Preoperative evaluation and surgical management of infants and toddlers with drug-resistant epilepsy

*Jonathan Pindrik, MD,^{1,2} Nguyen Hoang, MD,² Luke Smith, MD,² Mark Halverson, MD,³ Mary Wojnaroski, PhD,⁴ Kelly McNally, PhD, ABPP,⁴ Satyanarayana Gedela, MD, MRCP,⁵ and Adam P. Ostendorf, MD⁵

¹Division of Pediatric Neurosurgery, Department of Neurosurgery, ³Division of Pediatric Neuroradiology, Department of Radiology, and ⁴Section of Pediatric Psychology and Neuropsychology, Department of Pediatrics, Nationwide Children's Hospital; ²Department of Neurological Surgery, The Ohio State University College of Medicine; and ⁵Division of Child Neurology, Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, Ohio

OBJECTIVE Despite perioperative risks, epilepsy surgery represents a legitimate curative or palliative treatment approach for children with drug-resistant epilepsy (DRE). Several factors characterizing infants and toddlers with DRE create unique challenges regarding optimal evaluation and management. Epilepsy surgery within children < 3 years of age has received moderate attention in the literature, including mainly case series and retrospective studies. This article presents a systematic literature review and explores multidisciplinary considerations for the preoperative evaluation and surgical management of infants and toddlers with DRE.

METHODS The study team conducted a systematic literature review based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, targeting studies that investigated children < 3 years of age undergoing surgical treatment of DRE. Using the PubMed database, investigators selected peer-reviewed articles that reported seizure outcomes with or without developmental outcomes and/or perioperative complications. Studies were eliminated based on the following exclusion criteria: sample size < 5 patients; and inclusion of patients > 3 years of age, when demographic and outcomes data could not be separated from the cohort of patients < 3 years of age.

RESULTS The study team identified 20 studies published between January 1990 and May 2017 that satisfied eligibility criteria. All selected studies represented retrospective reviews, observational studies, and uncontrolled case series. The compiled group of studies incorporated 465 patients who underwent resective or disconnective surgery (18 studies, 444 patients) or vagus nerve stimulator insertion (2 studies, 21 patients). Patient age at surgery ranged between 28 days and 36 months, with a mean of 16.8 months (1.4 years).

DISCUSSION The study team provided a detailed summary of the literature review, focusing on the etiologies, preoperative evaluation, surgical treatments, seizure and developmental outcomes, and potential for functional recovery of infants and toddlers with DRE. Additionally, the authors discussed special considerations in this vulnerable age group from the perspective of multiple disciplines.

CONCLUSIONS While presenting notable challenges, pediatric epilepsy surgery within infants and toddlers (children < 3 years of age) offers significant opportunities for improved seizure frequency, neuro-cognitive development, and quality of life. Successful evaluation and treatment of young children with DRE requires special consideration of multiple aspects related to neurological and physiological immaturity and surgical morbidity.

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KEYWORDS drug-resistant epilepsy; epilepsy surgery; infants; toddlers; phase I evaluation; phase II monitoring

ABBREVIATIONS DNET = dysembryoplastic neuroepithelial tumor; DQ = developmental quotient; DRE = drug-resistant epilepsy; ECog = electrocorticography; EEG = electroencephalography; ESM = electrical stimulation mapping; ETLE = extratemporal lobe epilepsy; FCD = focal cortical dysplasia; FDG = fluorodeoxyglucose; ICEEG = intracranial electroencephalography; ICP = intracranial pressure; LTME = long-term monitoring electroencephalography; MCD = malformations of cortical development; MEG = magnetoencephalography; PET = positron emission tomography; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SEEG = stereotactic electroencephalography; SLA = stereotactic laser ablation; SWS = Sturge-Weber syndrome; TSC = tuberous sclerosis complex; VNS = vagus nerve stimulator.

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* J.P. and N.H. contributed equally to this work and share first authorship.

DRUG-RESISTANT epilepsy (DRE), defined as inadequate seizure control despite adequate trials of two antiseizure medications, represents a debilitating condition for adults and children.⁴⁷ A subset of patients with DRE may achieve seizure control following surgical intervention. While presenting notable challenges, pediatric epilepsy surgery within infants and toddlers (children < 3 years of age) offers significant opportunities for seizure freedom or reduction, developmental recovery and/or improvement, and enhanced quality of life for both patients and families.^{24,64,69} Cerebral plasticity during infancy and early childhood also offers potential benefits of enhanced functional recovery following surgery. However, young chronological and developmental age create unique challenges regarding presurgical evaluation (phase I monitoring), surgical planning, and decision-making due to increased risks from physiological immaturity and limited blood volume.

Improvements in presurgical evaluation, neuroimaging, neuro-anesthesia, and surgical technique have increased the safety and potential for favorable outcomes in the surgical management of DRE in very young patients. Many articles (mostly case series) have reported clinical outcomes with invasive epilepsy surgery involving children < 3 years of age. In this article, the authors provide a systematic literature review and explore special considerations for the preoperative evaluation and surgical management of infants and toddlers with DRE.

Methods

A systematic literature review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, analyzing data from studies reporting on children < 3 years of age undergoing surgical treatment of DRE and reported seizure outcomes with or without developmental outcomes and/or perioperative complications. Using the PubMed database, the study team searched for articles published from January 1985 through May 2018 with the following key terms: (“epilepsy surgery,” “epilepsy,” “resection,” “VNS,” “vagus nerve stimulation,” “callosotomy”) AND (“pediatric,” “toddlers,” “young,” “infancy,” “infants,” “children”). Additional manuscripts were found through reference lists from pertinent articles. Full-text English language studies published in peer-reviewed journals were selected. Studies were excluded based on the following: 1) sample size < 5 patients and 2) inclusion of patients older than 3 years, when demographic and outcomes data could not be separated from the cohort of patients less than 3 years of age. Eligible studies were evaluated critically based on study type and characteristics. From each qualifying study, investigators abstracted the following information: patient demographics, seizure etiology, surgical interventions, histopathology, seizure and developmental outcomes, and perioperative complications.

