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Article type : Research Article

Surgical Evaluation in Children Less Than Three Years of Age with Drug Resistant Epilepsy: Patient Characteristics, Diagnostic Utilization, and Potential for Treatment Delays

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/EPI.17124

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Keywords: pharmacoresistant, childhood epilepsy, epilepsy surgery

Text Pages: 16

Word Count: 3925

References: 29

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Figures: 0

Tables: 3

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Summary

Objective: Drug resistant epilepsy (DRE) occurs at higher rates in children less than three years old. Epilepsy surgery is effective, but rarely utilized in young children despite developmental benefits to early seizure freedom. The present study aims to identify unique patient characteristics and evaluation strategies in children less than three years 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 multi-centered, cross-sectional collaboration of 21 US pediatric epilepsy centers, collects prospective data on children under 18 years of age referred for epilepsy surgery evaluation. We compared patient characteristics, diagnostic utilization, and surgical treatment between children less than three years and those older undergoing initial presurgical evaluation. We evaluated patient characteristics leading to delayed referral (> 1 year) from DRE diagnosis in the very young.

Results: The cohort included 437 children, 71 (16%) less than three years of age at referral. Children evaluated before age three more commonly had abnormal neurological exams ($p=0.002$) and daily seizures ($p=0.001$). 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 ($p<0.001$) seizures and recommendation for palliative surgeries ($p<0.001$).

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

Keywords: pharmacoresistant, childhood epilepsy, epilepsy surgery

Introduction

Incidence of epilepsy is highest in the first years of life.[1-3] Drug resistant epilepsy (DRE) occurs in one third of all people with epilepsy with higher than average rates in children less than three years of age, ranging from 35-65%, 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.[4-7] Age of seizure onset less than one year and preexisting developmental delays predict development of DRE, yet a quarter of children without these characteristics will develop DRE within one year of seizure onset.[6] Early recognition and resolution of DRE is essential to optimize developmental outcome, as uncontrolled seizures at this critical period of brain development can result in developmental decline.[6]

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 less than three years.[8] 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.[4,9-11] 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.[12]

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When surgical therapy is employed in children less than three years with DRE, treatment frequently targets lesional epilepsy, and the abnormalities are more likely to be large multilobar or hemispheric pathologies. Prior studies have shown over 80% of children less than three years of age with DRE offered surgical therapy have a lesional MRI and over 50% underwent hemispherectomy or multilobar resections.[9,13-16] Given the underlying etiologies, these patients have high seizure burdens and significant developmental delays at the time of surgical referral. Yet among children less than three years of age with DRE, 48% have normal MRI and 26% are typically developing.[6,17] This disconnect suggests that surgical therapy in children less than three years is disproportionally offered to those with the most severe epilepsy presentations, while those that 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 less than three years, few studies have specifically examined epilepsy surgery in this age group.[9, 11-16] Most are retrospective in design and performed by single surgical centers, which can be limited by local policies, small cohorts, available technology, as well as 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 multi-center consortium, aims to define patient characteristics, evaluation strategies, and surgical techniques utilized in children less than three years of age referred for epilepsy surgery evaluation and explore potential contributors to decreased surgery referrals and/or utilization in this population.

Methods

The Pediatric Epilepsy Surgery Database, a project of the Pediatric Epilepsy Research Consortium (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: (i) admitted for pre-surgical epilepsy evaluation; (ii) discussed in a multidisciplinary epilepsy surgery conference; or (iii) undergo epilepsy surgery during the enrollment

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period. Patients are enrolled regardless of whether they ultimately progress to surgical therapy. Database enrollment began January 2018 and has enrolled consecutively since. Sites obtain institutional IRB 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. While 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 REDCap (Research Electronic Data Capture) database housed at Cook Childrens.[18-19] 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. While data is collected prospectively from enrollment, some data regarding epilepsy history and prior evaluation is 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 of onset, seizure types according to ILAE definitions[20], seizure frequency, failed therapies, and exam findings.

