Cerebral hemispherectomy: Hospital course, seizure, developmental, language, and motor outcomes


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Cerebral hemispherectomy
Hospital course, seizure, developmental, language, and motor outcomes

R. Jonas, MD; S. Nguyen, BS; B. Hu, MD; R.F. Asarnow, PhD; C. LoPresti, PhD; S. Curtiss, PhD; S. de Bode, PhD; S. Yudovin, RN, MN, PNP; W.D. Shields, MD; H.V. Vinters, MD, FRCP(C), FCAP; and G.W. Mathern, MD

Abstract—Objective: To compare hemispherectomy patients with different pathologic substrates for hospital course, seizure, developmental, language, and motor outcomes. Methods: The authors compared hemispherectomy patients (n = 115) with hemimegalencephaly (HME; n = 16), hemispheric cortical dysplasia (hemi CD; n = 39), Rasmussen encephalitis (RE; n = 21), infarct/ischemia (n = 27), and other/miscellaneous (n = 12) for differences in operative management, postsurgery seizure control, and antiepilepsy drug (AED) usage. In addition, Vineland Adaptive Behavior Scale (VABS) developmental quotients (DQ), language, and motor assessments were performed pre- or postsurgery, or both. Results: Surgically, HME patients had the greatest perioperative blood loss, and the longest surgery time. Fewer HME patients were seizure free or not taking AEDs 1 to 5 years postsurgery, but the differences between pathologic groups were not significant. Postsurgery, 66% of HME patients had little or no language and worse motor scores in the paretic limbs. By contrast, 40 to 50% of hemi CD children showed near normal language and motor assessments, similar to RE and infarct/ischemia cases. VABS DQ scores showed >5 points or more improvement postsurgery in 57% of patients, and hemi CD (+12.7) and HME (+9.1) children showed the most progress compared with RE (+4.6) and infarct/ischemia (−0.6) cases. Postsurgery VABS DQ scores correlated with seizure duration, seizure control, and presurgery DQ scores. Conclusions: The pathologic substrate predicted pre- and postsurgery differences in outcomes, with hemimegalencephaly (but not hemispheric cortical dysplasia) patients doing worse in several domains. Furthermore, shorter seizure durations, seizure control, and greater presurgery developmental quotients predicted better postsurgery developmental quotients in all patients, irrespective of pathology.

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McKenzie is credited with introducing cerebral hemispherectomy as a treatment for intractable epilepsy in 1938.1 He removed a cerebral hemisphere from a patient with spastic hemiparesis, and noted that seizures stopped postsurgery. It was not until Krynauw’s 1950 report, however, that hemispherectomy became a more widely accepted surgical treatment for intractable epilepsy.2 Enthusiasm for Krynauw’s study was based on successful postsurgical seizure control in 10 of 12 cases, and improvements in behavior, social interaction, and cognition.3 Despite these successes, in the late 1960s anatomic hemispherectomy fell into decline because up to one-third of patients developed delayed complications, ranging from hydrocephalus to superficial cerebral hemosiderosis with lethal consequences.4,5 In the 1970s, Rasmussen revitalized the procedure by partially removing portions of the central and temporal regions, and disconnecting the remaining cerebral cortex from the opposite hemisphere.6 Functional hemispherectomy achieved good seizure control without the delayed complications. Over the past two decades, coworkers of Rasmussen and others have devised additional modifications designed to further minimize the amount of resected brain while maintaining good postsurgery seizure control with fewer complications.7,9

Along with the progress in surgical technique over the past three decades, there has been an evolution in what constitutes appropriate pathologic sub-
strates for patients undergoing hemispherectomy. The earliest series were hemispherectomies performed mostly in adolescent and adult patients with a preexisting hemiplegia because of perinatal strokes or other acquired hemispheric injuries.\textsuperscript{9} Neuroimaging techniques developed since the mid- to late 1980s (i.e., MRI, PET) have identified additional pathologic substrates, often in younger patients, such as cortical dysplasia (CD), hemimegalencephaly (HME), and Rasmussen encephalitis (RE).\textsuperscript{10,11} Hence, over the past two decades younger patients with developmental and progressive pathologic substrates are referred for hemispherectomy. Furthermore, over this same time period reports have suggested that epilepsy surgery patients with CD or HME may have poorer postsurgery seizure and cognitive outcomes than those with perinatal infarcts and RE.\textsuperscript{12-23} These studies are difficult to compare with one another, however, because they often mix children undergoing hemispherectomy with nonhemispherectomy procedures (e.g., temporal lobectomy), or do not compare large enough sample sizes of different pathology groups.

Cerebral hemispherectomy for seizure control at The University of California, Los Angeles (UCLA) mirrors the evolution in pathologic substrates referred for surgery over the past two decades. The program began in 1986, and the earliest cases were usually children with perinatal infarcts. Over time the etiologies have changed with more cases of hemispheric CD, HME, and RE being referred for surgery at younger ages. The UCLA series numbers 115 patients through 2002, and because of this history and sample size we have an opportunity to discern if there are pre- and posthemispherectomy clinical factors that predict long-term seizure control and developmental outcomes. Based on our previous clinical observations and the literature, we hypothesized that pathologic substrate would predict outcomes. Specifically, children with HME and hemispheric CD would be the youngest and weigh the least at surgery compared with RE and perinatal infarct cases\textsuperscript{20}; HME cases would have the most difficult hospital course because of operative-related blood loss, and they would show the worst postsurgery seizure control, developmental, motor, and language performance compared with hemispheric CD and other pathology groups\textsuperscript{14}; and regardless of pathologic substrate, shorter seizure duration before surgery, seizure control after surgery, and better presurgery developmental quotients would predict the best development and neurologic outcomes posthemispherectomy.\textsuperscript{24}

