Epilepsy & Behavior 93 (2019) 22–28

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Outcome after hemispherotomy in patients with intractable epilepsy: Comparison of techniques in the Italian experience

Luca de Palma [a,1], Nicola Pietrafusa [a,1], Francesca Gozzo [b], Carmen Barba [c], Giusy Carfi-Pavia [a], Massimo Cossu [b], Alessandro De Benedictis [a], Lorenzo Genitori [c], Flavio Giordano [c], Giorgio Lo Russo [b], Carlo Efisio Marras [a], Veronica Pelliccia [b], Susanna Rizzi [c], Camilla Rossi-Espagnet [d], Federico Vigevano [a], Renzo Guerrini [c], Laura Tassi [b], Nicola Specchio [a,*]

[a] Department of Neuroscience and Neurorehabilitation, Bambino Gesù Children Hospital, Rome, Italy
[b] "Claudio Munari" Epilepsy Surgery Center, Department of Neuroscience, Niguarda Hospital, Milan, Italy
[c] Department of Neurosciences, Anna Meyer Pediatric Hospital, Florence, Italy
[d] Neuroradiology Unit, Imaging Department, Bambino Gesù Children's Hospital, Rome, Italy

ARTICLE INFO

Article history:
Received 27 September 2018
Revised 3 January 2019
Accepted 4 January 2019
Available online 16 February 2019

Keywords:
Hemispherotomy
Drug-resistant epilepsy
Epilepsy surgery
Outcome
Surgical technique

ABSTRACT

Objective: The objective of the study was to evaluate clinical characteristics and outcome of hemispherotomy in children and adolescents with hemispheric refractory epilepsy in an Italian cohort of patients.
Methods: We retrospectively evaluated the clinical course and outcome of 92 patients with refractory epilepsy who underwent hemispherotomy in three Italian epilepsy centers between 2006 and 2016. Three different approaches for hemispherotomy were used: parasagittal, modified parasagittal, and lateral.
Results: Mean age at epilepsy onset was 1.8 ± 2.51 years, and mean duration of epilepsy prior to surgery was 7.4 ± 5.6 years. Mean age at surgery was 9.2 ± 8.0 years. After a mean follow-up of 2.81 ± 2.4 years, 66 of 90 patients (two lost from follow-up, 73.3%) were seizure-free (Engel class I).
The etiology of epilepsy was related to acquired lesions (encephalomalacia or gliosis) in 44 patients (47.8%), congenital malformations (cortical dysplasia, hemimegalencephaly, other cortical malformations) in 38 (41.3%), and progressive conditions (Rasmussen or Sturge–Weber syndrome) in 10 patients (10.9%). Regarding seizure outcome, we could not identify statistically significant differences between vertical and lateral approaches ($p = 0.154$).
Seizure outcome was not statistically different in patients with congenital vs acquired or progressive etiologies ($p = 0.43$). Acute postoperative seizures (APOS) correlated with poor outcome ($p < 0.05$). On multivariate analysis, presurgical focal to bilateral tonic–clonic seizures (Odds Ratio (OR) = 3.63, 95% Confidence Interval (CI): 1.86–15.20, $p = 0.048$) independently predicted seizure recurrence. Twenty-one patients (22.8%) exhibited postoperative complications, with no unexpected and persistent neurological deficit. More than 50% of the patients completely tapered drugs.
Significance: Our data confirm hemispherotomy to be a safe and effective procedure in patients with drug resistant epilepsies due to hemispheric lesions. Presurgical focal to bilateral tonic–clonic seizures are the strongest predictor of seizure recurrence after surgery, independently from the type of hemispherotomy.

1. Introduction

Hemispherotomy is a surgical option for the treatment of intractable seizures due to hemispheric structural lesions [1]. Hemispherotomy techniques refer to different surgical approaches useful to functionally isolating the affected hemisphere from both ipsilateral and contralateral neural structures by transecting their projections and commissural fibers, with limited tissue resection [2]. These techniques represent an evolution of functional hemispherectomy introduced in the 1974 by Rasmussen. Since then, functional hemispherectomy and hemispherotomy remained a crucial tool in treating focal or hemispheric epilepsies with various etiologies [2–4]. These approaches are useful especially in early life, when the aim of surgery other than complete control of seizures also includes prevention of cognitive decline and behavioral disorders related to intractable seizures [5]. Various approaches to hemispherotomy have been described [1,4,6–13]. Two surgical techniques are more frequently used: the vertical parasagittal

* Corresponding author at: Division of Neurology, Bambino Gesù Children's Hospital, IRCCS, Rome, P.zza S. Onofrio 4, 00165 Rome, Italy.
E-mail address: nicola.specchio@opbg.net (N. Specchio).
[1] Both authors equally contributed to the manuscript.

https://doi.org/10.1016/j.yebeh.2019.01.006
1525-5050/

hemispherotomy [1] and the lateral hemispherotomy with a surgical route in – or around – the Sylvian fissure [4]. Recently, a modified vertical parasagittal hemispherotomy [14] – avoiding the lateral ventricle access – has also been reported.