Results

The initial search criteria identified 1710 studies from the PubMed database and exploration of reference lists from pertinent studies (Fig. 1). Twenty eligible stud-

FIG. 1. PRISMA flowchart for study selection. This diagram demonstrates the selection of peer-reviewed studies based on PRISMA guidelines and the study team's inclusion and exclusion criteria.

ies were identified; all were published between January 1990 and May 2017. This systematic search revealed no randomized controlled trials or prospective cohort studies satisfying the criteria for inclusion, as 2 notable studies were eliminated based on the inability to separate data for patients less than 3 years of age.^{23,55} All selected studies represented retrospective reviews, observational studies, and uncontrolled case series, representing low quality of evidence.

Within the 20 included manuscripts, data were available for 465 individuals who underwent resective or disconnective surgery (18 studies, 444 individuals total) or vagus nerve stimulator (VNS) insertion (2 studies, 21 individuals total) (Tables 1 and 2). The studies varied widely regarding number of patients, with a range of 5 to 116.^{21,69} Among these studies, patient age at surgery ranged between 28 days and 36 months, with a mean of 16.8 months.

Discussion

Summary of Literature Review

In contrast to the typical etiologies of DRE in older children and adults, the etiologies of DRE predominating in very young children included hemispheric syndromes such as Sturge-Weber syndrome (SWS), Rasmussen encephalitis, and hemimegalencephaly; malformations of cortical development (MCD) such as focal cortical dysplasia (FCD), polymicrogyria, and heterotopias; vascular malformations or stroke; tuberous sclerosis complex (TSC); neoplasms such as ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), other low-grade tumors, and malignant tumors; gliosis; and prior infection such as encephalitis (Table 1).^{30,35,40,44,45,50,51,69,70,73} Prevalence estimates of each etiology generally agreed with those reported by Harvey et al. in children younger than 4 years with DRE in an international survey of epilepsy procedures.³⁴ Overall, only approximately 1% of infants and toddlers with DRE (4 of 444) harbored hippocampal sclerosis.

The distinct etiologies of DRE in children below 3

TABLE 1. Summary of reported series of intracranial epilepsy surgery in children under 3 years of age

Authors & Year	No. of Pts	Age at Surgery (mean)	Etiology	Surgical Operation	Sz Outcome	Dev Outcome	Compl
Duchowny et al., 1990	5	2–11 mos (7.3 mos)	Gliosis, 2 (40%); neoplasm, 1 (20%); TSC, 1 (20%); idiopathic, 1 (20%)	Multilobar resection, 1 (20%); lobar/focal resection, 3 (60%); palliative/focal resection, 1 (20%)	Engel I, 3 (60%); Engel II, 1 (20%); Engel III, 1 (20%)	NR	NR
Chugani et al., 1993	20	6–33 mos (14.1 mos)	MCD, 11 (55%); gliosis, 4 (20%); hemimeg, 2 (10%); cystic malformation, 2 (10%); TSC, 1 (5%)	Hemispherotomy, 8 (40%); multilobar resection, 11 (55%); lobar/focal resection, 1 (5%)	Sz freedom, 13 (65%); 90% ctrl, 2 (10%); 75% ctrl, 1 (5%); no impr, 4 (20%)	No formal validated assessment	NR
Wyllie et al., 1996	12	2.5–29 mos (15.3 mos)	MCD, 5 (42%); neoplasm, 3 (25%); SWS, 3 (25%); hemimeg, 1 (8%)	Hemispherotomy, 5 (42%); multilobar resection, 2 (17%); lobar/focal resection, 5 (42%)	Engel I, 6 (50%); Engel II, 3 (25%); Engel III, 2 (17%); Engel IV, 1 (8%)	No formal validated assessment; report of 58% “catch-up” progress, 25% stable dev	Mortality, 1 (8%); SDH, 1 (20% of hemispherotomy pts)
Duchowny et al., 1998	31	0.9–36 mos (18.3 mos)	MCD, 18 (58%); neoplasm, 6 (19%); SWS, 2 (6%); hemimeg, 1 (3%); TSC, 1 (3%); other, 3 (9%)	Hemispherotomy, 14 (45%); multilobar resection, 3 (10%); lobar/focal resection, 14 (45%)	Sz freedom, 16 (61%); >90% ctrl, 4 (13%); <90% ctrl, 6 (19%)	No formal validated assessment; among Sz-free pts, 1 progressed; all Sz-free pts had stable dev	Mortality, 2 (6%)
Sugimoto et al., 1999	20	3–34 mos (15.3 mos)	MCD, 8 (35%); neoplasm, 3 (13%); SWS, 5 (22%); hemimeg, 3 (13%); peri-/postnatal infarction, 2 (9%); hippocampal sclerosis, 1 (4%); other, 1 (4%)	Hemispherotomy, 11 (48%); multilobar resection, 3 (13%); lobar/focal resection, 9 (39%)	Engel I, 12 (52%); Engel II, 3 (13%); Engel III, 6 (26%); Engel IV, 2 (9%)	NR	NR
Bittar et al., 2002	11	5–33 mos (15.0 mos)	Peri-/postnatal infarction, 3 (27%); neoplasm, 2 (18%); hemimeg, 2 (18%); MCD, 1 (9%); SWS, 1 (9%); TSC, 1 (9%); vascular malformations, 1 (9%); hippocampal sclerosis, 1 (9%)	Hemispherotomy, 7 (64%); lobar/focal resection, 4 (36%)	Sz freedom, 8 (73%); >90% reduction, 2 (18%); >75% reduction, 1 (9%)	No formal validated assessment; report of accelerated devl rate in 82%	Periop compl, 36%; unexpected neurol deficit, 1 (9%); HC, 3 (27%); pneumonia, 1 (9%); intraop hemorrhage, 1 (9%); postop coagulopathy, 1 (9%)
Kang et al., 2006	9	4–35 mos (19.5 mos)	MCD, 7 (78%); TSC, 2 (22%)	Lobar/focal resection, 6 (67%); functional disconnection, 3 (33%)	Engel I, 6 (67%); Engel II, 2 (22%); Engel III, 1 (11%)	NR	None
Battaglia et al., 2006	26	4–33 mos (8.5 mos)	MCD, 10 (38%); hemimeg, 7 (27%); neoplasm, 6 (23%); peri-/postnatal infarct, 2 (8%); SWS, 1 (4%)	Hemispherotomy, 7 (30%); multilobar resection, 8 (35%); lobar/focal resection, 8 (35%)	Engel I, 17 (65%); Engel II, 7 (27%); Engel III, 1 (6%); Engel IV, 1 (6%)	Impr in DQ/IQ, 2 (8%); stable DQ/IQ, 20 (77%); worse DQ/IQ, 4 (15%)	NR
Loddenkemper et al., 2007	24	3–33 mos (14 mos)	MCD, 12 (50%); hemimeg, 7 (29%); SWS, 2 (8%); neoplasm, 2 (8%); TSC, 1 (4%)	Hemispherotomy, 14 (58%); multilobar resection, 6 (25%); lobar/focal resection, 4 (17%)	Sz freedom, 17 (71%); >90% reduction, 5 (21%); >50% reduction, 1 (4%); no impr, 1 (4%)	BSID assessment; impr in DQ, 17 (71%); surgery at age <12 mos correlated w/ impr in DQ (p < 0.001)	NR

