Normal MRI, <i>n</i> = 1		
	Lobectomy	1 (100%), 24

Abbreviation: MRI, magnetic resonance imaging.

I at 24 months after left temporal lobectomy. Four were denied surgery (two genetic epilepsy, one nonepileptic, one multifocal), and the remaining patients were still undergoing evaluation. A total of 18 patients with early DRE with normal MRIs underwent evaluation at any age. Of these, seven had been offered and completed surgery. Four were denied surgery (two multifocal, one nonepileptic, one risk/benefit), and seven were still undergoing evaluation.

### 3.5 | Surgical therapy

Of the 34 patients <3 years old who had completed surgery, the mean follow-up was 23 months (range = 4–40 months; Table 4). Thirty-two (94%) had outcome at 1 year, and 18 (53%) had up to 2 years of follow-up postsurgery. Overall, 59% reported Engel I outcome, with mean follow-up of

21.9 ± 8.4 months. There were no significant differences between patients with seizure-free outcome versus those without among children <3 years old at referral, although the number of patients was small.

There was no difference in outcome among children referred for surgery before the age of 3 years comparing those undergoing early versus late epilepsy surgery. However, children undergoing palliative procedures were more often delayed for referral, yet all (*n* = 6) patients who underwent palliative epilepsy surgeries in this age group reported >50% seizure reduction (Engel I, *n* = 1; Engel II, *n* = 2; Engel III, *n* = 3).

## 4 | DISCUSSION

Relative to older children, patients referred for surgical evaluation before the age of 3 years are more likely to have



**TABLE 4** Seizure outcome for children referred for epilepsy surgery at <3 years of age

Characteristic	Seizure-free, <i>n</i> = 19	Not seizure-free, <i>n</i> = 15	<i>p</i>
Demographics			
Gender, M:F	9:10	7:8	.968
Race			
White	15	11	.183
Black	3	0	
Other	1	4	
Ethnicity			
Hispanic	2	6	.04
Non-Hispanic	17	9	
Unknown	0	0	
Insurance type			
Private	9	9	.564
Public	9	6	
Self-pay	1	0	
Epilepsy characteristics			
Type of seizure			
Focal	18	13	.410
Generalized	1	2	
Unknown	0	0	
Frequency of seizure			
Daily	13	10	.702
Weekly	4	3	
Monthly	2	1	
>Monthly	0	1	
Abnormal neurological exam	14	12	.666
Mean number of failed ASMs	2.2	3.5	.079
Abnormal MRI	18	15	.367
Ictal data on EEG			
Single focus	13	10	.683
Multifocal	3	3	
Generalized	0	0	
Mixed generalized	2	1	
Indeterminate	1	0	
Blank	0	1	
Ancillary testing			
0	6	8	.440
1	11	6	
>1	2	1	
Invasive monitoring			
1-stage	15	10	.420
2-stage	4	5	

(Continues)

TABLE 4 (Continued)

Characteristic	Seizure-free, <i>n</i> = 19	Not seizure-free, <i>n</i> = 15	<i>p</i>
Type of surgery			
Lesionectomy	5	4	.728
Lobectomy	7	4	
Lesionectomy/lobectomy	0	1	
Hemispherectomy	5	4	
Laser ablation	0	0	
Corpus callosotomy	0	0	
Neuromodulation	0	1	
Other	2	1	
Early referral (<1 year from DRE diagnosis)	13	8	.656

Abbreviations: ASM, antiseizure medication; DRE, drug-resistant epilepsy; EEG, electroencephalogram; F, female; M, male; MRI, magnetic resonance imaging.

daily or weekly seizures, and tend to have an abnormal neurologic examination. Although they more commonly have lesions on MRI and structural abnormalities (cortical malformations/cortical dysplasia) this did not reach the stated level of significance for our study, likely owing to small sample size. It can be inferred that our cohort (consisting only of referred patients) underrepresents those with DRE without MRI lesions, those with monthly or less frequent seizures, and those with normal examinations. This hypothesized group of younger patients with DRE represents an opportunity for improvement, as some of them might benefit from surgical treatment despite their lack of a clear lesion on imaging, abnormal examination, or frequent seizures. Shorter duration of uncontrolled seizures increases likelihood of seizure freedom following surgery, contributing to associated benefits in cognitive and developmental outcome.<sup>22</sup>