Different conditions might benefit from these techniques: multilobar or diffuse damage to one hemisphere (e.g., perinatal cerebral infarction or intracranial hemorrhage, hemiconvulsion-hemiplegia-epilepsy, and other sequelae of brain injury and/or infection), developmental lesions (e.g., focal cortical dysplasia [FCD], hemimegalencephaly, and other disorders of cortical development), and progressive dysfunctions of one hemisphere (e.g., Rasmussen's encephalitis and Sturge–Weber syndrome) [5,15,16].

Literature data indicate that a complete seizure control can be achieved in 50–90% of patients submitted to hemispherotomy [10,12,13,15,17–21]. Factors affecting seizure outcome have not been fully clarified, however, several authors [22] suggested that different etiologies and surgical techniques might partially explain variability in the outcomes. Holthausen et al. [23] reported the largest study on seizure outcome in a population of 333 hemispherectomies from 13 different centers with a minimum follow-up period of 6 months. The percentage of seizure-free patients was similar for anatomical/functional hemispherectomy and hemispherotomy (70.3% overall) with a clear trend towards a better performance of hemispherotomy (85.7% vs 64.3%). The rate of seizure-free patients was between 68 and 90% for the lateral approach [4,10,21] and between 77% and 91% for the parasagittal approach [13,24]. Better results have been reported in patients with Rasmussen encephalitis, Sturge–Weber syndrome, and vascular insults (77.6% seizure-free), if compared with cortical malformations and other etiologies (59.1% seizure-free). Acquired (i.e., encephalomalacia) and progressive etiologies (i.e., Rasmussen encephalitis) have a better seizure outcome than developmental ones (i.e., FCD) [22]. Moreover, in patients with developmental lesions, late seizure relapse can occur, therefore suggesting that in those cases, a longer follow-up period is appropriate to assess seizure outcome [25]. It is still unclear whether age at surgery [15,23] or the occurrence contralateral Electroencephalography (EEG) and brain Magnetic Resonance (MR) findings significantly influence outcome [25,26].

The aim of this study was to report a large series of patients with drug-resistant epilepsy assessed with similar presurgical evaluation protocols, and therefore operated using three different hemispherotomy techniques. Evaluation of seizure outcome in relation to surgical techniques and underlying etiologies was also reported.

2. Material and methods

2.1. Patient population and data collection

We retrospectively reviewed the medical records of 92 consecutive patients. All patients underwent hemispherotomy for medically refractory epilepsy due to hemispheric lesions in three main Italian epilepsy surgery centers between 2006 and 2016 (Niguarda Ca' Granda Hospital in Milan, Meyer Children Hospital in Florence, and "Bambino Gesù" Children's Hospital in Rome). Informed consent for all clinical procedures was obtained from all patients.

We collected the following data: age at seizure onset, age at surgery, seizure type, etiology, side of surgery, type of surgery, presence of acute postoperative seizures (APOS), and motor function. We also reviewed interictal and ictal scalp EEG, neurodevelopmental assessment, and neuroimaging studies including high-resolution MR imaging.

We defined the etiology as congenital (e.g., malformation of cortical development, hemimegalencephaly), acquired (e.g., perinatal infarction, bleeding), or progressive (e.g., Rasmussen encephalitis and Sturge–Weber) [5,15,22]. We stratified patients according to etiology and type of surgery. Fifty-four patients underwent lateral hemispherotomy (Niguarda Hospital), 19 vertical parasagittal hemispherotomy (Bambino Gesù Children's Hospital), 16 vertical parasagittal, and 3 modified extraventricular vertical parasagittal (Meyer Pediatric Hospital).

2.2. Surgical techniques

Vertical parasagittal hemispherotomy was performed according to the technique developed by Delalande et al. [13]. At Meyer Hospital, Firenze, a modified vertical parasagittal hemispherotomy was performed. This was designed with exposure of the midline and individualized extension of frontoparietal corticectomy. This approach is conceptually similar to perithalamic leucotomy with complete corpus callosotomy and commissurotomy as described in Delalande's technique, however, it entails the direct access to the corpus callosum through an interhemispheric approach coupled with either a ventricular or an extraventricular route [14] with different extent of corticectomy according to underlying pathology (i.e., more extended for ill-defined FCD which are often associated with widespread epileptogenicity). Lateral hemispherotomy allows to disconnect the hemisphere through a peri-insular approach, requiring only the removal of the fronto–parieto-temporal opercular cortices [10]. Different surgical approaches and hemispherotomy techniques have been used based on the background of neurosurgeons operating in three different centers in Italy. A detailed description of the procedures is available in Supplementary materials.

2.3. Statistical analysis

We performed statistical analysis using R, version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/). Prior to modeling, we summarized data with descriptive statistics for each variable including means, medians, and range for continuous variables and frequencies for categorical variables. An independent t-test and the Mann–Whitney U test with continuity correction were used for continuous variables; the analysis of variance (ANOVA) was used for the comparison of the mean of multiple groups with a Tukey's Honestly Significant Difference (HSD) post hoc analysis when necessary. For multiple testing, a correction was applied according to the Bonferroni rule. For dichotomous results, a chi-square test or Fisher's exact test was performed, as appropriate. The significance level for all tests was $p < 0.05$. All statistical tests were two-tailed. Outcome was defined following Engel epilepsy surgery outcome scale. Finally, based on the results of the first two levels of analyses and review of literature, some variables were attested in a binominal regression model (Engel class I vs classes II–IV) to determine predictors of seizure outcome. We included in the multivariate analysis those variables that are considered – in the literature – to be associated with outcome and that were considered of clinical interest.

