DETERMINANTS OF FUNCTIONAL OUTCOME AFTER PEDIATRIC HEMISPHEROTOMY

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SUMMARY

Objective: We aimed to evaluate determinants of functional outcome after pediatric hemispherotomy in a large and recent multicenter cohort.

Methods: We retrospectively investigated the functional outcomes of 455 children who underwent hemispherotomy in five epilepsy centers in 2000-2016. We identified determinants of unaided walking, voluntary grasping with the hemiplegic hand, and speaking through Bayesian multivariable regression modeling using missing data imputation.

Results: 75% of children were seizure-free, and 44% stopped antiseizure medication at a 5.1-year mean follow-up (range 1-17.1). 77% of children could walk unaided, 8% could grasp voluntarily, and 68% could speak at the last follow-up. Children were less likely to walk when they had contralateral MRI abnormalities (40/73 children; odds ratio (OR)=0.49 [0.28-0.86], p=0.04), recurrent seizures following hemispherotomy (62/109 children; OR=0.48 [0.28-0.86], p=0.04), and moderately (50/61 children; OR=0.21 [0.05-0.66], p=0.03) or severely impaired (127/199 children; OR=0.15 [0.03-0.42], p=0.001) intellectual functioning following hemispherotomy, but were more likely to walk when they were older at outcome determination (OR=1.11 [1.04-1.18], p=0.01). Children were unlikely to grasp voluntarily when they had Rasmussen encephalitis (0/61 children; OR=0.01 [0-0.16], p=0.001) or Sturge-Weber syndrome (0/32 children; OR=0.02 [0-0.33], p=0.007). Children were less likely to speak when they had contralateral MRI abnormalities (30/69 children; OR=0.34 [0.19-0.61], p=0.002) and longer epilepsy duration (OR=0.79 [0.67-0.92], p=0.01), but more likely to speak when they had Sturge-Weber syndrome (29/35 children; OR=3.89 [1.67-10.16], p=0.01), were older at surgery (OR=1.2 [1.04-1.41], p=0.04) and older at outcome determination (OR=1.18 [1.11-1.26], p<0.001).

Interpretation: Etiology and bilaterality of structural brain abnormalities were key determinants of functional outcome after hemispherotomy. Longer epilepsy duration affected language outcomes. Not surprisingly, walking and talking ability increased with older age at outcome evaluation.

INTRODUCTION

Hemispherotomy is defined by the disconnection – and, thus, the functional isolation – of one cerebral hemisphere from the remaining nervous system, often complemented by additional insular resection. Hemispherotomy accounts for 20-40% of current pediatric epilepsy surgery procedures, and candidates are commonly children with early onset drug-resistant epilepsy due to severe diffuse hemispheric lesions. Seizure freedom, the key objective of hemispherotomy, is attained by 66-85% of selected children[1–6], including infants with epileptic encephalopathy[7–10]. Although major complications – requiring invasive treatment or leading to unexpected permanent new deficits – have been reported in 14% of cases[11], these are often treatable, whereas new and permanent neurological deficits are rare. Despite the neurological deficits commonly preexisting in hemispherotomy candidates, including hemiparesis and hemianopia, postsurgical seizure freedom and antiseizure medication (ASM) cessation may lead to considerable developmental benefits[1,2,12]. Although multiple seizure outcome determinants have been identified[1,2,4,6,13], allowing to counsel families regarding the chances of postsurgical seizure freedom, there are fewer data on functional outcomes and their determinants after hemispherotomy. Postsurgical quality of life depends not only on seizure outcome but also on developmental and functional outcomes, such as motor and language impairments[14,15], e.g., the ability to walk unaided, ride a bicycle, and communicate verbally.

Etiology was a critical determinant of functional outcome following hemispherotomy in earlier cohorts[14,16]. Developmental substrates, particularly hemimegalencephaly, are associated with worse motor and language outcomes, while, among acquired substrates, perinatal stroke is associated with better outcomes. Recent improvements in neuroimaging, including high-resolution scanners[17], dedicated epilepsy protocols[18], and postprocessing tools[19], have widened the spectrum of etiologies amenable to hemispherotomy, underscoring the need to delineate their effect on functional outcomes in contemporary cohorts. In addition to etiology, contralateral MRI abnormalities are associated with seizure recurrence[2,6] and motor and language outcomes following hemispherotomy[12,20]. Current knowledge about functional outcomes derives from either smaller cohorts[20], which lacked the statistical power to adequately characterize functional outcomes in different etiologies, or from larger cohorts[12,16] that included hemispheric procedures performed as early as 1986, calling into question their applicability to contemporary cohorts, where insular resection, leading to higher rates of seizure freedom, has been increasingly implemented, and resection has been gradually replaced by disconnection, leading to comparable rates of seizure freedom but more favorable complication profiles[21].

This large and more recent European multicenter pediatric cohort, of which seizure outcomes were recently reported[6], provides a contemporary update of key functional outcomes following hemispherotomy and their determinants.

MATERIALS AND METHODS

Patient selection

In this retrospective multicenter cohort study, we included consecutive children aged ≤18 years at hemispherotomy in five European epilepsy surgery centers in 2000-2016 who were followed up for at least one year. Details of the full study cohort have been previously reported[6]. A subgroup has been included in previously published studies[1,3,6,8,10,22–25]. Each contributing center followed local ethics regulations, and the organizing center received approval from the institutional review board (KEK 2022-02174). We selected eligible patients from institutional databases and retrospectively reviewed their medical files.