Although MRI and video-EEG monitoring constituted the only testing for a plurality of the <3-year age group, a substantial number of younger patients had at least one ancillary test. Interestingly, increased utilization of ancillary testing in this younger and predominantly lesional population did not lead to improved outcome. Justification for selection of one testing regimen over another was not recorded, but it can be hypothesized that some modalities—those requiring sedation for younger patients or those based upon more complex cooperation, such as fMRI—would be used less frequently in younger patients. These factors may contribute to decreased utilization of epilepsy surgery in nonlesional patients for whom ancillary testing would facilitate surgical planning or determine candidacy, and the impact of additional testing in such a cohort cannot be determined from this study. However, many children <3 years of age are lesional and undergo large multilobar and hemispheric resections; thus, ancillary testing for sublobar localization may be unnecessary for most. Some modalities, in

particular MEG for infants, are not available at most centers, potentially leading to an underrepresentation of younger patients with that method of evaluation. At this point, it is speculative as to why young children without MRI abnormalities or abnormal examinations undergo epilepsy surgery evaluation less frequently. Perhaps there is a perception that these children may be more likely to have a self-limited epilepsy despite its early refractory course. However, a referral for epilepsy surgery should not be misconstrued to mean that the patient is a definite surgical candidate. This is the population that might best benefit from a more comprehensive evaluation, which may include ancillary testing that has been less utilized in this age group. Additionally, many centers have started to safely and successfully perform stereo-EEG for seizure localization in very young children with modified surgical techniques to address concerns regarding skull thickness.<sup>23–27</sup> With knowledge of some of the logistic barriers or inherent limitations to testing in this age group, careful selection of ancillary testing tailored to the patient may help identify appropriate surgical candidates and reduce lag time between the development of drug resistance and eventual surgery.

There was no significant racial disparity between younger and older patients in our cohort. It must be noted, however, that this speaks only to the apparently consistent workup and outcomes among referred patients at participating sites, and does nothing to indicate whether patients of all races and ages are equitably referred in the first place. A smaller proportion of <3-year-old patients live >100 miles from their study center, suggesting that patients from rural/remote areas may not be referred for evaluation of DRE as quickly. The authors hypothesize that rural patients are disproportionately managed more often by a general neurologist rather than an epileptologist. Interestingly, a similar phenomenon has been reported among adults, where greater distance from an

epilepsy surgical center was associated with a prolonged interval from time of DRE diagnosis to referral for surgical evaluation.<sup>28</sup>

Data on postsurgical seizure frequency are encouraging, as we found a high rate of Engel Class I (59%) and II (18%) outcomes a mean of 23 months out from surgery. This is similar to prior studies where Engel I and II outcomes were achieved in 90%,<sup>11,14</sup> although the current cohort had a greater proportion of focal resections (35% vs. 26%), and proportionately fewer multilobar and hemispherectomy surgeries.<sup>14</sup> It remains to be seen whether this degree of seizure remission proves durable in a younger population, and continued outcomes will be tracked by this PERC group. The developmental benefits of reduced seizures/medications following a successful surgery remain speculative. Prior studies show the majority of patients with successful early life epilepsy surgery have a stable developmental velocity ( $\pm 15$  developmental quotient [DQ]/intelligence quotient [IQ] points compared to presurgical evaluation), although these studies have been limited by recruitment bias (weighted toward patients with severe neurodevelopmental disability prior to surgery), small enrollment size, a lack of standardized developmental assessment tools, and limited duration of follow-up.<sup>14,29</sup> Factors previously demonstrated to have the highest association with developmental improvement include surgery at <12 months of age and shorter preoperative duration of epilepsy; spasm as a semiology also correlated with postsurgical developmental outcome, although not clearly independently of the prior two factors.<sup>11</sup> In this study, the duration from development of DRE to surgical referral was approximately 4 months and the duration from DRE diagnosis to surgery was 8 months. Although this duration is felt to be expedient in the setting of complex evaluations, opportunities for improvement still exist. The importance of longer interval follow-up to see potential developmental gains has also been noted, with Freitag and Tuxhorn noting a greater proportion of children with significant improvement further out from surgery (6% at 1 year vs. 22% at last known follow-up).<sup>30</sup> Ongoing challenges to developmental assessments in this age group include factors related to patient engagement, due to either age or disability, and inconsistent application of standardized assessment tools in the epilepsy clinic, necessitating a reliance on developmental pediatric and neuropsychology colleagues. Underlying genetic etiology of a structural DRE remains another potential independent contributor to overall developmental potential, which may significantly impact DQ/IQ even with Engel I or II outcomes. The current study precedes PERC's inclusion of neuropsychology elements before/after epilepsy surgery, which will allow