3. Results

3.1. Demographic data and clinical findings

Demographic data and clinical findings are summarized in Table 1. Patients, collected in three different epilepsy surgery centers, were homogeneous in terms of demographic data and clinical findings except for age at surgery which was lower in patients operated in Meyer Pediatric Hospital ($p = 0.002$). Our cohort consisted of 48 male and 44 female patients. Mean age at seizure onset was 1.8 years (standard deviation (SD): 2.51, range: 0.0–12.0); age at seizure onset was statistically different in patients with different etiologies ($p = 0.001$), with the lowest age at seizure onset in the group with congenital etiology. Mean duration of epilepsy prior to surgery was 7.4 years (SD: 5.6, range: 0.2–17.7). Mean age at surgery was 9.2 years (SD: 8.0, range: 0.2–36.2), 10 patients were older than 18 years at surgery. Age at surgery was lower in the group with congenital etiology vs the groups with acquired and progressive etiology (7.3 vs 10.4 of the other two groups, $p = 0.02$, see Fig. 1). Fifty-seven (62%) patients had motor and 67 (72.8%) language delay.

Table 1
Preoperative clinical data.

	Overall (92), n. of pts (%) or mean years (±SD, range)
Gender: M/F	48/44 (47.8% M)
Mean age at seizure onset	1.8 (±2.5, 0.0–12.0)
Mean age at surgery	9.2 (±8.08, 0.17–36.17)
Epilepsy duration	7.4 (±7.3, 0.07–36.07)
Seizure type:	
Only focal seizures	62 (67.4%)
Focal to bilateral t–c seizure	28 (30.4%)
Etiology:	
Congenital	38 (41.3%)
FCD I	5 (5.4%)
FCD II	14 (15.2%)
Hemimegalencephaly	8 (8.7%)
Other cortical mal. including (polymicrogyria, FCD III, etc.)	11 (11.9%)
Acquired:	44 (47.8%)
Encephalomalacia (postischemic, posthemorrhagic, postinfectious, posttraumatic)	28 (30.4%)
Gliosis	16 (17.4%)
Progressive:	10 (10.9%)
Rasmussen encephalitis	7 (7.6%)
Sturge–Weber syndrome	3 (3.3%)
Prior surgery	28 (30.4%)
Hemispherotomy side (R/L)	52/38 (56.5% R)
Type of hemispherotomy:	
LH	54 (58.7%)
VPH	19 (20.6%)
VPH modified	19 (20.6%)

n. = number; pts= patients; SD = standard deviation; M = males; F = females; t–c = tonic–clonic; FCD = focal cortical dysplasia; R = right; L = left; LH = lateral hemispherotomy; VHP = vertical parasagittal hemispherotomy.

All patients had focal seizures, 28 (30.4%) presented also focal to bilateral tonic–clonic seizures; 68 patients (73.1%) experienced multiple seizures per day. Patients were taking an average of 2.7 antiepileptic drugs (AEDs) at the time of surgery while the mean number of previous AEDs was 5.9.

3.2. Antecedents

Twenty-seven patients (29.3%) had a history of perinatal hypoxia (19 of them with acquired etiology), and five (5.4%) experienced febrile seizures. A family history of epilepsy was observed in 14 patients (15.2%).

3.3. Additional data on previous surgery

Before hemispherotomy, 25 (27.2%) patients had a previous surgical approach. For details, see Supplementary Table 1.

3.4. Magnetic Resonance Imaging (MRI) findings

Brain MR revealed encephalomalacia in 49 (53.2%), cortical malformation in 24 (26.1%), hemimegalencephaly in eight (8.7%), Rasmussen encephalitis in six (6.5%), Sturge–Weber syndrome in three (3.3%), and unspecified in two (2.2%) patients. Fifty-two patients (56.5%) had right hemisphere lesion. No patient had significant contralateral brain MR abnormalities. Unilobar pathology was found in 6 (6.6%) patients whereas multilobar and hemispheric structural abnormalities were seen, respectively, in 37 (40.2%) and 49 (53.2%) cases.

3.5. Pathology

Based on histopathological results, 38 patients (41.3%) had a congenital etiology, 44 (47.8%) acquired, and 10 (10.8%) progressive. For details, see Table 1.

3.6. EEG findings

Interictal slow abnormalities were documented in 74 patients (81.3%) and interictal epileptiform abnormalities in 85 (92.4%). Hemispheric slow and epileptiform abnormalities in 34 (36.9%) and 43 (46.7%) patients, respectively. Seventy-three patients (79.3%) had at least one seizure documented by video-EEG, and the average of seizure recorded was 10.4 (SD: +14.4, range: 1–66). Eighty-five patients (92.4%) had significantly asymmetric EEG findings.