Functional outcome

The three main functional outcome measures assessed at the last follow-up were: 1) *unaided walking,* dichotomized as yes (able to walk unaided) or no, 2) *voluntary hemiplegic hand function,* dichotomized as yes (able to grasp voluntarily with the hemiplegic hand, e.g., to take an object, open the door) or no, and 3) *speaking,* dichotomized as yes (able to speak in short sentences or age-appropriately) or no. We only included children ≥2 years at the last follow-up when assessing speech

outcomes. Functional outcome data for this study were retrieved retrospectively from the institutional databases, as entered by pediatric neurologists and supplemented by developmental pediatricians or neuropsychologists in children investigated with standardized tests.

Patient characteristics

We classified the underlying etiology into three main categories and seven subcategories, according to MRI and histopathology: 1) developmental, including hemimegalencephaly, polymicrogyria, and other developmental; 2) acquired, including stroke and other acquired; and 3) progressive, including Rasmussen encephalitis and Sturge-Weber syndrome. *Significant MRI abnormalities contralateral* to the operated hemisphere, as noted in the original neuroradiological reports, were retrospectively reviewed by experienced pediatric neurologists and neurosurgeons and included hemispheric atrophy, major sulcation abnormalities, indistinct gray-white differentiation, extensive white matter abnormalities or loss, and contralateral ventricular dilatation. Subtle abnormalities, such as mild sulcation variants, small single white matter lesions, or isolated subtle T2 hyperintensity areas without tissue loss, ventricular dilatation, and cortical/subcortical involvement, were not noted[1,2,6].

Patients underwent vertical parasagittal hemispherotomy in Fondation Rothschild, Paris, or lateral periinsular/perisylvian/transsylvian hemispherotomy in the other centers. We recorded *major surgical complications*[6,26], defined as unwanted, unexpected, and uncommon events[26] following hemispherotomy requiring invasive treatment or leading to irreversible neurological deterioration or deficits for over three months, i.e., hydrocephalus requiring shunt placement, hemorrhage requiring intervention, intracranial infection, brain swelling causing symptoms or requiring intervention, and sinus thrombosis. Thus, the expected worsening of an incomplete hemiparesis or hemianopia after a hemispherotomy was not considered a complication. We defined *seizure freedom* to align with the Engel Ia outcome, i.e., completely seizure-free – including auras – since surgery at the last follow-up[27]. *Postsurgical ASM policies* followed standard practices in each center.

Postoperative cognitive development was considered a possible determinant of motor outcome, and its evaluation was derived from standardized tests (n=303) or, in children who did not undergo formal neuropsychological testing, from clinical assessments by the treating pediatric neurologists, developmental pediatricians, and/or neuropsychologists (n=70), as reported in the files. Standardized cognitive and/or intellectual functioning evaluation was performed by variable tests yielding intelligence quotient (IQ) or developmental quotient (DQ) according to patient age and common practice in each center. We excluded motor development scales since these would be negatively impacted by novel hemiparesis. Intellectual functioning at the last follow-up, based on standardized tests or clinical assessment, was categorized as normal (IQ > 85), mildly impaired (IQ 70–84), moderately impaired (IQ 50–69), or severely impaired (IQ < 55).

Statistical analysis

We first performed descriptive statistics on the independent variables, then bivariate analysis assessing differences between groups of patients with different functional outcomes, and finally, multivariable analysis to identify determinants of favorable functional outcomes.

We reported mean and standard deviation for continuous variables and frequencies and percentages for categorical variables. We performed bivariate analysis separately for each of the three functional outcomes (unaided walking, grasping, speaking) by Wilcoxon's rank sum and Fisher's exact test, considering the following independent variables: epilepsy duration, age at surgery, contralateral MRI abnormalities, etiology, major surgical complications, postsurgical seizure freedom, antiseizure medication (ASM) use, age at last postsurgical follow-up, and intellectual functioning (except for speaking, since intellectual functioning is partly determined by language domains). Missing data concerned 3.6% of entries in contralateral MRI abnormalities, 0.2% in epilepsy duration, 17.1% in intellectual functioning, 0.7% in unaided walking, 11.8% in voluntary grasping with the hemiplegic hand, and 1.8% in speaking. We addressed missing data by multiple imputations[25], and thus generated ten imputed datasets for performing multivariable analysis. In the multiple imputations, we applied polynomial frequentist regression for variables with multiple categories, frequentist logistic

regression for binary variables, and predictive mean matching for continuous variables, including the etiology subgroups and excluding the main etiology categories and all other abovementioned independent variables.

To identify determinants of functional outcomes, we used a Bayesian multi-level generalized mixed effect logistic regression model based on the Bernoulli distribution and the Cauchy[29] (median=0, average absolute deviation=2.5) priors to prevent biases due to complete separation, with the centers as random effects. Using this methodology allowed us to incorporate potential differences between centers, as it enhances robustness in unbalanced data. This model handled the multiple imputed datasets using the brms package[30]. We report the derived median odds ratios [OR]s, credible interval [CI] presenting the 89% probability range containing probable values[31,32], and the two-sided *p*-values based on the probability of direction threshold of 0.95. We report OR per year for continuous variables such as epilepsy duration, age at surgery, and age at the last follow-up. We established statistical significance at two-sided *p*-values of ≤0.05. We performed all statistical analyses by R[33] using RStudio[34] (2022.02.3).