**Methods.** *Presurgery evaluation.* The cohort consisted of cerebral hemispherectomy patients operated at UCLA’s Pediatric Epilepsy Surgery Program from 1986 to 2002 (n = 115). The total UCLA pediatric resective surgery series (n = 268) includes the aforementioned hemispherectomy cases (43%), temporal lobe resections for limbic seizures (TLE; 17%), and nonlimbic lobar or multilobar resections (nonhemispherectomy/non-TLE; 40%).\textsuperscript{19} Informed consent was obtained to use clinical data for research studies, and preoperatively all children had antiepilepsy drug (AED) treatment resistant seizures. The standardized presurgery evaluation included detailed history and neurologic examinations, interictal and ictal scalp EEG, and when appropriate, intracarotid amobarbital injections (Wada test) or functional MRI for evaluation of memory or speech representation. Neuroimaging studies included high-resolution MRI and \textsuperscript{18}fluoro-2-deoxyglucose (FDG) PET.

**Pathologic classification.** Hemispherectomy patients were classified into the following pathologic categories based on neuroimaging (MRI and PET; figure 1) and histopathology of the resected specimen.\textsuperscript{25} HME (see figure 1A, n = 16) patients had severe CD on histopathology (cortical dyslamination, large heterotopias, cytomegalic

**Figure 1.** MRI scans showing representative examples of hemispherectomy patients by pathologic classification. Axial MRI images are oriented left/right as shown in A. (A) This child began seizing within days of birth from a right hemimegalencephaly. Surgery was performed at 3.5 months of age. Notice the enlarged right cerebral hemisphere compared with the left side. (B) This 12-year-old began seizing at age 3 years from a left hemispheric cortical dysplasia consisting of polymicrogyria (arrow) and white matter heterotopias (by pathology). Notice that the left cerebral hemisphere is not enlarged relative to the other side. (C) This 6.5-year-old began with new onset seizures at age 5.5 years that progressed to epilepsy partialis continua of the foot followed by the hand on the left body. MRI shows T2 signal change in the motor-sensory region on the right (arrows), and pathology confirmed histopathologic findings consistent with Rasmussen encephalitis. (D) An 8.5-year-old with known difficult birth history and early onset left body hemiparesis began with seizures at age 6 years. MRI shows a large infarct in the right middle cerebral artery distribution.
neurons, balloon cells), and neuroimaging showed an enlarged cerebral hemisphere often with partial or hemispheric pachygyria. Hemispheric CD (Hemi CD; see figure 1B, n = 39) cases had severe to mild CD on histopathology, and neuroimaging indicated a relatively normal sized cerebral hemisphere without lissencephalic-like features compared with the other side. The MRI/histopathology often showed polymicrogyria, subcortical heterotopias, and other neuronal migrational abnormalities. Together with the HME group, these two categories exemplify abnormalities of cortical development, but with a difference in degree of anomaly.

RE (see figure 1C, n = 21) cases had histopathologic findings consistent with RE.27,28 Neuroimaging often showed regions of signal change on T2 or FLAIR MRI consistent with inflammation, and depending on the duration of seizures there was or was not accompanying cerebral atrophy. This group represents a form of progressive pathology. Infarct/ischemia (see figure 1D, n = 27) patients had medical histories and neuroimaging findings usually indicating perinatal ischemic injury mostly to one cerebral hemisphere. Most cases showed signs of brain infaracts in the middle cerebral artery distribution on MRI (see figure 1D). Other children had hemispheric cerebral atrophy consistent with unilateral acquired brain injury. While the initial injury is mostly unilateral, there is the possibility of asymmetrical bilateral damage in this patient group.

Other/miscellaneous (n = 12) cases could not be classified into the previous four categories and were grouped together. Seven patients had medical histories and pathologic confirmation of viral or bacterial encephalitis prior to the onset of their epilepsy, two patients had a history of severe head trauma, two had Sturge-Weber syndrome, and one had a large hemispheric brain tumor (ganglioglioma).

Hemispherectomy technique. From 1986 to 2002, three hemispherectomy techniques were utilized at UCLA, and there was a progressive and overlapping change in technique over time. Initially, anatomic hemispherectomy (n = 37) was performed exclusively from 1986 to 1990.19 In 1990, Rasmussen’s functional hemispherectomy (n = 32) was introduced, and for the following years both techniques were performed together until 1997. From 1997 to present we have used a modified lateral hemispherotomy (n = 46).20 The distribution of patients by pathology categories and hemispherectomy technique was not different (χ²; p = 0.51). Therefore, over the time course of this study each pathologic category contains patients having undergone every hemispherectomy technique in a proportion that is not significantly different.

Clinical variables. Clinical information was selected to survey presurgery and operative variables, along with postoperative seizure control, and pre- or postsurgery language, developmental, and motor functions. This information was abstracted from the medical record or through postsurgery interviews. The list of variables is shown in table 1, and those requiring further definition are indicated in the following.

Duration of seizures was defined as the age at surgery minus age at seizure onset in years.

Operative blood loss (mL/kg) was defined as the change in total red cell mass, and calculated as follows: red cell mass in the circulating vascular volume at the start of surgery (starting hematocrit times estimated vascular volume at 75 mL/kg), minus red cell mass at the end of surgery (ending hematocrit times vascular volume), plus red cell mass given during surgery (mL of packed red cells times hematocrit of transfused blood). Assuming a hematocrit of 40, replacement of total blood volume would equal to 30 mL/kg.

