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Original Article

Physical Growth of the Contralateral Cerebrum is Preserved After Hemispherotomy in Childhood

Patrick J. Pan, MD [a], Henrik E. Ullman, MD [a], Gary W. Mathern, MD [b], Noriko Salamon, MD, PhD [a,*]

[a] Department of Radiology, UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California
[b] Department of Neurosurgery, UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California

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ABSTRACT

Background: Hemispherotomy can be an effective treatment for refractory childhood epilepsy. However, the extent of postoperative brain development after hemispherotomy remains incompletely understood. This study aims to provide an anatomic foundation in assessing development of the contralateral hemisphere, by measuring volumetric growth after hemispherotomy.
Methods: Eleven patients with hemimegalencephaly, Rasmussen's encephalitis, and cerebral infarction who underwent hemispherotomy before age 12 years, an immediate preoperative magnetic resonance imaging, and at least three years of follow-up magnetic resonance imagings were retrospectively analyzed. The volume of the contralateral hemisphere was measured before and after surgery. Growth curves were compared with those of healthy individuals from an open database. The growth rate relative to the healthy individuals ("catch-up rate") was calculated.
Results: A positive volumetric growth of the contralateral hemisphere was observed across all pathologies. The hemimegalencephaly subgroup underwent hemispherotomy at the earliest time and had the largest postoperative growth rate, which exceeded that of healthy individuals. The Rasmussen subgroup underwent surgery at the second earliest time and had an intermediate growth rate, which was similar to that of healthy individuals. The infarction subgroup underwent surgery at the latest time and had the slowest growth rate, which was less than that of healthy individuals.
Conclusions: The contralateral hemisphere continues to increase in volume after hemispherotomy in childhood. Further studies with a larger sample size and correlation with cognitive outcomes may aid in characterizing the prognosis after hemispherotomy.

Introduction

Hemispheric disconnective surgery can be an effective treatment for refractory epilepsy in childhood when a nonfocal, hemispheric structural abnormality is present. The earliest surgical approach, termed "anatomical hemispherectomy," involves removing the entire diseased cerebral hemisphere. Although it was effective in seizure control, this technique was associated with delayed complications such as hydrocephalus and hemosiderosis, because of repetitive hemorrhages into the large resection cavities. In the 1970s, Rasmussen and his contemporaries made popular a technique, which combined subtotal hemispherectomy and disconnection of the remaining diseased hemisphere. This technique, termed "functional hemispherectomy," successfully reduced the delayed complications, whereas achieving comparable seizure outcomes. Since then, various techniques have been proposed to balance the amount of tissue removed, postoperative complications, and effectiveness in seizure control. Many of the newer techniques are termed "hemispherotomy" to emphasize the partial cortical removal. At our institution, we employed a "modified lateral hemispherotomy," which is highlighted by early ligation of the middle cerebral artery in the proximal sylvian fissure to reduce operative blood loss and routine removal of thalamus, basal

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* Communications should be addressed to: Salamon; Professor of Radiology, Vice Chair of Academic Affairs, Chief of Diagnostic Neuroradiology, David Geffen School of Medicine at UCLA; 757 Westwood Plaza; Room 1621; Los Angeles, CA 90095-1721.
E-mail address: NSalamon@mednet.ucla.edu (N. Salamon).

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ganglia, and associated deep structures to improve long-term seizure control.[1,2]

Hemimegalencephaly, Rasmussen encephalitis, and cerebral infarction are common seizure etiologies in children who may benefit from hemispherotomy. Although improvement in motor, cognitive, and intellectual functions in children after hemispherotomy is readily observed, the extent of postoperative brain development remains incompletely understood.[3-5]

Whether a developing brain is more or less susceptible to insult is still under debate. Anderson et al.[3] have introduced a "recovery continuum" hypothesis in which timing of insult to an early brain may affect development by a mixed effect of plasticity and vulnerability. In patients who undergo hemispherotomy, the insult is twofold and includes the native insult caused by the underlying pathology as well as the iatrogenic insult caused by the surgery. Further characterization of the trajectory of postoperative development is needed, not only to optimize the timing for surgery but also to plan postoperative rehabilitation and to provide a more accurate prognosis. What has complicated the clinical investigation is the nature of functional brain development, which is complex and nonlinear. Lesions may have specific effects depending on the trajectory of the cortical regions involved, and the region-specific level of maturation. Furthermore, cognitive function develops as an interaction between genes and environment and is constantly evolving in the pediatric age range, making individual differences difficult to separate from cognitive changes directly related to surgery.[6] The preoperative status may also be an independent predictor of recovery.[5]

