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RESEARCH ARTICLE

Not surgical technique, but etiology, contralateral MRI, prior surgery, and side of surgery determine seizure outcome after pediatric hemispherotomy

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Abstract

Objective: We aimed to assess determinants of seizure outcome following pediatric hemispherotomy in a contemporary cohort.

Methods: We retrospectively analyzed the seizure outcomes of 457 children who underwent hemispheric surgery in five European epilepsy centers between 2000 and 2016. We identified variables related to seizure outcome through multivariable regression modeling with missing data imputation and optimal group matching, and we further investigated the role of surgical technique by Bayes factor (BF) analysis.

Results: One hundred seventy seven children (39%) underwent vertical and 280 children (61%) underwent lateral hemispherotomy. Three hundred forty-four children (75%) achieved seizure freedom at a mean follow-up of 5.1 years (range 1 to 17.1). We identified acquired etiology other than stroke (odds ratio [OR] 4.4, 95% confidence interval (CI) 1.1–18.0), hemimegalencephaly (OR 2.8, 95% CI 1.1–7.3), contralateral magnetic resonance imaging (MRI) findings (OR 5.5, 95% CI 2.7–11.1), prior resective surgery (OR 5.0, 95% CI 1.8–14.0), and left hemispherotomy (OR 2.3, 95% CI 1.3–3.9) as significant determinants of seizure recurrence.

Christine Bulteau and Dorottya Cserpan share second authorship.

Martin Tisdall and Kees Braun share last authorship.

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We found no evidence of an impact of the hemispherotomy technique on seizure outcome (the BF for a model including the hemispherotomy technique over the null model was 1.1), with comparable overall major complication rates for different approaches.

Significance: Knowledge about the independent determinants of seizure outcome following pediatric hemispherotomy will improve the counseling of patients and families. In contrast to previous reports, we found no statistically relevant difference in seizure-freedom rates between the vertical and horizontal hemispherotomy techniques when accounting for different clinical features between groups.

KEYWORDS
hemispheric surgery, hemispherotomy, pediatric epilepsy, seizure outcome

1 | INTRODUCTION

Hemispherotomy is an established surgical treatment for drug-resistant epilepsy, with seizures commonly manifesting in infancy and early childhood due to diffuse unihemispheric lesions. In pediatric epilepsy centers, hemispherotomy accounts for 20%–40% of surgical procedures,[1] with significantly increasing utilization over the past decades.[2] Seizure control, the main objective of hemispherotomy, is achieved in most carefully selected pediatric patients,[3–7] including infants with early severe epileptic encephalopathy,[8,9] with relatively low complication rates.[10] Despite the inherent functional deficits following hemispherotomy, including commonly preexisting hemiparesis and homonymous hemianopia, children may achieve substantial cognitive benefits following postsurgical seizure cessation and drug discontinuation.[3,4,11] However, although hemispherotomy has been performed in children for almost half a century, patient selection criteria are still evolving.

Etiology has been identified as a critical determinant of seizure freedom following hemispherotomy. Hemimegalencephaly has been associated with reduced chances of seizure freedom, whereas, among acquired etiologies, perinatal stroke has been associated with increased chances of seizure freedom.[3,7,12,13] Recent improvements in neuroimaging have opened the prospect of hemispherotomy to an ever-widening spectrum of etiologies, underscoring the need to redefine their impact on seizure outcomes in contemporary cohorts. Beyond etiology, contralateral electroencephalography (EEG) and magnetic resonance imaging (MRI) abnormalities have been investigated extensively regarding their impact on postsurgical seizure freedom. Although it has been widely acknowledged that contralateral EEG findings do not preclude seizure freedom,[3,4,14,15] the impact of contralateral MRI abnormalities, increasingly revealed by high-resolution MRI, remains under debate.[3,4,16]

Key Points

- Three-fourths of children were seizure-free after hemispherotomy at long-term follow-up
- Acquired etiology other than stroke and hemimegalencephaly determined seizure recurrence
- Contralateral magnetic resonance imaging (MRI) findings, prior resective surgery, and left hemispherotomy determined seizure recurrence
- The vertical and horizontal hemispherotomy technique did not differ in seizure-free rates

