Received: 19 November 2023 | Revised: 13 April 2024 | Accepted: 3 May 2024

DOI: 10.1002/epi4.12965

Epilepsia Open® Open Access

ORIGINAL ARTICLE

Trends, outcomes, and complications of surgery for lesional epilepsy in infants and toddlers: A multicenter study

Carmen Barba[1,2] | **Veronica Pelliccia**[3] | **Laura Grisotto**[4] | **Luca De Palma**[5] | **Giulia Nobile**[6] | **Francesca Gozzo**[3] | **Martina Revay**[3] | **Giusy Carfi-Pavia**[5] | **Massimo Cossu**[3,7] | **Flavio Giordano**[2,8] | **Alessandro Consales**[7] | **Alessandro De Benedictis**[9] | **Elena Cavallini**[2] | **Cristina Mion**[2] | **Claudia Accolla**[2] | **Nicola Specchio**[5] | **Lino Nobili**[6,10] | **Renzo Guerrini**[1,2] | **Laura Tassi**[3]

[1]Neuroscience Department, Meyer Children's Hospital IRCCS, Florence, Italy

[2]University of Florence, Florence, Italy

[3]"C. Munari" Epilepsy Surgery Center, Niguarda Hospital, Milan, Italy

[4]Department of Statistics, Computer Science, Application "G. Parenti" (DiSIA), University of Florence, Florence, Italy

[5]Neurology, Epilepsy and Movement Disorders, EpiCARE, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[6]Child Neuropsychiatry, IRCCS, Istituto Giannina Gaslini, Genoa, Italy

[7]Child Neurosurgery, IRCCS, Istituto Giannina Gaslini, Genoa, Italy

[8]Neurosurgery Department, Meyer Children's Hospital IRCCS, Florence, Italy

[9]Neurosurgery Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[10]DINOGMI, University of Genoa, Genoa, Italy

Correspondence
Carmen Barba, Neuroscience Department, Meyer Children's Hospital IRCCS, Florence, Italy.
Email: carmen.barba@meyer.it

Laura Tassi, C. Munari" Epilepsy Surgery Center, Niguarda Hospital, Milan, Italy.
Email: laura.tassi@ospedaleniguarda.it

Abstract

Objective: To assess seizure and developmental outcomes, their predictors, and complications in 160 children who, between 1998 and 2022, underwent surgery for lesional epilepsy with curative intent before the age of 3 years. To compare trends in epilepsy surgery in this age group before and after the year 2014.

Methods: Retrospective multicenter study. Descriptive and univariate analyses, and multivariable models for all outcomes.

Results: These 160 patients (76 F; 47.5%) underwent 169 surgeries (age at surgery 20.4 ± 9.4 months). At the last follow-up (77 ± 57.4 months), 121 patients (75.6%) were in Engel class I, 106 (66.2%) of whom were in Engel class Ia. Antiseizure medications were stopped in 84 patients (52.5%). Complications requiring reoperations were observed in 16 patients (10%; 9.5% of surgeries) and unexpected permanent deficits in 12 (7.5%; 7.1% of surgeries). Postoperative cognitive functions remained unchanged in 56 patients (44.4%), improved in 51 (40.5%), and worsened in 19 (15.1%). Multivariable analyses showed that the probability of achieving Engel class Ia was lower when the duration of epilepsy was longer, patients underwent preoperative video-EEG, and unexpected postoperative permanent deficits occurred. Cognitive improvement after surgery was associated with lower preoperative seizure frequency, better preoperative developmental level, and a longer postoperative follow-up. FCDII and tumors were the histopathologies carrying a higher probability of achieving seizure freedom, while polymicrogyria was associated with a lower probability of cognitive improvement. The number of patients operated on after 2014 was higher than before (61.3% vs. 38.7%), with stable outcomes.

Significance: Epilepsy surgery is effective and safe in infants and toddlers, although the complication rate is higher than seen in older patients. Shorter duration of epilepsy, lower seizure frequency, no need for video-EEG, tumors, and some malformations of cortical development are robust predictors of seizure and cognitive outcome that may be exploited to increase earlier referral.

Plain Language Summary: This study analyzed the results of epilepsy surgery in 160 children who had been operated on before the age of 3 years at four Italian centers between 1998 and 2022. At the last follow-up (77 ± 57.4 months), 121 patients (75.6%) were free from disabling seizures, of which 106 (66.2%) were completely seizure-free since surgery. Major surgical complications occurred in 28 patients (17.5%), which is higher than observed with epilepsy surgery in general, but similar to hemispheric/multilobar surgery. Postoperative cognitive function remained unchanged in 56 patients (44.4%), improved in 51 (40.5%), and worsened in 19 (15.1%). Epilepsy surgery is effective and safe in infants and toddlers.