Blood given in pediatric ICU. Calculated as the total volume of packed red cells (mL) given in the pediatric ICU (PICU) for the first 3 postsurgery days times the hematocrit of transfused blood (60 divided by patient’s weight (kg)). This assesses continued blood replacement in the postoperative period.

Crystalloids and albumin given in the operating room. The total crystalloids and albumin given in the operating room (OR) was calculated as total mL/kg (continuous variable), and the transfusion of platelets, fresh-frozen plasma (FFP), and cryoprecipitate (cryo) was classified as being given or not (yes/no; nominal variable).

Surgery time. The time, in hours, from entering the operating room to arrival in postanesthesia recovery department (anesthesia plus operating time).

<table>
<thead>
<tr>
<th>Table 1 Clinical variables abstracted from medical record or by interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Presurgery</td>
</tr>
<tr>
<td>Sex (female/male)</td>
</tr>
<tr>
<td>Side resected (left/right)</td>
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<tr>
<td>History of infantile spasms</td>
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<tr>
<td>Weight at surgery, Kg</td>
</tr>
<tr>
<td>Age at seizure onset, y</td>
</tr>
<tr>
<td>Age at surgery, y</td>
</tr>
<tr>
<td>Duration of seizures*</td>
</tr>
<tr>
<td>Operative</td>
</tr>
<tr>
<td>Blood loss in OR, cc/kg*</td>
</tr>
<tr>
<td>Crystalloids in OR, cc/kg</td>
</tr>
<tr>
<td>Albumin in OR, cc/kg</td>
</tr>
<tr>
<td>Fresh frozen plasma, yes/no</td>
</tr>
<tr>
<td>Platelets given in OR, yes/no</td>
</tr>
<tr>
<td>Cryo given in OR, yes/no</td>
</tr>
<tr>
<td>Length of PICU stay, d</td>
</tr>
<tr>
<td>Hospital stay, d</td>
</tr>
<tr>
<td>Abnormal PT/PTT in OR, yes/no</td>
</tr>
<tr>
<td>Lowest platelet count in OR</td>
</tr>
<tr>
<td>Lowest blood pH in OR</td>
</tr>
<tr>
<td>Worse base deficit in OR</td>
</tr>
<tr>
<td>Lowest body temperature in OR</td>
</tr>
<tr>
<td>Surgery time*</td>
</tr>
<tr>
<td>Blood given in PICU, cc/kg*</td>
</tr>
<tr>
<td>Ventriculostomy, yes/no; duration</td>
</tr>
<tr>
<td>Postsurgery</td>
</tr>
<tr>
<td>Seizure control at 0.5, 1, 2, and 5 y*</td>
</tr>
<tr>
<td>Antiseizure medications at 0.5, 1, 2, and 5 y*</td>
</tr>
<tr>
<td>Vineland Developmental Assessments, 0.5 to 2 y*</td>
</tr>
<tr>
<td>Spoken Language Scale and motor skill in paretic limbs*</td>
</tr>
</tbody>
</table>

See text for definition.

OR = operating room; PICU = pediatric intensive care unit; PT/PTT = prothrombin time/partial thromboplastin time.

Postsurgery seizure control. Utilized a previously published scale of seizure frequency from 1 to 5 recorded for a 1-month interval at 6 months, 1 year, 2 years, and 5 years after surgery.20 Seizure frequency was scored as class 1, no seizures; class 2, 1 seizure per month; class 3, 2 to 4 seizures per month; class 4, 5 to 30 seizures per month; and class 5, more than 30 seizures per month. Information was obtained by direct patient or family contact, and was confirmed independently by one individual (S.Y.). For patients requiring reoperation for recurrent seizures, postsurgery seizure control began with the final hemispherectomy procedure, and seizures after the failed first operation were excluded from the analysis.

Postoperative antiepilepsy medications. Recorded the number of AEDs taken by the patient at the time of presurgery evaluation, and at 6 months, 1 year, 2 years, and 5 years postsurgery. Pre- and postsurgery developmental attainments. Developmental levels were assessed using the Adaptive Behavior Composite scale (ABC) of the Vineland Adaptive Behavior Scales (VABS) as previously published.21,23 The VABS was chosen because many...
of the children functioned at such a low developmental level that they were unable to participate in other cognitive tests, and the Vineland assessment could be administered over the age range of this cohort. ABC scales were reported as developmental quotients (developmental age/actual age x 100). The VABS is a semistructured caregiver interview containing 261 items that assess communication, daily living, and socialization skills. Motor skill assessments were excluded because of the hemiparesis associated with hemispherectomy. The ABC scale of the VABS aggregates scores across the aforementioned domains to provide a global index of developmental attainment; VABS interviews were conducted within 2 weeks before surgery and between 6 months and 2 years postsurgery. If multiple postsurgery assessments were available, the one closest to 2 years postsurgery was used. VABS ABC scales are expressed as standard scores with a mean (SD) of 100 ± 15 in the general population, and represent a child’s level of functioning relative to children of the same chronological age.