Following the reduced use of anatomic hemispherectomy due to its perceived increased mortality and morbidity, several surgical techniques have been proposed that gradually transitioned from resection toward a focus on disconnection. The most prevalent current techniques, lateral and vertical hemispherotomy,[3–5,13] have been developed and performed in different epilepsy centers with similar success. However, because each center commonly uses only one approach, these techniques have not been compared regarding their efficacy and morbidity until recently. In contrast to the findings of a multicentric Italian study[17] and four consecutive meta-analyses,[10,18–20] a recent multicentric international study[21] reported shorter time-to-seizure recurrence and increased seizure recurrence odds for lateral compared to vertical hemispherotomy, fueling an ongoing debate on the impact of surgical techniques on seizure outcomes. The findings of that

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multicentric study,[21] however, derive from a comparison between 72 vertical and 600 lateral hemispherotomies performed as early as the 1980s, with the difference in efficacy between techniques becoming apparent only at more than 6 years after surgery (i.e., among fewer than 100 patients with long-term follow-up), thus reducing both the validity and the applicability of these findings to contemporary cohorts.

This large European multicenter study aimed to assess the determinants of seizure freedom following pediatric hemispherotomy. In particular, we investigated whether or not the surgical approach-vertical or horizontal—was independently related to seizure outcome, to provide more insight as to the superiority of one technique over the other.

2 | MATERIALS AND METHODS

In this retrospective multicentric cohort study, we included consecutive children (age at surgery ≤18 years) who underwent hemispherotomy in five epilepsy surgery centers in Europe between 2000 and 2016 and had at least 1 year of follow-up. All contributing centers followed local ethics regulations, and the organizing center received institutional review board approval for the study. A subset of the patients has been included in previously reported cohorts.[3,5,9,21–25]

We identified eligible patients from clinical databases maintained by the individual hospitals and we retrospectively reviewed their medical records. Etiology was classified into three main categories (developmental, acquired, and progressive) and seven subcategories (stroke, acquired-other, hemimegalencephaly, polymicrogyria, developmental-other, Rasmussen encephalitis, and Sturge–Weber syndrome), according to MRI and histopathology. Significant MRI findings contralateral to the affected hemisphere were noted.[3,4] Subtle abnormalities, such as small single white matter lesions, mild sulcation anomalies or isolated areas of subtle T2 hyperintensity without ventricular dilatation, tissue loss, and cortical/subcortical involvement, were not considered as significant contralateral MRI findings for analysis.[3,4]

Patients underwent either vertical parasagittal hemispherotomy (Fondation Rothschild, Paris) or lateral peri-insular/perisylvian/transsylvian hemispherotomy (other centers). We excluded patients with other types of hemispheric disconnection, such as decortication or anatomic hemispherectomy from analysis. Only data from the first procedure were included for patients who underwent a redo hemispherotomy procedure. We recorded major complications,[26] defined as those requiring invasive treatment, or those leading to unexpected neurological deficits for over 3 months or to irreversible neurological deterioration. Seizure freedom was classified as Engel class Ia and noted at last follow-up.[27] Postsurgical medication policies followed common practices in each of the centers.

We performed univariate analysis using Wilcoxon's rank sum and Fisher's exact test, with age at surgery, epilepsy duration, contralateral MRI findings, etiology, prior resective surgery, side of hemispherotomy, type of hemispherotomy, and postsurgical follow-up duration as independent variables for seizure outcome. Missing data were addressed by multiple imputation,[28] thus generating 10 imputed data sets for multivariable analysis. We used polynomial regression for variables with multiple categories, logistic regression for binary variables, and predictive mean matching for continuous variables. For this step, we included the etiology subcategories (and excluded the main categories) and considered all independent variables except for follow-up duration.

Furthermore, we used logistic regression to identify determinants of hemispherotomy types. For significant variables, we then matched the vertical to the horizontal hemispherotomy groups with the MatchThem[29] package within the imputed data set using Mahalanobis distance metrics and the optimal matching method. Correction for centers was not possible because these applied either a vertical or lateral hemispherotomy technique. We used Rubin's rule to pool the estimated parameters, standard errors, confidence intervals, and *p*-values from the imputed data sets.

We used multivariable logistic regression with (1) age at surgery, epilepsy duration, contralateral MRI findings, etiology, prior resective surgery, side of hemispherotomy, type of hemispherotomy, and postsurgical follow-up duration as independent variables for *seizure recurrence*; and with (2) age at surgery, etiology, and type of hemispherotomy as independent variables for *major complications* (hydrocephalus, other major complications, pooled major complications). We checked the assumptions of linearity, response distribution, independence, and multicollinearity of the logistic regression model, and we removed variables having a variance inflation factor >5. As classical frequentist models are known for their inability to provide evidence in favor of the null hypothesis, we compared the logistic models of seizure outcome and major complications with and without the inclusion of surgery type by the Bayes factor (BF)[30] to assess the role of surgery type in explaining the seizure outcome.[31] Statistical significance was established at two-sided *p*-values of ≤.05. All statistical analyses were performed by RStudio (2022.02.3).