KEYWORDS

developmental outcome, infants, predictors, seizure outcome, surgical treatment

1 | INTRODUCTION

Drug resistance emerges early after epilepsy onset in most children with seizures starting under 3 years of age, and is associated with higher mortality rates and poorer intellectual performances.[1] Surgical treatment may represent the only curative therapeutic option in selected children with drug-resistant epilepsy, with a demonstrated superiority over medical treatment[2] and rates of seizure freedom ranging between 51.5% and 74.7%.[3] Notwithstanding, epilepsy surgery remains largely underused, especially in children.[4–6]

Some studies[3,7] have suggested that the earlier the age at surgery and the shorter epilepsy duration the better seizure outcome, thus generating a growing interest in surgical treatment for children in pre-school age.[8–13]

Despite the reported favorable seizure outcomes in over 50% of children operated on before the age of three,[12–14] a recent systematic review concluded that evidence supporting the efficacy of surgery in this age group is of low quality.[12] Variables such as the type of epilepsy, etiology, early postoperative seizures, and extent of surgery have been suggested as possible predictors of seizure outcome in infants and toddlers.[8,15,16] However, the small sample size of most previous surgical series makes it difficult to draw definite conclusions on the actors influencing surgical results.

The few studies[10,12,14] that assessed postoperative developmental outcome suggested preoperative cognitive level and postoperative seizure freedom would influence it. Finally, while the mortality rate following epilepsy surgery in infants and young children is known to be low,[12] the types and percentages of surgical complications have yet to be fully defined.[9,14,17]

Key points

- At the last follow-up (77 ± 57.4 months), 121/160 patients (75.6%) were in Engel class I, of which 106 (66.2%) were in Engel class Ia.
- Need for video-EEG, longer duration of epilepsy, and postoperative unexpected permanent deficits predicted a worse seizure outcome.
- The complication rate was higher than observed with epilepsy surgery in general, but similar to hemispheric/multilobar surgery.
- Postoperative cognitive functions remained unchanged in 56 patients (44.4%), improved in 51 (40.5%), and worsened in 19 (15.1%).
- The number of patients operated on after 2014 was higher than before (61.3% vs. 38.7%).

In this multicenter Italian study, we aimed at assessing seizure and developmental outcomes and their predictors, along with surgical complications in a cohort of 160 children who underwent surgery before the age of three. Additionally, we assessed the trends in epilepsy surgery in this age group before and after 2014. We chose this calendar year to follow up on a previous survey on the trends in pediatric epilepsy surgery in Italy.[5]

2 | METHODS

This is a retrospective multicenter study involving four Italian epilepsy surgery centers, three of which are pediatric only. The participating centers were identified through an epidemiological survey.[5]

Each center provided information on patients surgically treated since its inception who met the following criteria: (a) age at surgery below 3 years; (b) intended curative epilepsy surgery; (c) at least 1 year of follow-up; and (d) preoperative EEG and brain magnetic resonance imaging (MRI) available for review. Exclusion criteria were (a) progressive metabolic and genetic diseases and (b) lack of informed consent.

All patients included in the study were prospectively registered in each center's database.

The study was approved by the Pediatric Ethics Committee of Tuscany Region, Italy.

2.1 | Study protocol

For each patient, centers were asked to provide information about: (a) general characteristics: sex, age at seizure onset, antecedents, that is, family history, febrile seizures, perinatal period, any neurological deficits; (b) preoperative developmental status assessed through standardized scales,[18] that is, Griffiths Mental Developmental Scales-Extended Revised, Italian versions of the Wechsler Scales and Vineland Adaptative Behavior Scales,[19] and categorized as normal, borderline, mild, moderate, severe global developmental delay (GDD); (c) epilepsy characteristics: age at seizure onset, seizure frequency (no seizures, daily, weekly, monthly, yearly), seizure types (focal seizures, epileptic spasms or both), topography (lobe and hemisphere) and extent (unilobar vs multilobar) of the seizure onset zone (SOZ) assessed through non-invasive and, if necessary, invasive investigations, number and type of antiseizure medications (ASMs), duration of epilepsy (i.e., time from seizure onset to surgery); (d) preoperative investigations: conventional brain MRI categorized as unrevealing or lesional, prolonged (>24 h) scalp video-EEG recording, and stereo-electroencephalography (Stereo-EEG); (e) surgery: age at surgery (the earliest surgery being the index intervention for patients with repeated surgery), type, side and extent (unilobar vs multilobar) of last surgery, having undergone multiple surgeries, complications categorized as major that is, death, complications[20] requiring reoperation, unexpected permanent deficits (motor, hemianopia, etc.) and minor and transient complications. that is, infections, anemia, metabolic, endocrinological problems, etc.; (f) histopathological findings[21,22] categorized as glial scars (post-traumatic, postischemic, etc.), malformations of cortical development (MCD), that is, focal cortical dysplasia (FCD) type I, FCD type II, hemimegalencephaly, polymicrogyria, nodular heterotopia, tuberous sclerosis, hippocampal sclerosis (HS; associated or not with FCD IIIA), epileptogenic tumors (associated or not with FCD IIIB), Rasmussen encephalitis, vascular abnormalities (including Sturge–Weber and cavernomas), hypothalamic hamartoma, and uninformative (when no specific histopathologic lesion was detected); (g) duration of postoperative follow-up (from last surgery in case of multiple surgeries) and (h) outcomes (the last surgery being the index intervention for patients with repeated surgery) at last follow-up: seizure outcome according to Engel's scoring scale,[23] ASM discontinuation categorized as no treatment change, reduced, stopped, stopped and re-started for seizure recurrence, and cognitive outcome categorized as improved, worsened or unchanged based on the transition between the five preoperative developmental categories, that is, normal, borderline, mild, moderate, severe GDD. For the evaluation of cognitive outcome, we included only patients whose developmental status was assessed pre- and postoperatively using standardized tools. To ensure consistency across centers, an experienced neuropsychologist centrally reviewed all the results of the developmental assessments.