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TABLE 1. Summary of reported series of intracranial epilepsy surgery in children under 3 years of age

Authors & Year	No. of Pts	Age at Surgery (mean)	Etiology	Surgical Operation	Sz Outcome	Dev Outcome	Compl
Maton et al., 2008	13	6–33 mos (14 mos)	Neoplasm, 6 (46%); MCD, 4 (31%); peri-/postnatal infarction, 1 (8%); gliosis, 1 (8%); encephalitis, 1 (8%)	Lobar/focal resection, 13 (100%)	Engel I, 10 (77%); Engel II, 2 (15%); Engel IV, 4 (31%)	NR	Periop compl, 3 (23%); stroke w/ permanent hemiparesis, 2 (15%); infection/HC, 1 (8%)
Steinbok et al., 2009	116	1–35 mos (15.8 mos)	MCD, 57 (49%); neoplasm, 22 (19%); SWS, 19 (16%); hemimeg, 8 (7%); peri-/postnatal infarction, 1 (1%); TSC, 1 (1%); gliosis, 1 (1%); other, 10 (9%); encephalitis, 1 (1%)	Hemispherectomy, 40 (34%); lesionectomy, 35 (30%); cortical resection, 33 (28%); temporal lobectomy, 7 (6%); corpus callosotomy, 1 (1%)	Engel I, 72 (67%); Engel II, 15 (14%); Engel III, 12 (11%); Engel IV, 8 (7%)	Impr in dev'l delay, 55%; stable dev'l delay, 33%; worse dev'l delay, 12%	Periop compl, 55%; infection, 11%; HC, 5%; SDH/EDH, 3%
Gowda et al., 2010	15	1.5–6 mos (4 mos)	MCD, 8 (53%); hemimeg, 6 (40%); TSC, 1 (7%)	Hemispherectomy, 11 (73%); multilobar resection, 3 (20%); lobar/focal resection, 1 (7%)	Engel I, 6 (46%); Engel II, 2 (15%); Engel III, 3 (23%); Engel IV, 2 (15%)	NR	Periop compl, 5 (33%); aseptic meningitis, 4 (27%); cerebral infarct, 1 (7%)
Dunkley et al., 2011	42	3–36 mos (20 mos)	MCD, 26 (62%); hemimeg, 5 (12%); SWS, 5 (12%); neoplasm, 2 (5%); peri-/postnatal infarction, 1 (2%); TSC, 1 (2%); hippocampal sclerosis, 1 (2%)	Hemispherectomy, 27 (23%); multilobar resection, 4 (3%); lobar/focal resection, 11 (9%)	Sz freedom, 20 (48%); >90% reduction, 13 (31%); >75% reduction, 4 (10%); >50% reduction, 2 (5%); no impr, 4 (10%)	BSID & GSMD assessment; no sig change in cog ability following surgery ($p = 0.5$); decline in dev, 26%; improvement in dev, 13% (all w/ IS)	Early compl, 0 (0%); HC, 5 (20% of pts undergoing hemispherectomy)
Iwatani et al., 2012	6	5–26 mos (15.5 mos)	MCD, 4 (66%); hemimeg, 1 (17%); PVL, 1 (17%)	Hemispherectomy, 2 (33%); cortical resection, 2 (50%); multilobar dissection, 1 (17%); corpus callosotomy, 1 (33%)	Engel I, 4 (67%); Engel III, 2 (33%)	Improved motor function, 6 (100%); improved DA, 5 (83%)	None
Ramantani et al., 2013	30	5–33.5 mos (20 mos)	MCD, 18 (60%); hemimeg, 6 (20%); neoplasm, 3 (10%); peri-/postnatal infarction, 3 (10%)	Hemispherectomy, 16 (47%); multilobar resection, 7 (21%); lobar/focal resection, 11 (32%)	Engel I, 22 (73%); Engel II/III, 5 (17%); Engel IV, 3 (10%)	Stable dev velocity, 75%; worse dev velocity, 25%; positive corr btwn pre- & postop dev'l status; neg corr btwn postop dev'l status & EOR	Surgical compl, 15%; HC, 4 (25% of pts undergoing hemispherectomy); ICH, 1 (6%)
Kumar et al., 2015	25	11 days–11.5 mos (4.7 mos)	MCD, 10 (40%); hemimeg, 8 (32%); peri-/postnatal infarction, 2 (8%); neoplasm, 1 (4%); SWS, 1 (4%); TSC, 1 (4%); gliosis, 1 (4%); other, 1 (4%)	Hemispherectomy, 16 (64%); grid-based resection, 7 (28%); lobar/focal resection, 9 (36%)	Engel I, 20 (80%); Engel II, 2 (8%); Engel IV, 3 (12%)	NR	Periop compl, 9 (36%); HC, 5 (20%); mortality, 1 (4%); infection, 1 (4%)
Jenny et al., 2016	19	5–36 mos	MCD, 7 (37%); neoplasm, 3 (16%); hemimeg, 2 (11%); peri-/postnatal infarction, 1 (5%); SWS, 1 (5%); TSC, 3 (16%); hippocampal sclerosis, 1 (5%); hamartoma, 1 (5%)	Hemispherectomy, 4 (21%); lobar/focal resection, 15 (79%)	Engel I, 17 (89%); Engel III/IV, 2 (11%)	NR	Periop compl, 15.3% overall (incl infants & children/adolescents); intraparenchymal ICH, 1 (5%)