3 | RESULTS

Our cohort included 457 children (250 male; Table 1). Mean age at seizure onset was 1.9 years (standard deviation [SD] 2.9, range 0.0–8.0), mean duration of

TABLE 1 Clinical characteristics of our cohort in relation to seizure outcome.

	Seizure freedom, $N = 344$[a]	Seizure recurrence, $N = 113$[a]	*p*-value[b]	Overall, $N = 457$[a]
Etiology: main categories				
Acquired	125 (78%)	36 (22%)	.22	161 (35%)
Developmental	135 (71%)	55 (29%)		190 (42%)
Progressive	84 (79%)	22 (21%)		106 (23%)
Etiology: subcategories				
Stroke	116 (82%)	26 (18%)	.008*	142 (31%)
Other acquired	8 (44%)	10 (56%)		18 (4.0%)
Hemimegalencephaly	48 (66%)	25 (34%)		73 (16%)
Polymicrogyria	26 (72%)	10 (28%)		36 (7.9%)
Other developmental	61 (75%)	20 (25%)		81 (18%)
Rasmussen encephalitis	57 (83%)	12 (17%)		69 (15%)
Sturge–Weber syndrome	27 (75%)	9 (25%)		36 (7.9%)
Contralateral MRI findings				
No	296 (82%)	67 (18%)	<.001*	363 (83%)
Yes	34 (45%)	41 (55%)		75 (17%)
Epilepsy duration (years)	3.9 (0.1–16.3)	3.5 (0.1–17.8)	.17	3.8 (0.1–17.8)
Age at surgery (years)	5.8 (0.1–17.8)	5.2 (0.2–17.8)	.14	5.7 (0.1–17.8)
Side of hemispherotomy				
Right	178 (80%)	45 (20%)	.030*	223 (49%)
Left	166 (71%)	68 (29%)		234 (51%)
Prior resective surgery				
No	326 (76%)	101 (24%)	.07	427 (94%)
Yes	17 (61%)	11 (39%)		28 (6.2%)
Type of hemispherotomy				
Lateral	210 (75%)	70 (25%)	.91	280 (61%)
Vertical	134 (76%)	43 (24%)		177 (39%)
Follow-up duration (years)	5.0 (1.0–17.1)	5.3 (1.0–15.5)	.26	5.1 (1.0–17.1)

Note: Patients who achieved seizure freedom (Engel class Ia) differed significantly ($p < .05$*) from those who had seizure recurrence (all other outcomes) as to the etiology subcategories, contralateral magnetic resonance imaging (MRI) findings, and side of hemispherotomy but not as to the type of hemispherotomy. Values are presented as numbers *n* (%) or their mean (range), and percentages are calculated row-wise for the seizure outcome columns, and column-wise for the overall rates in our cohort.

[a]*n* (%); mean (range).

[b]Fisher's exact test; Wilcoxon rank-sum test.

epilepsy 3.8 years (SD 3.7, range 0.1–17.8), and mean age at surgery 5.7 years (SD 4.8, range 0.1–17.8). Mean follow-up duration was 5.1 years (SD 3.9, range 1–17.1): 193 patients (42%) had 5-year, and 66 (14%) had 10-year follow-up. Two hundred eighty patients (61%) underwent lateral hemispherotomy (111 peri-insular, 96 perisylvian, 73 transsylvian) and 177 (39%) underwent vertical parasagittal hemispherotomy. Left- (51%) and right-sided (49%) hemispherotomies were equally represented.

One hundred sixty-one children (35%) children had an acquired, 190 (42%) a developmental, and 106 (23%) a progressive etiology (Table 1). We classified as "other acquired" cases with post-infectious epilepsy ($N = 15$), including hemiconvulsion-hemiplegia-epilepsy syndrome ($N = 5$), and as "other developmental" children with hemispheric cortical dysplasia ($N = 72$) and Aicardi syndrome ($N = 4$). Seventy-five children (16%) had contralateral MRI findings, including 37 of 158 (23%) of those with acquired, 34 of 175 (19%) of those with developmental, and 4 of 105 (4%) of those with progressive etiology. Twenty-eight children (6%) had undergone previous non-hemispheric resective surgery, including 19 of 189 (10%) with developmental, 6 of 105 (6%) with progressive, and 3 of 161 (2%) with acquired etiology. Missing data comprised 0.4% of entries in etiology subgroups, 4.4% in contralateral MRI findings, 0.2% in epilepsy duration, and 0.4% in previous surgery.