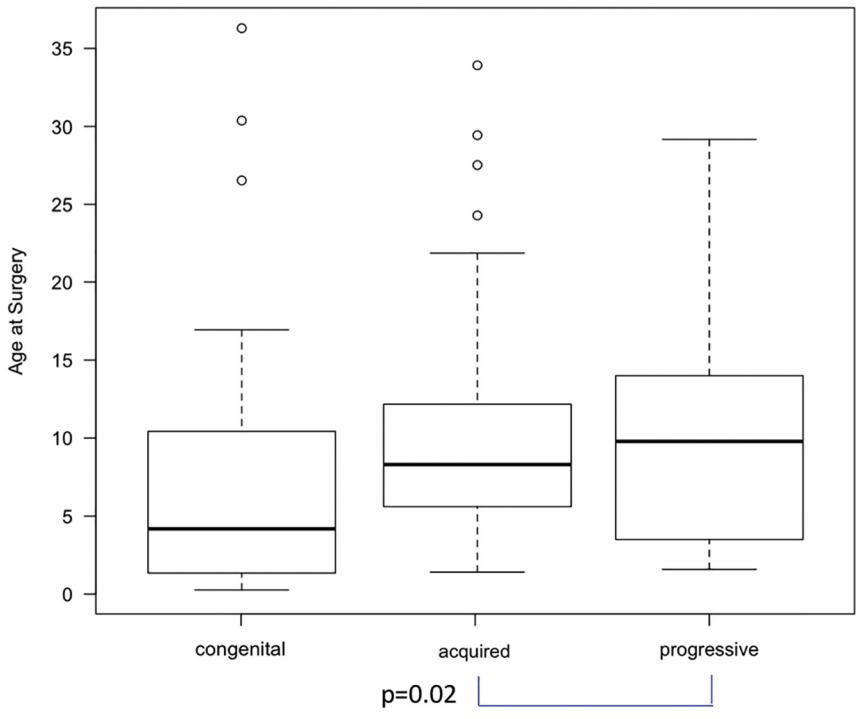

Fig. 1. Box plot showing the age at surgery in the three different groups of etiology. The median age at surgery is significantly lower in the group with congenital etiology.

3.7. Preoperative and postoperative neurologic findings

Eighty-five (92.4%) patients presented with hemiparesis and 69 (75%) other neurologic impairments including psychomotor delay (50, 54.3%), hemianopsia (9, 9.8%), spastic quadriparesis (1, 1.1%), strabismus (5, 5.4%), facial palsy (2, 2.2%), hypotonia (4, 4.3%), and other visual disturbances (5, 5.4%).

In the postoperative course, the hemiparesis remained unchanged at the last follow-up in 44 out of 85 patients (51.7%). In those patients, mean age at surgery was 9.08 years (SD: 7.8, range: 0.16–34.0). Worsening of hemiparesis at the last follow-up was seen in 37 out of 85 (43.5%) patients with a mean age at surgery of 9.41 years (SD: 8.52, range: 0.5–36.2). Hemiparesis improved in 4 children (4.7%) with a mean age at surgery of 8.7 years (SD: 7.58, range: 1.2–16.9). No statistical differences were found adjusting the data by etiology and type of surgery ($p = 0.97$) between the three groups of patients with different functional outcome.

Data about neuropsychological evaluation are limited and inconclusive and, therefore, not reported.

3.8. Surgical procedures and early postoperative course

Nineteen patients (20.6%) underwent vertical parasagittal hemispherotomy ("Bambino Gesù" Hospital), and 54 (58.8%) received a lateral hemispherotomy with peri-insular approach ("Niguarda" Hospital). In 19 patients operated at "Meyer" Hospital, a modified vertical parasagittal-modified approach with an interhemispheric approach coupled with ventricular (16 patients) or extraventricular (3 patients) approach was applied [14].

In our cohort, there were no perioperative mortalities. Overall, 21 patients (22.8%) presented with postoperative complications: early sequelae included intracranial hemorrhage, ischemia, infection, hydrocephalus, and hygroma (see Table 2). We did not find statistically significant differences between the various techniques in terms of surgical complications (vertical vs lateral approaches, $p = 0.154$). All complications did not provoke permanent deficits or mortality.

3.9. Seizure outcome

Two patients were lost at follow-up after an uneventful acute postoperative period. We analyzed data on seizure outcome in 90 patients (Table 3 and Fig. 2).

At the mean follow-up of 2.81 years (SD: 2.41, range: 0.1–16.6), 66 out of 90 patients (73.3%) achieved seizure freedom (Engel I), and 34 out of 66 (53.0%) were off anticonvulsants at last follow-up. Nineteen out of 66 patients (28.8%) started AED withdrawal at time of data collection. Twenty-two patients out of 31 with at least 3-year follow-up were seizure-free (70.9%).

At univariate analysis, only the presence of APOS revealed a significant association with seizure outcome ($p < 0.05$).

Eight patients (8.7%) experienced seizures in the early postoperative period: 4 with FCD II, 3 with encephalomalacia, and 1 with other cortical malformation. Seizure semiology was similar to the preoperative one in all cases. Seizure recurrence in the perioperative period significantly correlated with poor seizure outcome ($p < 0.05$) at long-term follow-up. Seizure outcome did not significantly correlate with the type of hemispherotomy (lateral vs parasagittal approach, $p = 1$).

