Impact of intraoperative 3-T MRI with diffusion tensor imaging on hemispherectomy

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ABSTRACT

OBJECTIVE Hemispherectomy can produce remarkable seizure control of medically intractable hemispheric epilepsy in children, but some patients continue to have seizures after surgery. A frequent cause of treatment failure is incomplete surgical disconnection of the abnormal hemisphere. This study explores whether intraoperative 3-T MRI with diffusion tensor imaging (DTI) during hemispherectomy can identify areas of incomplete disconnection and allow complete disconnection during a single surgery.

METHODS The charts of 32 patients with epilepsy who underwent hemispherectomy between January 2012 and July 2014 at the Florida Hospital for Children were reviewed. Patients were grouped as having had curative or palliative hemispherectomy. To assess the completeness of disconnection when the surgeon considered the operation completed, intraoperative 3-T MRI-DTI was performed. If incomplete disconnection was identified, additional surgery was performed until MRI-DTI sequences confirmed satisfactory disconnection. Seizure outcome data were collected via medical records at last follow-up.

RESULTS Of 32 patients who underwent hemispherectomy, 23 had curative hemispherectomy and 9 had palliative hemispherectomy. In 11 of 32 surgeries, the first intraoperative MRI-DTI sequences suggested incomplete disconnection and additional surgery followed by repeat MRI-DTI was performed. Complete disconnection was accomplished in 30 of 32 patients (93.8%). Two of 32 disconnections (6.3%) were incomplete on postoperative imaging. Cross-sectional results showed that 21 of 23 patients (91.3%) who had curative hemispherectomy remained free of seizures (International League Against Epilepsy Class 1) at a median follow-up of 1.7 years (range 0.4–2.9 years). The longitudinal seizure freedom after curative hemispherectomy was 95.2% (SE 0.05) at 6 months, 90.5% (SE 0.06) at 1 year, and 90.5% (SE 0.05) at 2 years.

CONCLUSIONS Intraoperative 3-T MRI-DTI sequences can identify incomplete disconnection during hemispherectomy and allow higher rates of complete disconnection in a single surgery. Higher rates of complete disconnection seem to achieve better seizure-free outcome following modified functional hemispherectomy.

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KEY WORDS epilepsy; curative hemispherectomy; palliative hemispherectomy; magnetic resonance imaging; seizure outcome; surgery

Since hemispherectomy was introduced as treatment for epilepsy by McKenzie in 1938,13,16 various technical modifications have been developed to improve seizure-free outcomes and minimize surgical complications.4,19–24 The original procedure, the anatomical hemispherectomy, although initially successful in creating seizure control, was associated with unacceptable delayed complications and was largely abandoned.5,7,9,18,25–28 Rasmussen19 postulated, and later proved, that a more limited resection, with disconnection of remaining hemispheric tissue, was as effective in seizure control as the anatomical procedure, but associated with much lower rates of late complications. Rasmussen’s approach has been further modified to allow even less tissue removal, with more elegant and less invasive disconnection methods.20

Usually, hemispherectomy is offered to patients with...
unilateral electroencephalography (EEG) abnormalities or hemispheric lesions. Recent series have demonstrated that patients with bilateral EEG abnormalities or structural lesions can also benefit from hemispherectomy. This so-called palliative hemispherectomy can result in both improved seizure control and quality of life,\(^3,^{11}\) as long as the most disabling seizure activity can be localized to a single hemisphere and there are no additional neurological deficits associated with the surgery.

Despite this surgical evolution, recently published hemispherectomy series report rates of seizure freedom between 61% and 80%,\(^2,^3,^8,^{10,17,24}\) The most frequent cause of surgical failure is incomplete disconnection of frontal-basal cortex, followed by incomplete resection of corpus callosum and insular cortex.\(^26\) Ensuring complete disconnection can be particularly challenging in younger patients with dysmorphic brains. Although intraoperative imaging can provide useful anatomical information, it is possible to miss areas of incomplete disconnection with this approach. Frequently, the residual connections are only detected on postoperative diffusion tensor imaging (DTI) sequences. We chose to examine the benefit of intraoperative 3-T MRI with DTI for achieving complete disconnection and better seizure outcome in modified functional hemispherectomy.