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In univariate analysis (Table 1), seizure outcome differed significantly according to the etiology subcategory ($p = .008$), the presence of contralateral MRI findings ($p < .001$), and the side of hemispherotomy ($p = .03$). Seizure freedom was achieved in 75% of lateral and 76% of vertical procedures. Seizure-freedom rates according to etiology are given in Figure 1.

In multivariable logistic regression, contralateral MRI findings (odds ratio [OR] 5.5, 95% confidence interval [CI] 2.7–11.1), prior resective surgery (OR 5.0, 95% CI 1.8–14.0), left hemispherotomy (OR 2.3, 95% CI 1.3–3.9), acquired etiology other than stroke (OR 4.4, 95% CI 1.1–18.0), and hemimegalencephaly (OR 2.8, 95% CI 1.1–7.3) were identified as significant determinants of seizure recurrence (Figure 2, Table S1).

The lateral and vertical hemispherotomy groups differed significantly in univariate analysis for their distribution of main etiology categories and subcategories ($p < .001$), and for epilepsy and postsurgical follow-up duration (Table 2). Multivariable regression modeling revealed that only etiology subcategories and follow-up duration differed independently between the two groups; therefore data were matched according to these two variables. We obtained an estimated Bayes factor (or BF) of 1.1 in favor of the outcome determination model containing the surgery type compared to the model not containing the surgery type. This finding indicates no impact of surgery type on seizure outcome.

Pooled major complications related to surgery occurred in 14% of our cohort; 11% of children developed hydrocephalus with a need for ventriculoperitoneal shunt placement or ventriculocisternostomy, and 4% had other major complications. Although etiology and age at surgery were not independently related to the occurrence of major complications in multivariable analysis (Table S2), type of surgery was related to the development of hydrocephalus, with OR 2.3 (95% CI 1.17–4.59) for vertical hemispherotomy ($p = .016$) with substantial evidence suggested by the Bayes factor (BF: 7.0), but not to the occurrence of pooled major complications (OR 1.42, 95% CI 0.79–2.57, $p = .2$; BF: 0.63).

Only one child died as a direct complication of surgery; this was a 6-month-old boy with Sturge–Weber syndrome who developed hypoxia and bradycardia and died within a few hours of surgery.

4 | DISCUSSION

Our study offers valuable insights into the independent determinants of seizure outcomes and major complications following hemispherotomy in children, drawing from a large and contemporary multicenter cohort, in which specific etiology categories were established with current diagnostic approaches. Acquired etiology other than stroke, hemimegalencephaly, contralateral MRI findings,