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Neurological exam 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 after failing two appropriate antiseizure medications (ASM) 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 determined at the discretion of the treating center. 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 of EEG localization of seizure onset; discordant, defined as localization outside of 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, 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.[21]

For the purposes of this study, patients undergoing an initial presurgical evaluation were included. Patients previously evaluated for surgery and presenting for repeat evaluation or those with prior epilepsy surgery were excluded. To describe characteristics unique to children less than three years referred for surgical evaluation, the cohort was initially divided into patients less than three 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

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referral (≤3.0 y vs > 3.0 y). Categorical variables were compared using Pearson chi-square 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 <0.001 following Bonferonni correction for multiple variables. After identifying characteristics of meaningful difference between patients referred less than three years and those older, we sought to determine factors which may delay epilepsy surgery despite DRE diagnosis less than three years of age. We define early DRE when diagnosed before age three years. Early referral for epilepsy surgery was defined when a child was referred for evaluation within one year of DRE diagnosis. Among all children with seizure onset less than three 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 of DRE diagnosis was unknown, we compared characteristics of those with unknown age of DRE to those with known age for meaningful differences. Patients with early DRE and early referral were compared to those with referral greater than one year from DRE diagnosis for characteristics leading to delayed evaluation. Finally, among children referred at age less than three years, we compared children seizure free to those not following surgery to identify characteristics that may predict outcome.

Results

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

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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 less than three years of age at the time of presurgical referral. Within this cohort, the mean age of seizure onset was 0.7 years (n=71, SD 0.62), mean age of DRE diagnosis 1.2 years (n=54, SD 0.81), mean age at referral for surgical evaluation 1.5 years (n=71, SD 0.86), and mean age of surgery 1.8 years (n=34, range 0.3-3.8 years, SD 0.98). The characteristics of patients less than three years 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 three years lived in closer proximity to referral centers (p=0.05).

While the type of seizures and number of failed ASMs were similar between the groups, children referred at age less than three years more commonly had abnormal neurological examinations (p=0.002), daily seizures (p=0.001), abnormal MRI results (p=0.042), and known etiologies (p=0.04) at the time of referral.

Evaluation Strategies

Specific evaluations performed by age at referral are presented in Table 2. Compared to children referred after age three years, those referred at younger age underwent less ancillary testing. MRI was obtained as part of the evaluation in all children less than three years of age. Of these, 55 (77%) were performed using 3T MRI, 15 (21%) 1.5 T, and 64 (90%) included at least one thin slice (i.e.1mm) sequence. The mean age at MRI was 1.4 years (SD 0.85) with the majority of MRI studies done after the age of referral for phase I evaluation. Eleven MRIs interpreted as normal were obtained at a mean age of 1.35 years (SD 0.35). Sixty children less than three years had abnormal MRI findings, 33 (55%) were multilobar or hemispheric (22 cortical malformations, 4 encephalomalacia, 7 other), while 27 (45%) were unilobar

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abnormalities (20 focal cortical dysplasias (FCD), 4 tumor with/without FCD, 3 vascular lesions). Of the unilobar lesions, 13 were frontal, 10 temporal, 2 parietal, and 1 occipital. Among children less than three years at referral, 34 (48%) had only MRI/VEEG, 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. FDG-PET was used most commonly and with similar frequency compared to older children. While other neuroimaging (SPECT, MEG, fMRI, other) was used less frequently in children under three 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 less than three years had a surgical decision rendered, 45 (80%) recommended for surgery. Thirty four (76%) had completed surgery. Seventy-three percent of children less than three years at referral underwent single stage procedures. When invasive monitoring was required, methods of evaluation were similar regardless of age at referral. Twelve children less than three years were recommended for invasive monitoring and nine underwent subsequent resective surgery (8 lesionectomy/lobectomy, 50% Engel 1 at mean 24 m; 1 hemispherectomy, Engel 4 at 26 months). All cases using invasive monitoring had abnormal MRIs with the majority (8, 66%) having unilobar lesions. Three of the four cases with multifocal lesions undergoing invasive monitoring underwent multilobar resective procedures (33% Engel 1 at mean 26 months).