Pre- and postsurgery language assessments. For children who were too young to be expected to speak (i.e., children <8 months of age at time of surgery), no presurgery language data were collected. For children who did not yet speak or were speaking primarily in one- to two-word utterances language was assessed by means of the MacArthur Communicative Development Inventories (MCDI). For children who consistently produced two-word or longer utterances, language samples were collected. Language samples were audio tape recorded, transcribed, and analyzed for grammatic and lexical content, and each language sample or MCDI assigned a Spoken Language Rank (SLR) as previously published using the following six-point scale: SLR = 0, no language; SLR = 1, fewer than 20 words; SLR = 2, more than 20 words but no word combinations; SLR = 3, short telegraphic utterances typical of the root infinitive (RI) stage in normal language development; SLR = 4, beyond the RI (root infinitive/telegraphic) stage with only occasional errors in the use of functional category elements but no complementizer phrase (CP) embeddings (e.g., relative clauses and other clausal embeddings); SLR = 5, fluent speech plus CP embeddings (but not the full complement of error free structures in the mature grammar); and SLR = 6, mature grammar. The age at postsurgery language interview and duration from surgery were also recorded.

Postsurgery motor function assessments. At the time of postsurgery language assessment, a subgroup of children had functional evaluations of the paretic motor system via a parental interview containing 261 items that assess communication, daily living, and socialization skills. Motor skill assessments were excluded because of the hemiparesis associated with hemispherectomy. The ABC scale of the VABS aggregates scores across the aforementioned domains to provide a global index of developmental attainment; VABS interviews were conducted within 2 weeks before surgery and between 6 months and 2 years postsurgery. If multiple postsurgery assessments were available, the one closest to 2 years postsurgery was used. VABS ABC scales are expressed as standard scores with a mean (SD) of 100 ± 15 in the general population, and represent a child’s level of functioning relative to children of the same chronological age.

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Postsurgery motor function assessments. At the time of postsurgery language assessment, a subgroup of children had functional evaluations of the paretic motor system via a parental interview and questionnaire. If the parent reported that the child could walk, run, ride a bicycle, and climb stairs, each positive answer was given 0.5 points (total of 2 points). If the child could skip he or she received 1.0 point. Alternately if he or she could only jump up and down on one leg he or she received 0.5 points, and if he or she could do it with either leg he or she received 0.5 points (total of 1 point). If the child could kick with both legs he or she received 1 point, and if he or she could do it with either leg he or she received 0.5 points (total of 1 point). Total score for the lower extremity was the sum of the three assessments (2 + 1 + 1 = 4). The upper extremity was assessed by determining if a child could grasp with the whole hand, grasp with a pincer hold, open/close the hand, carry objects with the hand, raise the arm to shoulder height, and bend and straighten the elbow. Each positive answer was counted as one point for a total of six points. The lower and upper extremity scores were added together for a total possible of 10 points, indicating close to normal upper and lower extremity function.

Data analysis. Data were entered into a database and analyzed using a statistical program (StatView 5; SAS Institute Inc., Cary, NC). Differences between pathologic categories (independent variable) involving continuous dependent variables were statistically compared using an analysis of variance (ANOVA), and further compared between subgroups using the Games-Howell post hoc test, which was developed for comparisons of unequally sized samples and heterogeneous variances. The reader should recognize that ANOVA or other statistical methods might not be reliable tests with severely non-normally distributed data. Comparison between pathology groups using nominal dependent variables was performed using χ² tests. Other statistical tests used where appropriate included linear and multiple regression analyses and analysis of covariance (ANCOVA). Results were considered significantly different at a minimal level of significance of p < 0.05.

Results. Pathologic categories. The distribution of cases by pathologic category, hemispherectomy technique, sex, and side resected is shown in table 2. The most frequent pathology in this hemispherectomy series was developmental (HME and hemi CD; 47.8%), followed by infarct/ischemia (23.5%), RE (18.3%), and other/misc (10.4%). This is a young hemispherectomy cohort with a median age at surgery of 3.5 years. Twenty-six cases (23%) were 1 year or less, and 54 (47%) were 3 years or less at hemispherectomy. The youngest patient at hemispherectomy was 6 weeks of age, and the lowest weight was 4.5 kg (different patients). In this series, 46.9% were females, and 59.1% had left sided hemispherectomy. Sex, side resected, and hemispherectomy technique were not different between pathologic categories (χ² tests; p > 0.34).

Of the clinical variables noted in table 1, those that were significantly different by pathologic classification or pre- versus postsurgery assessments are shown in tables 3 and 4, supplementary tables E1 through 3 (available online at www.neurology.org), and figure 2. Table 3 shows mean (±SD) data, and ANOVA and χ² p values. The remainder of the results will sequentially discuss the significant findings in presurgery, operative, and postsurgery subsections. The reader may assume that if a variable from table 1 is not shown in table 3, then that variable was not significantly different by pathologic category.