RESULTS

The study cohort comprised 455 children (249 male) (**Table 1**). Etiology was acquired in 160 (35%) children, developmental in 190 (42%), and progressive in 105 (23%). Contralateral MRI abnormalities were noted in 73 (16%) children and concerned 37/158 (23%) of acquired, 34/175 (19%) of developmental, and 4/104 (4%) of progressive etiology. The mean age at seizure onset was 1.9 years (standard deviation [SD] 2.9, range 0–14.3), the mean epilepsy duration was 3.8 years (SD 3.7, range 0.1-17.8), and the mean age at surgery was 5.7 years (SD 4.8, range 0.1-17.8).

280 (62%) patients had lateral hemispherotomy (73 transsylvian, 96 perisylvian, 111 peri-insular), and 175 (38%) had vertical parasagittal hemispherotomy. Right (49%) and left-sided hemispherotomies were evenly proportioned. 66 (15%) children had major surgical complications, concerning 19/160 (12%) cases of acquired, 33/190 (17%) cases of developmental, and 14/105 (13%) cases of progressive etiology. For more details, see our previous work[6].

The mean follow-up duration was 5.1 years (SD 3.9, range 1-17.1)[6]: 43% of children had a follow-up of at least 5 years and 15% at least 10 years. The mean age at the last follow-up was 10.8 years (SD 5.8, range 1.3-27.6): 112 (25%) of children were <6 years old, 291 (64%) 6-18 years old, and 52 (11%) ≥ 18 years at last follow-up. 343 (75%) of children achieved postsurgical seizure freedom; 245 (71%) of these children (54% of the total cohort) were seizure-free and had withdrawn all ASM.

Postoperative intellectual functioning categories were available for 373 children, with 323 (87%) categorized as impaired: 60 (16%) as mildly, 63 (17%) moderately, and 200 (54%) as severely impaired.

Functional outcomes and determinants

Walking unaided

342 (77%) of children could walk unaided at the last follow-up (**Table 1**). In bivariate analysis, walking unaided was related to etiology (Fisher's exact test, $p<0.001$, with, e.g., Rasmussen encephalitis and stroke having good and hemimegalencephaly poor outcomes, **Figure 1A**), lack of contralateral MRI abnormalities (Fisher's exact test, $p<0.001$), older age at surgery (Wilcoxon rank sum test, $p<0.001$), longer epilepsy duration (Wilcoxon rank sum test $p<0.001$), older age at outcome determination (Wilcoxon rank sum test, $p<0.001$), achieving seizure freedom (Fisher's exact test, $p<0.001$), having a higher intellectual functioning (Fisher's exact test, $p<0.001$), having ASM withdrawn (Fisher's exact test, $p<0.001$), and having no major surgical complications (Fisher's exact test, $p=0.016$).

In the multivariate analysis, older age at outcome determination (OR=1.11 [1.04-1.18], $p=0.01$) was identified as a significant determinant of walking unaided, while contralateral MRI abnormalities (OR=0.49 [0.28-0.86], $p=0.04$), recurrent seizures (OR=0.48 [0.28-0.86], $p=0.04$), and moderately (OR=0.21 [0.05-0.66], $p=0.03$) or severely impaired (OR=0.15 [0.03-0.42], $p=0.001$) intellectual

functioning were significantly associated with not walking unaided. Epilepsy duration, age at surgery, side of surgery, surgical complications, and continued ASM use had no significant impact on ambulatory outcomes (**Figure 2A**, **Table 2**).

Voluntary grasping with the hemiplegic hand

30 (8%) of the children could grasp voluntarily with their hemiplegic hand at the last follow-up (**Table 1**). In bivariate analysis, voluntary grasping was related to etiology (Fisher's exact test, $p<0.001$, e.g., stroke and polymicrogyria having good, and Rasmussen encephalitis and Sturge Weber syndrome poor outcomes, **Figure 1B**), older age at surgery (Wilcoxon rank sum test, $p=0.12$), older age at outcome determination (Wilcoxon rank sum test, $p=0.03$), and longer epilepsy duration (Wilcoxon rank sum test, $p=0.003$).

In the multivariate analysis, Rasmussen encephalitis (OR=0.01 [0-0.16], $p=0.001$) and Sturge-Weber syndrome (OR=0.02 [0-0.33], $p=0.007$), compared to stroke, were significant negative determinants of voluntary grasping. Contralateral MRI abnormalities, epilepsy duration, age at surgery, seizure outcome, follow-up duration, intellectual functioning, major surgical complications, and continued ASM use had no significant independent impact on grasping (**Figure 2B**, **Table 2**).

Speaking short sentences or age-appropriately

297 (68%) children could speak short sentences or age-appropriately at the last follow-up (**Table 1**). In bivariate analysis, good verbal outcome related to etiology (Fisher's exact test, $p<0.001$, with stroke, polymicrogyria, Rasmussen encephalitis, and Sturge Weber syndrome having good, and hemimegalencephaly poor outcomes, **Figure 1C**), lack of contralateral MRI abnormalities (Fisher's exact test, $p<0.001$), older age at surgery (Wilcoxon rank sum test, $p<0.001$), longer epilepsy duration (Wilcoxon rank sum test, $p<0.001$), older age at outcome determination (Wilcoxon rank sum test, $p<0.001$), achieving seizure freedom (Fisher's exact test, $p<0.001$), and having ASM withdrawn (Fisher's exact test, $p<0.001$).