2.2 | Statistical analysis

We conducted a descriptive analysis with categorical variables presented as frequencies or percentages, and continuous variables as means ± SD.

We investigated possible differences in several clinical preoperative, surgical, and postoperative variables (see above) between different groups of patients with:

1. age at surgery under vs over 1 year old;
2. age at seizure onset under vs over 1 year old;
3. calendar year of surgery before 2014 vs after 2014.

Specifically, to assess group differences, we carried out Pearson χ^2 tests of independence or Fisher's exact test, when appropriate, for categorical variables and Student *t*-test for continuous variables. We subsequently analyzed these different outcomes at the last follow-up: Engel class Ia vs IB–IV outcome, Engel class I vs class II–IV, and ASM complete discontinuation vs persistence to medical treatment and cognitive outcomes categorized as improved, worsened, or unchanged.

We used logistic regression models or ordered logistic regression models for the outcomes adjusted for the

recruiting center and specified robust standard error for intragroup correlations to consider a possible correlation between patients belonging to the same center. We performed univariate and multivariable models for all outcomes. We calculated ORs and 95% confidence intervals (CIs) from the fitted models. We also verified the possible confounding effect of the variable "center." The univariate analyses were used to select the covariates for the multivariate analyses; only the covariates with a p-value ≤0.05 in the univariate models were included in the multivariable models. Then, to further select the covariates of the final models, we used a backward method, removing the terms with p-value >0.05 from the models.

We conducted all statistical analyses using the STATA version 16.0 (StataCorp. 2016. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP).

3 | RESULTS

3.1 | Descriptive analysis

We included 160 patients (76 F, 47.5%) operated on between February 1998 and March 2022 with a mean age at surgery of 20.4 ± 9.4 months (range 2–35 months). They represented 11% (range: 8.5–16.8%) of all patients under the age of 18 years undergoing epilepsy surgery in the four participating centers. Eight patients operated on before the age of 3 years were excluded from the final sample, of whom 5 underwent tumoral lesionectomies after a single unprovoked seizure, 2 had a postoperative follow-up of <1 year, and one received palliative surgery.

Fifty-five patients (34.4%) had antecedents, and specifically, 39 (24.4%) had a family history of epilepsy or other neurological disorders, and 16 (10%) had prenatal or perinatal distress.

Neurological examination was abnormal in 55 patients (34.4%), of which 38 exhibited lateralized motor deficits, 7 hypotonia or impairment of gross motor skills, 5 language delays, and 5 oculomotor or visual field defects.

In 130 patients (81.2%) seizures had started before the age of 1 year, but only 40 (25%) underwent surgery before the age of 1 year. The mean duration of epilepsy until the first operation was 13.6 ± 8.4 months (range 1–34).

Seizure frequency was reported to be daily in 117 patients (73.6%), weekly in 13 (8.2%), monthly in 13 (8.2%), and yearly in 2 (1.3%). Fourteen patients (8.8%) had no seizures in the 6 months before surgery. However, they either had a history of drug resistance and were on polytherapy or had highly epileptogenic lesions with a great risk of drug resistance.[24] For the remaining one child, data on seizure frequency were missing. Of the 146 drug-resistant patients, 127 (79.4%) had never experienced a beneficial period of seizure freedom after epilepsy onset.

Regarding seizure type, 109 (68.1%) patients exhibited focal seizures only, 18 (11.3%) had epileptic spasms only and 33 (20.6%) manifested both focal seizures and epileptic spasms.

Fifty-five (34.4%) patients were on ≥ three ASM, 53 (33.1%) on monotherapy, and 52 (32.5%) on two medications.