Presurgery. Most presurgery variables (see table 1) differed by pathologic substrate (see table 3). Age at seizure onset for RE cases was older than the other four pathology groups, and HME patients had a younger age at...
Table 3 Clinical variables significantly different by pathologic substrate in hemispherectomy patients (mean ± SD or no. of cases)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HME</th>
<th>Hemi CD</th>
<th>RE</th>
<th>Infarct/ischemia</th>
<th>Misc/other</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presurgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at seizure onset, y</td>
<td>0.1 ± 0.16</td>
<td>0.5 ± 1.4</td>
<td>4.9 ± 2.3</td>
<td>1.9 ± 2.2</td>
<td>1.3 ± 2.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at surgery, y</td>
<td>1.5 ± 1.2</td>
<td>2.7 ± 3.3</td>
<td>7.8 ± 4.1</td>
<td>8.3 ± 7.2</td>
<td>7.7 ± 8.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Seizure duration, y</td>
<td>1.4 ± 1.1</td>
<td>2.2 ± 2.9</td>
<td>3.0 ± 2.7</td>
<td>6.4 ± 6.2</td>
<td>6.4 ± 6.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight at surgery, Kg</td>
<td>10 ± 4.1</td>
<td>15 ± 12</td>
<td>31 ± 17</td>
<td>25 ± 13</td>
<td>34 ± 29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infantile spasms, yes/total</td>
<td>9/16 (56)</td>
<td>19/38 (50)</td>
<td>0/21 (0)</td>
<td>9/27 (33)</td>
<td>5/13 (38)</td>
<td>0.0013</td>
</tr>
<tr>
<td><strong>Operative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood loss OR, mL/kg</td>
<td>80 ± 74</td>
<td>36 ± 25</td>
<td>23 ± 22</td>
<td>21 ± 19</td>
<td>18 ± 12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood ICU, mL/kg</td>
<td>21 ± 13</td>
<td>12 ± 7.7</td>
<td>13 ± 8.6</td>
<td>13 ± 7.0</td>
<td>9.1 ± 8.1</td>
<td>0.038</td>
</tr>
<tr>
<td>Lowest blood pH</td>
<td>7.31 ± 0.06</td>
<td>7.37 ± 0.05</td>
<td>7.37 ± 0.08</td>
<td>7.39 ± 0.06</td>
<td>7.38 ± 0.06</td>
<td>0.0018</td>
</tr>
<tr>
<td>Surgery time, h</td>
<td>12 ± 1.8</td>
<td>10 ± 2.2</td>
<td>11 ± 2.4</td>
<td>9.3 ± 1.3</td>
<td>9.0 ± 1.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Post-minus pre-Vineland D/Q, 6–24 mo</td>
<td>+9.1 ± 16</td>
<td>+13 ± 15</td>
<td>+4.6 ± 4.9</td>
<td>−0.6 ± 14</td>
<td>−5.8 ± 1</td>
<td>0.026</td>
</tr>
<tr>
<td>Presurgery Spoken Language Rank (SLR)</td>
<td>0.33 ± 0.5</td>
<td>0.17 ± 0.38</td>
<td>3.6 ± 1.9</td>
<td>1.9 ± 2.1</td>
<td>1.2 ± 1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postsurgery SLR</td>
<td>1.4 ± 1.8</td>
<td>3.4 ± 2.0</td>
<td>4.6 ± 1.5</td>
<td>3.8 ± 2.3</td>
<td>2.6 ± 2.4</td>
<td>0.0056</td>
</tr>
<tr>
<td>Postsurgery motor score</td>
<td>1.6 ± 1.7</td>
<td>4.6 ± 2.4</td>
<td>4.7 ± 1.8</td>
<td>5.3 ± 1.7</td>
<td>4.5 ± 2.3</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Post hoc statistical analysis showed the following statistically significant differences by variable:

Age at seizure onset: RE cases had older ages than the other four categories (p < 0.0001), and infarct/ischemia were older than HME patients (p = 0.0019).

Age at surgery: RE were older than HME and hemi CD, and infarct/ischemia were older than HME and hemi CD patients (p < 0.0001).

Duration of seizures: Infarct/ischemia had longer durations than HME and hemi CD (p < 0.0004).

Weight at surgery: RE cases weighed more than HME and hemi CD cases (p < 0.0002), and infarct/ischemia cases weighed more than HME and hemi CD cases (p < 0.01).

Blood loss in OR: HME had more blood loss than the other four pathology categories (p < 0.0001).

Blood given in pediatric ICU: HME had more blood given than the other four pathology categories (p < 0.037).

Lowest OR blood pH: HME had lower intraoperative blood pH compared with hemi CD, infarct/ischemia, and other/misc categories (p < 0.002).

Surgery time: HME had longer operative time compared with infarct/ischemia and other/misc groups (p = 0.0001).

HME = hemimegalencephaly; CD = cortical dysplasia; RE = Rasmussen encephalitis; OR = operating room; ICU = intensive care unit.

Seizure onset than infarct/ischemia cases (see table 3 legend). HME and hemi CD cases were younger and weighed less at surgery than RE and infarct/ischemia patients. Likewise, a history of infantile spasms was more frequent in HME and hemi CD cases compared with infarct/ischemia and RE cases. By comparison, seizure duration before surgery was shorter for HME and hemi CD cases compared with infarct/ischemia cases.

**Operative.** Four variables were significantly different by pathologic category (see table 3). Blood loss during surgery and blood given postsurgery in the PICU was greater in HME patients compared with the other four pathology groups. Operative blood loss was greater than one blood volume equivalent (30 mL/kg) in 79% of HME cases compared with 57% of the hemi CD, 15% of the RE, 17% of the infarct/ischemia, and 25% of the other/misc group. It might be expected from the perioperative blood loss, the lowest intraoperative blood pH was found in HME cases compared with hemi CD, infarct/ischemia, and other/misc categories. Similarly, surgery time was longer in HME patients compared with infarct/ischemia and other/misc cases.