**Methods**

**Data Collection**

All patients who underwent a modified functional hemispherectomy at Florida Hospital for Children between January 2012 and July 2014 were included in the study. Clinical, EEG, imaging, and surgical data were collected via retrospective chart review. Seizure outcome data were collected via medical records at last follow-up. Seizure classification was based on the video EEG–documented seizures. Etiology was determined from clinical, imaging, and pathology results. Hemispherectomy cases were classified as palliative if seizure activity was identified as originating from independent ictal foci in both hemispheres during preoperative evaluation. If seizure onset was determined to be unihemispheric, the surgery was classified as curative hemispherectomy. The International League Against Epilepsy (ILAE) seizure outcome score was collected from the last follow-up record. The ILAE classification\(^27\) is as follows: 1) completely seizure free, no auras; 2) only auras, no other seizures; 3) 1–3 seizure days per year, with or without auras; 4) 4 seizure days per year to 50% reduction of baseline seizure days, with or without auras; 5) < 50% reduction of baseline seizure days to 100% increase of baseline days, with or without auras; and 6) > 100% increase of baseline seizure days, with or without auras.

Approval by the Florida Hospital Institutional Review Board was obtained before initiation of this retrospective study. Patients’ families gave consent prior to participation in our registry.

**Preoperative Evaluation**

Patients underwent detailed preoperative evaluation including 5-day video EEG, 3-T MRI (Siemens), FDG-PET, ictal and interictal technetium-99m SPECT with subtraction ictal SPECT coregistered to MRI (SISCOM), and neuropsychological evaluation. If necessary, magnetoecephalography, functional MRI, and Wada testing were performed. The surgical decision for hemispherectomy was made based on consensus of the Florida Hospital comprehensive epilepsy board meeting.

**Intraoperative Procedures**

A modified functional hemispherectomy technique involved resection of the temporal lobe, posterior frontal lobe, and anterior parietal lobe, followed by a complete corpus callosotomy and frontal and posterior temporal/occipital disconnections. All surgeries were performed by 1 surgeon (J.B.). Neuronavigation (Stryker) was used during surgery. After the first disconnection attempt, T2-weighted axial and T2-weighted coronal images were obtained by intraoperative 3-T MRI (Siemens) utilizing DTI. The MRI parameters were as follows: axial T2-weighted using number of excitations 2, TR 4200 msec, TE 95 msec with 4-mm slices (4 minutes); coronal T2-weighted using number of excitations 1, TR 4700 msec, TE 119 msec with 2-mm slices (7 minutes); and DTI using number of excitations 1, TR 4800 msec, TE 95 msec with 4-mm slices (3 minutes). Intraoperative 3-T MRI with DTI results were reviewed by the neurosurgeon, neuroradiologists, and epileptologists to confirm satisfactory disconnection. If incomplete disconnection was identified, the surgeon continued the operation to achieve complete disconnection. When DTI suggested intact white matter connections, we located them using our updated post-intraoperative MRI navigation coordinates. We adjusted the frameless navigation based on intraoperative scan data. A second intraoperative MRI-DTI was then performed to confirm completion of the disconnection. After disconnection was confirmed, insular electrocorticography (ECoG) was performed in 19 patients intraoperatively. If epileptiform discharges were found on insular ECoG, insular resection was continued until epileptiform discharges ceased on repeat insular ECoG.

**Statistical Analysis**

Kaplan-Meier survival analysis was used to calculate the longitudinal seizure freedom rate in the patients who underwent curative hemispherectomy. All statistical analyses were performed using SPSS 19 (SPSS, Inc.).