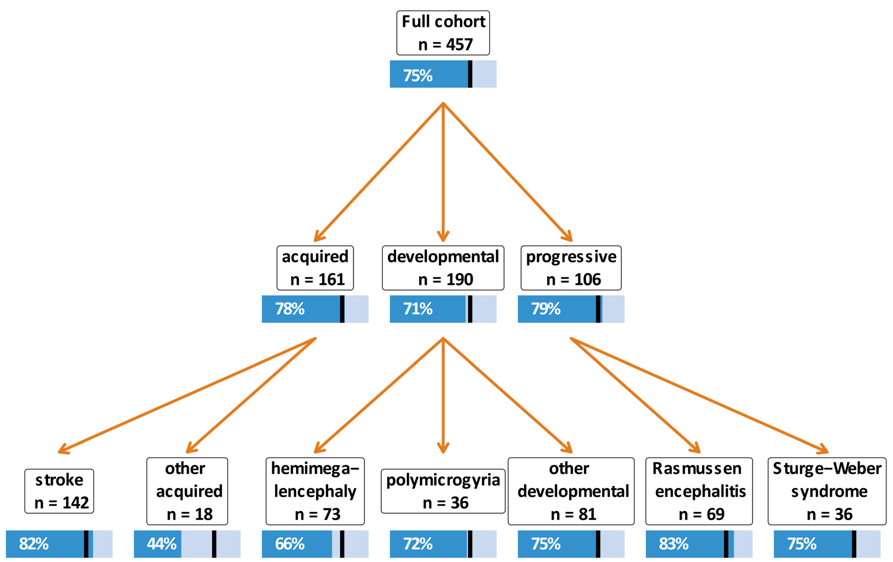

FIGURE 1 Seizure-outcome rates according to etiology. Seizure-freedom rates were comparable among the three main etiologies but showed considerable variation among the etiology subcategories. The dark and light blue parts of each bar correspond to the rates of seizure freedom (Engel Ia) and seizure recurrence (all other outcomes), whereas the black vertical line represents the mean seizure-freedom rate of 75% for our full cohort. The logistic regression model revealed increased odds of postsurgical seizure recurrence for patients with hemimegalencephaly (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.1–7.3) and acquired etiology other than stroke (OR 4.4, 95% CI 1.1–18.0).

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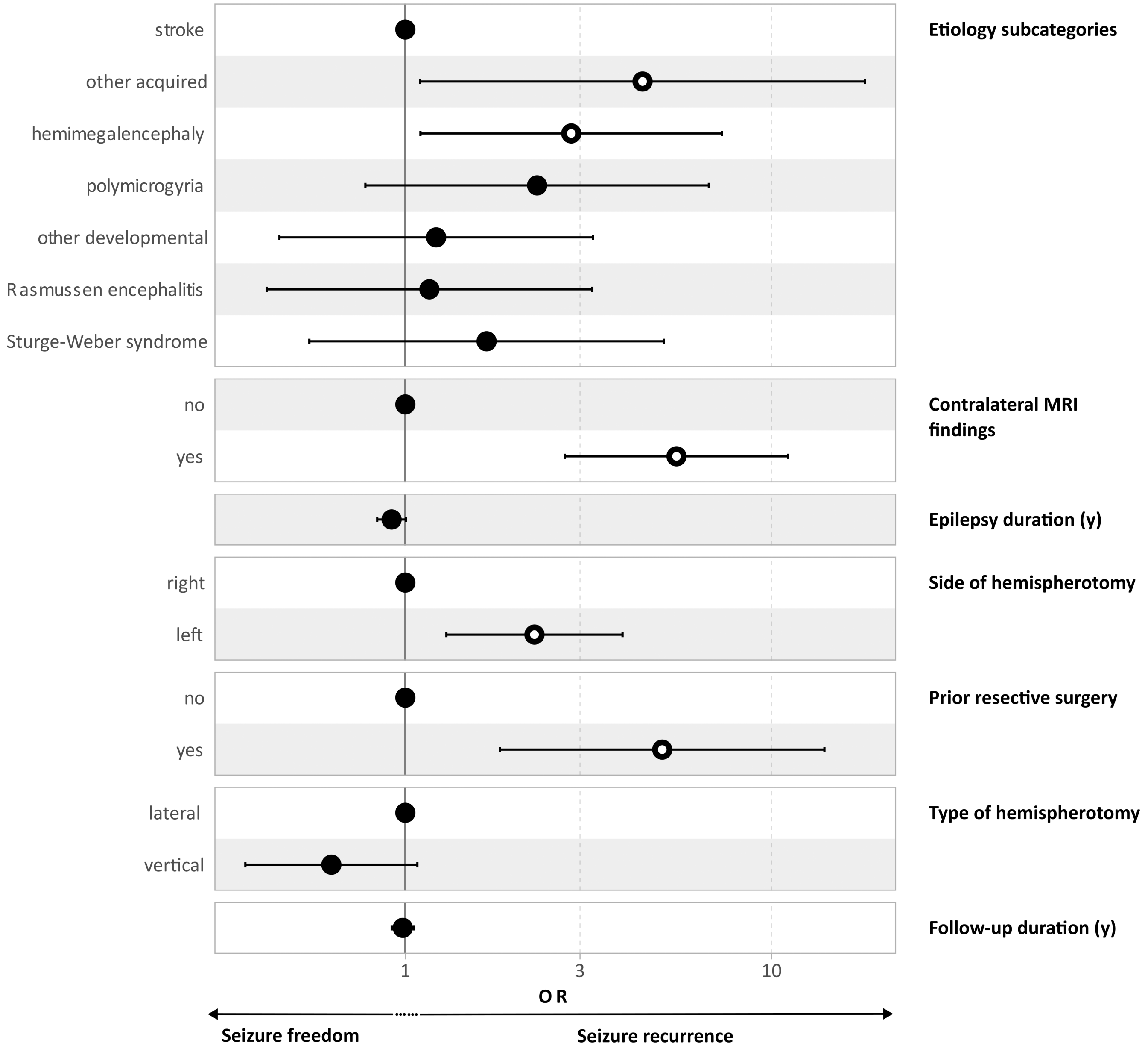