Table 4 Percentage of hemispherectomy patients seizure free at 0.5, 1, 2, and 5 years postsurgery by pathology, n (%)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>0.5 Year</th>
<th>1.0 Year</th>
<th>2 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemimegalencephaly</td>
<td>15 (73.3%)</td>
<td>14 (57.1%)</td>
<td>13 (46.1%)</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>Hemi CD</td>
<td>37 (78.4%)</td>
<td>32 (81.2%)</td>
<td>29 (82.7%)</td>
<td>15 (60.0%)</td>
</tr>
<tr>
<td>RE</td>
<td>20 (75.0%)</td>
<td>16 (81.2%)</td>
<td>15 (66.7%)</td>
<td>8 (62.5%)</td>
</tr>
<tr>
<td>Infarct/ischemia</td>
<td>27 (85.2%)</td>
<td>24 (75.0%)</td>
<td>22 (72.7%)</td>
<td>14 (71.4%)</td>
</tr>
<tr>
<td>Other/Misc.</td>
<td>13 (76.9%)</td>
<td>11 (81.8%)</td>
<td>9 (55.6%)</td>
<td>7 (42.8%)</td>
</tr>
</tbody>
</table>

*p Value* 0.89 0.45 0.15 0.51

CD = cortical dysplasia; RE = Rasmussen encephalitis.
Operative morbidity and mortality. Overall, 27% (n = 31) of hemispherectomy patients had postoperative problems ranging from serious (n = 4), moderate (n = 16), to minor (n = 11). Of the serious complications, there are two known deaths in this cohort. One death occurred in a 7-month-old with HME who died intraoperatively from excessive blood loss, and the case has been previously published. A second hemispherectomy patient in the infarct/ischemia group died many months postsurgery due to shunt failure. In addition, there were two emergent reoperations for acute epidural/subdural hematomas (hemi CD and infarct/ischemia).

Of the moderate complications, 16 patients had late reoperations for recurrent seizures or to repair skull defects. Of the 14 reoperations for recurrent seizures (the other 2 were for nonseizures), 4 (33%) were in the HME category, 8 (21%) in the hemi CD, and 2 (9%) in the RE group. Of the 14 reoperations for seizures, seizure control after the second surgery was achieved in 7 (50%) cases. The minor complications include nine cases of postsurgery ventricular infections that were successfully treated with antibiotics, and one case each of a transient cranial nerve III palsy and inappropriate antidiuretic hormone (ADH). Numerically, HME patients had more operative complica-

Figure 2. Linear regression analyses comparing postsurgery Vineland Adaptive Behavior Scale (VABS) developmental quotients (DQ) with seizure duration (upper left), and averaged postsurgery seizure scores (upper right). R and p values are shown for the upper row. Lower row shows box plots with pre-, post- (lower left), and post- minus presurgery VABS developmental quotients (lower right). Box plots indicate the median, 25th to 75th percentiles, and individual data points outside the range of 1.5 standard deviations of the mean. Post-Pre Vineland DQ: post hoc tests revealed that hemispheric cortical dysplasia had improved differences in DQ scores compared with infarct/ischemia and other/misc groups (**p < 0.05).
tions (37.5%) compared with the other pathology categories (25%), but the differences were not significant ($\chi^2; p = 0.16$). Shunts, which were not considered an operative complication, were necessary in 39.6% of hemispherectomy patients, and there was no significant difference between HME (27%), hemi CD (46%), RE (29%), infarct/ischemia (44%), and other/misc (45%) cases.

**Postsurgery seizure control.** Presurgery all hemispherectomy patients had uncontrolled epilepsy (seizure score 4 or 5), and the mean seizure scores were not different by pathologic category (ANOVA; $p = 0.10$). Postsurgery follow-up information was available on all but two hemispherectomy patients (see above). Posthemispherectomy, 78.6% of patients were seizure free at 6 months ($n = 112$), 76.3% at 1 year ($n = 97$), 70.4% at 2 years ($n = 88$), and 58.0% at 5 years ($n = 50$). The decline in seizure-free patients from 2 to 5 years postsurgery is similar to all extratemporal pediatric epilepsy surgery patients (hemispherectomy and nonhemispherectomy) with similar pathologic substrates and seizure types. Numerically, fewer HME patients were seizure free at 1, 2, and 5 years postsurgery compared with the other pathology categories, but the differences were not significant at any time interval ($\chi^2; p > 0.15$; see table 4). Age at surgery ($p > 0.34$) and duration of seizures ($p > 0.22$) did not correlate with seizure control (Class 1 through 5) at 0.5, 1, 2, or 5 years posthemispherectomy. For hemispherectomy patients with persistent seizures, 79% had postsurgery seizure scores of 4 or 5 indicating they had more than one seizure per week.

**Postsurgery AED usage.** Presurgery, all patients except 2 (2%) were taking AEDs, the mean ($\pm$SD) AED per patient was 2.6 $\pm$ 1.1, and the number of AEDs per patient did not differ by pathology category (HME, 2.5 $\pm$ 0.9; hemi CD, 3.0 $\pm$ 1.2; RE, 2.7 $\pm$ 1.0; infarct/ischemia, 2.3 $\pm$ 1.0; other/misc, 2.3 $\pm$ 1.4; ANOVA, $p = 0.23$). Posthemispherectomy, 11.2% of patients were no longer taking AEDs at 6 months, 25.0% at 1 year, 42.9% at 2 years, and 38.2% at 5 years (supplementary table E1, available online at www.neurology.org). Numerically, HME patients were taking more AEDs 2 years postsurgery (mean $\pm$ SD; 1.7 $\pm$ 1.2) compared with the other pathology groups (0.8 $\pm$ 0.9), but the difference was not significant ($p = 0.07$).

**Pre- and postsurgery developmental attainment.** VABS interviews were conducted on 57.4% ($n = 66$) of patients, either presurgery ($n = 58$) and/or postsurgery ($n = 52$). Of these, 44 patients (38%) had both pre- and posthemispherectomy assessments. To determine if patients who had VABS interviews were representative of the entire cohort, we compared presurgery variables (shown in table 1) in those hemispherectomy cases that did and did not have Vineland assessments, and found no differences ($p > 0.075$). The mean ($\pm$SD) follow-up interval was 1.56 $\pm$ 0.56 years for postsurgery VABS interviews.