As part of the presurgical evaluation, in all patients, a brain structural abnormality was demonstrated using 1.5 or 3 T MRI: 78 on the right side (48.7%) including one in the right cerebellar peduncle, and 78 (48.7%) on the left. A hypothalamic hamartoma was found in the 4 remaining (2.5%) children. Prolonged scalp video-EEG monitoring was performed in 125 patients (78.1%) and stereo-EEG in 11 (6.9%). Preoperative cognitive assessment through standardized scales was available for 140 (87.5%) patients and revealed normal development in 26 (18.6%); borderline level in 19 (13.6%); mild GDD in 18 (12.9%); moderate GDD in 23 (16.4%); and severe GDD in 54 (38.6%).

Surgery was unilobar in 87 (5.0%) patients, including 41 (25.6%) lesionectomies+ corticectomies; 24 (15%) isolated lesionectomies and 18 (11.2%) lobectomies, and multilobar in 73 (45.6%), including 41 (25.6%) hemispheric surgeries. Hypothalamic hamartomas were treated with laser interstitial thermal therapy (LITT) in two patients, and with endoscopic disconnection and open microsurgery in one each. Nine patients (5.6%) required two surgeries, bringing the total to 169 operations.

At histopathology, we found FCD in 74 patients (50 FCDII, 24 FCDI, 46.2%), tumors associated or not with FCDIIIb in 32 (20%), gliotic scars in 14 (8.7%), hemimegalencephaly in 9 (5.6%), vascular anomalies in 9 (8 Sturge–Weber syndrome, 1 cavernoma, 5.6%), tuberous sclerosis in 7 (4.4%), polymicrogyria in 5 (3.1%), nodular heterotopia in 2 (1.2%), hypothalamic hamartoma in 2 (1.2%), hippocampal sclerosis in 2 (1.2%), and Rasmussen encephalitis in 1(0.6%). In the remaining 3 patients (1.9%), histopathology results were not available either due to the type of surgery (LITT in two hypothalamic hamartomas) or because specimens were too small (one suspected FCD).

Follow-up duration was 77 ± 57.4 months (range 12–297 months). At the last follow-up, 121 patients (75.6%) were in Engel class I, 106 (66.2%) of whom were in class Ia.

In addition, we observed minor complications in 23 patients (12 infections, 5 anemia, 2 metabolic, and 4 endocrinological problems; 14.4% of patients, 13.6% of surgeries), complications requiring reoperations in 16 (10% of patients and 9.5% of surgeries), and unexpected permanent deficits in 12 (7.5% of patients and 7.1% of surgeries). In addition, 138 patients (86.25%) could walk

after the operation compared to 83 (51.9%) who did before surgery. Notably, 37 patients were younger than 12 months old, and 31 were between 12 and 18 months old at the time of surgery. Among the 138 patients who could walk at the last follow-up, 132 were older than 18 months.

Information on postoperative developmental outcomes through standardized scales was available for 126 patients. Concerning the timing of postoperative cognitive testing, 49 patients were assessed 12 months after surgery, 21 between 12 and 24 months, and 56 after 24 months. Cognitive performances remained unchanged in 56 patients (44.4%), improved in 51 (40.5%), and worsened in 19 (15.1%).

ASMs had been completely discontinued in 84 patients (52.5%), remained unchanged since surgery in 39 (24.4%), had been reduced in 28 (17.5%), and stopped and then restarted in 9 (5.6%).

3.2 | Statistical comparison between groups

When comparing patients operated on before 1 year of age with those operated on after 1 year of age, we found that all children undergoing SEEG belonged to the latter group ($p = 0.037$) (Table S1). In addition, hemispherotomy was the most frequent type of surgery in children operated on before 1 year of age (45%) and corticectomy+ lesionectomy in those operated on after 1 year of age (27.5%, $p = 0.042$). The percentage of unexpected permanent deficits after surgery was higher in children operated on before 1 year of age compared with those operated on after the first year (15% vs. 5%; $p = 0.038$). However, we did not find significant differences in terms of seizure and cognitive outcome between the two age groups.

Children with seizure onset before the age of 1 year were more likely to have antecedents (50% vs 30.8%; $p = 0.046$), and abnormal neurological examination (39.2% vs 13.3%, $p = 0.005$), to experience daily seizures (77.5% vs. 56.7%, $p = 0.007$) and complications requiring re-intervention (12.3% vs. 0%, $p = 0.030$) compared to those with seizure onset after the age of 1 year. Children with seizure onset before the age of 1 year were more likely to exhibit severe GDD (44.6%) while those with seizure onset after the age of 1 year were more likely to have normal cognitive skills (35.7%) ($p = 0.013$). Finally, those with seizure onset after the first year had a lower probability of achieving Engel class I and Ia outcomes (28.5% vs. 6.7%, $p = 0.007$ and 37.7% vs. 16.7%, $p = 0.028$, respectively).