**Results**

**Patient Data**

Thirty-two patients had hemispherectomy during the study period (Table 1). Twenty-three procedures were curative and 9 were palliative hemispherectomy. Two patients with chronic Rasmussen encephalitis showed independent ictal foci in both hemispheres, classified as palliative hemispherectomy. The other patients who had palliative hemispherectomies showed bilateral independent ictal foci with 3 ischemia, 2 bilateral cortical malformations, and 2 unknown etiologies. Thirteen (7 curative and 6 palliative) of 32 patients had a history of epilepsy surgery. Results of preoperative evaluation are shown in Table 2. Eight (6
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Intraoperative Procedures

Intraoperative MRI-DTI was done after the first attempt at disconnection. Figure 1 is an example of intraoperative MRI-DTI showing the status of disconnection. Residual connection with the corpus callosum (Fig. 1A, arrow) and frontal-basal cortex (Fig. 1B, arrow) were identified during the first trial and complete disconnection was confirmed during the second trial (Fig. 1C and D). Following disconnection, the epileptogenicity of the insular cortex was assessed with intraoperative insular ECoG in 19 patients. Epileptiform insular cortex was resected in 5 of 19 patients who underwent insular ECoG.

Surgical Outcomes

Complete disconnection was accomplished in 30 of 32 patients (93.8%), with 11 undergoing a second intraoperative MRI after further resection (Table 3). The other 2 of 32 (6.3%) were found to have incomplete disconnection postoperatively, but technical difficulties did not allow an intraoperative DTI sequence to be obtained. Fifteen brain areas with incomplete disconnection were identified intraoperatively (11 patients) or postoperatively (2 patients): 5 anterior genu, 5 posterior corpus callosum, 4 frontal-basal cortices, and 1 temporal cortex. Two patients had 2 different areas of incomplete disconnection. Postoperative hydrocephalus developed in 7 of 32 patients (21.9%), requiring ventriculoperitoneal shunt placement between 7 and 52 days (median 17 days) after hemispherectomy. No patient had postoperative infection requiring surgical management, and no mortality occurred. All 11 patients (2 curative, 9 palliative) with breakthrough seizures showed seizure onset from the nonoperated hemisphere.

Pathology Results

Findings from neuropathological evaluation of the surgically resected specimens included focal cortical dysplasia, hippocampal sclerosis, Rasmussen encephalitis, evidence of neonatal ischemic events, and 1 case of unusual axonal dystrophy (Table 4). The most common finding was various forms of focal cortical dysplasia. These were

TABLE 1. Profiles of 32 patients who underwent hemispherectomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall, N = 32</th>
<th>Hemispherectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at seizure onset, yrs (range)*</td>
<td>0.54 (0–65.0)</td>
<td>0.58 (0–65.0)</td>
</tr>
<tr>
<td>Median age at op, yrs (range)*</td>
<td>7.6 (0.5–65.4)</td>
<td>7.16 (0.5–65.4)</td>
</tr>
<tr>
<td>Median interval from seizure onset to op, yrs (range)</td>
<td>4.1 (0.1–17.7)</td>
<td>3.4 (0.1–15.7)</td>
</tr>
<tr>
<td>Etiology, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia/stroke</td>
<td>11 (34.4)</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>Hemimegalencephaly</td>
<td>2 (6.3)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Extensive dysplasia</td>
<td>15 (46.9)</td>
<td>12 (52.2)</td>
</tr>
<tr>
<td>Rasmussen encephalitis</td>
<td>4 (12.5)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Seizure type, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal seizures only (w/ w/o evolvement to both hemispheres)</td>
<td>20 (62.5)</td>
<td>14 (60.9)</td>
</tr>
<tr>
<td>Focal &amp; generalized seizures</td>
<td>12 (37.5)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Generalized seizure only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Previous op, no. (%)†</td>
<td>13 (40.6)</td>
<td>7 (30.4)</td>
</tr>
</tbody>
</table>

* Three patients were older than 18 years.
† Nine patients had corpus callosotomy, 2 had lobar resection, 1 had corpus callosotomy and lobar disconnection, and 1 had incomplete disconnection of functional hemispherectomy at an outside hospital.