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TABLE 1. Summary of reported series of intracranial epilepsy surgery in children under 3 years of age

Authors & Year	No. of Pts	Age at Surgery (mean)	Etiology	Surgical Operation	Sz Outcome	Dev Outcome	Compl
Gröppel et al., 2018	20	3–32 mos (16.2 mos)	MCD, 10 (50%); peri-/postnatal infarction, 5 (25%); neoplasm, 2 (10%); SWS, 2 (10%); gliosis, 1 (5%)	Hemispherectomy, 11 (55%); lobar/focal resection, 9 (45%)	ILAE 1a, 13 (65%); ILAE 1, 1 (5%); ILAE 3, 1 (5%); ILAE 4, 5 (25%)	Median SIQ score improved postop by 22%; Sz-free infants showed greater increase than toddlers in SIQ (28% vs 20%)	Periop compl, 5 (25%); HC, 3 (15%); DVT, 1 (5%); hyponatremia, 1 (5%)
Combined total	444	28 days–36 mos (16.8 mos)	MCD, 220 (50%); neoplasm, 62 (14%); SWS, 41 (9%); hemimeg, 59 (13%); peri-/postnatal infarction, 22 (5%); TSC, 14 (3%); gliosis, 10 (2%); cystic malformations, 2 (<1%); vascular malformations, 1 (<1%); hippocampal sclerosis, 4 (1%); other, 18 (4%)	Hemispherectomy, 186 (42%); multilobar resection, 50 (11%); lobar/focal resection, 200 (45%); corpus callosotomy, 4 (1%)	Sz-free/Engel I, 283 (64%)	Dev'l impr, 8–71%; 3 studies demonstrated impr in majority of pts; dev'l stability, 33–77%; 3 studies demonstrated stability in majority of pts; dev'l decline, 12–26%; no studies demonstrated decline in majority of pts	Surgical/periop compl reported, 0–55%; mortality reported, 0–8%

BSID = Bayley Scales of Infant Development; cog = cognitive; compl = complications; ctrl = control; dev = development; dev'l = developmental; DQ = developmental quotient; EDH = epidural hematoma; Engel = Engel class; EOR = extent of resection; GSMD = Griffiths Scales of Mental Development; HC = hydrocephalus; hemimeg = hemimegalencephaly; ICH = intracranial hemorrhage; ILAE = International League Against Epilepsy class; impr = improvement; intraparench = intraparenchymal; IQ = intelligence quotient; IS = infantile spasms; MCD = malformations of cortical development; neg = negative; neurol = neurological; NR = not reported; pos = positive; pts = patients; PVL = periventricular leukomalacia; SDH = subdural hematoma; sig = significant; SIQ = social interaction quotient; SWS = Sturge-Weber syndrome; Sz = seizure; TSC = tuberous sclerosis complex.

years of age require different surgical approaches. In this systematic review, approximately 90% of surgeries involved extratemporal resections, multilobar resections, or hemispherectomies/hemispherotomies. In contrast, temporal lobe and anteromesial temporal resections comprise more than 50% of epilepsy surgeries performed in older children and adults.^{34,62} Anatomical hemispherectomy and functional hemispherotomy accounted for 42% of epilepsy surgeries performed in infants and toddlers, representing a much higher frequency than similar extensive surgery in older patients.