The only preoperative variable of significant frequency difference after 2014 was an abnormal preoperative neurological examination (24.2% vs. 40.8%, $p < 0.0001$). In addition, there was a higher percentage of children with improved developmental status among those operated on before the calendar year 2014, (60.4%), while there was a higher percentage of children with unchanged cognitive levels among those operated after 2014 (53.4%) ($p < 0.0001$).

We observed a higher number of operated patients after 2014 than before 2014 (61.3% vs. 38.7%, $p = 0.006$).

3.3 | Univariate analyses

The results of the univariate analyses are summarized in Table S2. Selected covariates from univariate analyses are listed in Table S3.

3.4 | Multivariable analysis

3.4.1 | Predictors of Engel class Ia outcome

The probability of achieving Engel's class Ia outcome was lower when the duration of epilepsy increased (OR = 0.988, $p = 0.016$), and when unexpected permanent deficits occurred after surgery (OR = 0.209, $p = 0.010$), while it was higher when patients did not necessitate video-EEG (OR = 5.064, $p < 0.0001$) (Table 1).

In addition, patients with tumors had a higher probability (OR = 6.562, $p < 0.0001$) and patients with hypothalamic hamartoma and nodular heterotopia had a lower probability of achieving Engel class Ia outcome (OR = 0.225, $p = 0.025$, and OR = 0.237, $p = 0.040$, respectively) than those with FCD II.

3.4.2 | Predictors of Engel class I outcome

The probability of achieving Engel's class I outcome was lower when the patients experienced high seizure frequency (OR = 0.516, $p < 0.0001$) and higher when patients were not submitted to video-EEG (OR = 1.789, $p < 0.0001$) (Table 2). In addition, patients with tuberous sclerosis and nodular heterotopia had a lower probability of achieving Engel class I outcome than those with FCD II (OR = 0.198, $p = 0.031$; OR = 0.407, $p = 0.001$, and OR = 0.381, $p < 0.0001$ respectively).

3.4.3 | Predictors of complete ASM withdrawal after surgery

The probability of completely stopping ASM after surgery was lower when patients had high seizure frequency (OR = 0.529, $p < 0.0001$) (Table 3). Patients with

TABLE 1 Multivariable analysis.

Engel's class Ia vs class Ib-IV outcome at last FU					
		ORs	**LL95%CI**	**UL95%CI**	***p*-value**
FU Duration		0.988	0.979	0.998	**0.016**
Video-EEG (Ref: Yes)	No	5.064	3.808	6.736	**<0.0001**
Pathologies (Ref. FCDII)	FCDI	1.818	0.599	5.519	0.292
	HMG	1.379	0.084	22.704	0.822
	Tumors[a]	6.561	4.084	10.541	**<0.0001**
	Gliotic scars[a]	0.370	0.077	1.768	0.213
	VA	0.402	0.072	2.239	0.298
	TSC	0.102	0.008	1.303	0.079
	PMG	1.000			
	RE	1.000			
	NH	0.225	0.068	0.747	**0.025**
	HH	0.237	0.06	0.936	**0.040**
	HS[a]	1.000			
Unexpected permanent deficits (Ref: No)	Yes	0.209	0.064	0.683	**0.010**

Note: Significant *p* values are in bold.

Abbreviations: CI, confidence interval; EEG, electroencephalogram; FCD, focal cortical dysplasia; FU, follow-up; HH, hypothalamic hamartoma; HMG, hemimegaloencephaly; HS, hippocampal sclerosis; NH, nodular heterotopia; ORs, odds ratios; PMG, polymicrogyria; RE, Rasmussen encephalitis; Ref, reference category; TSC, tuberous sclerosis complex; VA, vascular anomalies.

[a]With or without FCDIII.

tumors had a higher probability and those with vascular anomalies and TSC had a lower probability of stopping ASM than those with FCD II(OR = 4.425, $p = 0.043$; OR = 0.158, $p < 0.0001$, and OR = 0.319, $p = 0.007$, respectively).

3.4.4 | Predictors of change in developmental status after surgery

The probability of cognitive improvement after surgery was lower when patients had high seizure frequency (OR = 0.547, $p < 0.0001$) and when patients did not undergo video-EEG (OR = 0.330, $p < 0.0001$), and higher as the duration of follow-up increased (OR = 1.015, $p < 0.0001$) (Table 4). Patients with preoperative borderline level, moderate, and severe GDD had a higher probability of experiencing cognitive improvement after surgery than those with normal preoperative developmental level (OR = 8.008, $p < 0.0001$, OR = 15.271, $p < 0.0001$, and OR = 15.794, $p < 0.0001$ respectively). Patients with FCD type I and nodular heterotopia had a higher probability of experiencing an improvement in their cognitive performances after surgery compared to those with FCD type II (OR = 5.242, $p = 0.001$; OR = 4.118, $p = 0.001$), while patients with polymicrogyria had a lower probability to do so (OR = 0.247, $p < 0.0001$).