TABLE 2. Presurgical evaluation of 32 patients who underwent hemispherectomy

<table>
<thead>
<tr>
<th>Method of Detection &amp; Lesion Type</th>
<th>Overall, N = 32</th>
<th>Hemispherectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of Detection &amp; Lesion Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interictal EEG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateralizing</td>
<td>20 (62.5)</td>
<td>18 (78.3)</td>
</tr>
<tr>
<td>Nonlateralizing</td>
<td>12 (37.5)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>22 (68.8)</td>
<td>22 (95.7)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>4 (12.5)</td>
<td>* (4.3)</td>
</tr>
<tr>
<td>Bilateral independent</td>
<td>6 (18.8)</td>
<td>0</td>
</tr>
<tr>
<td>MRI†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>24 (75.0)</td>
<td>21 (91.3)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>6 (18.8)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>PET</td>
<td>n = 27</td>
<td>n = 20</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>22 (81.5)</td>
<td>17 (65.0)</td>
</tr>
<tr>
<td>Nonlateralizing</td>
<td>5 (18.5)</td>
<td>3 (15.0)</td>
</tr>
</tbody>
</table>

All values reported as number of patients (%).
* The patient had a history of ruptured cerebral aneurysm. All other measures indicated right hemisphere origin of seizure except diffuse onset of ictal EEG.
† MRI lesions include cortical abnormalities, white matter changes, and evident brain lesions.
classified based on the new ILAE classification proposed by the ILAE task force and ranged from ILAE Type I (subtle abnormalities of cortical lamination) to Type III (those associated with other pathologies, e.g., Rasmussen encephalitis, perinatal stroke, and so on).1

Seizure Outcomes

Cross-sectional results showed 21 of 23 patients (91.3%) who underwent curative hemispherectomy remained free of seizures (ILAE Class 1) at median follow-up of 1.7 years (range 0.4–2.9 years) (Fig. 2). The longitudinal freedom from seizure after curative hemispherectomy was 95.2% (SE 0.05) at 6 months, 90.5% (SE 0.06) at 1 year, and 90.5% (SE 0.05) at 2 years (Fig. 3). Two patients with incomplete disconnection following curative hemispherectomy remained free of seizures during the follow-up period. For palliative hemispherectomy, 8 of 9 patients (88.9%) had a greater than 50% seizure reduction compared with baseline: ILAE Class 2 (n = 1), Class 3 (n = 1), and Class 4 (n = 6). One of 9 patients showed a less than 50% seizure reduction (ILAE Class 5) (Fig. 2).

Discussion

Hemispheric disconnection surgery is a complicated, multistep procedure. It is typically performed over several hours and can be particularly challenging when the affected hemisphere is poorly organized and the patient is very young. Many hemispherectomy failures are found on postoperative evaluation to have incomplete disconnection.

Intraoperative 3-T MRI-DTI allowed us to assess technical comprehensiveness of the first surgical attempt at hemispheric disconnection and to achieve a complete disconnection in a single surgical session.

Complete disconnection has been reported in 12.9%–

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Overall, N = 32</th>
<th>Hemispherectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasmussen encephalitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>FCD (ILAE Type IIID)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>FCD (ILAE Types III/MCD)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Others*</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

*Includes other pathologies without FCD including mesial temporal sclerosis, remote infarctions, gliosis, radiation necrosis post tumor, and 1 case of an unusual form of infantile axonal dystrophy.

* For 2 patients, the MRI magnet either could not be brought into the operating room or did not function properly during that surgery. Both patients remained free of seizures during the follow-up.

† Two patients had multiple areas of incomplete disconnection.
54.5% of patients following hemispheric disconnection surgery.\textsuperscript{6,14} When reoperation resulted in improved seizure control, incomplete disconnection was considered the cause of failure at first surgery.\textsuperscript{6} Recently, DTI was selectively used for 8 patients with persistent seizures after hemispherectomy to detect residual white matter association fiber connecting the 2 hemispheres.\textsuperscript{12} Incomplete disconnection was identified on DTI in all patients, and 5 patients became free of seizures after repeat surgery.