While surgery was performed at similar rates regardless of age at referral, children less than three years more often underwent large procedures (i.e. hemispherectomy), while older children more commonly underwent neuromodulation or thermal ablation procedures, though this did not meet the stated level of significance. As a result, pathological specimens were more commonly available for children less than three years. Malformations of cortical development were more commonly reported in children less than three years, likely owing to size of malformations and tendency to offer resections in this age group. Surgical procedures were intended to be definitive in the majority of patients regardless of age, though palliative procedures were less

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common in children less than three years. Type of surgery related to MRI findings is described in Table 3. When patients were denied surgery, the reasons were similar between the groups.

Early DRE and Time to Surgery Referral

Having identified characteristics unique to children less than three 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 less than three years) who were referred for surgical evaluation. Of these, 176 (87%) qualified as having DRE at the time of referral.

The age of DRE diagnosis was known for 143 (81.3%), 79 (55%) had early DRE diagnosis and 64 (45%) were older than three years at diagnosis of DRE. We were unable to determine the age of DRE diagnosis in 33 (18.8%) patients due 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 y, p=0.03), longer duration between seizure onset and referral (6.2 vs 4.6, p=0.04), and had failed fewer ASMs (2.4 vs 3.5, p=0.001). For children in whom age of becoming drug resistant was unknown, they were less often African American (p=0.043), lived further away from the surgical center (p=0.023), and more often had focal seizures (p=0.028). There were no significant differences among children with epilepsy onset less than three years with early DRE compared to those with later DRE diagnosis.

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 one year of DRE diagnosis and the rest had delayed referrals. There were significant differences between those referred early versus late with regards to mean age at referral (1.5 vs 5.9 y, p<0.001), duration from

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seizure onset to referral (0.9 vs 5.2 y, p<0.001), and failed ASMs prior to referral (2.7 vs 5.2, p<0.001). Children with delayed referrals for epilepsy surgery were more likely to have abnormal neurological examinations (p=0.037), generalized (p=0.03) or focal aware (p<0.001) seizure types, and recommended for surgeries that were intended to be palliative (p<0.001).

Unique populations

There were 11 children with normal MRIs referred for epilepsy surgery evaluation prior to age three years. Of these, only one has been offered surgery and is Engel 1 at 24 months post left temporal lobectomy. Four were denied surgery (2 genetic epilepsy, 1 nonepileptic, 1 multifocal) and the remaining patients are still undergoing evaluation. There were a total of 18 patients with early DRE with normal MRIs that underwent evaluation at any age. Of these, seven have been offered and completed surgery. Four were denied surgery (2 multifocal, 1 nonepileptic, 1 risk/benefit) and seven are still undergoing evaluation.

Surgical Therapy

Of the 34 patients less than three years that have completed surgery, the mean follow-up is 23 months (range 4-40 months). Thirty-two (94%) had outcome at one year, and 18 (53%) had up to two years follow-up post surgery. Overall, 59% reported Engel 1 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 less than three years at referral, though the number of patients was small.

There was no difference in outcome among children referred for surgery before age three 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 that underwent palliative epilepsy surgeries in this age group reported >50% seizure reduction (1, Engel 1; 2, Engel 2; 3, Engel 3).

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Discussion

Relative to older children, patients referred for surgical evaluation before the age of three years are more likely to have daily or weekly seizures, and tend to have an abnormal neurologic exam. While they more commonly have lesions on MR imaging 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 drug resistant epilepsy without MR lesions, those with monthly or less frequent seizures, and those with normal exams. 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 exam, or frequent seizures. Indeed, shorter duration of uncontrolled seizures increases likelihood of seizure freedom following surgery contributing to associated benefits in cognitive and developmental outcome.[22]

While MRI and video EEG monitoring constituted the only testing for a plurality of the less than three-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 does 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, in fact, contribute to decreased utilization of epilepsy surgery in non-lesional 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 less than three years of age are lesional and undergo large multilobar and hemispheric resections, thus ancillary testing for sublobar localization may be unnecessary for most.