Single factor linear regression analysis of the VABS ABC scales showed that the best postsurgery DQs were associated with shorter seizure durations prior to surgery ($p = 0.0071$), and better postsurgery seizure control ($p = 0.014$; figure 2, top row). Of patients with seizure durations of 3 years or less, 52% had postsurgery VABS ABC DQ scores above 50, compared with 13% who had seizure durations greater than 3 years. Similarly, 30% of posthemispherectomy patients who were seizure free at all postsurgery time intervals (Score 1) had VABS DQs above 50 compared with only 13% with postsurgery seizures (Score $>2$). In a second analysis we performed a multiple regression ANCOVA with seizure duration, postsurgery seizure score, and pathology as the independent variables, and Vineland DQ scores as the dependent variable. The ANCOVA statistical analysis showed that seizure duration ($p = 0.0081$) and postsurgery seizure control ($p = 0.016$), but not pathologic classification ($p = 0.25$) correlated with postsurgery VABS ABC DQs without two-way or three-way interactions between the independent variables ($p > 0.77$). In other words, the best postsurgery VABS DQs were associated with shorter seizure duration prior to hemispherectomy (2 to 3 years or less) and postsurgery seizure control, regardless of the pathologic substrate.

Pre- and postsurgery VABS ABC DQs did not differ by pathologic classification, but the difference from post- versus pre-DQs was different by pathology group (see table 3, figure 2, lower row). The average ($\pm$SD) presurgery VABS ABC DQs for all hemispherectomy patients was 33.9 $\pm$ 19 (range 6 to 81), and there were no differences among pathologic categories (ANOVA; $p = 0.56$; see figure 2, lower left). Presurgery, 15.1% of all hemispherectomy patients had ABC DQs greater than 50. By pathology category, presurgery 0% of HME cases, 35% of hemi CD, 11% of RE, and 6% of infarct/ischemia cases had DQ scores over 50. There were also no differences between pathologic categories in postsurgery VABS ABC DQs (37.4 $\pm$ 17; range 4 to 80; see table 3 and figure 2, lower left; $p = 0.094$). Postsurgery, 29.2% of hemispherectomy patients had DQs more than 50, with 11% in the HME group, 47% in the hemi CD, 29% for RE, and 24% for infarct/ischemia cases. As might be expected, pre- and postsurgery VABS ABC DQ scores from the same patient positively correlated with each other ($r = +0.61; p < 0.0001$).

Most patients showed an increase in postsurgical VABS ABC DQs compared to presurgery, and the degree of improvement varied by pathologic substrate (see figure 2, lower right). The mean ($\pm$SD) increase in post- vs presurgery VABS ABC DQ for all hemispherectomy patients was 5.3 $\pm$ 15 (range $−39$ to $+41$). There was a significant effect of pathology category (ANOVA; $p = 0.026$) with the hemi CD group showing the best improvement compared with infarct/ischemia and other/misc patient groups (see figure 2, lower right; $p < 0.046$). Repeating the statistical analysis (ANCOVA) with pathology group and presurgery DQ scores as the independent variables and the post- vs pre-DQ differences as the dependent variable found that both independent variables were significant without a significant interaction ($F/p$ value; pathology group, 3.1/0.027; presurgery DQ, 16.1/0.0003; interaction, 1.04/0.40). In other words, the differences in pre- vs postsurgery DQ scores between pathology groups remain significant after accounting for presurgery DQ scores.

Overall, 57% of hemispherectomy patients showed $+5$ points or better change in pre- versus postsurgery VABS DQs. However, 27% showed between $+5$ and $−5$ change, and 16% showed $−5$ point or greater decrease in DQ scores. Six (13.6%) patients, whose presurgery DQ scores were from 5 to 30, had $+20$ point or more improvements in postsurgery DQ scores. Four were hemi CD and two were HME, and all but one was seizure free. By comparison, 3 (6.8%) patients had $−20$ point or greater decline in postsurgery DQ scores. Their presurgery DQ scores were 40, 58, and 80. Two were infarct/ischemia and one was a viral
encephalitis case, and all continued to have epilepsy after hemispherectomy. In sum, 84% showed unchanged or improved VABS DQs after hemispherectomy with the greatest improvement occurring in patients with hemi CD and HME, although these patients often began with DQ scores less than 50.

Long-term postsurgery SLR and motor assessments of paretic limbs. Language samples were collected from 59% (n = 68) of patients, either pre- (n = 60) or postsurgery (n = 68) or both. Of these, 59 (51%) patients had both pre- and postsurgery assessments. To determine if patients who had language assessments were representative of the entire cohort, we compared presurgery variables (shown in table 1) in those hemispherectomy cases that did or did not have language assessments, and found no differences (p > 0.18). The mean (±SD) follow-up interval for postsurgery language/motor assessments was 6.2 ± 3.5 years, and there was no difference in follow-up interval by pathologic category (ANOVA; p = 0.69). The average age (± SD) at most recent postsurgery language evaluation was 10.7 ± 4.8 years. As would be expected based on their age at operation, 70% of patients did not speak or had fewer than 20 spoken words prior to hemispherectomy (SLR < 1; see supplementary table E2, available online at www.neurology.org). Presurgery, a few RE and infarct/ischemia cases had SLRs of 3 or above, and most of the HME and hemi CD cases did not speak (SLR = 0). Thus, postsurgery SLR scores were different by pathology category with RE cases showing higher SLRs than the other four groups (see table 3 and supplementary table E-2 available online at www.neurology.org; p < 0.0001).