In our center, intraoperative 3-T MRI-DTI was routinely performed during hemispherectomy. We used frameless navigation, and adjusted the navigation based

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{A flow chart showing cross-sectional seizure outcomes after hemispherectomy. ILAE Class 1 = seizure free; ILAE Class 2 = only auras; ILAE Class 3 = 1–3 seizure days per year; ILAE Class 4 = 4 seizure days per year to 50% reduction of baseline seizure days; ILAE Class 5 = < 50% reduction of baseline seizure days.\textsuperscript{27} The overall median follow-up is 1.7 years (range 0.4–2.9 years).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{survival.png}
\caption{Longitudinal seizure outcomes in curative hemispherectomy (n = 23). Kaplan-Meier survival curves illustrate seizure-free rates at various postoperative time intervals. Figure is available in color online only.}
\end{figure}
on updated scan data. DTI was therefore “seeing” intact white matter connections while intraoperative MRI easily located the updated areas to remove. The total time commitment for the intraoperative scan is roughly 40–50 minutes from start to finish. It took approximately 15–20 minutes to prepare the patient for the scan. The actual scan time is less than 20 minutes, and the time it takes to review the studies is approximately 5–10 minutes. DTI data were sufficient to easily and rapidly identify areas of incomplete disconnection. In 11 of 32 patients (34.4%), disconnections were found to be incomplete on initial intraoperative MRI-DTI. In all 11 cases, when areas of residual connection were suggested on intraoperative MRI, structural connections were identified and divided during surgery. Repeat intraoperative imaging confirmed the completeness of disconnection following the additional attempt.

Incomplete disconnection does not always result in seizure recurrence, but it does appear to increase that risk. In our series, 34.4% of patients benefitted from intraoperative 3-T MRI-DTI, allowing us to obtain a complete disconnection during a single surgery. Without intraoperative DTI, these patients would have had incomplete surgical disconnection and been put at a higher risk of seizure recurrence. Our 2 surgical failures occurred without the benefit of intraoperative DTI, because the MRI scanner was out of order during that surgery.

Seizure Outcomes

Longitudinal analysis provides a reasonable assessment of seizure outcomes in series with variable durations of follow-up. In a recent longitudinal study of 186 patients who underwent hemispherectomy, the seizure freedom rate was 78% at 6 months, 76% at 1 year, and 71% at 2 years. A meta-analysis of long-term seizure outcome following hemispherectomy showed 61% (95% CI 54–68) seizure-free outcome in 169 patients. In our study, the seizure freedom rate after curative hemispherectomy was 95.2% (SE 0.05) at 6 months, 90.5% (SE 0.06) at 1 year, and 90.5% (SE 0.05) at 2 years.

Palliative Surgery

Palliative hemispherectomy was chosen in cases where most disabling seizures originated from 1 hemisphere and where hemispherectomy would allow improved seizure control and quality of life without additional neurological deficit. The benefit of palliative functional hemispherectomy was reported in several case series. Lupashko and colleagues reported a child with refractory status epilepticus who underwent palliative hemispherectomy to control seizures. Ciliberto et al. reported 7 patients who underwent palliative hemispherectomy, with 3 patients achieving seizure freedom (Engel Epilepsy Surgery Outcome Scale Class I) and all patients experiencing improved quality of life. Ilyas and colleagues reported that 5 of 9 patients had a greater than 50% seizure reduction (ILAE Classes 1–4), and 4 of 9 showed a less than 50% reduction (ILAE Class 5) than baseline. In our study, 8 of 9 patients had a greater than 50% seizure reduction (ILAE Classes 2–4), and in 1 of 9, the seizure burden decreased (ILAE Class 5).

Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Baumgartner. Acquisition of data: Kim, Seo, Schroff, Chen. Analysis and interpretation of data: Kim, Seo, Schroff. Drafting the article: Kim, Chen. Critically revising the article: Lee. Reviewed submitted version of manuscript: Baumgartner. Approved the final version of the manuscript on behalf of all authors: Baumgartner. Statistical analysis: Kim, Chen. Administrative/technical/material support: Chen.

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