Larger areas of resection or disconnection improve seizure outcomes in this young age group. Reported seizure-freedom rates for infants and toddlers undergoing surgical treatment of DRE vary between 45% and 90% overall and 65% and 85% specifically for young patients undergoing hemispherotomy or hemispherectomy.^{12,13,15,20–22,30,31,35,40,42,45,50–53,58,59,69,70,73} Sugimoto et al. demonstrated more

favorable postsurgical outcomes in young patients with SWS and low-grade gliomas as compared to MCD, while reporting superior seizure outcomes for patients undergoing hemispherectomy (82% Engel class I or II) as opposed to focal cortical resection (50% Engel class I or II).⁷⁰ In another retrospective series, young patients with DRE due to SWS who underwent complete cortical resection or hemispherectomy/hemispherotomy had better rates of seizure freedom (94%) than those who underwent subtotal resection (30%).¹³ Hemimegalencephaly and cortical dysplasia typically confer worse prognoses regarding seizure outcomes without surgery.^{35,50,69} Despite these challenges, Honda et al. reported an acceptable seizure-freedom rate (66.7%) in infants with hemimegalencephaly following early hemispherotomy, with the patients who did not gain seizure freedom achieving significantly reduced seizure frequency and improved quality of life.³⁵ VNS insertion has provided for seizure reduction in 33%–66% of children less than 3 years of age, with a 0%–13% rate of surgical complications (device infection), although data are limited due to lower utilization rates in very young children (Table 2).^{27,75}

In open intracranial surgery, targeted plans may incorporate preoperative studies and/or invasive monitoring to better define extents of resection. Chugani et al. demonstrated the utility of positron emission tomography (PET) in the surgical treatment of young patients (age range 5 months to 3 years) with DRE and infantile spasms.¹⁶ The authors reported consistent findings of abnormal cerebral glucose metabolism (typically hypo-metabolism, 18/23) in all patients studied, with good correlation to interictal and ictal electrographic abnormalities during scalp long-term monitoring electroencephalography (LTME). Given these concordant phase I monitoring findings, the surgical team performed single-stage operations involving cortical resection (15/23) or hemispherectomy (8/23), without the need for invasive testing and with favorable seizure outcomes (65% Engel class I; 78% with ≥ 90% seizure reduction or control).¹⁵ Other published data highlight limitations of noninvasive testing. Snead et al. demonstrated that only 2 of 13 (15%) children with DRE exhibited concordant findings between fluorodeoxyglucose (FDG)-PET and chronic invasive monitoring.⁶⁷ In young children, given the higher

TABLE 2. Summary of reported series on VNS insertion in children under 3 years of age

Authors & Year	No. of Pts	Age Range, mos (mean)	Etiology	Sz Outcome	Dev Outcome	Complications
Zamponi et al., 2008	6	6–31 (17.8)	Malignant migrating partial epilepsy of infancy, 3 (50%); peri-/postnatal infarction, 1 (17%); hemimeg, 1 (17%); TSC, 1 (17%)	Sz freedom, 1 (17%); 60–90% reduction, 4 (67%); no impr, 1 (17%)	No sig impr	None
Fernandez et al., 2015	15	12–35 (26)	Aicardi syndrome, 3 (20%); Miller-Dicker syndrome, 1 (7%); neuronal migration disorder, 1 (7%); genetic w/o brain malformation, 1 (7%); perinatal insult, 1 (7%); idiopathic, 3 (20%)	Improved, 2 (14%); unchanged, 8 (57%); worse, 4 (29%)	NR	Device infection, 2 (13%)

prevalence of extratemporal lobe epilepsy (ETLE), FDG-PET may fail to recognize congenital structural anomalies like MCD or may inadequately estimate the extent of the epileptogenic zone.⁶⁷

In the context of discordant (or insufficient) phase I monitoring findings, invasive monitoring may determine the epileptogenic zone and identify eloquent cortex. Intracranial electroencephalography (ICEEG) has been performed safely and effectively in young children using intraoperative electrocorticography (ECog) or extraoperative subdural LTME. Sugimoto et al. reported the ability to identify epileptiform discharges during intraoperative ECog from all study patients (23/23) 0–3 years of age undergoing single-stage surgery for DRE with various etiologies.⁷⁰ In that retrospective series, nearly 80% (18/23) of patients exhibited concordant localization of ictal and interictal abnormalities, while 43% (10/23) showed concordant localization of intraoperative ECog and preoperative ictal scalp LTME findings.⁷⁰ Duchowny et al. demonstrated the safety and utility of extraoperative subdural LTME with reduced arrays (due to smaller cortical surface areas) in children below 3 years of age.^{20,21} In their retrospective study, the authors described subdural grid insertion in 11 of 31 patients undergoing subsequent phase II monitoring, sensorimotor electrical stimulation mapping (ESM) with direct cortical stimulation, and epileptogenic zone and lesion resection sparing eloquent cortex.²⁰ Similarly, Maton et al. described subdural electroencephalography (EEG) electrode insertion in 6 (of 20) young patients with successful localization of the epileptogenic zone (but with less success with ESM).⁵²

Newer paradigms offer the potential for less-invasive strategies in the evaluation and treatment of patients with DRE. While applied more frequently in older children and adults, stereotactic electroencephalography (SEEG) with robotic-arm assistance and stereotactic thermal coagulation or laser ablation (SLA) represent minimally invasive options. Cossu et al. performed a retrospective study of a series of young children (8/15 < 36 months of age) undergoing SEEG for DRE and reported acceptable mortality (1/15), morbidity, and success rates (80% Engel class I or II) following resection or radiofrequency thermal coagulation.¹⁷ Intracerebral electrodes also facilitated ESM.¹⁷