4 | DISCUSSION

In this multicenter study including 160 children operated on before the age of 3 years, 121 (75.6%) were in Engel class I of whom 106 (66.2%) were in class Ia at the last follow-up (77 ± 57.4 months). ASMs had been completely discontinued in 84 patients (52.5%) and reduced in 28 (17.5%).

A recent systematic review and meta-analysis[13] including 401 patients operated before the age of 3 years exhibited favorable outcomes, defined as Engel I and II or ILAE score of 1 or 2, in 68%. Another systematic review of operations performed between 1979 and 2020[12] reported the average chance of Engel Ia outcome to vary between 7% and 76% in different centers. With this study, we have confirmed in a larger cohort the satisfactory surgical results previously observed in this age group,[9,10,14,17,25,26] in terms of achieving seizure freedom after surgery. We also demonstrated that discontinuing or reducing ASMs is possible in most patients. In children, ASM withdrawal is associated with improved developmental outcomes.[27] In our study, the 40.5% percentage of children cognitively improved after surgery is largely superior to the 26% indicated in a previous systematic review[13] on early surgical approaches in pediatric epilepsy. In a single US center surgical series,[9] including 31 operated children under 3 years of age, family perception of accelerated development was not confirmed by formal testing, with patients who were severely impaired before surgery

TABLE 2 Multivariable analysis.

Engel class outcome I vs. II–IV					
		OR	**LL95%CI**	**UL95%CI**	***p*-value**
Video-EEG (Ref: Yes)	No	1.789	1.486	2.153	**<0.0001**
Seizure frequency (trend)		0.516	0.361	0.739	**<0.0001**
Pathologies (Ref. FCDII)	FCDI	1.248	0.630	2.474	0.525
	HMG	1.075	0.062	18.642	0.961
	Tumors[a]	8.421	0.713	99.483	0.091
	Gliotic scars[a]	1.290	0.364	4.573	0.694
	VA	0.799	0.184	3.466	0.765
	TSC	0.198	0.139	0.280	**<0.0001**
	PMG	1.000			
	RE	1.000			
	NH	0.407	0.244	0.679	**0.001**
	HH	0.381	0.239	0.607	**<0.0001**
	HS[a]	1.000			

Note: Significant *p* values are in bold.

Abbreviations: CI, confidence interval; EEG, electroencephalogram; FCD, focal cortical dysplasia; FU, follow-up; GDD, global developmental delay; HH, hypothalamic hamartoma; HMG, hemimegaloencephaly; HS, hippocampal sclerosis; NH, nodular heterotopia; ORs, odds ratios; PMG, polymicrogyria; RE, Rasmussen encephalitis; Ref, reference category; TSC, tuberous sclerosis complex; VA, vascular anomalies.

[a]With or without FCDIII.

TABLE 3 Multivariable analysis.

ASM withdrawal at last FU					
		OR	**LL95%CI**	**UL95%CI**	***p*-value**
Seizure frequency (trend)		0.529	0.396	0.707	**<0.0001**
Video-EEG (Ref: Yes)	No	1.629	1.050	2.528	**0.029**
Pathologies (Ref. FCDII)	FCDI	1.251	0.690	2.268	0.461
	HMG	3.048	0.655	14.174	0.155
	Tumors[a]	4.425	1.047	18.705	**0.043**
	Gliotic scars[a]	0.462	0.128	1.671	0.239
	VA	0.158	0.070	0.357	**0.000**
	TSC	0.319	0.139	0.730	**0.007**
	PMG	1.000			
	RE	1.000			
	NH	1.000			
	HH	0.852	0.405	1.793	0.673
	HS[a]	1.000			

Note: Significant *p* values are in bold.

Abbreviations: ASM, antiseizure medication; CI, confidence interval; EEG, electroencephalogram; FCD, focal cortical dysplasia; FU, follow-up; GDD, global developmental delay; HH, hypothalamic hamartoma; HMG, hemimegaloencephaly; HS, hippocampal sclerosis; NH, nodular heterotopia; ORs, odds ratios; PMG, polymicrogyria; RE, Rasmussen encephalitis; Ref, reference category; SD, speech delay; TSC, tuberous sclerosis complex; VA, vascular anomalies.