This study aims to provide an anatomic foundation in assessing development of the contralateral hemisphere in patients who had hemispherotomy in childhood by measuring volume growth after surgery. The specific goals of this study are (1) to measure volume of the healthy hemisphere before and after hemispherotomy, (2) to compare volume growth by underlying pathology, and (3) to compare the volume growth with normal healthy subjects of the same age group from the existing literature.

Methods

Patient selection

In this Institutional review board-approved study, patients who underwent a hemispherotomy at our institution before age 12 years, between year 2003 and 2014, were retrospectively identified. Inclusion criteria were (1) the presence of an underlying pathology of hemimegalencephaly, Rasmussen encephalitis, or cerebral infarction; (2) a preoperative magnetic resonance imaging (MRI) study within 1 month of surgery; and (3) at least one follow-up MRI more than three years after the hemispherotomy. MRI brain studies were queried from the institutional picture archiving and communication system. A brief chart review was performed to acquire the patient demographics and to evaluate the effectiveness in seizure control.

Measuring contralateral hemispheric volume

MRI studies, which contained a T2-weighted axial sequence covering the entire cerebral hemispheres with a slice thickness of 4 mm or less, performed routinely without an acute finding such as abnormal axial collection or hydrocephalus were used for measurements. We chose a T2-weighted sequence for its better tissue contrast. Keller et al.[7] attempted automated segmentation, a common method in measuring brain volume in diseases such as multiple sclerosis and found the results suboptimal in our cohort because of the postoperative nature and various degrees of anatomic distortion. Therefore they resorted to manual contouring of the healthy hemisphere. The total volume of contralateral hemisphere was measured by manually tracing the hemisphere on each of the consecutive slice using three-dimensional software (Visage 7; Visage Imaging, Inc, San Diego, CA, USA). Conventional definition of the cerebral hemisphere, as illustrated by Keller et al.,[7] was applied (Fig 1).

Comparing volumetric brain growth to healthy control subjects

The growth curve of the contralateral hemisphere was created for each patient by plotting the hemispheric volume against age. In each curve the first data point represented the immediate preoperative hemispheric volume, and the subsequent data points represented volume measured at subsequent follow-up MRI scans. A growth curve for healthy children and adolescents was calculated by fitting a linear curve between the natural logarithm of age and the mean hemispheric volume from the Neurodevelopmental MRI Database created and maintained by Dr. John E. Richards at the University of South Carolina (Fig 2).[8,9]

Quantitative comparison of volumetric brain growth between diagnoses

To quantitatively evaluate the volumetric growth rate with respect to pathology, the following metrics were calculated. First, we calculated the difference in hemispheric volume between a patient and the healthy control subjects of the same age:

$$\begin{aligned}\text{Differential volume (mL)} \\ &= \text{hemispheric volume of a patient (mL)} \\ &- \text{hemispheric volume of age} \\ &- \text{controlled healthy individuals (mL)}\end{aligned}$$

A positive differential volume reflects a volume surplus, whereas a negative value reflects volume deficit for a patient at a given time point. Subsequently, we designated the "catch-up volume" to represent changes in the differential volume over the follow-up period:

$$\begin{aligned}\text{Catch} - \text{up volume (mL)} \\ &= \text{differential volume at the last available MRI (mL)} \\ &- \text{differential volume at the immediately} \\ &\quad \text{preoperative MRI (mL)}\end{aligned}$$

The catch-up volume accounts for the expected age-related growth, and therefore minimizes the confounding factor of different ages at surgery. A positive catch-up volume reflects that a patient's hemisphere has grown at a faster rate than that of the healthy control subjects, and a negative catch-up volume reflects a slower growth rate. Finally, to account for the variable follow-up periods among our cohort, we calculated the "catch-up rate" by dividing the catch-up volume by the total duration of the follow-up:

$$\text{Catch} - \text{up rate (mL/year)} = \text{catch} - \text{up volume (mL)/follow} - \text{up duration (year)}$$

Single-factor analysis of variance was used to test the null hypothesis that the means of catch rates in all three subgroups are equal.