In the multivariate analysis, Sturge-Weber syndrome (OR=3.89 [1.67-10.16], $p=0.01$, compared to stroke), older age at surgery (OR=1.21 [1.04-1.41], $p=0.04$), and older age at outcome determination (OR=1.18 [1.11-1.26], $p<0.001$) were identified as significant positive determinants of speaking, while contralateral MRI abnormalities (OR=0.34 [0.19-0.61], $p=0.002$) and longer epilepsy duration (OR=0.79 [0.67-0.92], $p=0.01$) were acknowledged as significant negative determinants. Side of surgery, surgical complications, seizure outcome, and continued ASM use had no significant impact on speaking (**Figure 2C, Supplementary Table 2**).

DISCUSSION

This large and contemporary multicenter cohort study provides insightful information about the independent determinants of functional outcomes in children following hemispherotomy. The two key outcome determinants – specific etiology categories and bilateral structural brain abnormalities - could be established with current diagnostic approaches. The proportion of children who could walk and talk expectedly increased with longer-follow up – i.e., at an older age. Unaided walking was less frequent in children who were not seizure-free and those with impaired intellectual functioning. Talking age-appropriately was less frequent in children with longer epilepsy duration and more frequent in those older at surgery. These observations underscore the importance of early surgery[35] but also show that older children may profit considerably from this intervention[1].

Seizure and functional outcomes

This cohort's 75% seizure freedom rate is higher than the 61% rate reported in the so-far largest monocenter study (n=115) on functional outcomes[12]. Given the broader range of etiologies and growing complexity of surgical cases in the past few decades, this seizure-freedom rate is remarkable, particularly since our outcomes were determined after a 5-year mean follow-up, with almost half of the children followed for ≥5 years. The relatively long follow-up interval allows for assessing the long-term effects of different determinants on functional outcomes. The distribution of functional outcomes, particularly of walking and talking at the last follow-up, is comparable between

the two studies (77% vs. 83% in the past study, and 68% vs. 70%, respectively)[12]. The stable rate of postsurgical impairment over time is encouraging, considering that the decision to offer hemispherotomy in extensive unliteral pathology is more liberal now than in the past, maximizing chances of seizure control while fully accepting possible neurological deficits, particularly in younger children profiting from higher functional plasticity[8,10,35,36].

Walking unaided

Contralateral MRI abnormalities first emerged as predictive of less favorable ambulation outcomes in a monocentric study[2], to be later confirmed by a larger study[12]. The potential for recovery of proximal motor strength, critical for walking after hemispherotomy, largely depends on compensatory mechanisms offered by the contralateral hemisphere, namely the preservation of the ipsilateral corticospinal tract and the axonal sprouting of the intact, crossed corticospinal tract at the medullary level[37]. Bilateral cortical abnormalities limit the potency of these functional recovery mechanisms.

Intellectual functioning has emerged as another key determinant of ambulation. Although children with higher intellectual functioning are expected to be more alert, attentive, receptive, responsive, and thus capable of grappling with various motor tasks and achieving motor milestones, this relation has not been demonstrated in the specific context of children undergoing hemispherotomy.

Our study is the first to demonstrate that ***older age at outcome determination*** relates to a higher chance of walking unaided. Improvements in motor performance have been previously related to longer follow-up – but not to the inherently related older age at outcome determination – in a study where standardized investigations were performed at set intervals up to two years after surgery[38]. Gross motor performance is determined not only by the integrity of the remaining brain but also by cognitive recovery – which may take longer – and by the child's attention and motivation, possibly profiting from seizure cessation and ASM withdrawal over time.

Voluntary grasping with the hemiplegic hand

Although hemispherotomy invariably leads to contralateral hemiparesis, residual motor function differs between the upper and lower extremities, and hand function is most severely compromised[39]. The ipsilateral corticospinal tract, which may be preserved in early unilateral lesions, mainly innervates truncal, leg, and proximal rather than distal arm muscles. While 77% of children could walk, only 8% could grasp voluntarily with their hemiplegic hand. This retained functionality is, however, crucial for all key bimanual activities of daily living.

Children with Rasmussen encephalitis and Sturge-Weber syndrome were unlikely to grasp voluntarily, in line with previous findings of preserved voluntary grasping only in pre- or perinatally acquired lesions, such as stroke, as opposed to lesions occurring later in life and related to progressive ***etiology***[39–41]. Unilateral destructive motor system lesions acquired in early life can prompt the preservation of ipsilateral corticospinal hand-innervating connections, which usually are only transient, thus permitting the contralesional hemisphere to govern motor functions of the paretic hand[40,42,43]. Until what exact time point during development – late pre- or perinatally – ipsilateral corticospinal hand innervation can be preserved remains unclear.

Adaptive plasticity mechanisms of the developing brain thus underlie a time when the brain is less vulnerable to injury, allowing for the preservation of motor functions in pre- or perinatal stroke. Some cortical malformations, such as hemispheric dysplasia, may still harbor motor function, thus leading to a deterioration of arm strength and hand function after hemispherotomy[40,43,44]. Others, such as polymicrogyria, may harbor little or no function[45–47], forcing the use of the ipsilateral corticospinal tract from early intrauterine development onward, explaining the preservation of hand function before and after hemispherotomy. Progressive etiologies occurring later in life, following a period of normal brain development, will preclude the possibility of ipsilateral innervation[48].

In addition to the predictive value of underlying etiology, visual analysis and diffusion tractography of the corticospinal tracts on presurgical MRI and transcranial magnetic stimulation[49–52] may enable prediction of the postsurgical motor recovery and, thus, considerably improve presurgical counseling. Asymmetrical brainstem and structural corticospinal tract connectivity reflect motor reorganization

involving ipsilateral corticospinal projections, which predict preserved grasping following hemispherotomy[40,49,53].