Despite potentially catastrophic presentations during early life, infants and toddlers with DRE may achieve seizure freedom or substantial seizure reduction following surgery. Retrospective studies have demonstrated greater rates of seizure freedom in children 3 years of age

or younger compared to patients 4–17 years of age.⁴⁰ Reported rates of seizure freedom following epilepsy surgery in infants and toddlers range between 48% and 89.5%, including 65%–85% following hemispherotomy or hemispherectomy.^{6,13,15,35,37,40,50,51,69,70,73} In general, patients with ETLE exhibit lower rates of seizure freedom (56%–68% Engel class I) than patients with TLE undergoing temporal lobectomy (60%–100%).^{25,40} However, infants and toddlers experience a higher prevalence of ETLE and may respond better to resection, with seizure freedom rates as high as 82%.^{25,40} Earlier surgical intervention increases the likelihood of success, as a meta-analysis has shown that preoperative epilepsy duration of 7 years or less represented a positive predictive factor for Engel class I outcome.²⁵ Earlier surgical intervention also may foster improvements in global development and neuro-cognition by decreasing the disruptive effects of refractory seizures and interictal abnormalities.^{13,20,25,35,40,51,68,73}

Young patients with structural hemispheric abnormalities and DRE often exhibit contralateral hemiparesis, other neurological deficits (contralateral hemianopia), cognitive impairments, and developmental delay.^{30,69} Consequently, many epilepsy surgical teams advocate earlier surgical intervention to optimize seizure control, functional retention or recovery, and neuro-cognitive development.^{6,13,35,37,51} Retrospective studies have reported significant improvements in global, motor, and speech development following functional hemispherotomy or cortical resections in young patients with DRE and preoperative developmental delay.^{15,37,73} For example, earlier intervention represented a positive predictive factor for developmental improvement in young SWS patients with DRE and baseline developmental impairments.¹³ Similarly, shorter preoperative seizure duration was associated with improved postoperative developmental quotients (DQs) within infants undergoing hemispherotomy for hemimegalencephaly.³⁵ Additional retrospective studies have demonstrated an inverse relationship between age at the time of surgery and developmental progression, with infants exhibiting greater DQ increases following hemispherectomy or focal resection.⁵¹ In particular, Loddenkemper et al. showed that infants with epileptic spasms demonstrated the greatest improvement developmentally following surgery (with 71% of infants overall demonstrating improved DQ), independent of seizure outcome.⁵¹ Retrospective studies demonstrated a significant direct correlation (or nonsignificant trend) between postoperative seizure freedom and improved development.^{35,69} Even without developmental or cognitive im-

FIG. 2. Radiographic appearance of progressive myelination. Axial T2-weighted brain MRI sequences obtained at 2 (A), 3 (B), 4 (C), 9 (D), 13 (E), 17 (F), 23 (G), and 28 (H) months of age demonstrating changes in imaging appearance of cortical and subcortical regions with age. (The images were obtained in a child who underwent repeated screening for atypical teratoid rhabdoid tumor due to a known *SMARCB1* genetic mutation risk factor.) Initially the cortex appears hypo-intense compared to white matter, but the white matter becomes hypo-intense as myelination continues. During stages of this process, the distinction between cortical and white matter becomes difficult, thereby complicating evaluation of cortical thickness, white matter arborization, and the contour of the gray-white matter junction.

provement, young children may preserve neuro-cognitive function following epilepsy surgery.^{6,50} Eliminating disruptive influences of epileptiform activity from the aberrant hemisphere may preserve contralateral function and optimize chances for developmental recovery and progression, especially during infancy and critical periods of brain maturation.^{15,35,40,50,51,69}

Resections involving eloquent cortex in younger patients may take advantage of greater neural plasticity that offers better hope for functional recovery.^{40,50} Even without functional improvement, young patients undergoing hemispherotomy may retain the same degree of hemiparesis postoperatively and continue to ambulate.⁷³

Enhanced seizure outcomes, improved developmental progress, and greater neural plasticity represent compelling reasons for considering early surgical intervention in infants with DRE. When weighing risks and benefits, catastrophic DRE, with status epilepticus and developmental regression, may prompt earlier surgical intervention during infancy.^{13,35,50,51} However, evaluation and treatment of these young children requires special modifications at each step to optimize outcomes and reduce complications.

Special Considerations in Neuroradiology

Relative immaturity and anticipated development of the infant brain influence radiographic examination of young patients during phase I evaluation. Typically requiring

at least 1.5 or 3.0 T for adequate evaluation of children with DRE, brain MRI allows analysis of gyral and sulcal patterns, cortical thickness, distinction of the gray-white matter junction, cortical signal intensity, subcortical white matter signal intensity, ventricular wall contours, white matter arborization patterns, and regional brain volume. High-resolution MRI may demonstrate subtle findings, including the “transmantle” sign involving white matter signal abnormalities extending toward the ependymal surface of the ventricle.^{5,8,32,41,46,48,49} While many articles have described imaging findings of MCD, few reports have explored the impact of age and cerebral development on the radiographic depiction of MCD.