[a]With or without FCDIII.

continuing to function in the severely impaired range. These largely variable findings might indicate that parallel evaluations of adaptative performances, quality of life, and neuropsychological testing would better weigh the impact of epilepsy surgery on younger children and their families.[28]

The most frequent pathologies we observed were FCD and tumors, diagnosed in 46.2% and 20% of patients. These results confirm those of previous large-scale pediatric surgical series,[29] and surgical studies including children younger than 3 years of age.[8,14,16,17] We found patients

TABLE 4 Multivariable analysis.

Cognitive outcome					
		OR	LL95%CI	UL95%CI	*p*-value
Seizure frequency (trend)		0.547	0.404	0.741	**<0.0001**
Video-EEG (Ref:Yes)	No	0.330	0.280	0.390	**<0.0001**
Pathologies (Ref. FCDII)	FCDI	5.242	1.956	14.045	**0.001**
	HMG	0.971	0.577	1.633	0.911
	Tumors[a]	1.409	0.253	7.861	0.696
	Gliotic scars[a]	0.697	0.382	1.272	0.240
	VA	4.124	0.701	24.264	0.117
	TSC	0.910	0.010	82.645	0.967
	PMG	0.247	0.119	0.512	**<0.0001**
	RE	1.000			
	NH	4.118	1.780	9.530	**0.001**
	HH	1.447	0.033	63.608	0.848
	HS[a]	1.000			
FU Duration		1.015	1.011	1.020	**<0.0001**
Preoperative cognitive development (Ref: Normal)	Borderline	8.008	3.432	18.684	**<0.0001**
	Mild GDD	1.484	0.573	3.840	0.416
	Moderate GDD	15.271	3.487	66.876	**<0.0001**
	Severe GDD	15.794	3.466	71.974	**<0.0001**

Note: Significant *p* values are in bold. Cognitive outcome ordinal variable: 0: worsened, 1: unchanged, 2: improved.

Abbreviations: CI, confidence interval; EEG, electroencephalogram; FCD, focal cortical dysplasia; FU, follow-up; GDD, global developmental delay; HH, hypothalamic hamartoma; HMG, hemimegaloencephaly; HS, hippocampal sclerosis; NH, nodular heterotopia; ORs, odds ratios; PMG, polymicrogyria; RE, Rasmussen encephalitis; Ref, reference category; TSC, tuberous sclerosis complex; VA, vascular anomalies.

[a]With or without FCDIII.

with tumors to have the highest probability of achieving Engel class Ia outcome and stopping ASM while those with vascular anomalies, nodular heterotopia, hypothalamic hamartoma, and TSC to face worse outcomes than FCDII. These findings are in line with previous series on pediatric epilepsy surgery in general and under 3 years of age,[15] and suggest a favorable seizure outcome associated with tumors.[3,7,30] Contrasting findings have been reported for MCDs,[3,7,31] possibly due to the different ways they were classified and grouped in the various studies.

We performed 73 (45.6%) multilobar resections/disconnections, including 41 (25.6%) hemispherotomies, 9 multiple surgeries, and 11 stereo-EEGs. These figures demonstrate that most children under the age of 3 can be cured through unilobar resections/disconnections, and single direct surgery, which could reduce the delay before surgery. The type and side of surgery did not statistically influence seizure or cognitive outcome, as also reported in some studies[8,9] but not in others.[32]

Our multivariable analysis, aimed at analyzing predictors of seizure outcome, found that the probability of obtaining an Engel's class Ia outcome was lower as the duration of epilepsy increased and when unexpected permanent deficits occurred after surgery, while it was higher when patients did not necessitate preoperative video-EEG. Well-demarcated lesions such as tumors or FCD can be resected without ictal Video-EEG recordings, but lesions associated with complex anatomo-electroclinical correlations such as polymicrogyria, may require video-EEG monitoring and are at higher risk of unsatisfactory seizure outcome.[33] In a multicenter pediatric surgical series,[8] 34 (48%) patients had only MRI/video-EEG, 31 (44%) had one additional ancillary test (PET, MEG, FMRI, SPECT, etc.), and six (8%) had more than one such tests. Ancillary tests were most often performed in challenging presentations, that is, with unrevealing MRI or extended MCDs to better define the area to be resected/disconnected.[16]

The negative correlation between follow-up duration and the probability of achieving sustained seizure freedom confirms the results of a recent meta-analysis on pediatric epilepsy surgery in general.[3]

Regarding surgical complications, we observed no deaths but complications requiring reoperations in 17 children (10.6% of patients and 10% of surgeries) and unexpected permanent deficits in 12 (11.9% of patients

and 11.2% of surgeries). These figures confirm that the complication rate in this age group[9,14,34] is higher than observed in epilepsy surgery in general, that is, 5.1% for minor and 1.5% for major complications,[35] but close to that of hemispheric/multilobar resections/disconnections.[31] that are more frequently performed in younger children.[34] However, 86.25% of patients were able to walk after surgery compared to 51.9% before surgery. Even considering that nearly all patients who could walk at the last follow-up were older than 18 months, our observation suggests that most children undergoing surgery before the age of 3 can achieve normal motor milestones. This may be related to multiple factors, including the greater brain plasticity in this age group[36] and easier access to postoperative education and rehabilitation if seizure freedom is achieved.