FIGURE 2 Significant determinants of seizure relapse following hemispherotomy. Multivariable analysis of the data after matching the vertical and horizontal group for significant covariate differences. Acquired etiology other than stroke (odds ratio [OR] 4.4, 95% confidence interval [CI] 1.1–18.0), and hemimegalencephaly (OR 2.8, 95% CI 1.1–7.3), contralateral MRI findings (OR 5.5, 95% CI 2.7–11.1), prior resective surgery (OR 5.0, 95% CI 1.8–14.0), and left hemispherotomy (OR 2.3, 95% CI 1.3–3.9), were identified by logistic regression as independent significant determinants of seizure recurrence (marked by empty circles). OR > 1 indicates greater odds of seizure recurrence. Details of the model are shown in Table S2.

prior resective surgery, and left hemispherotomy were significant independent determinants of seizure recurrence. In contrast to previous reports, we found no independently significant impact of hemispherotomy technique on seizure outcome when accounting for disparities in clinical features between the lateral and vertical groups. Although vertical hemispherotomy carried a higher risk of hydrocephalus in our study, surgical technique was not significantly related to the overall occurrence of major complications. In addition to improving patient selection, counseling, and prognostication, these insights support the notion that different hemispherotomy techniques, as performed in different experienced institutions, are associated with comparable chances of surgical success.

4.1 | Seizure outcome

The 75% rate of long-term seizure freedom in the present study is toward the higher end of the 62%–80%

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TABLE 2 Clinical characteristics of the vertical and horizontal hemispherotomy subgroups.

	Horizontal, $N = 280$	Vertical, $N = 177$[a]	p-value[b]
Coded etiology			
Acquired	126 (45%)	35 (20%)	<.001*
Developmental	102 (36%)	88 (50%)	
Progressive	52 (19%)	54 (31%)	
Sub-coded etiology			
Stroke	115 (41%)	27 (15%)	<.001*
Other acquired	11 (3.9%)	7 (4.0%)	
Hemimegalencephaly	42 (15%)	31 (18%)	
Polymicrogyria	15 (5.4%)	21 (12%)	
Other developmental	45 (16%)	36 (21%)	
Rasmussen encephalitis	33 (12%)	36 (21%)	
Sturge–Weber syndrome	19 (6.8%)	17 (9.7%)	
Contralateral MRI			
No	234 (84%)	129 (82%)	.60
Yes	46 (16%)	29 (18%)	
Epilepsy duration (years)	4.1 (0.1–17.8)	3.2 (0.1–16.1)	.003*
Age at surgery (years)	5.9 (0.1–17.8)	5.2 (0.2–17.4)	.07
Side of hemispherotomy			
Right	140 (50%)	83 (47%)	.56
Left	140 (50%)	94 (53%)	
Prior resective surgery			
No	263 (94%)	164 (94%)	>.99
Yes	17 (6.1%)	11 (6.3%)	
Follow-up duration (years)	4.2 (1.0–17.1)	6.5 (1.0–15.0)	<.001*

Note: The two groups differed significantly ($p < .05$*) regarding the main etiologies, etiology subcategories, epilepsy, and follow-up durations. Values are presented as numbers n (%) or their mean (range).

[a]n (%); mean (range).

[b]Fisher's exact test; Wilcoxon rank-sum test.

range reported by a recently published large multicentric study[21,22] and three meta-analyses,[10,18,19] all including patients who underwent hemispheric procedures as early as the 1970s. This finding is particularly reassuring, considering the broader spectrum of etiologies and the increased complexity of surgical cases in recent years. In addition, the long-term mean follow-up of 5.1 years with almost one-half of the cohort followed for ≥5 years after surgery enables us to ascertain the long-term impact of different determinants of seizure outcome.