For instance, chronological age and brain maturity influence the imaging appearance of FCD. Due to incomplete myelination, FCD may appear relatively indistinct radiographically during earlier ages but may become more apparent as myelination progresses.^{28,49} On T2-weighted sequences, myelination causes a hypo-intense (dark) signal within subcortical white matter. The cerebral cortex appears hypo-intense compared to white matter in full-term infants. This relationship reverses as myelination advances, such that cerebral cortex and white matter may demonstrate similar signal intensity during this transition (Fig. 2). Therefore, repeat imaging beyond 24–30 months of age is warranted for infants with DRE and initial unremarkable MRI and may elucidate a previously occult FCD.^{5,28,41} Given these nuances, radiographic interpretation should

FIG. 3. Simple gyral and sulcal pattern. Coronal T2-weighted brain MR image obtained shortly after birth in a premature infant (31 weeks' gestational age) demonstrating a relatively simplified gyral and sulcal pattern. Primary sulci appear present but relatively shallow, while secondary sulcation appears underdeveloped. Additionally, the sylvian fissures seem relatively wide and the cerebral convexities exhibit smooth contours. While raising concerns in full-term infants, these radiographic findings may remain within the normal range for significant degrees of prematurity.

be performed by an individual with specialized training and/or expertise in pediatric neuroimaging.^{8,32}

The radiographic assessment of gyral and sulcal pattern development is also influenced by patient age. For instance, radiographic examination of a premature infant with seizures may suggest the presence of abnormally simplified gyral and sulcal patterns, when this may represent normal gyral development for corrected age (Fig. 3). If structural imaging fails to disclose an obvious lesion, other phase I findings, including PET, may guide focused MRI review.¹⁶ Age-related nuances of PET include relatively low cerebral glucose metabolism in infants, complicating recognition of subtle hypo-metabolic anomalies,^{16,67} and lentiform nucleus and brainstem hyper-metabolism in infants with infantile spasms.¹⁶ As an additional functional imaging modality, magnetoencephalography (MEG) may augment phase I evaluation, but with uncertain benefit, given the paucity of published data within this younger age group. In addition to localizing primary motor and somatosensory cortex, MEG may identify interictal dipoles neighboring structural lesions, providing useful information for surgical planning.⁹

Special Considerations in Neurology

Infants and toddlers undergoing presurgical evaluation require distinct modifications compared to older children or adults. Several factors related to young chronological and developmental age impact preoperative phase I monitoring, including head size, behavioral concerns, incomplete myelination, and dynamic brain maturation. Small

cephalic dimensions may necessitate use of an International 10–10 system EEG montage or preclude the use of sphenoidal electrodes.⁷³ Behavior, such as irritability, impulsivity, and inability to follow commands, presents logistical challenges, including difficulty maintaining consistent video coverage during LTME and inadequate response testing.⁷⁴ Therefore, young patients benefit from involvement of supporting or ancillary staff (child life, music therapy, etc.).

In addition to difficulties collecting adequate LTME data, seizure classification and EEG interpretation are challenging in younger patients. While frequently helpful in older children and adults, seizure semiology may contribute less information regarding lateralization and localization in infants due to inability to communicate, frequent nonspecific stereotyped body movements, unclear changes in level of consciousness, and/or inconsistent head deviation (ipsilateral or contralateral to hemispheric ictal onset). For example, bilateral or diffuse torso and extremity movements may suggest generalized seizure activity despite the presence of focal EEG changes.¹⁹ Ictal EEG recordings may also appear more generalized or diffuse, as with epileptic spasms or diffuse tonic seizures, even in the setting of an epileptogenic lesion. Interictal EEG abnormalities may be absent, multifocal, or diffuse (as with hypsarrhythmia). In contrast to older children and adults, infants and toddlers with DRE experience more frequent seizures and are at greater risk for status epilepticus.⁶⁹ Nevertheless, the increased seizure frequency may allow shorter admissions for phase I or phase II monitoring.²⁰

Phase II monitoring presents obstacles for safety and data interpretation in younger patients. Disruptive behavior or agitation may result in damage or displacement of indwelling ICEEG electrodes. Despite these risks and challenges, ICEEG—including insertion of subdural grid and strip electrodes and SEEG—has been used safely and effectively in infants and toddlers.^{18,74} Sedating medications (including midazolam) used to decrease these risks may suppress seizure activity, alter ESM or other neurophysiology results, and require prolonged intubation.² Dexmedetomidine and chloral hydrate, however, do not interfere with electrophysiological data and may facilitate safe data collection.^{26,33}

Useful ESM has been reported in infants and toddlers, though with lower success rates and requirements for higher current application.^{10,38,72} For instance, adequate primary motor cortex stimulation in young children may require up to 20 mA of current and longer train durations (25 seconds) during extraoperative ESM (using 50-Hz biphasic pulses of 0.2-msec duration).^{14,20} Intraoperative ESM also may be limited by age, but has been performed during tumor resection in children as young as 3 years with currents up to 12.5 mA.⁶⁵ Furthermore, language ESM is less successful in children below the age of 10 years and represents an improbable task in infants and toddlers.^{52,63}

Other neurophysiological studies can assist in locating eloquent cortex and critical anatomical landmarks in younger patients. Somatosensory evoked potentials provide more reliable and efficient identification of the central sulcus as compared to ESM in children below 5 years of age.²⁹ High gamma electrocorticography (ECog) may

also assist identification of primary sensorimotor cortex in young children.⁷² Noninvasive adjuncts for ESM include resting-state functional MRI, MEG, and transcranial magnetic stimulation, although data and availability are limited.^{3,60,72}

Special Considerations in Neuropsychological Assessment

Neuropsychological evaluation represents an essential component of the presurgical evaluation for patients with DRE, yet few studies have described formal neurodevelopmental testing in infants and toddlers.^{39,51,61} Standardized evaluation may reveal previously unrecognized developmental and cognitive strengths or weaknesses, foster early developmental and behavioral interventions or postsurgical rehabilitative efforts, and identify family psychosocial needs during the epilepsy surgery process. Given the high rates of distress among parents of young children with medical needs and the potential negative impact of parental distress on child development, addressing psychosocial needs early may contribute substantially to patient outcome.³⁶ Younger age of seizure onset and longer preoperative duration of epilepsy represent risk factors for poor neuropsychological function and behavior in young patients, highlighting the importance of proper evaluation before and after epilepsy surgery.^{7,22,42,53,66,71}