for a greater capacity in assessing potential long-term benefits in future studies.

There are relatively few studies of epilepsy surgery in the very young. To our knowledge, this study is the largest cohort to date capturing the presurgical evaluation in children younger than 3 years. It also appears to be the first to describe in detail the presurgical workup for this age group. The participating programs cover a range of sizes, include academically affiliated and private institutions, and draw from both larger and smaller populations and catchment areas. Although the sample size is comparable to prior studies, the prospective ascertainment in this study reduces potential sources of bias. The overall demographic distributions in this study appear comparable to other pediatric epilepsy cohorts and US demographics, although this does not address the potential for systemic health disparities.

Limitations of this study include a potential referral bias in younger patients toward those with lesional DRE; the proportion of <3-year-old patients with DRE and normal MRIs in the general population is not captured in these data. We also lack complete data on the chronologic progression from first seizure to DRE. A long period between a patient's first seizure and their referral for surgical evaluation may represent an unnecessary delay, or may simply reflect a patient whose seizures were well controlled for a period of time before blossoming into more refractory epilepsy. We did not collect surgical complications in our dataset and, therefore, cannot make conclusions on safety of surgery in the very young, although only one patient in this cohort was deceased following surgery related to underlying malignancy.

Epilepsy surgery in children <3 years of age with DRE is an effective treatment, leading to substantial and sustained seizure reduction in most patients. Key differences between these young patients and other pediatric patients include the higher presurgical seizure burden, presence of larger lesions, and relative paucity of referrals during the early life period for patients with normal imaging and/or neurologic examination. This warrants not only a deeper investigation into the prevalence of nonlesional DRE in children <3 years old, but also an exploration of the biopsychosocial factors that may be hindering a more timely surgical evaluation.

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#### CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## REFERENCES