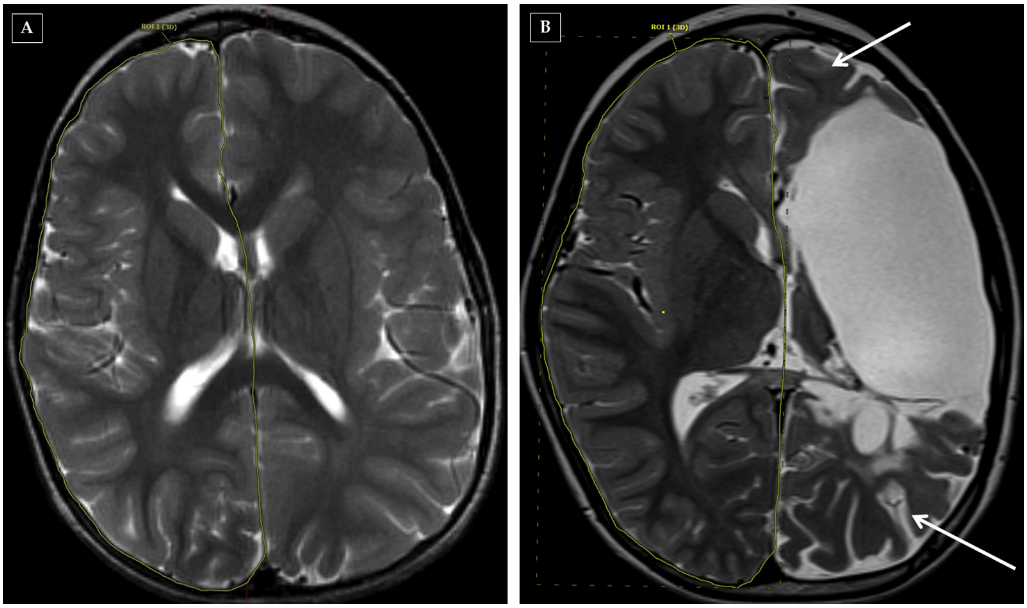

FIGURE 1. Axial T2-weighted images of a patient with left hemimegalencephaly who had a modified lateral hemispherotomy at age two years and four months. Three-dimensional manual contouring is represented by the yellow outline of the right hemisphere on (A) preoperative examination two weeks before surgery and (B) postoperative examination four years and 10 months after surgery. Note the atrophy in the unremoved portions of left hemisphere (arrows) despite preserved vascular supply, and the nonatrophic right hemisphere. The color version of this figure is available in the online edition.

Results

A total of 11 patients who met the inclusion criteria were retrospectively identified (Table).

The preoperative diagnoses were confirmed through pathologic examination of the removed specimens. Among these patients, five had hemimegalencephaly, three had Rasmussen encephalitis, and three had cerebral infarction. The range of age at surgery was 0.3 to 10.8 years (median 4.4 years), with the hemimegalencephaly subgroup receiving the surgery earliest in life (0.3 to 4.4 years), followed by Rasmussen (3.0 to 5.2 years) and infarction (8.6 to 9.9 years) subgroups. The age at follow-up MRI available was 3.0 to 9.9 years after surgery (median 4.7 years). All these patients underwent modified lateral hemispherotomy and achieved zero or rare (less than three per year) disabling seizures (Engel class I/II).

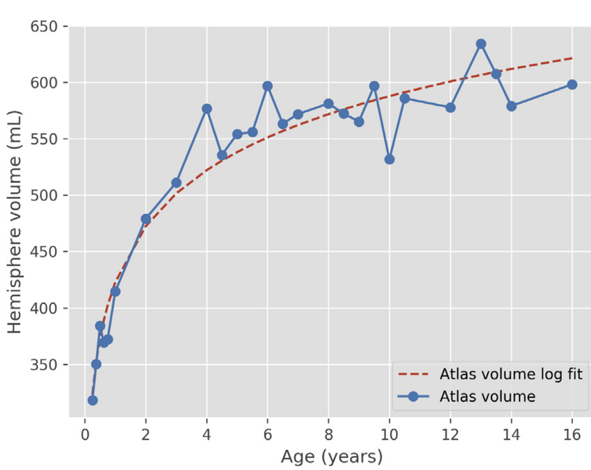

FIGURE 2. Hemispheric volume growth curve of healthy individuals. The data points were adapted from the Neurodevelopmental MRI Database maintained by Dr. John E. Richards at the University of South Carolina, with permission[8,9] The logarithmic curve (dashed line) was fitted to the database and used as control in this study. The color version of this figure is available in the online edition.