Special Considerations in Neurosurgery

Special considerations in the neurosurgical management of young patients with DRE relate to soft tissue handling, positioning, body weight and blood volume, extent of resection, anticipated seizure outcomes, and potential for functional recovery. Care must be taken when positioning young patients in rigid fixation due to their thin, immature calvaria. Some authors recommend less than 20 lbs pressure in patients at the ages of 1–2 years¹¹ to decrease the risks of skull or dural penetration, intracranial hemorrhage, or CSF leakage, while others (including the author) avoid rigid fixation in patients less than 3 years of age.¹

Compression devices (Raney clips) along scalp edges should be used sparingly to prevent skin necrosis and allow for optimal wound healing. Infants are at high risk of intraoperative hypothermia and subsequent coagulopathy due to poor body temperature regulation. This requires external warming devices (e.g., 3M Bair hugger), prophylactic warming of blood products and fluids, and close attention by the anesthesiology team. Perioperative blood loss represents the leading cause of mortality in infants and toddlers undergoing epilepsy surgery.^{56,57} During the first 12 weeks of life, hemoglobin values decrease to a physiological nadir around 9.0 g/dl and may not return to normal until 6 months of age, when the infant's bone marrow becomes the main site of hematopoiesis.⁴ To help determine the necessity and/or timing of transfusion, estimations of total blood volume (TBV) as a function of body weight (stratified by age) have been reported previously: preterm neonates (100 ml/kg); full-term neonates (90 ml/kg); infants ≤ 1 year of age (80 ml/kg); and patients 1–12 years of age (75 ml/kg).⁶⁸ When estimated blood loss (EBL) exceeds 13 ml/kg in young patients, there is a higher risk of needing a blood transfusion.⁴

FIG. 4. Expansive duraplasty during insertion of subdural grid and strip electrodes. This intraoperative photograph demonstrates the senior author's (J.P.) incorporation of an expansive duraplasty during the first stage surgery for a 2-year-old boy with TSC and DRE, in preparation for chronic invasive ICEEG long-term monitoring. The expansive duraplasty accommodates the additional volume contributed by subdural grid and strip electrodes and reduces the risks related to cortical compression and mass effect.

Despite close attention to hemostasis and blood transfusions, certain surgical procedures involve anticipated blood loss that exceeds levels that are safe or tolerable for young patients. Functional hemispherotomy, anatomical hemispherectomy, and extensive cortical resections may lead to significant blood loss, especially in infants with hemimegalencephaly or SWS, in whom perioperative transfusions averaged 34 ml/kg.^{13,30,35,43,50} Voluminous blood transfusions ranging from 320 to 550 ml are reported in young patients (5 years or less) undergoing hemispherotomy, hemispherectomy, or hemidecortication.⁵² In these cases, preplanning staged surgical approaches may reduce surgical and anesthetic risk. The need for transfusion of other factors, including platelets and fresh frozen plasma (FFP), must also be considered. We do not typically use tranexamic acid or reconstituted whole blood.¹¹

Anesthesia protocols for epilepsy surgery typically account for the performance of motor mapping or ICEEG, and whether elevated intracranial pressure (ICP) may become a concern. Intraoperative postresection ECoG helps guide extent of resection in conjunction with the findings of phase I/II monitoring. Special considerations must be given to the risks of elevated ICP with subdural grid insertion in infants and toddlers. Rates of cerebral edema

in children undergoing subdural electrode insertion may reach as high as 14%.¹⁷ At the time of subdural electrode placement, use of an expansive duraplasty may minimize the risk of intracranial hypertension, with a low risk of CSF leakage (Fig. 4).

Typically high seizure frequency and antiseizure medication discontinuation may permit shorter durations of extraoperative ICEEG in younger patients.⁶⁹

Newer diagnostic and treatment paradigms incorporate SEEG with robotic-arm assistance and radiofrequency thermal coagulation or stereotactic laser ablation (SLA) as less-invasive options. Despite the technical challenges of achieving cranial immobilization and satisfying threshold skull thickness (≥ 2 mm) for peg fixation (to insert the depth electrodes), SEEG and SLA represent potentially useful, less-invasive strategies for evaluating and treating DRE in younger patients.¹⁷ Published data remain limited for both modalities in infants and toddlers.

Conclusions

Preoperative evaluation and surgical management of infants and toddlers with DRE offer substantial opportunities for favorable outcomes regarding seizure frequency and neuro-cognitive development. Young chronological and developmental age, physiological immaturity, small body size, and low blood volumes present nuances and unique challenges in the assessment and management of this young population. Epilepsy surgery represents a safe and effective treatment strategy for infants and toddlers with DRE, but requires modifications in evaluation and management from multiple disciplines.

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Disclosures

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

Author Contributions

Conception and design: Pindrik, Gedela, Ostendorf. Acquisition of data: Pindrik, Hoang, Halverson. Analysis and interpretation of data: Pindrik, Hoang, Smith, Halverson, Ostendorf. Drafting the article: Pindrik, Hoang, Smith, Halverson, Wojnaroski, McNally, Gedela. Critically revising the article: Pindrik, Hoang, Halverson, Wojnaroski, McNally, Ostendorf. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Pindrik. Study supervision: Pindrik, Ostendorf.

Correspondence

Jonathan Pindrik: Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, OH. jonathan.pindrik@nationwidechildrens.org.