Determinants of *speaking short sentences or age-appropriately*

Contralateral MRI abnormalities negatively impacted motor and language outcomes, in line with a previous large monocentric study[12]. The functional outcome relies on how the residual critical function at risk for loss of the disconnected hemisphere is balanced against the integrity and plasticity reserve, enabling gains in the contralateral hemisphere[12]. Continued postsurgical cognitive (particularly language) development occurs preferentially in children with a relatively normal contralateral hemisphere[2]. Recently developed advanced MRI techniques allow the detection of subtle contralateral MRI abnormalities, particularly in children with hemimegalencephaly and other developmental etiologies, where the malformation may be more striking on one hemisphere but affect both, with hemispherotomy performed on the most affected side[54,55].

Etiology emerged as a key outcome determinant in all three functional domains. The impact of etiology on language outcome has been demonstrated in earlier monocentric studies[14,16,56] and a recent meta-analysis[55] but was contradicted by a recent large monocentric study[12], which did, however, display a trend for more favorable language outcomes in children with progressive etiology. Our observations pointed to better language outcomes, independent of the side of surgery, in children with Sturge Weber syndrome, an overtly underrepresented etiology in past studies[55].

However, an important selection bias may have influenced the observed determinants of language outcome. The decision to proceed to hemispherotomy is less likely in children whose language function is expected to deteriorate after surgery. Therefore, hemispherotomy is generally indicated only in 1) children before the age of 4 years when language lateralization is still permitted bilaterally, 2) children – independent of age - with a large, destructive epileptogenic lesion that occurred early in life, ensuring already existing contralesional language lateralization, 3) children with developmental hemispheric lesions, in whom functional studies proved contralesional language lateralization, and 4) children older than 4 years with rare and super refractory epilepsy courses – such as in Rasmussen's encephalitis – when surgical relief of seizures justifies an anticipated decrease of language function.

Children who were **older at surgery** were more likely to speak than those operated at younger age. While a recent meta-analysis identified no relation between age at surgery and language outcome[55], younger age at hemispherotomy has been associated with impairments in language development in a large monocentric study[12], and superior cognitive (including language) outcomes were associated with older age at surgery in previous smaller cohorts[1,57]. This effect may be appreciated within the context of early vulnerability[58], resulting in less favorable cognitive and functional outcomes in earlier compared to later brain injury, despite the increased functional plasticity attributed to the developing brain[59]. This observation should not, however, be perceived as a reason to postpone hemispherotomy in younger children but rather encourage physicians to also offer hemispherotomy to older, more intact children, who may profit considerably from this intervention[1]. In smaller-size past studies, younger age at surgery corresponded to children with developmental etiology, such as hemimegalencephaly, with their inherent cognitive impairments. In comparison, older age at surgery corresponded to children with stroke and language lateralization permitting hemispheric surgery without the aggravation of functional deficits. Therefore, it cannot be ruled out that any correlations of age at surgery with functional outcomes may reflect a candidate selection bias rather than a true effect of age on these outcomes.

Although the negative impact of **longer epilepsy duration** on overall cognitive and adaptive outcomes after hemispherotomy has been supported by earlier studies[3,7,16,60], more recent studies have failed to identify such a relation. However, a shorter time when seizures impact the developing brain likely leads to more favorable outcomes[1,2,12,61]. We found that children with longer epilepsy duration were less likely to speak in short sentences or age-appropriately, supporting the current incentive for early surgical intervention[35,62] to avert the damage caused by the ongoing seizure activity and ASM to the developing brain and to allow the resumption of cognitive development through sensitive periods of brain maturation[63]. Epilepsy duration and ASM withdrawal are two modifiable

determinants of cognitive development[7,8,64], stressing the significance of early intervention for optimal cognitive outcomes.

Children were more likely to speak at **older age at outcome determination**. While an earlier hemispherotomy study has demonstrated a positive effect of time passing on cognitive and adaptive functioning[3], a later study failed to confirm improved language outcomes over time[61]. The importance of older age at outcome evaluation may reflect the combined impact of older age at surgery and longer follow-up duration, enabling key language achievements over time despite the reduced developmental velocity. The large cohort size and long mean follow-up of 5.1 years, extending up to 17 years, may have allowed the detection of this effect. Further studies are required to gain insights into long-term brain reorganization and cognitive recovery mechanisms.

Limitations

Given its retrospective multicenter design, our study has several limitations, including the accountability for differences among regions and countries in socioeconomic factors or the availability, intensity, and robustness of postsurgical rehabilitation programs. However, our observations are representative of a large geographic region and a wide range of etiologies within the largest cohort to date, supporting their applicability and generalizability. Further limitations arise from applying a simplistic ambulatory, hand function, and language assessment as the only feasible approach to homogenize multicenter data across different epilepsy centers, countries, age groups, and functional levels. However, we focused on the practical limitations in daily life activities, which are bound to have a higher impact than meticulously analyzed changes in muscle strength or cognitive tests. Finally, our analysis may have been impacted by the lack of statistical power in some etiology subgroups (e.g., other acquired), limiting the applicability of our findings to these less frequently encountered etiologies. Given the rapidly widening spectrum of etiologies considered for hemispherotomy, future studies may succeed in reaching the critical cohort size in these subgroups to provide more meaningful results.