4.2 | Determinants of seizure outcome

Specific etiology, including acquired etiology other than stroke and hemimegalencephaly, was identified as an independent significant determinant of seizure relapse. In contrast, no significant outcome difference was found between the main etiology categories of developmental, progressive, and acquired epilepsy substrates. This finding highlights the complexity of surgical decision-making in contemporary cohorts. The often-used although rather crude etiological trichotomy of past decades has been superceded by more precise approaches aiming at more precise counseling and prognostication. In past studies, acquired etiologies—of which stroke accounted for the vast majority—have been linked to optimal seizure outcome.[12,13] Large multicenter cohorts, as available in the present study, are required to include sufficient numbers of patients with rare and potentially poorer-outcome etiologies (comprising mainly post-infectious epilepsies) in the acquired etiology group that is dominated by better-outcome strokes. Specific categorization of etiology offers the potential of more precise counseling and prognostication.[32] Finally, our findings corroborate the reduced chances of seizure control in hemimegalencephaly, one of the key developmental epilepsy substrates before the introduction of

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advanced MRI technology,[3,7,33] in a contemporary cohort. Although most developmental etiologies amenable to hemispherotomy are caused by somatic mutations, a higher mosaicism load with possibly bilateral expression[34] may explain a higher rate of surgical failures in hemimegalencephaly compared to other malformations, such as multilobar cortical dysplasia.

Significant contralateral MRI findings were associated with seizure recurrence in our cohort, thus supporting the impact of MRI abnormalities on postsurgical seizure outcome.[4,19,20] However, the criteria for "significant" MRI abnormalities have not always been clearly defined in previous studies, and often remain dependent on the subjective interpretation of the observer. This ambiguity may underpin disparities reported in past studies[3,4,16] and is expected to evolve further with the use of improved neuroimaging techniques. Beyond seizure freedom, contralateral MRI abnormalities have been shown previously to hinder presurgical cognitive development and postsurgical cognitive improvements[4] and result in lower language function.[11] Although these findings suggest caution in cases with bihemispheric MRI abnormalities, they should not be perceived as an absolute contraindication for hemispherotomy, provided that seizure semiology and ictal EEG abnormalities are predominantly unihemispheric. Nevertheless families should be carefully counseled in such circumstances.

Previous non-hemispheric resective surgery has been associated with seizure recurrence.[22] In our study, among the children who underwent previous surgery and had seizure recurrence after hemispherotomy, no specific etiology or type of previous surgery was found to be overrepresented. This observation is surprising because reoperation has been reported as particularly beneficial for selected children with pharmacoresistant epilepsy associated with extensive unilateral cortical dysplasia who did not respond to an initial limited resection.[9,23,35,36] In very young children, insufficient MRI delineation of focal cortical dysplasia (FCD) and lack of preexisting neurological deficits may limit the direct offer or acceptance of hemispherotomy, resulting in a lesser, subhemispheric resection with the hope of significant seizure reduction without additional postsurgical deficits.[23] However, due to incomplete myelination,[37] contralateral MRI abnormalities may also escape detection during specific time windows in infancy, possibly contributing to surgical failure. Finally, it should be noted that reoperations in pediatric epilepsy surgery reflect the incorrect delineation of the epileptogenic zone within the ever-widening and increasingly challenging spectrum of surgical candidates, where genetic substrates may ultimately explain surgical failures in developmental etiologies.[38]

Left hemispherotomy was associated with seizure recurrence in our cohort, in contrast with a previous meta-analysis[19] and a recent large multicentric study.[22] Although two monocentric studies have also suggested higher rates of seizure freedom for right as opposed to left hemispheric procedures (72% vs 59%[6] and 95% vs 73% for right- vs left-hemispheric procedures[3]), this difference did not reach statistical significance. In children, the opportunity to benefit from marked brain plasticity for language reorganization in early life[39] may dictate a more liberal indication for left-sided hemispherotomy, even in more challenging cases with lower chances of seizure freedom. This window of opportunity is crucial, since satisfactory transfer may only occur for certain aspects of linguistic abilities after the age of 8 years.[40,41]

4.3 | Comparing hemispherotomy techniques

We found no significant impact of surgical technique on long-term seizure outcomes when applying two different statistical approaches. First, multivariable regression analysis of the cohort failed to demonstrate an independent significant effect of technique on outcome. Second, when matching both groups for significant covariate differences, Bayesian analysis revealed no influence of adding surgical techniques to the outcome model, with a Bayes factor of only 1.1 (currently defined as "not worth more than a bare mentioning"[30]). In addition, the recent study that suggested more durable seizure freedom following vertical compared to lateral hemispherotomy[21] derived from subgroups of only 72 vertical vs 600 lateral procedures. We have, however, investigated the impact of surgical technique in more balanced subgroups of 177 vertical and 280 lateral procedures, bolstering subgroup comparability by matching for crucial clinical features. In addition, although the majority of hemispherotomies analyzed in the previous study were reportedly performed after 2000, some procedures dated as far back as 1986,[22] whereas our study represents a more contemporary cohort. Finally, the previous multicenter study[21] underscored that seizure-freedom rates significantly declined over time, most noticeably at 6 years after hemispherotomy. In particular, differences in seizure outcome between the surgical groups increased with longer follow-up duration. In that study, however, only 22% of children had a 5-year, and only 4% had a 10-year follow-up, corresponding to a considerably lower proportion of children with long follow-up duration than in our cohort (42% 5-year, 14% 10-year). The lack of significant difference in seizure outcome despite an even longer relative follow-up duration in our cohort reinforces our observations.