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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 MR abnormalities or abnormal exams 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 who might best benefit from a more comprehensive evaluation that 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 for skull thickness.[23-27] 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 with a reduced 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 amongst 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 less than 3 year patients live more than 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 amongst adults, where greater distance from an epilepsy surgical center was associated with a prolonged interval from time of DRE to referral for surgical evaluation.[28]

Data on post-surgical 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

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surgery. This is similar to prior studies where Engel 1 & 2 outcomes were achieved in 90%[11,14], although the current cohort had a greater proportion of focal resections (35% vs 26%), and proportionately fewer multilobar and hemispherectomy surgeries.[14] 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 (+/- 15 DQ/IQ points of presurgical evaluation), although these studies have been limited by recruitment bias (weighted towards patients with severe neurodevelopmental disability prior to surgery), small enrollment size, a lack of standardized developmental assessment tools, and limited duration of follow-up.[14,29] Factors previously demonstrated to have the highest association with developmental improvement include surgery at <12 months of age and shorter pre-operative duration of epilepsy; spasm as a semiology also correlated with post-surgical developmental outcome, although not clearly independent of the prior two factors.[11] In this study, the duration from development of DRE to surgical referral was approximately four months and the duration from DRE diagnosis to surgery was eight months. While 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 & Tuxhorn noting a greater proportion of children with significant improvements further out from surgery (6% at 1 year vs 22% at last known follow-up).[30] Ongoing challenges to developmental assessments in this age group include factors related to patient engagement, either due to age or disability, and inconsistent application of standardized assessment tools in epilepsy clinic, necessitating a reliance on developmental pediatric and neuropsychology colleagues. Underlying genetic etiology of a structural drug-resistant epilepsy remains another potential independent contributor to overall developmental potential, which may significantly impact DQ/IQ even with Engel 1 or 2 outcomes. The current study precedes PERC's inclusion of neuropsychology elements pre-/post-epilepsy surgery, which will allow for a greater capacity in assessing potential long-term benefits in future studies.

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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 pre-surgical evaluation in children younger than three years of age. It also appears to be the first to describe in detail the pre-surgical workup for this age group. The participating programs cover a range of sizes, include academic affiliated and private institutions, and draw from both larger and smaller populations and catchment areas. While 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 appears 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 towards those with lesional DRE; the proportion of less than 3 year patients with DRE and normal MRIs in the general population is not captured in this 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 – though only one patient in this cohort is deceased following surgery related to underlying malignancy.

Epilepsy surgery in children less than 3 years of age with DRE is an effective treatment, leading to a substantial and sustained seizure reduction in most patients. Key differences between these young patients and other pediatric patients include the higher pre-surgical seizure burden, presence of larger lesions, and a 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 non-lesional DRE in children less than three years, but also an exploration of the biopsychosocial factors that may be hindering a more timely surgical evaluation.

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Disclosures: 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.

Key Points:

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

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Table 1: Baseline patient characteristics compared by age at referral

	< 3y at referral (n=71)	>3 y at referral (n=366)	p-value
Demographics			0.93
Gender (M:F)	33:38	168:198	
Race			0.31
White	51 (72%)	283 (77%)	
Black	11 (15%)	33 (9%)	
Other	9 (13%)	50 (14%)	
Ethnicity			0.13
Hispanic	12 (17%)	40 (11%)	
Non-Hispanic	59 (83%)	314 (86%)	
Unknown	0	12 (3%)	
Insurance type			0.29
Private	35 (49%)	222 (61%)	
Public	35 (49%)	138 (38%)	
Self pay	1 (2%)	4 (1%)	