CONCLUSION

In this multicenter study investigating functional outcomes after hemispherotomy, etiology and bilaterality of structural brain abnormalities have arisen as key determinants. In addition, longer epilepsy duration affects language outcomes. Knowledge of independent determinants of functional outcomes after pediatric hemispherotomy is critical for counseling patients and families.

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 contributions from WO, CB, and MT. All authors reviewed, edited, and approved the final version of the manuscript.

POTENTIAL CONFLICTS OF INTEREST

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

DATA AVAILABILITY

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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FIGURE LEGENDS

Figure 1. Functional outcomes depend on etiology.
A. Rates of unaided walking showed considerable variation among the three main etiologies and the etiology subcategories. A black vertical line marks our full cohort's mean unaided walking rate of 77%. B. Rates of voluntary grasping showed considerable variation both among the three main etiologies and among the etiology subcategories. A black vertical line marks our full cohort's mean voluntary grasping rate of 8%. C. Rates of speaking showed considerable variation among the three main etiologies and the etiology subcategories. A black vertical line marks the mean speaking rate of 68% for our full cohort. The numbers of etiology groups differ due to missing values.

Figure 2. Significant determinants of functional outcomes in the multivariable analysis.
OR>1 and blue bars indicate significantly greater median odds of walking, grasping, or speaking, while OR<1 and red bars indicate significantly lower median odds. Bars represent the 89% credible intervals; significance was established at $p \leq 0.05$.

FIGURES

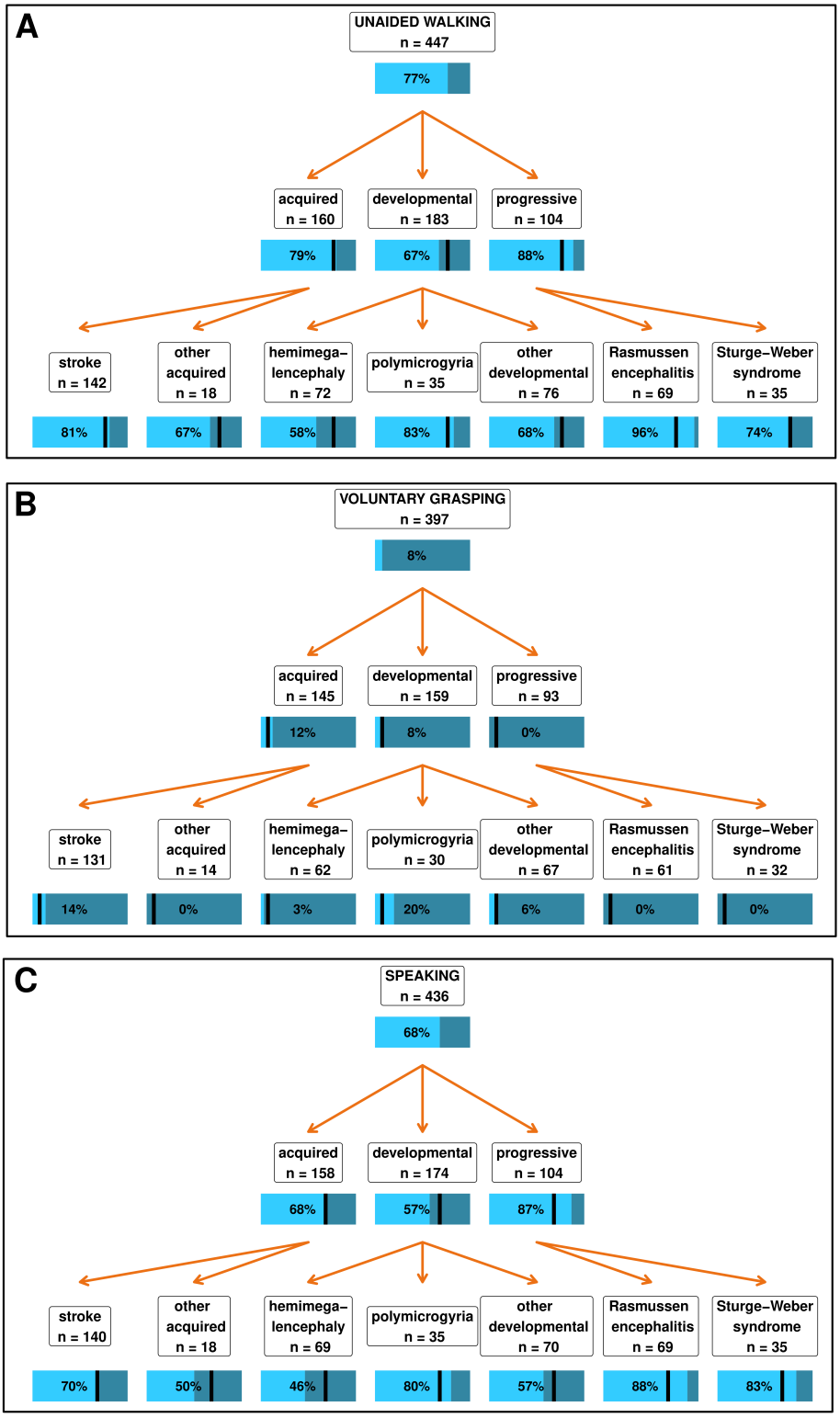

Figure 1.