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Although complication data, not reported in the recent large multicentric study,[21] are critical for weighing the potential benefit of the different hemispherotomy techniques against their associated risks, overall major complication rates did not differ significantly between hemispherotomy techniques in our study, although hydrocephalus occurred more often in the vertical hemispherotomy cohort. This observation is in line with previous cohort studies[3,5,7,13,42,43] and a recent meta-analysis[18] suggesting comparable overall rates of major surgical complications in vertical vs lateral hemispherotomy cohorts. Our findings thus corroborate that the vertical and lateral hemispherotomy techniques are similarly effective for seizure control, with acceptable and comparable safety profiles, when performed by skilled epilepsy neurosurgeons. Finally, although past studies have linked surgical complications, particularly hydrocephalus, to the underlying etiology,[44] the key determinant of seizure outcome, etiology, had no significant impact on major complications in our study. In contrast, hydrocephalus was recorded more frequently in children undergoing vertical compared to lateral hemispherotomy. The impact of hemispherotomy technique on both seizure outcome and major surgical complications, particularly hydrocephalus, should be analyzed in the context of the different etiology subcategories and different age groups in sufficient sample sizes, which are available only within the scope of multicentric collaborative studies. This approach will facilitate the selection of the appropriate hemispherotomy technique with the highest chances of seizure freedom and the lowest risks of major surgical complications for each individual patient.

4.4 | Limitations

Our study has several limitations originating from its retrospective multicentric design. First, candidate selection for hemispherotomy differs between centers, and accounting for these center effects is impeded by the use of the vertical technique in a single center. Nevertheless, the subgroups of vertical vs lateral hemispherotomy were balanced for sample size and matched for variables that differed independently between the two subgroups, thus strengthening our results. Second, surgical failure due to incomplete resection and disconnection, as opposed to incorrect surgical hypothesis, can be verified only by analyzing the postsurgical MRI, preferably including tractography studies. Although this analysis was not within the scope of our study, the inclusion of structural and functional MRI data in future studies will be beneficial to disentangle the effect of different determinants of surgical failure in hemispherotomy. Third, surgical experience is undoubtedly crucial in obtaining complete disconnection, thus increasing the chances of seizure freedom, irrespective of patient selection and surgical technique. Although variables such as documentation of incomplete disconnection have not been accounted for in our analysis, it must be noted that the majority of hemispherotomies were performed by two experienced neurosurgeons in each center throughout the time period of the study, thus closely mirroring an expertise-based real-world trial of different hemispherotomy techniques.

5 | CONCLUSION

Our study demonstrates independent determinants of seizure outcome and complications following hemispherotomy in children, drawing from a large and contemporary multicenter cohort. New insights regarding specific etiology, contralateral MRI findings, and side of surgery may improve patient selection, counseling, and prognostication. In contrast to previous reports, we found no significant impact of hemispherotomy technique on seizure outcome when accounting for disparities in clinical features between the lateral and vertical groups. In skilled hands, different hemispherotomy techniques, as performed in different institutions, apparently bear comparable chances of surgical success with comparable risks of major surgical complications.

AUTHOR CONTRIBUTIONS

GR, CB, MT, and KB contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. GR, DC, and KB drafted the manuscript and prepared the figures with significant contribution from WO and MT. All authors reviewed, edited, and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Helen Cross has served as a paid consultant for Zogenix/UCB, Takeda, and Biocodex, and/or has received grants or contracts from GW Pharma/Jazz, Stroke Therapeutics, Ultragenyx, and Marinius. Georgia Ramantani has received payments to her institution from NEUROCRINE, EISAI, and Takeda. Martin Tisdall has received payments from Medtronic, Renishaw, Optima, MicroMed, LivaNova, and Dixi. The remaining authors have no conflicts of interest. We confirm that we have read the

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Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

INFORMED CONSENT

All participants provided written informed consent, where applicable.

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

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