Only imaging examinations free of hydrocephalus or abnormal mass effect were measured in this study.

A positive volumetric growth was observed in all patients within the follow-up periods. The largest increase was observed in the hemimegalencephaly subgroup (271.62 ± 32.5 mL), followed by Rasmussen (58.5 ± 15.6 mL) and infarction (8.5 ± 2.6 mL) subgroups. Fig 3 shows the growth curves grouped by diagnosis in relation to the healthy control subjects.

The catch-up volumes for the hemimegalencephaly, Rasmussen, and infarction subgroups were +97.5 ± 57.0, +5.7 ± 15.2, and −18.8 ± 9.5 mL. The catch-up rates for the hemimegalencephaly, Rasmussen, and infarction subgroups were +16.9 ± 8.1, +0.9 ± 3.1, and −6.2 ± 3.2 mL/year (Fig 4). The hemimegalencephaly subgroup demonstrated a growth rate exceeding that of healthy control subjects, The Rasmussen subgroup demonstrated a growth rate similar to the healthy control subjects, and the infarction subgroup demonstrated a slower growth rate.

When the mean catch-up rates were compared between the subgroups, analysis with single-factor analysis of variance failed to demonstrate statistical significance ($P = 0.099$).

Discussion

Hemispherotomy was effective in lowering seizure frequency in our cohort. The disease processes investigated in this study are quite different in nature. Hemimegalencephaly is a developmental disease marked by diffuse abnormality involving a hemisphere. Rasmussen's encephalitis occurs progressively in an otherwise normally developed brain. Infarction is typically limited in a single region of the brain and is nonprogressive in nature. Despite the differences, a positive volumetric growth of the contralateral hemisphere after hemispherotomy was observed across pathologies. This finding is encouraging and suggests that the growth potential of the brain is at least partially preserved in these children.

TABLE.
Demographics of 11 Patients Who Met Inclusion Criteria for This Study

Patient	Diagnosis	Gender	Side of Hemispherotomy	Age at Surgery (year)	Age at Last Available MRI (year)
1	HME	M	Left	2.4	7.1
2	HME	M	Left	4.4	11.5
3	HME	F	Right	0.3	9.4
4	HME	M	Left	0.5	4.1
5	HME	F	Right	0.3	10.2
6	RAS	F	Right	5.2	10.3
7	RAS	M	Right	3.0	6.0
8	RAS	M	Right	4.5	11.5
9	INF	F	Left	8.7	11.7
10	INF	M	Left	9.9	13.1
11	INF	F	Left	8.6	11.7

Abbreviations:
F = Female
HME = Hemimegalencephaly
INF = Infarction
M = Male
MRI = Magnetic resonance imaging
RAS = Rasmussen encephalitis

Qualitatively, different growth rates among the subgroups are observed. Although statistical analysis failed to show significance, this may be related to the small sample size. A confounding factor is timing of hemispherotomy, which may be influenced by the type of pathology. In patients with hemimegalencephaly, hemispherotomy is often performed at a younger age, because of early onset of intractable epilepsy and the need to protect the contralateral hemisphere from repetitive seizure insult. The earlier timing of hemispherotomy in hemimegalencephaly may lead to a better recovery because of a stronger plasticity of the younger brain. This observation is in accordance with a developmental study by Loddenkemper et al., which showed that patients who receive epilepsy surgery at a younger age have a lower preoperative developmental quotient, and a greater increase after surgery.[4] Furthermore, the abnormally enlarged hemisphere may deprive the contralateral hemisphere of space and nutrition, and on removal of the diseased hemisphere, the contralateral hemisphere may resume its full growth potential.[10]

On the other end of the spectrum, children with epilepsy secondary to infarctions may exhaust medical treatments before surgery is considered, because of its nonprogressive nature. Therefore this subgroup often receives hemispherotomy at a later age. Rasmussen encephalitis is a nondevelopmental but progressive disease, whose clinical timing for surgery may come in between. The later surgical timing of these two diseases in this cohort may be associated with the smaller volumetric growth observed.