3.10. Multivariate analysis

In multivariate binomial logistic regression, focal to bilateral tonic–clonic seizures were independently predictive of seizure recurrence in the regression model showed in Supplementary Table 2. Patients with focal to bilateral tonic–clonic seizures were 3.63 times (95% CI: 1.86–15.20, $p = 0.048$) more likely to fail hemispherectomy.

4. Discussion

In this multicenter study, we described a cohort of patients who underwent hemispherotomy for medically refractory epilepsy and highlighted predictive factors related to seizure freedom. In all centers involved in this study, hemispherotomy was the surgical technique chosen because of specific experience of surgeons and because of smaller skin incision and bone flap, with both reduced blood loss and exposure of large venous sinuses [2]. Specifically, we assessed if different surgical approaches might modify seizure freedom rates and overall morbidity.

Our study compares parasagittal with lateral disconnective approaches, demonstrating that using either of these surgical techniques does not influence seizure freedom rate. Unexpected complications were quite low, with a prevalence of hygroma and hydrocephalus in the parasagittal approach if compared with lateral approaches (26% vs 11%). None of the patients had permanent deficits related to complications, indicating that both procedures are safe.

The overall seizure-free survival (Engel I) after hemispherotomy was 73.3%. This finding is in line with earlier reports [10,12,13,15,17,20,21,25,27–29] and emphasizes that hemispherotomy is a highly effective treatment option. In our patients, the benefits of hemispherotomy were durable over time (70.9% at 3 years), in line with other studies [13], despite the overall increase in patient complexity and new surgical techniques [22,23]. In a recent systematic review of 29 papers including 1161 patients, the overall seizure freedom rate for hemispherotomy was 76.0% [22], a slightly lower rate than previously reported (85.7%) [23]. The durability of results found in patients treated with hemispherotomy is not described in focal neocortical resections [30].

While the overall rate of seizure freedom is stable among published series and techniques [22], it was quite clear from the first reported series [23] that etiology influences outcome. In particular, patients with acquired and progressive etiologies had a postsurgical seizure freedom rate of 77.6% [23] while patients with developmental etiology – especially in older reports – had worse outcome (59.1%) [23]. In our cohort, we observed an overall lower seizure freedom rate for patients with developmental etiologies if compared with acquired lesions (67.6% vs 76.7%), although not statistically significant. In previous studies, no direct comparative analysis was done in order to evaluate differences based on surgical techniques in relation to etiology. Looking at our results, the use of different surgical techniques for hemispherotomy does not influence the seizure freedom rate.

The multivariate analysis did not reveal a correlation between seizure-free outcome and gender, age at surgery, age of seizure onset, etiology, and side of surgery, seizure semiology, and interictal EEG abnormalities (including bilateral EEG abnormalities). This finding is in

Table 2
Rate of early postsurgery complication.

Type of surgery	Intracranial hemorrhage	Ischemia	Infection	Hydrocephalous	Hygroma	Total
VPH (19 pts)	0	0	0	5(26.3%)	1(5.2%)	6(31.6%)
mVPH (19 pts)	0	0	2(10.5%)	3(15.8%)	1(5.3%)	6(31.6%)
LH (54 pts)	2(3.7%)	1(1.8%)	0	6(11.1%)	0	9(16.6%)
Total (92 pts)	2(2.2%)	1(1.1%)	2(2.2%)	14(14.2%)	2(2.2%)	21(22.8%)

pts: patients; VPH: vertical parasagittal hemispherotomy; LH: lateral hemispherotomy; m: modified.

Table 3
Seizure outcome.

	Engel I group (66), n. (%) or mean years (±SD, range)	Not Engel I group (24), n. (%) or mean years (±SD, range)	p-Value
Gender: M/F	37/29 (56.0% M)	11/13 (45.8% M)	0.53
Mean age at seizure onset	1.69 (±2.17, 0.0–10.0)	2.23 (±3.2, 0.0–12.0)	0.46
Mean age at surgery	8.78 (±7.7, 0.16–36.1)	10.25 (±8.9, 0.6–30.2)	0.49
Epilepsy duration	7.14 (±7.4, 0.06–36.1)	8.02(±6.9, 0.5–21.2)	0.61
Seizure type:			
Only focal seizures	48 (77.4%)	14 (22.6%)	0.29
Focal to bilateral t–c seizure	18 (64.3%)	10 (35.7%)	
Etiology:			
Congenital	25 (67.5%)	12 (32.5%)	Congenital vs not congenital, p = 0.43
Acquired	33 (76.7%)	10 (23.3%)	
Progressive	8 (80%)	2 (20%)	
Prior surgery	18 (64.3%)	10 (35.7%)	0.29
Hemispherotomy side (R/L)	38/28 (73.1% R, 73.7% L)	14/10 (26.9% R, 26.3% L)	1
Type of hemispherotomy:			LH vs VPH, p = 0.5
LH	38 (73.1%)	14 (26.9%)	LH vs mVPH, p = 0.6
VPH	16 (84.2%)	3 (15.8%)	VPH vs mVPH, p = 0.2
VPH modified	12 (63.2%)	7 (36.8%)	LH vs VPH + mVPH, p = 1
Acute postoperative seizures	0 (0.0%)	8 (100%)	<0.05

n. = number; pts = patients; SD = standard deviation; M = males; F = females; t–c = tonic–clonic; FCD = focal cortical dysplasia; R = right; L = left; LH = lateral hemispherotomy; VHP = vertical parasagittal hemispherotomy; m = modified.

line with previous papers, in which data coming from different surgical approaches are frequently mixed and a clear-cut conclusion is difficult to be drawn [15,25,27,31–35].