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Distance to surgical center			0.05
<50 miles	44 (62%)	181 (49%)	
51-100 miles	15 (21%)	63 (17%)	
101-500 miles	10 (14%)	109 (30%)	
>500 miles	2 (3%)	13 (4%)	
Epilepsy Characteristics			0.06
Type of seizure			
Focal	65 (92%)	307 (84%)	
Generalized	4 (6%)	44 (12%)	
Unknown	2 (1%)	13 (4%)	
Frequency of seizure			0.001
Daily	43 (61%)	122 (33%)	
Weekly	14 (20%)	123 (34%)	
Monthly	8 (11%)	73 (20%)	
>Monthly	6 (8%)	46 (13%)	
Abnormal neurological exam	48 (68%)	165 (45%)	0.002
Mean number of failed ASMs	2.66 (SD 1.9)	3 (SD 1.9)	0.16
Abnormal MRI	60 (85%)	253 (69%)	0.04

Table 2: Diagnostic Utilization and Surgical Treatment

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Diagnostic Test	< 3y at referral (n=71)	>3 y at referral (n=366)	p-value
Ictal Data on EEG			0.44
Single Focus	39 (55%)	180 (49%)	
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%)	
>1 Ancillary test	6 (8%)	108 (30%)	
PET	33 (46%)	188 (51%)	0.75
SPECT	5 (7%)	88 (24%)	0.006
MEG	6 (8%)	70 (19%)	0.05
fMRI	0 (0%)	99 (27%)	<0.001
Other[1]	1 (1%)	25 (7%)	
Surgery			
Surgical decision rendered	56 (79%)	283 (77%)	0.77
Surgery Offered	45 (80%)	219 (77%)	0.90
Surgery Denied	11	64	0.70
Inadequate data	4	25	
Multifocal	2	17	
Nonepileptic	1	2	

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Risks/benefit	1	6	
Other	5[2]	13[3]	
Invasive monitoring	12 (27%)	99 (45%)	0.07
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%)	0.85
Type of surgery			0.01
-Lesionectomy	11 (32%)	42 (23%)	
-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%)	
Intent of Surgery			0.11
-Definitive	28 (82%)	105 (67%)	
-Palliative	6 (18%)	57 (35%)	
Pathology[3]			0.001
-Inflammatory	0	5 (3%)	
-Malformation	22 (65%)	25 (15%)	

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-MTS[4]	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%)	

1: Wada, transcranial magnetic stimulation, and Curry source localization; 2: other comprised 2 seeking care elsewhere, 2 needing additional testing, and 1 declined; 3: other comprised 3 needing additional testing, 2 are still considering surgery, and 8 have declined; 3: may have >1 pathology reported; 4: MTS=mesial temporal sclerosis

Table 3: Type of surgical treatment based on MRI findings

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

Table 4: Seizure outcome for children referred for epilepsy surgery < 3 years of age

	Seizure Free N = 19	Not Seizure Free N = 15	p-value
Demographics			

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Gender (M:F)	9:10	7:8	0.968
Race			0.183
White	15	11	
Black	3	0	
Other	1	4	
Ethnicity			0.04
Hispanic	2	6	
Non-Hispanic	17	9	
Unknown	0	0	
Insurance type			0.564
Private	9	9	
Public	9	6	
Self pay	1	0	
Epilepsy Characteristics			
Type of seizure			0.410
Focal	18	13	
Generalized	1	2	
Unknown	0	0	

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Frequency of seizure			0.702
Daily	13	10	
Weekly	4	3	
Monthly	2	1	
>Monthly	0	1	
Abnormal neurological exam	14	12	0.666
Mean number of failed ASMs	2.2	3.5	0.079
Abnormal MRI	18	15	0.367
Ictal Data on EEG			0.683
Single Focus	13	10	
Multifocal	3	3	
Generalized	0	0	
Mixed generalized	2	1	
Indeterminate	1	0	
Blank	0	1	
Ancillary Testing			0.440

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0	6	8	
1	11	6	
>1	2	1	
Invasive monitoring			0.420
1 Stage	15	10	
2 Stage	4	5	
Type of surgery			0.728
-Lesionectomy	5	4	
-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 (< 1y from DRE diagnosis)	13	8	0.656

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