Several limitations are present in this study. Most importantly, growth in cerebral volume may not necessarily correlate with improvement in cognitive function. In healthy children, the relationship between gray matter[11] and white matter[12] development and cognitive function is well documented. Although this relationship has also been shown in preterm infants,[13] traumatic brain injury,[14] and attention deficit hyperactivity disorder,[15] an association has not been established specifically for hemispherotomy patients. Furthermore, the inherent heterogeneity among individuals makes the interpretation of individual patients difficult, as a low cerebral volume may be within the normal variation and not related to pathology.[16] In addition, the small sample size of this study limits the statistical power, and studies with larger cohorts remain needed.

Further studies may also evaluate segmented brain volumes of the gray and white matter, or regional volumes of the hippocampus, as epilepsy is associated with reduced volumes of the white matter and hippocampus.[17,18] Measuring segmented and regional brain volumes may help understand brain recovery after hemispherotomy. For example, in a posthemispherotomy patient, increase in white matter and hippocampal volumes that is proportionally more than increase in the remaining brain may be attributed to cessation of epilepsy, in addition to the expected

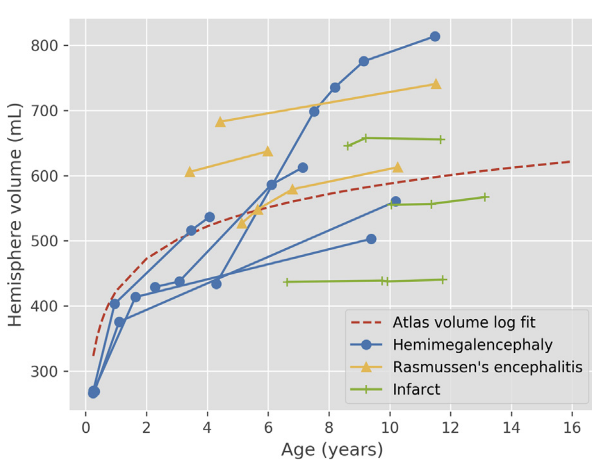

FIGURE 3. Volumetric growth of the contralateral hemisphere after hemispherotomy in all 11 patients, grouped by diagnosis. The growth curve of the healthy control subjects (dashed line) is the same as in Figure 2.

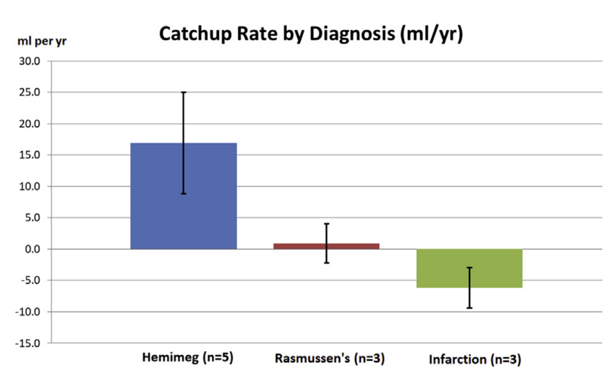

FIGURE 4. "Catch-up rate" by pathologies. The hemimegalencephaly subgroup demonstrated a growth rate convincingly exceeding that of healthy control subjects (mean = +16.9, SE = 8.1, mL/year), the Rasmussen subgroup demonstrated a growth rate similar to the healthy control subjects (mean = +0.9, SE = 3.1, mL/year), and the infarction subgroup demonstrated a slower growth rate than the healthy control subjects (mean = −6.2, SE = 3.2, mL/year). SE, standard error.

postoperative growth. This information could carry a prognostic value in cognitive development. Advanced imaging modalities such as diffusion tensor imaging or functional MRI may also help by demonstrating correlation between the volume growth and the increased amount of cortical activation and functional connectivity.

Conclusions

Across different pathologies, patients who received childhood hemispherotomy for epilepsy have a positive volumetric growth of the contralateral hemisphere. Further studies with a larger number of patients and correlation with cognitive outcomes are needed to determine whether such brain growth can predict developmental outcomes.

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