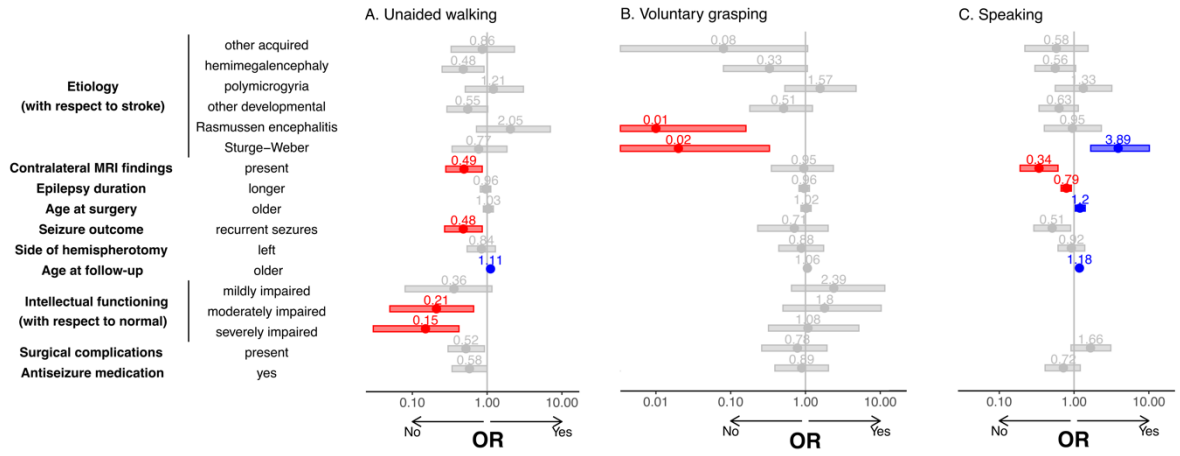
A. Unaided walking
B. Voluntary grasping
C. Speaking
Etiology (with respect to stroke)
other acquired
hemimegalencephaly
polymicrogyria
other developmental
Rasmussen encephalitis
Sturge–Weber
Contralateral MRI findings
present
Epilepsy duration
longer
Age at surgery
older
Seizure outcome
recurrent sezures
Side of hemispherotomy
left
Age at follow-up
older
Intellectual functioning (with respect to normal)
mildly impaired
moderately impaired
severely impaired
Surgical complications
present
Antiseizure medication
yes
0.10
1.00
10.00
0.01
No
Yes
OR

Figure 2.

TABLES

Clinical features, N	WALKING UNAIDED yes 342[1]	WALKING UNAIDED no 105[1]	WALKING UNAIDED *p*-value[2]	VOLUNTARY GRASPING WITH THE HEMIPLEGIC HAND yes 30[1]	VOLUNTARY GRASPING WITH THE HEMIPLEGIC HAND no 367[1]	VOLUNTARY GRASPING WITH THE HEMIPLEGIC HAND *p*-value[2]	SPEAKING SHORT SENTENCES/ SPEAKING AGE-APPROPRIATELY yes 297[1]	SPEAKING SHORT SENTENCES/ SPEAKING AGE-APPROPRIATELY no 139[1]	SPEAKING SHORT SENTENCES/ SPEAKING AGE-APPROPRIATELY *p*-value[2]
Etiology: main categories, 455			**<0.001**			**<0.001**			**<0.001**
acquired	127 (79%)	33 (21%)		18 (12%)	127 (88%)		107 (68%)	51 (32%)	
developmental	123 (67%)	60 (33%)		12 (8%)	147 (92%)		100 (57%)	74(43%)	
progressive	92 (88%)	12 (12%)		0 (0%)	93 (100%)		90 (87%)	14 (13%)	
Etiology: subcategories, 455			***<0.001***			***<0.001***			***<0.001***
stroke	115 (81%)	27 (19%)		18 (14%)	113 (86%)		98 (70%)	42 (30%)	
other acquired	12 (67%)	6 (33%)		0 (0%)	14 (100%)		9 (50%)	9 (50%)	
hemimegalencephaly	42 (58%)	30 (42%)		2 (3%)	60 (97%)		32 (46%)	37 (54%)	
polymicrogyria	29 (83%)	6 (17%)		6 (20%)	24 (80%)		28 (80%)	7 (20%)	
other developmental	52 (68%)	24 (32%)		4 (6%)	63 (94%)		40 (57%)	30 (43%)	
Rasmussen encephalitis	66 (96%)	3 (4%)		0 (0%)	61 (100%)		61 (88%)	8 (12%)	
Sturge-Weber syndrome	26 (74%)	9 (26%)		0 (0%)	32 (100%)		29 (83%)	6 (17%)	
Contralateral MRI findings, 437			***<0.001***			>0.99			***<0.001***
no	290 (81%)	68 (19%)		24 (8%)	297 (93%)		256 (73%)	95 (27%)	
yes	40 (55%)	33 (45%)		5 (7%)	64 (93%)		30 (43%)	39 (57%)	
Epilepsy duration (y), 454	4.0 (0.1-16.1)	3.0 (0.1 - 17.8)	***<0.001***	5.1 (0.8-16.1)	*3.5 (0.1-17.8)*	***0.003***	4.1 (0.1-17.8)	3.1 (0.1-16.0)	***<0.001***
Age at surgery (y), 455	6.3 (0.1-17.8)	3.8 (0.2-17.8)	***<0.001***	7.3 (0.8-17.1)	*5.5 (0.1-17.8)*	***0.012***	6.7 (0.1-17.8)	3.9 (0.2 - 16.6)	***<0.001***
Side of hemispherotomy, 455			0.82			0.70			0.54
right	168 (77%)	50 (23%)		16 (8%)	177 (92%)		141 (67%)	71 (33%)	
left	174 (76%)	55 (24%)		14 (7%)	190 (93%)		156 (70%)	68 (30%)	
Age at follow-up (y), 455	11.7 (1.6-27.6)	8.0 (1.3-20.8)	***<0.001***	12.9 (3.7-22.5)	10.5 (1.6-27.6)	**0.03**	12.4 (2.1-27.6)	7.8 (2.1-21.4)	***<0.001***
Seizure outcome, 455			***<0.001***			0.38			***<0.001***
seizure freedom	280 (83%)	58 (17%)		25 (8%)	*273 (92%)*		243 (74%)	87 (26%)	
seizure recurrence	62 (57%)	47 (43%)		5 (5%)	*94 (95%)*		54 (51%)	52 (49%)	
Intellectual functioning, 373			***<0.001***			*0.06*			
normal	49 (98%)	1 (2%)		1 (2%)	*45 (98%)*				
mildly impaired	53 (88%)	7 (12%)		7 (12%)	*52 (88%)*				
moderately impaired	50 (82%)	11 (18%)		7 (13%)	*45 (87%)*				
severely impaired	127 (64%)	72 (36%)		10 (5%)	*175 (95%)*				
Antiseizure medication, 454			***<0.001***			0.45			***<0.001***
withdrawn	218 (86%)	35 (14%)		19 (9%)	*201 (91%)*		195 (78%)	55 (22%)	
continued	124 (64%)	70 (36%)		11 (6%)	*166 (94%)*		102 (55%)	84 (45%)	
Surgical complications, 455			***0.016***			0.60			0.56
no	301 (79%)	82 (21%)		27 (8%)	312 (92%)		252 (67%)	122 (33%)	
yes	41 (64%)	23 (36%)		3 (5%)	55 (95%)		45 (73%)	17 (27%)	