- Camfield CS, Camfield PR, Gordon K, Wirrell E, Dooley JM. Incidence of epilepsy in childhood and adolescence: a population-based study in Nova Scotia from 1977 to 1985. *Epilepsia*. 1996;37:19–23.
- Wirrell EC, Grossardt BR, Wong-Kisiel LC, Nickels KC. Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study. *Epilepsy Res*. 2011;95:110–8.
- Aabert KM, Gunnes N, Bakken IJ, Søråas CL, Berntsen A, Magnus P, et al. Incidence and prevalence of childhood epilepsy: a nationwide cohort study. *Pediatrics*. 2017;139:1–9.
- Vignoli A, Peron A, Turner K, Scornavacca GF, La Briola F, Chiesa V, et al. Long-term outcome of epilepsy with onset in the first three years of life: findings from a large cohort of patients. *Eur J Paediatr Neurol*. 2016;20:566–72.
- Berg AT, Zelko FA, Levy SR, Testa FM. Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes: a prospective cohort study. *Neurology*. 2012;79:1384–91.
- Berg AT, Wusthoff C, Shellhaas RA, Loddenkemper T, Grinspan ZM, Saneto RP, et al. Immediate outcomes in early life epilepsy: a contemporary account. *Epilepsy Behav*. 2019;97:44–50.
- Wirrell E, Wong-Kisiel L, Mandrekar J, Nickels K. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: a retrospective, population-based study. *Epilepsia*. 2012;53:1563–9.
- Baud MO, Perneger T, Racz A, Pensel MC, Elger C, Rydenhag B, et al. European trends in epilepsy surgery. *Neurology*. 2018;91:96–106.
- Duchowny M, Jayakar P, Resnick T, Harvey AS, Alvarez L, Dean P, et al. Epilepsy surgery in the first three years of life. *Epilepsia*. 1998;39:737–43.
- Jenny B, Smoll N, El Hassani Y, Momjian S, Pollo C, Korff CM, et al. Pediatric epilepsy surgery: could age be a predictor of outcomes? *J Neurosurg Pediatr*. 2016;18:235–41.
- Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E. Developmental outcome after epilepsy surgery in infancy. *Pediatrics*. 2007;119:930–5.
- Pindrik J, Hoang N, Smith L, Halverson M, Wojnaroski M, McNally K, et al. Preoperative evaluation and surgical management of infants and toddlers with drug-resistant epilepsy. *Neurosurg Focus*. 2018;45:1–12.
- Gowda S, Salazar F, Bingaman WE, Kotagal P, Lachhwani DL, Gupta A, et al. Surgery for catastrophic epilepsy in infants 6 months of age and younger. *J Neurosurg Pediatr*. 2010;5:603–7.
- Dunkley C, Kung J, Scott RC, Nicolaides P, Neville B, Aylett SE, et al. Epilepsy surgery in children under 3 years. *Epilepsy Res*. 2011;93:96–106.
- Sugimoto T, Otsubo H, Hwang PA, Hoffman HJ, Jay V, Snead OC III. Outcome of epilepsy surgery in the first three years of life. *Epilepsia*. 1999;40:560–5.
- Wyllie E, Comair YG, Kotagal P, Raja S, Ruggieri P. Epilepsy surgery in infants. *Epilepsia*. 1996;37:625–37.
- Coryell J, Gaillard WD, Shellhaas RA, Grinspan ZM, Wirrell EC, Knupp KG, et al. Neuroimaging of early life epilepsy. *Pediatrics*. 2018;142:e20180672.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377–81.
- Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software partners. *J Biomed Inform*. 2019;95:103208.
- Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522–30.
- Engel J, Van Ness P, Rasmussen T, Ojemann I. Outcome with respect to epileptic seizures. In: Engel J Jr, editor. *Surgical treatment of the epilepsies*. 2nd ed. New York, NY: Raven Press; 1993. p. 609–21.
- Gracia CG, Yardi R, Kattan MW, Nair D, Gupta A, Najm I, et al. Seizure freedom score: a new simple method to predict success of epilepsy surgery. *Epilepsia*. 2015;56:359–565.
- Karsonovich T, Alexander A, Graber S, O'Neil BR. Placement of leads for stereotactic electroencephalography without the use of anchor bolts: technical note. *J Neurosurg Pediatr*. 2020;18:1–6.
- Taussig D, Dorfmueller G, Fohlen M, Jalin C, Bulteau C, Ferrand-Sorbets S, et al. Invasive explorations in children younger than 3 years. *Seizure*. 2012;21:631–8.
- Taussig D, Chipaux M, Fohlen M, Dorison N, Bekaert O, Ferrand-Sorbets S, et al. Invasive evaluation in children (SEEG vs subdural grids). *Seizure*. 2020;77:43–51.
- Liu Y, Chen G, Chen J, Zhou J, Su L, Zhao T, et al. Individualized stereoelectroencephalography evaluation and navigated resection in medically refractory pediatric epilepsy. *Epilepsy Behav*. 2020;112:107398.
- Kim LH, Parker JJ, Ho AL, Pendharkar AV, Sussman ES, Halpern CH, et al. Postoperative outcomes following pediatric intracranial electrode monitoring: a case for stereoelectroencephalography (SEEG). *Epilepsy Behav*. 2020;104(pt A):106905.
- Roberts JI, Hrazdil C, Wiebe S, Sauro K, Hanson A, Federico P, et al. Feasibility of using an online tool to assess appropriateness for an epilepsy surgery evaluation. *Neurology*. 2014;83:913–9.
- Pulsifer MB, Brandt J, Salorio CF, Vining EPG, Carson BS, Freeman JM. The cognitive outcome of hemispherectomy in 71 children. *Epilepsia*. 2004;45:243–54.
- Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. *Epilepsia*. 2005;46(4):561–7.

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