The EEG characteristics of patients undergoing hemispherotomy has been widely debated in recent years, and whether interictal or ictal EEG could be misleading in selecting patients with epileptogenic hemispheric lesions is still unsolved [32,35]. Looking only in ictal EEG pattern, it has been reported in a large monocentric study on 170 children that nonlateralized ictal EEG pattern does not correlate with seizure recurrence after surgery [36]. Our study cannot provide a definitive answer to this topic: all patients presented with focal epilepsy with clear anatomo-electroclinical correlations with the affected hemisphere, prompting us to consider the epileptogenic zone to be consistent with the hemispheric structural abnormality in all cases. We also agree, however, that the use of only interictal EEG without a careful analysis of seizure semiology, especially if a large perisylvian lesion is present (i.e., a poroencephalic cyst), could be misleading [35], but this specific point was not part of our study.

The predictive value of MRI has been largely debated, especially concerning the predictive value of contralateral structural abnormalities on outcome [27,32]. We excluded from our study patients with major abnormalities in the contralateral hemisphere, as previous evidences suggested a worse surgical outcome in such cases [32]. The presence of subtle abnormalities, such as reduction in the volume of the unaffected hemisphere, doubtful focal gyral abnormalities, and slight white matter hyperintensities, [25] was not considered in our analysis.

The univariate and multivariate analysis revealed that seizure recurrences in the early postoperative period, and preoperative focal to

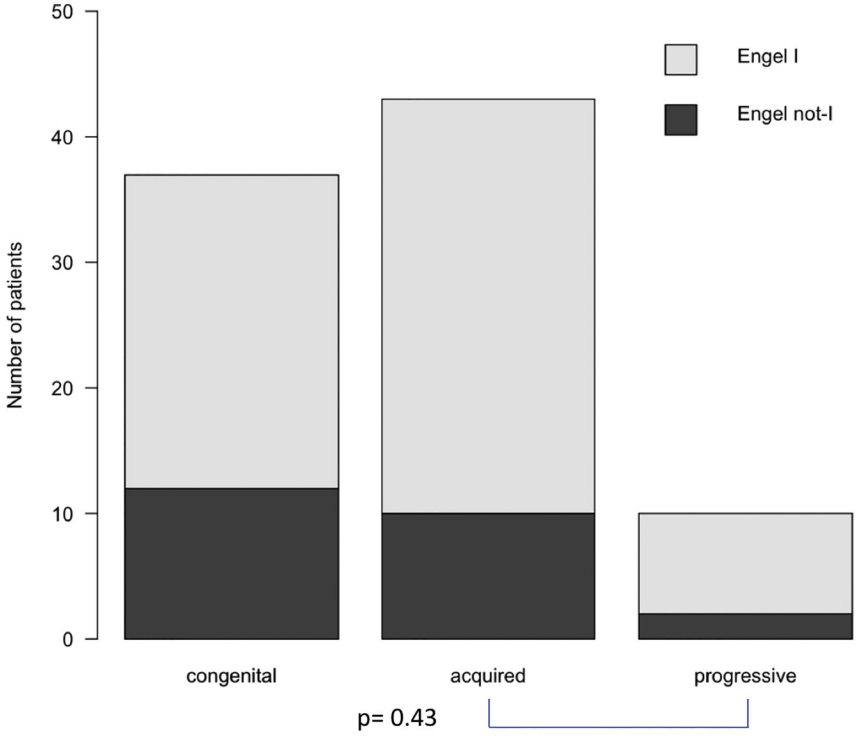

Fig. 2. Column chart showing the outcome in the three different groups of etiology. There is no statistically significant difference regarding outcome related to etiology.

bilateral tonic–clonic seizures, are strong predictors of seizure relapse in the long-term follow-up. A correlation between early postoperative seizures and long-term relapse had already been hypothesized [32]. Conversely, preoperative focal to bilateral tonic–clonic seizures had not been previously associated with a worse outcome.

Our study has some limitations including a possible bias in patients' diagnostic and therapeutic procedures due to the retrospective nature and multicentric collection of data, the lack of standardized postoperative neuropsychological evaluations, and the relatively few data coming from functional studies, such as Fluorodeoxyglucose - Positron Emission tomography (FDG-PET) and High Density -EEG (HD-EEG) or Magnetoencephalography (MEG). However, all patients were evaluated with a uniform presurgical work-up, mainly based on the anatomo-electroclinical correlations [37].