[1]n (%); Mean (Range)

[2]Fisher's exact test; Wilcoxon rank sum test

Table 1. Clinical features of our cohort and their impact on the functional outcomes of speaking, walking, and grasping in bivariate analysis. For each clinical characteristic, we show the number of children (N) for whom data were available and describe them as mean (range) for continuous variables and counts n (%) for categorical variables. Percentages are calculated row-wise for the available data.

	WALKING		GRASPING		SPEAKING	
Variable	*OR (CI)*	*p value*	*OR (CI)*	*p value*	*OR (CI)*	*p value*
Stroke	1 (-)	-	1 (-)	-	1 (-)	-
Other acquired	0.86 (0.33-2.32)	0.8	0.08 (0-1.07)	0.12	0.58 (0.22-1.54)	0.37
Hemimegalencephaly	0.48 (0.25-0.91)	0.07	0.33 (0.08-1.06)	0.13	0.56 (0.3-1.05)	0.14
Polymicrogyria	1.21 (0.51-3.06)	0.73	1.57 (0.53-4.75)	0.5	1.33 (0.56-3.2)	0.59
Other developmental	0.55 (0.29-1.02)	0.12	0.51 (0.18-1.24)	0.23	0.63 (0.34-1.14)	0.21
Rasmussen encephalitis	2.05 (0.72-7.01)	0.28	0.01 (0-0.16)	**0.001**	0.95 (0.4-2.32)	0.92
Sturge-Weber syndrome	0.77 (0.34-1.84)	0.64	0.02 (0-0.33)	**0.007**	3.89 (1.67-10.16)	**0.01**
Contralateral MRI abnormalities	0.49 (0.28-0.86)	**0.04**	0.95 (0.35-2.36)	0.93	0.34 (0.19-0.61)	**0.002**
Epilepsy duration	0.96 (0.81-1.12)	0.66	0.96 (0.82-1.13)	0.71	0.79 (0.67-0.92)	**0.01**
Age at surgery	1.03 (0.89-1.21)	0.8	1.02 (0.87-1.19)	0.83	1.2 (1.04-1.41)	**0.04**
Seizure recurrence	0.48 (0.27-0.86)	**0.04**	0.71 (0.23-2.01)	0.61	0.51 (0.29-0.9)	0.06
Left surgery	0.84 (0.54-1.29)	0.51	0.88 (0.44-1.75)	0.77	0.92 (0.61-1.39)	0.76
Age at follow-up	1.11 (1.04-1.18)	**0.01**	1.06 (0.97-1.15)	0.31	1.18 (1.11-1.26)	**<0.001**
Mild impairment	0.36 (0.08-1.16)	0.17	2.39 (0.65-11.51)	0.31	-	-
Moderate impairment	0.21 (0.05-0.66)	**0.03**	1.8 (0.5-10.29)	0.49	-	-
Severe impairment	0.15 (0.03-0.42)	**0.001**	1.08 (0.32-5.18)	0.93	-	-
Combined complications	0.52 (0.3-0.92)	0.07	0.78 (0.26-1.94)	0.68	1.66 (0.91-3.1)	0.17
Current ASM	0.58 (0.34-1)	0.11	0.89 (0.39-2.03)	0.82	0.72 (0.41-1.21)	0.3

Table 2. Determinants of functional outcomes, as identified in the multivariable analysis according to the median odds ratio (OR), credible intervals (CI), and p-value. An odds ratio higher than 1 is associated with the ability to walk unaided, grasp voluntarily with the hemiplegic hand, speak short sentences, and speak age-appropriately. The threshold of significance was set at two-sided *p*-values of ≤0.05.