Finally, a negative predictor of Engel class I outcome and ASM withdrawal was a high seizure frequency. Better surgical results have been reported in patients operated on without experiencing prior drug resistance,[24] particularly in those with FCD where the failure of one ASM has been associated with a substantial risk of pharmacoresistance.[37] This observation aligns with our finding that 79.4% of our patients developed de novo drug-resistance.

Regarding cognitive outcome,[41–43] we confirmed that presurgical developmental scores are a predictor of postoperative cognitive outcome.[16,20,38,39] In line with previous studies, cognitive improvement was observed less frequently in children with normal development than in those with GDD of any level of severity,[9,40] showing an association between preoperative normal cognitive level and stable age-appropriate scores after surgery. In contrast, pre-existing cognitive deficits were more likely to improve over time. Accordingly, we found that patients requiring video EEG, which potentially reflects a globally more complex clinical picture, exhibited better postoperative cognitive performances.

A high seizure frequency was also positively correlated with cognitive decline, which may indicate a detrimental effect of more severe epilepsy on cognitive function.[41,42] The likelihood of cognitive improvement increased with a longer follow-up duration, which is in line with the few available studies on long-term postoperative outcomes in children showing stable or improved developmental trajectories over time.[39,43] Finally, cognitive outcome was also influenced by etiology, with patients with polymicrogyria exhibiting the poorest performance following surgery, a finding likely related to their low preoperative cognitive scores and unfavorable seizure outcome.

While assessing trends in epilepsy surgery before and after 2014, we observed an increase in the number of patients undergoing surgery over time. This trend appears to be related to the establishment and development of new epilepsy surgery centers. However, we did not find differences over time in the types of surgery and etiologies, complication rates, and seizure outcomes. The higher percentage of children with unchanged postoperative cognitive levels among those operated on after 2014 may be related to the shorter duration of their follow-up.

The consequences of this study are limited by its retrospective design and multicenter nature and the possible variation in the referral of patients from different centers. Additionally, there was variability in the timing of cognitive testing between centers, which could have partially influenced the evaluation of postoperative changes. However, the robust statistical methodology we applied considered both the correlation between patients belonging to the same center and the confounding effect of the centers. All the involved centers have a high level of expertise in epilepsy, with regular participation at quarterly meetings of the Commission of Epilepsy Surgery of the Italian League Against Epilepsy and adoption of clinical care pathways following national[44,45] and international[46,47] recommendations. These activities have contributed to achieving standardized practice and satisfying surgical results, which have remained stable over time.[5,48]

5 | CONCLUSIONS

We demonstrated, in a large cohort, that surgery in the first 3 years of life is effective, with 75.6% of patients reaching Engel class I outcomes and 52.5% withdrawing ASMs. Although the rate of complications was higher than that of epilepsy surgery in general, no deaths were reported, most children were able to walk independently after surgery and 40.5% experienced improved cognitive performances.

The robust predictors of seizure and cognitive outcome we identified, such as the presence of tumors or some malformations of cortical development, duration of epilepsy, high seizure frequency, and the need for video-EEG to elucidate complex anatomo-electro-clinical correlations, could help to identify the best candidates for epilepsy surgery, optimize preoperative counseling to families, and increase early referral.

ACKNOWLEDGMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This study was partly conducted in the framework of the ERN EpiCARE. We thank Dr Simona Cappelletti (Bambino Gesù Hospital, Rome) for her support to this study.

FUNDING INFORMATION

No funding was received for conducting this study.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as Tables S1-S3. Additional data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

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.

ORCID

Carmen Barba https://orcid.org/0000-0001-5445-5842
Giulia Nobile https://orcid.org/0000-0002-9957-7760
Massimo Cossu https://orcid.org/0000-0002-1891-7648
Alessandro Consales https://orcid.org/0000-0002-4354-6906
Alessandro De Benedictis https://orcid.org/0000-0002-5414-198X
Nicola Specchio https://orcid.org/0000-0002-8120-0287
Lino Nobili https://orcid.org/0000-0001-9317-5405
Renzo Guerrini https://orcid.org/0000-0002-7272-7079
Laura Tassi https://orcid.org/0000-0002-0632-7296

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Barba C, Pelliccia V, Grisotto L, De Palma L, Nobile G, Gozzo F, et al. Trends, outcomes, and complications of surgery for lesional epilepsy in infants and toddlers: A multicenter study. Epilepsia Open. 2024;00:1–11. https://doi.org/10.1002/epi4.12965