5. Conclusions

In conclusion, our study confirms, in a large cohort, that hemispherotomy is a safe and highly effective technique for the treatment of drug-resistant epilepsies due to unilateral large brain lesions, and that, using the different adaptations of such procedure, does not influence the long-term outcome. Moreover, as per low morbidity rate, early surgery should be proposed in patients with hemispheric epilepsies in which usually, seizures are very disabling and negatively influence the global developmental skills and quality of life. The occurrence of preoperative focal to bilateral tonic–clonic seizures should be considered as a bad prognostic predictor and should be discussed with surgeons and families.

Acknowledgments

We wish to thank the patients and their families for the participation in this study. We wish also to thank the Epilepsy Surgery Commission of Italian League Against Epilepsy (LICE).

Funding sources

This manuscript had no funding.

Ethical publication statement

We confirm that we have read the Journal position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.01.006.

References

[1] Otsuki T. Hemispherotomy and multilobar surgery. In: Arzimanoglou A, Cross JH, Gaillard WD, Holthausen H, Jayakar P, Kahane P, Mathern G, editors. Pediatric epilepsy surgery, 33. John Libbey Eurotext Ltd.; 2017. p. 387–98.
[2] De Ribaupierre S, Delalande O. Hemispherotomy and other disconnective techniques. Neurosurg Focus 2008;25:E14. https://doi.org/10.3171/FOC/2008/25/9/E14.
[3] Rasmussen T. Hemispherectomy for seizures revisited. Can J Neurol Sci 1983;10:71–8.
[4] Villemure JG, Mascott R. Peri-insular hemispherectomy: surgical principles and anatomy. Neurosurgery 1995;37:975–81.
[5] Devlin AM, Cross JH, Harkness W, Chong WK, Harding B, Vargha-Khadem F, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. Brain 2003;126:556–66. https://doi.org/10.1093/brain/awg052.
[6] Shimizu H, Maehara T. Modification of peri-insular hemispherotomy and surgical results. Neurosurgery 2000;47:367–73.
[7] Danielpour M, Von Koch CS, Ojemann SG, Peacock WJ. Disconnective hemispherectomy. Pediatr Neurosurg 2001;35:169–72. https://doi.org/10.1159/000050417.
[8] Schramm J, Kral T, Clusmann H. Transsylvian keyhole functional hemispherectomy. Neurosurgery 2001;49:891–901.
[9] De Almeida AN, Marino R, Aguiar PH, Teixeira MJ. Hemispherectomy: a schematic review of the current techniques. Neurosurg Rev 2006;29:97–102. https://doi.org/10.1007/s10143-005-0011-7.
[10] Villemure JG, Daniel RT. Peri-insular hemispherotomy in paediatric epilepsy. Childs Nerv Syst 2006;22:967–81. https://doi.org/10.1007/s00381-006-0134-3.
[11] Binder DK, Schramm J. Transsylvian functional hemispherectomy. Childs Nerv Syst 2006;22:960–6. https://doi.org/10.1007/s00381-006-0131-6.
[12] Marras CE, Granata T, Franzini A, Freri E, Villani F, Casazza M, et al. Hemispherotomy and functional hemispherectomy: indications and outcome. Epilepsy Res 2010;89:104–12. https://doi.org/10.1016/j.eplepsyres.2009.09.006.
[13] Delalande O, Bulteau C, Dellatolas G, Fohlen M, Jalin C, Buret V, et al. Vertical parasagittal hemispherotomy: surgical procedures and clinical long-term outcomes in a population of 83 children. Neurosurgery 2007;60:19–32. https://doi.org/10.1227/01.NEU.0000249246.48299.12.
[14] Giordano F, Spacca B, Barba C, Mari F, Pisano T, Guerrini R, et al. Vertical extraventricular functional hemispherotomy: a new variant for hemispheric disconnection. Technical notes and results in three patients. Childs Nerv Syst 2015;31:2151–60. https://doi.org/10.1007/s00381-015-2788-1.
[15] Ramantani G, Strobl K, Stathi A, Brandt A, Schubert-Bast S, Wiegand G, et al. Reoperation for refractory epilepsy in childhood: a second chance for selected patients. Neurosurgery 2013;73:695–704. https://doi.org/10.1227/NEU.0000000000000081 [discussion 704].
[16] van der Kolk NM, Boshuisen K, van Empelen R, Koudijs SM, Staudt M, van Rijen PC, et al. Etiology-specific differences in motor function after hemispherectomy. Epilepsy Res 2013;103:221–30. https://doi.org/10.1016/j.eplepsyres.2012.08.007.
[17] Cook SW, Nguyen ST, Hu B, Yudovin S, Shields WD, Vinters HV, et al. Cerebral hemispherectomy in pediatric patients with epilepsy: comparison of three techniques by pathological substrate in 115 patients. J Neurosurg Pediatr 2004;100:125–41. https://doi.org/10.3171/ped.2004.100.2.0125.
[18] Basheer SN, Connolly MB, Lautzenhiser A, Sherman EMS, Hendson G, Steinbok P. Hemispheric surgery in children with refractory epilepsy: seizure outcome, complications, and adaptive function. Epilepsia 2007;48:133–40. https://doi.org/10.1111/j.1528-1167.2006.00909.x.
[19] Terra-Bustamante VC, Inuzuka LM, Fernandes RMF, Escorsi-Rosset S, Wichert-Ana L, Alexandre V, et al. Outcome of hemispheric surgeries for refractory epilepsy in pediatric patients. Childs Nerv Syst 2007;23:321–6. https://doi.org/10.1007/s00381-006-0212-6.
[20] Torres CV, Fallah A, Ibrahim GM, Cheshier S, Otsubo H, Ochi A, et al. The role of magnetoencephalography in children undergoing hemispherectomy. J Neurosurg Pediatr 2011;8:575–83. https://doi.org/10.3171/2011.8.PEDS11128.
[21] Schramm J, Kuczaty S, Sassen R, Elger CE, von Lehe M. Pediatric functional hemispherectomy: outcome in 92 patients. Acta Neurochir 2012;154:2017–28. https://doi.org/10.1007/s00701-012-1481-3.
[22] Griessenauer CJ, Salam S, Hendrix P, Patel DM, Tubbs RS, Blount JP, et al. Hemispherectomy for treatment of refractory epilepsy in the pediatric age group: a systematic review. J Neurosurg Pediatr 2015;15:34–44. https://doi.org/10.3171/2014.10.PEDS14155.Disclosure.
[23] Holthausen H, May TW, Adams CT, Andermann F, Comair Y, Delalande O, et al. Seizures post hemispherectomy. In: Tuxhorn I, Holthausen H, Boenigk H, editors. Paediatric Epilepsy Syndromes and Their Surgical Treatment. London: John Lib- bey; 1997. p. 749–73.
[24] Dorfer C, Czech T, Dressler A, Gröppel G, Mühlebner-Fahrngruber A, Novak K, et al. Vertical perithalamic hemispherotomy: a single-center experience in 40 pediatric patients with epilepsy. Epilepsia 2013;54:1905–12. https://doi.org/10.1111/epi.12394.
[25] Jonas R, Nguyen S, Hu B, Asarnow RF, LoPresti C, Curtiss S, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 2004;62:1712–21.
[26] Lew SM, Koop JI, Mueller WM, Matthews AE, Mallonee JC. Fifty consecutive hemispherectomies: outcomes, evolution of technique, complications, and lessons learned. Neurosurgery 2014;74:182–94. https://doi.org/10.1227/NEU.0000000000000241.
[27] Hallbook T, Ruggieri P, Adina C, Lachhwani DK, Gupta A, Kotagal P, et al. Contralateral MRI abnormalities in candidates for hemispherectomy for refractory epilepsy. Epilepsia 2010;51:556–63. https://doi.org/10.1111/j.1528-1167.2009.02335.x.
[28] Dagar A, Chandra PS, Chaudhary K, Avnish C, Bal CS, Gaikwad S, et al. Epilepsy surgery in a pediatric population: a retrospective study of 129 children from a tertiary care hospital in a developing country along with assessment of quality of life. Pediatr Neurosurg 2011;47:186–93. https://doi.org/10.1159/000334257.
[29] Jeong A, Strahle J, Vellimana AK, Limbrick DD, Smyth MD, Bertrand M. Hemispherotomy in children with electrical status epilepticus of sleep. J Neurosurg Pediatr 2017;19:56–62. https://doi.org/10.3171/2016.8.PEDS16319.
[30] De Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011;378:1388–95. https://doi.org/10.1016/S0140-6736(11)60890-8.
[31] Lettori D, Battaglia D, Sacco A, Veredice C, Chieffo D, Massimi L, et al. Early hemispherectomy in catastrophic epilepsy. A neuro-cognitive and epileptic long-term follow-up. Seizure 2008;17:49–63. https://doi.org/10.1016/j.seizure.2007.06.006.