Posthemispherectomy assessments showed that many children had acquired considerable language, and there was a difference of SLR by pathology category (see supplementary table E-2). Nearly half (47%) of the hemispherectomy children showed long-term postsurgery SLRs of 5 or above, indicating fully developed language, while 26% did not speak or had less than 20 spoken words (SLR < 1). Of the posthemispherectomy cases who did not acquire language (SLR = 0), four were in the HME group, even though the mean (±SD) age at postsurgery language sampling was 7.3 ± 4.0 years, similar to the hemi CD cases (8.3 ± 3.3; p = 0.58). An equal number (4) with SLR of 0 were in the infarct/ischemia group, even though the age at surgery was similar to the RE cases. Postsurgery SLR scores were different by pathology group with RE cases showing higher SLRs than the other four groups (see table 3 and supplementary table E-2 available online at www.neurology.org; p < 0.0001).

Posthemispherectomy patients found pre- and postsurgery differences to be more relevant for hemispherectomy patients than those with HME, hemi CD, RE, and infarct/ischemia cases. Postsurgery VABS assessments showed +5 points or more improvement in DQ scores in 57% of hemispherectomy patients, and hemi CD patients had the most improved DQ scores compared with RE and other/misc cases (see figure 2). Furthermore, postsurgery VABS DQ scores correlated with shorter seizure duration (see figure 2) and both DQ and SLR scores correlated with postsurgery seizure control.

It is important to note the potential limitations of this study when interpreting our results. For example, we had very few patients with Sturge-Weber syndrome (n = 2), and this group has a high rate of posthemispherectomy seizure control and excellent language prognosis. Therefore our results are likely to be more relevant for hemispherectomy patients with HME, hemi CD, RE, and infarct/ischemia as pathologic substrates, and may or may not be applicable to other pathology groups. Similarly, the median age at surgery for our study was 3.5 years, and our results should be compared cautiously with older hemispherectomy cohorts, in which the pathologic substrates more often reflect atrophic etiologies.
nally, we were only able to assess a portion of our hemispherectomy patients for postsurgery developmental, language, and motor assessments, often because families lived a long distance from UCLA, they declined participation, or the children were not developmentally mature enough to participate in the language and motor studies. The group of patients with data showed similar presurgery characteristics with the entire cohort, and our sample sizes were large enough to find significant differences in VABS, language, and motor outcomes between HME and the other pathology groups. However, larger sample sizes may be necessary to detect differences between hemi CD, RE, and infarct/ischemia subgroups.

Previous studies of epilepsy surgery patients in the modern neuroimaging era have suggested that patients with CD or HME have poorer postsurgery seizure outcomes and neurologic development compared with other pathology groups. For example, 52 to 61% of children under 2.5 to 3 years of age are reported to be seizure free postsurgery, but these studies include a higher incidence of tumors and operations other than hemispherectomy, compared with our report. Surgical series of CD patients indicate that 11 to 50% are seizure free postsurgery, but these studies involve multiple types of resective surgeries in children and/or adults and do not compare CD with other pathology groups from the same institution. Likewise, reports indicate that 38 to 60% of hemispherectomy patients with CD are seizure free compared with 67 to 88% with RE and infarct/ischemia etiologies, but these studies do not distinguish between HME and hemi CD pathologic substrates. There are hemispherectomy studies that have compared HME with hemi CD cases, but they have 10 patients or less in each group, and do not include other pathologic groups for comparison. Collectively, they report that 37% (15/41) of HME and 58% (14/24) of hemi CD patients are seizure free postsurgery, and 11% (2/18) of HME and 33% (2/6) of hemi CD patients have postseizure DQ scores greater than 50. However, these hemispherectomy studies have not compared pathology subgroups for differences in postsurgery language and/or motor assessments.

The results of our study agree but also disagree with previous conclusions. For example, we found that HME cases were the most challenging surgically, and pre- and postsurgery very few children had DQ scores above 50. In contrast, we found that hemi CD children, who had similar ages at surgery as the HME cases, were no more difficult to manage perioperatively and had similar seizure outcomes, AED usage, VABS DQ assessments, and language and motor scores as RE and infarct/ischemia cases. While HME patients had the least probability of postsurgery seizure control (58.3%), it was higher in our series than previously reported (37%; see above references). Furthermore, the HME group showed an improvement in postsurgery VABS DQ scores that averaged +9 points (see figure 2), and two of the six cases with +20 points or more improvement in DQ scores were HME children. Hence, our results agree with previous studies that HME cases are less likely to be seizure free posthemispherectomy, and most patients will have significant impairments as assessed by developmental, language, and motor tests. However, a proportion of HME patients clearly benefited from the surgery with regard to seizure control and postsurgery DQ scores, which is significant given the high mortality of similar children with intractable symptomatic epilepsy. Just as importantly, 77.9% of hemi CD cases were seizure-controlled posthemispherectomy, and many showed improved DQ scores, and language and motor assessments similar to RE and infarct/ischemia cases. Thus, younger hemi CD patients benefited equally or better from cerebral hemispherectomy compared with older RE and infarct/ischemia pathology groups, which are the traditional types of patients referred for surgery. These findings support the notion that not all CD patients do poorly with regards to seizure control and neurologic outcomes after cerebral hemispherectomy.

There are few previous studies in the contemporary medical literature examining neurologic outcomes posthemispherectomy. Based on their findings and our data, at least three factors are consistently associated with the best postsurgery developmental, language, or motor outcomes, irrespective of the pathologic substrate: 1) higher presurgery developmental attainments, 2) shorter seizure durations before surgical intervention, and 3) postsurgery seizure control.

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Cerebral hemispherectomy: Hospital course, seizure, developmental, language, and motor outcomes


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