[32] Boshuisen K, Van Schooneveld MMJ, Leijten FSS, De Kort GAP, Van Rijen PC, Gosselaar PH, et al. Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy. Neurology 2010;75:1623–30. https://doi.org/10.1212/WNL.0b013e3181fb4400.
[33] Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7:525–37. https://doi.org/10.1016/S1474-4422(08)70109-1.
[34] Ciliberto MA, Limbrick D, Powers A, Titus JB, Munro R, Smyth MD. Palliative hemispherotomy in children with bilateral seizure onset. J Neurosurg Pediatr 2012;9:381–8. https://doi.org/10.3171/2011.12.PEDS11334.
[35] Wyllie E, Lachhwani DK, Gupta A, Chirla A, Cosmo G, Worley S, et al. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. Neurology 2007;69:389–97. https://doi.org/10.1212/01.wnl.0000266386.55715.3f.
[36] Moosa ANV, Gupta A, Jehi L, Marashly A, Cosmo G, Lachhwani D, et al. Longitudinal seizure outcome and prognostic predictors after hemispherectomy in 170 children. Neurology 2013;80:253–60. https://doi.org/10.1212/WNL.0b013e31827dead9.
[37] Kahane P, Landré E, Minotti L, Francione S, Ryvlin P. The Bancaud and Talairach view on the epileptogenic zone: a working hypothesis. Epileptic Disord 2006;8:16–26.